1 INTRODUCTION TO PHARMACOLOGY

- Pharmacology is the study of drugs.
- Proper dosages are defined in pharmacology.
- Uses, non-uses, how the drug works, and adverse effects are studied in pharmacology.
- Pharmacology is used to prescribe drugs to patients so that diseases can be cured and prevented.

How To Apply Pharmacology 00:01:04

- If a 6-month-old baby is having a fever, paracetamol is given to the baby in syrup/oral drops form (Dosage form), and if the drug is leading to vomiting, then paracetamol can be given through rectal (routes of administration).
- If a five-year-old child weighing 20 kg has to be given PCT, then the dose of the drug can be decided by pharmacology. PCT dose is 10mg/kg/dose. So for a child weighing 20 kg, 200 mg PCT is given per dose.
- If a 42-year-old patient is having a fever and tablet is given. In the prescription, the drug name should be written in capitals with the dosage and the no. of times the drug should be taken in patient's understandable language.
- Rx
  Tab. "PARACETAMOL" 500MG
  Three times daily after food
- For pregnant women, paracetamol is safe, always ask a woman whether she is married and pregnant or not.
- Lactating mother also should be considered while prescribing drugs.
- For Liver disease patients and chronic alcoholics, the dose of the drug should be decreased.
- Diabetic and hypertensive patients should be considered to avoid drug interaction.
- Antidote of the drug should be given in case of toxicity, if there is toxicity due to consumption of high doses of paracetamol then N acetylcysteine should be given.

Rational Prescribing 00:12:00

- Right drug should be given to the right patient at the right dose.
- Right time of the drug should be known.
- Right duration and right documentation should also be considered in prescribing drugs.

What is drug?

- Word drug is obtained from the French word drogue which means herb.
- Drug is an active chemical entity used to diagnose, prevent, treat, or cure diseases.
- **WHO Definition:** Any substance/product intended to modify or explore physiological/pathological state for the benefit of the recipient.

Pharmacokinetics 00:16:10

- It is also called what the body does to drugs.
- Understanding how the drug is absorbed, distributed, metabolized, and excreted.

Pharmacodynamics

- It is what the drug does to the body.

Pharmacotherapeutics

- Use of knowledge of a drug or disease to treat/cure/prevent disease is called pharmacotherapeutics.

Chemotherapy 00:18:40

- Chemotherapy means to kill cells.
- Cells are killed in cancer and microbial infections.

Clinical Pharmacology 00:19:55

- Scientific study of drugs.

Pharmacy

- It is the art of preparing and dispensing drugs.

Toxicology

- It is the study of toxins or chemicals in the body.

General Pharmacology 00:21:20

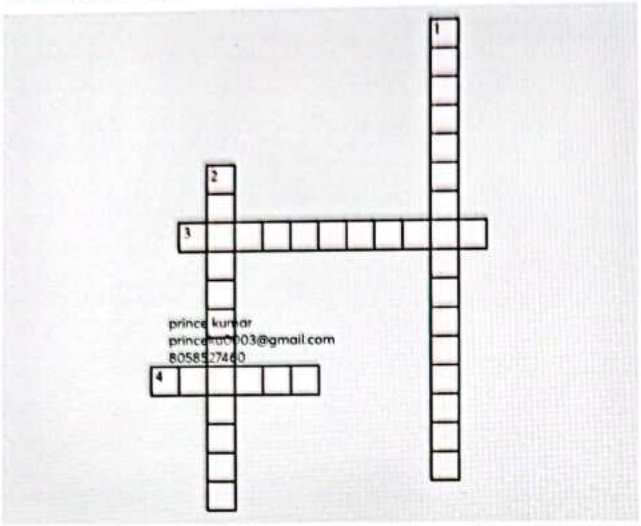
- Deals with pharmacokinetics, pharmacodynamics, adverse effects of the drug and how to develop a new drug

Systemic Pharmacology

- Deals with all the systems in pharmacological aspects.

CROSS WORD PUZZLES

Crossword Puzzle 1



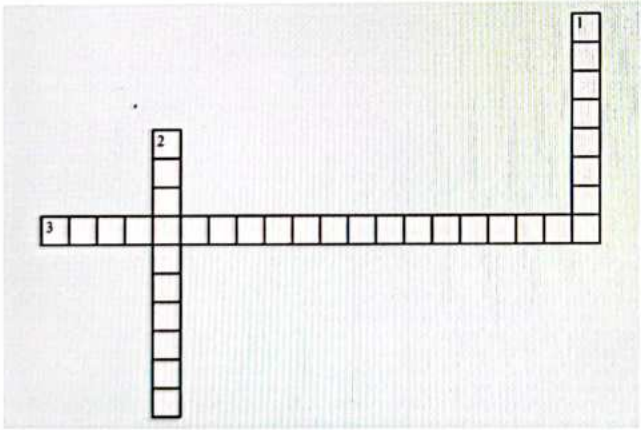
Across

3. N acetylcysteine is the antidote for_____.
4. Word drug is obtained from the French word_____.

Down

1. _____is also called what the body does to drugs.
2. _____ is the study of drugs.

Crossword Puzzle 2



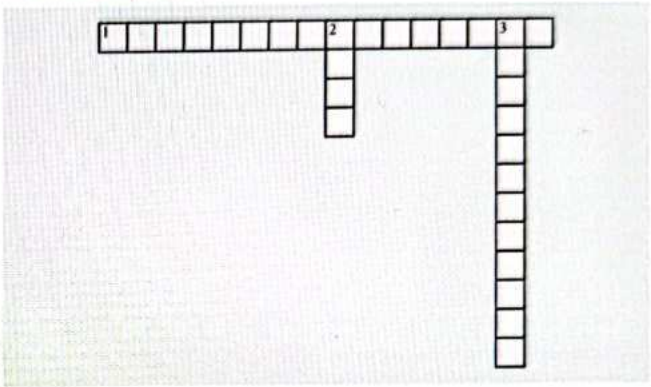
Across

3. _____is the scientific study of drugs.

Down

1. _____is the art of preparing and dispensing drugs.
2. _____is the study of toxins or chemicals in the body.

Crossword Puzzle 3



Across

1. _____is called what the drug does to the body.

Down

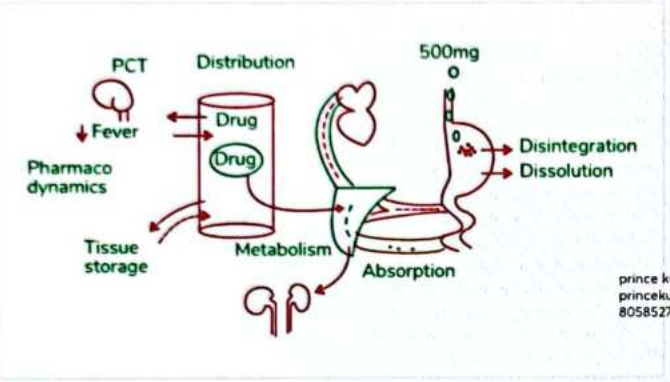
2. _____is any substance/product intent to modify or explore physiological/pathological state for the benefit of the recipient.
3. _____means to kill cells.

2 PHARMACOKINETICS ABSORPTION

Pharmacokinetics

- Pharma means drugs and kinetics stands for movement.
- Pharmacokinetics is, what the body does to the drug:
  - Absorption of the drugs.
  - Distribution of the drug.
  - Metabolism of the drug.
  - Excretion

Paracetamol



- During fever, paracetamol is the standard drug that is given. When a patient consumes the tablet, it passes through the oesophagus where the tablet is first disintegrated and then it is dissolved, in the stomach and intestine. From the intestine, it gets absorbed and reaches the liver. Then it goes to the heart from where it is distributed to the site of action. Then it is metabolised and excreted out of the body.
- The site of action of paracetamol is to decrease the fever in the brain.
- There is a separate branch for this decrease of fever which is called Pharmacodynamics. It is basically what the drug does to the body.
- In the case of certain drugs are stored under tissue storage for a very long time and comes out of it very slowly.
- Once the drug has produced action it has to come back and be excreted from the body.
- The major site of drug excretion is in the Kidney through urine. It can be excreted in the bile also.

Drug Absorption 00:09:08

- There are various routes of drug administration, from various routes the drug has to reach the blood vessels also called systemic circulation.
- So, drug absorption is the transportation of drugs from the routes of administration to the systemic circulations.
- In between, there are processes which help them, called drug transport mechanisms. There are two types of transport:
  - **Passive:** No energy or ATP is required. It is divided into two parts:
    - **Simple Diffusion:** The movement of drugs from a high concentration to a low concentration is called simple diffusion.
    - **Facilitated Diffusion:** It is a carrier-mediated transporting system for example GLUT.
  - **Active:** Energy is required, there are two variants:
    - **Symport:** It means the same direction. Example: SGLT- 1 & 2.
    - **Antiport:** Different direction. Example: H+ K+ ATPase and Na+ K + ATPase.

- The most common mode of drug transportation is Simple diffusion.
- There are other ways of drug absorption such as endocytosis for Vitamin B_{12} and pinocytosis for Liposomal anticancer drugs.
- There are two important properties of the drug they can be:
  - **Lipid soluble drugs:** They are also called Non-Ionized drugs. They can easily cross the membrane.
  - **Water Soluble drugs:** They are also called Ionized drugs. Water-soluble drugs cannot cross the membrane easily. They can be easily cleared out of the body.

Routes of drugs administration 00:18:00

- **Systemic Route:** In the systemic root, the drug is distributed throughout the body.
  - **Enteral Route:** Anything that is related to GIT is enteral. Oral, Rectal, sublingual and Trans buccal.
  - **ParEnteral Route:** Beyond intestine. There are two types:
    - → Injection: I.V, I.M, Subcutaneous, intradermal and Intra-osseous.
    - → Non-Injection: Transdermal and Inhalation.

- **Local Route:** The drug acts locally only in the place where it is given. There are two important classes:
  - Topical:
    - → Eye, ear and Nasal drops.
    - → Applied on the skin and mucous membrane.
  - Deeper tissues:
    - → Intrathecal: The drug is given into the spinal cord.
    - → Intra articular: The drug is given in the joint spaces.
    - → Intra-arterial.
- Many times, some of the routes overlap for example the nasal route can be a local route depending on the drugs.
- Suppose a patient uses a nasal drop for a running nose, the

Drop will act locally and constrict the blood vessels. It acts as systemic when desmopressin nasal spray is used.

Factors affecting drug absorption

Chemical Nature of the drugs.

- Weak Acid:
  - Aspirin
  - Barbituric acid
  - Antibiotic- Penicillin's & cephalosporins
  - Loop diuretics
  - Thiazide diuretics.
- Weak Base:
  - Atropine
  - Morphine
  - Amphetamine

Acidic drug → acidic medium ⇒ L.S. (N.I) ⇒ Cross Membrane Easily ⇒ ↑A

Basic drug → Basic Medium [alkaline] → L.S [N.I] ⇒ Cross Membrane Easily ⇒ ↑A

- If the drug and the medium are the same they are lipid soluble and easily absorbed.

Acidic drug – basic medium → W.S (I) = Not easily Cross Membrane

Basic drug – acidic medium → "Easily cleared"

- When the drug and the medium are different it will be water soluble which makes it hard to cross the membrane.
- Aspirin is absorbed in the stomach because the pH of the stomach is acidic and Aspirin is also acidic.
- The pH of the intestine is slightly basic which is why morphine is absorbed in the intestine.

Food Factors

- Whenever a drug is given orally food will interfere.
- Drugs given before food: PPI, Levothyroxine etc. given before food because the food may interfere with the absorption of the drug.
- Fatty food increases the absorption of the drug. Examples- Lumefantrine, Griseofulvin, Bedaquiline, and Efavirenz (It should not be given with food because it increases absorption and which has adverse effects such as neuropsychiatric adverse effects.)
- Now there are two types of iron Fe3+ and Fe2+. Iron needs an acidic environment to convert from Fe3+ to Fe2+ which gets absorbed. The combination of iron + Vitamin C is rational.
- PPI + Iron is not recommended since it reduces iron absorption.
- Tetracycline + milk will lead to an increase in the size and the tetracycline absorption will reduce.
- The oral route has variable absorption.

Area of absorbing surface:

- The area of the surface and the absorbing capacity is directly proportional.
  - Irrespective of whether the drug is acidic or basic maximum absorption occurs in the small intestine.
  - Drugs are also absorbed from the large intestine.

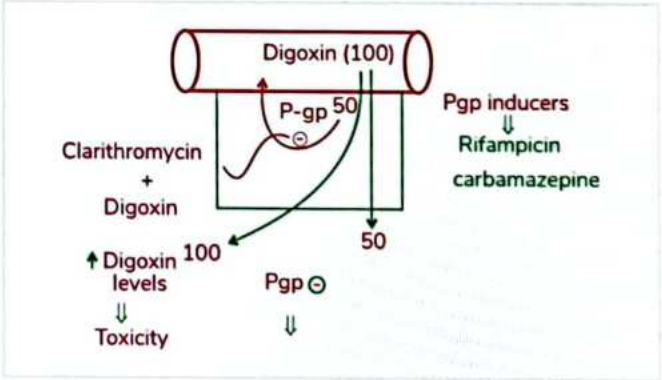
Blood flow of absorbing area

- Blood flow to the absorbing area is directly proportional.
- For instance, whenever an injection is given to the patient that area is rubbed so that the blood flow in that area increases and results in faster absorption.
- In anaphylactic shock, the drug of choice is adrenaline, which is given intramuscular over subcutaneously due to the blood flow of the muscle is comparatively higher.

GIT diseases

- In the case of diarrhea, drug absorption will decrease.
- In constipation, the drug absorption increases.

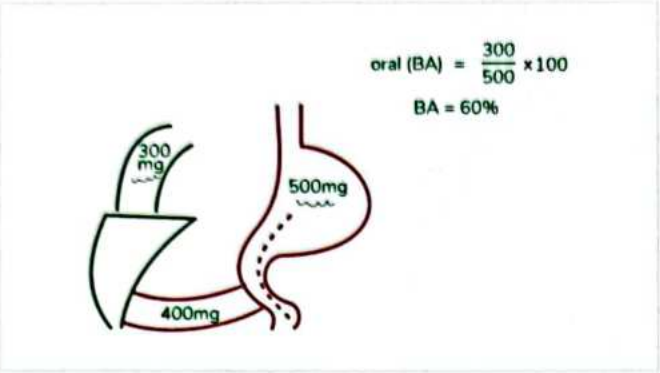
P- glycoprotein



- It is an efflux pump, efflux means throwing out. It is present in the intestine, Placenta and Blood-brain barrier.
  - Digoxin is used in the management of congestive heart failure. For instance, when 100 digoxin is given, 50 will enter and 50 will be thrown out by these cells.
  - The problem is when digoxin is given with another drug clarithromycin (it is an antibiotic). Clarithromycin + digoxin will lead to toxicity.
- Pgp inducer drugs - Rifampicin, carbamazepine.
- Pgp inhibitors drugs - Quinidine, Amiodarone, verapamil.
- The cancer cell in the body increases the p-glycoprotein to fight the Anti-cancer drugs. This leads to resistance to anti-cancer cells.

Bioavailability

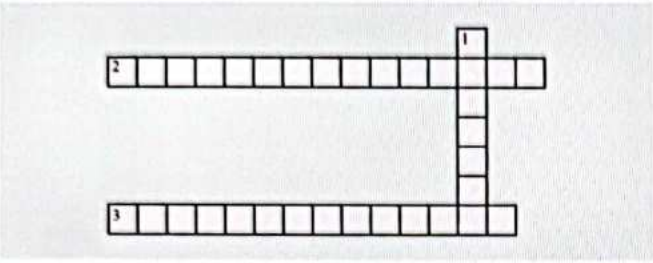
00:57:14



- Bioavailability stands for the fraction of the drug available for systemic action in unchanged form. For instance, oral 500 mg Paracetamol is given. After the first pass metabolism and absorption process the left-over Paracetamol is 300 mg. The fraction of the Paracetamol given and what is left is bioavailability.
- The bioavailability of any drugs given through I.V. is 100%.
- The routes that have the First pass metabolism are:
  - Oral
  - Rectal
    - → Internal haemorrhoidal vein- 50% 1st pass
    - → External haemorrhoidal vein- No 1st pass
- Bioavailability depends on two factors:
  - Absorption- Directly proportional to bioavailability.
  - First pass metabolism- Inversely proportional to bioavailability.
- The reason why IV route has 100% bioavailability is because it has no absorption and first pass metabolism.
- The bioavailability is <100% when a drug is given through the IM route even though it has no first pass metabolism because there is absorption.
- Drugs with high first pass metabolism:
  - Nitrates- To avoid first pass metabolism these are given sublingually. If given orally, it should be given with a higher dose.
  - Hydrocortisone and Lignocaine- Given by parenteral route.
  - Propranolol, Salbutamol, Verapamil and Morphine- Given orally (But given by increasing dose).
- The following route has the fast rate of absorption:
  - Inhalation- Lungs have a large surface area. More the surface area, the more the absorption.

CROSS WORD PUZZLES

Crossword Puzzle 1



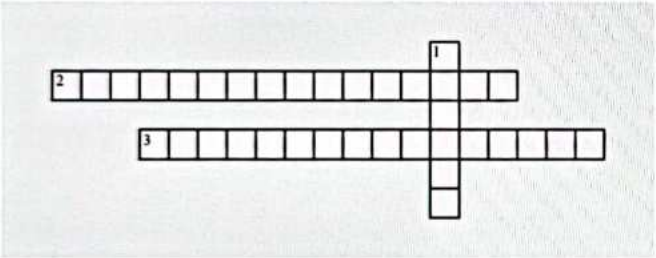
Across

2. The _____ of any drugs given through I.V. is 100%.
3. Maximum absorption occurs in the _____.

Down

1. _____ is used in the management of congestive heart failure.

Crossword Puzzle 2



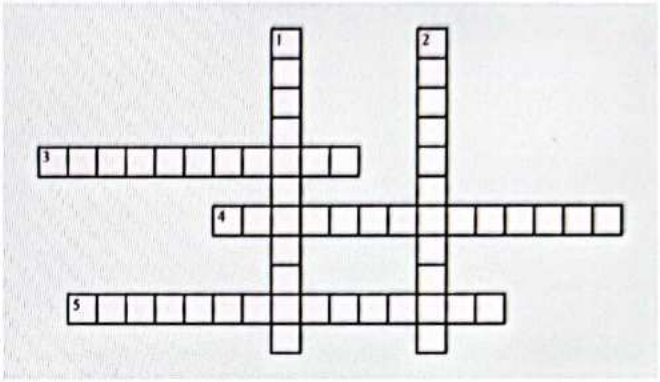
Across

2. _____ is also called what the body does to the drug.
3. There is a separate branch for this decrease in fever which is called _____.

Down

1. The major site of drug excretion is in the _____ through urine.

Crossword Puzzle 3



Across

3. _____ the drug is given into the spinal cord.
4. _____ the drug is given in the joint spaces.
5. The movement of drugs from a high concentration to a low concentration is called _____.

Down

1. _____ for Liposomal anticancer drugs.
2. The other ways of drug absorption such as _____ for Vitamin B12.

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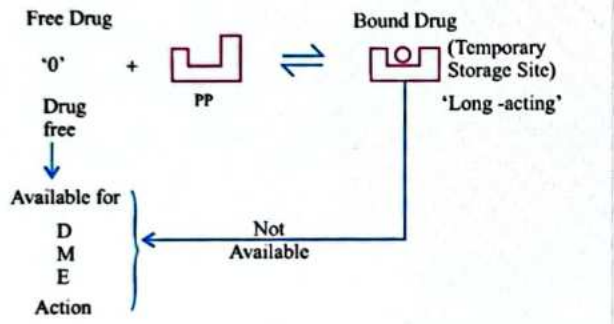
3 PHARMACOKINETICS DRUG DISTRIBUTION AND PLASMA PROTEIN BINDING

Plasma Proteins

00:00:35

- There are two important plasma proteins:
  - Albumin – acidic drugs bind to the albumin. Eg. Furosemide
  - Alpha-1 acid glycoprotein – basic drugs bind to the alpha-1-glycoprotein. Eg. Lignocaine (local anesthetic and an antiarrhythmic drug).

- All the drugs cannot bind to the plasma protein. Only certain drugs can bind.



Free drugs	Bound drugs
• A drug that is not attached to the plasma protein. • If free drugs are more, they become bound. • Free drugs are available for distribution, metabolism, excretion, and action.	• When the drug binds to the plasma protein • If bound drugs are more, they will release the free drugs and there will be a balance. • Bound drugs are not available for distribution, metabolism, excretion, and action. • The bound drug is like a temporary storage site for a drug. • If the drug is bound, it is usually longer acting. • The highly plasma protein-bound drugs are Warfarin, Tolbutamide, and Diazepam. ○ For eg., Diazepam is in 90% bound form and 10% free form. Only a few drugs have this property.

Displacement Reaction

- When the drugs are bound, there is a chance of displacement reaction.
- Eg.1: A drug (Warfarin) is sitting in a plasma protein. If a patient who is on Warfarin is given Sulfonamide (an antimicrobial drug that kills the microbes). Sulfonamide will kick the Warfarin out. As a result, the free Warfarin level increases which will lead to toxicity.
- Eg 2: An endogenous substance called Bilirubin. If Sulfonamide is used for a newborn, it can displace Bilirubin. As a result, the free bilirubin level increases and it can cross the blood-brain barrier which can cause Kernicterus (also known as Jaundice).

Important Information

- All the drugs cannot bind to the plasma protein.
- Do not combine Warfarin and Sulfonamide since it increases the risk of bleeding.
- Bilirubin is an endogenous substance. Sulphonamide can displace the Bilirubin in the newborn and cause Kernicterus (jaundice).
- Free drugs are available for distribution, metabolism, excretion, and action whereas bound drugs are not available for all these.

Clinical Applications

CASE 1

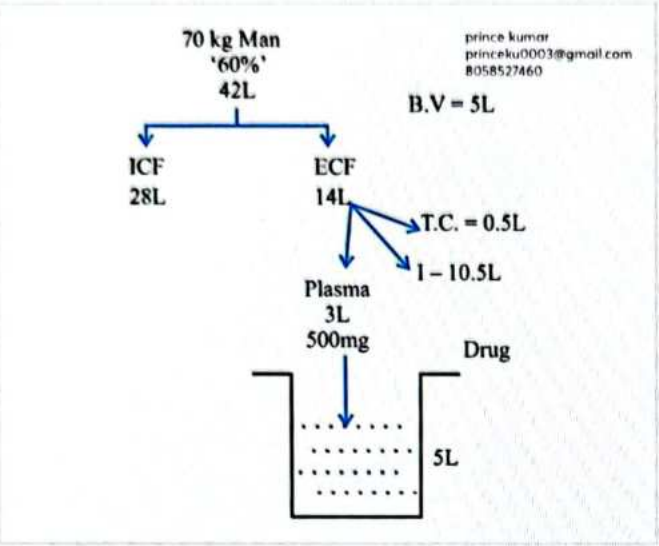
- The patient has Hypoalbuminemia (albumin levels are less). The acidic drug Furosemide is given to this patient because the patient has edema. Furosemide binds to the albumin because it is less acidic. If a normal dose is given, albumin levels will be less, and thus, Furosemide cannot bind more. So, there is an increase in the free levels of Furosemide. Therefore, in this patient, the Furosemide dose should be reduced.

CASE 2

- The patient has Myocardial Infarction (MI). During MI, there is a chance of arrhythmia particularly Ventricular arrhythmia (VT). In this case, Lignocaine is used. If the patient has MI with VT, there is a condition that for any inflammatory conditions, the production of alpha-1-glycoprotein is increased. If a normal dose of Lignocaine is given there is an increase in bound form and a decrease in free form. If free forms are fewer it will work less. So, the dose of Lignocaine should be increased a bit.

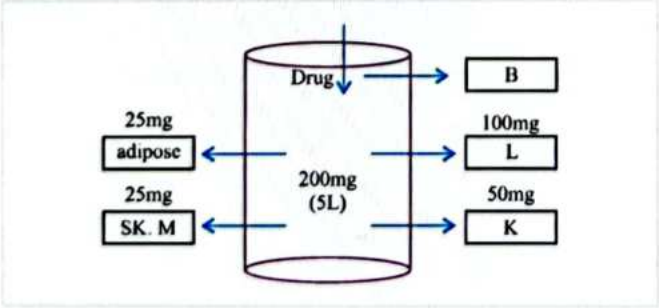
Volume of Distribution (VD) 00:13:25

- Normal volume of distribution in a 70 kg man:



- Distribution is the volume in which the drug is uniformly distributed at the same plasma concentration.
- When the drug is given, it is distributed evenly.
  - For eg. The jar is filled with 5L of water. In this jar, 500mg of the drug is added. This drug gets dissolved and is distributed in 5L.
  - Eg. 2. The same jar has blood vessels and 5L of plasma. To calculate the Plasma Concentration (PC), if 500mg of the drug is given and is evenly distributed, there will be 100 mg in every liter.
  - If the drug is not getting distributed and stays only in the blood vessel. Then the Volume of Distribution (VD) is given by:

    VD = Dose administered/Plasma concentration (PC)
    = 500mg/100mg/L
    = 5L
- In a real-life situation, the drug has to go out and get distributed evenly. For eg. If a drug is given to the patient, it does not stay in the blood vessel. It has to go out.



- When the drug is given, the drug moves toward the brain, Liver, and Kidney. More the blood flows, the more absorption. These organs will get more drugs.
- Skeletal muscles and Adipose tissues have the least amount of blood flow, respectively.
- E. g. When a person receives 500mg of a medicine, the substance enters the blood vessels. From the 500 mg, 25 mg is delivered to the skeletal muscles, 100 mg to the liver, 100 mg to the kidney, and 25 mg to the adipose tissues. 200mg of the 300mg total that leaves 5L's plasma stays there. The PC will therefore be 200 mg/5 L = 40 mg/L.
- The PC here has decreased because the drug is distributed to the other tissues.
- The Volume of Distribution = Dose administered/PC
  = 500 mg/40 mg/L
  = 12.5 L
- If the drugs stay in the blood vessel, the VD is less. If the drug goes out, the VD increases.
- VD is expressed in liters. For e.g., VD = 10 L/kg. If the patient is 70 kgs, then VD will be 10 x 70 = 700 liters.

Apparent Volume of Distribution

- It is the hypothetical volume because there are multiple compartments in the body.
- Chloroquine has aVD of around 13,000 liters. This means that this drug does not stay in the plasma. It stays outside the blood vessel.
- If the VD values are more, the drug is going out of blood vessel.

Properties that keep the drug inside the blood vessels

- These are known as low-volume of distribution drugs
- Water-soluble
- Ionized
- Large size or large molecular weight
- Plasma protein binding

Properties that make the drug go out of the blood vessels

- These are known as high volume of distribution drugs
- Lipid soluble
- Non-ionized
- Small size or low molecular weight
- Tissue Protein-bound drugs – tissue proteins are outside the blood vessels which means they have high VD.

Importance

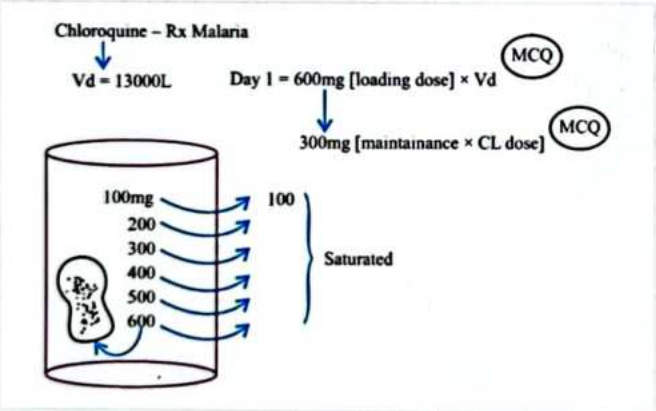
- Suppose a drug has to be designed for a pregnant woman. In the pregnant woman, the drug goes to the placenta, and then the fetus may get affected. Therefore, a low-VD drug should be designed for a pregnant woman.
- A drug with low Vd is Heparin. It is an anticoagulant of choice in pregnancy. It is water soluble, big in size, and will not go through the placenta and affect the fetus.
- The highly plasma-bound drugs also help in pregnancy because they are less free. They cannot cross the placenta easily. Eg. Propylthiouracil – is used in 1st-trimester hypothyroidism.

- Suppose a patient comes with drug poisoning and the drug has low VD. Another drug poison has high VD. For which poison, dialysis should be done??
  - Dialysis is not useful if a drug has high VD or a drug is highly plasma protein bound.
  - If the drug is staying outside the blood vessel, then dialysis will have no use.
  - If the drug is present in the blood vessel, the drug will go to the dialysis machine, get dialyzed, and come back.
  - In low VD also, if the drugs are highly plasma protein (PP) bound, they cannot be removed.
  - The exception is that in low VD, the drugs are highly PP bound because PP is not removed by dialysis. So dialysis is not used in these two situations
  - The MNEMONIC used for these high VD drugs (dialysis should not be done):

    Better - BZDs (Diazepam) – it is highly PP bound.
    Care - Chloroquine (has the highest VD of 13000L)
    A - Amphetamine
    V - Verapamil
    O - Organophosphates/Opioids
    I - Imipramine
    D - Digoxin

Chloroquine

00:33:15



- Used to treat malaria.
- It has a VD of 13000L
- If 100 mg of chloroquine is given, it has to work in the RBC and kill the parasite. If 100 mg is given, all the 100 will go out.
- At one point, even the tissues outside will get saturated and will not allow more entry.
- If 600 mg is given then it will stay and kill the protozoa.
- Initially (on day 1), a dose of 600 mg is given and this dose is called the Loading Dose.
- The loading dose is given depending on the VD.
- After 8 hours, 300 mg of Maintenance Dose is given. It depends on the clearance of the drug.

- The Loading dose of the drug is given by

$$\text{Loading Dose} = \frac{\text{Target P.C} \times \text{Vd}}{F}$$

  - Target P.C = Target plasma concentration
  - V.D= Volume of distribution
  - F= Bioavailability

Barriers of Distribution

00:36:50

- The drug does not enter certain places.

- **Blood-Brain Barrier (BBB):**
  - Parkinson's disease is treated with the drug levodopa. In this illness, there is less dopamine. Dopamine cannot be used because the blood-brain barrier's enzymes metabolise it, preventing it from reaching the brain. Levodopa is administered for this purpose because it penetrates the brain where it transforms into dopamine.
  - The brain also has an efflux pump called P-glycoprotein. Whenever some drug enters, it is thrown out. It is also for protection.
  - Many times this BBB may be breached if there is inflammation. If there is meningitis and inflammation, this BBB may not be intact and certain drugs can penetrate during inflammation.

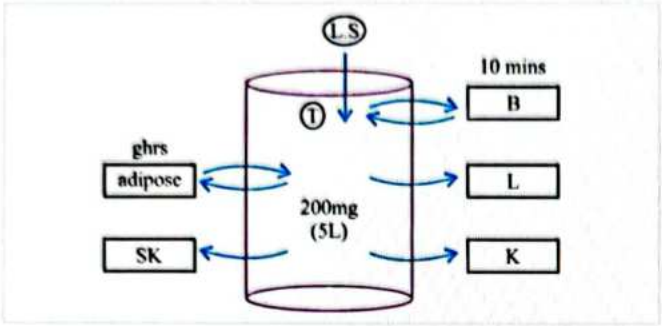
- **Placental Barrier:**
  - It is not as efficient as BBB.
  - It also has P-glycoprotein and enzymes for protection so the drugs will not enter.

Important Information

- Vd is the distribution in which the drug is uniformly distributed.
- Chloroquine has a Vd of 13,000L.
- Apparent Vd is the hypothetical volume of distribution.
- A low-Vd drug should be given to a pregnant woman. A drug with low Vd properties is Heparin.
- The Loading Dose depends on the volume of distribution and the Maintenance dose depends on the clearance of the drug.
- The placental barrier is not as efficient as the BBB barrier.
- Even though Ethanol and Lithium are water soluble, they are small in size and can enter the placenta and cause Teratogenicity.

Redistribution

00:40:10



Thiopentone

- It is used as an inducing agent in anesthesia.
- It is ultra short-acting. It acts only for 10 minutes.
- Highly lipid soluble.
- When thiopentone is given in the vein, from the vein it goes to the heart, and from the heart, it gets distributed to the brain.
- In the brain, it has a fast onset of action. It can enter the brain so easily because the drug is highly lipid-soluble.
- The patient becomes conscious after 10 min because the drug has undergone redistribution and it works only for 10 min in the brain.
- The drug is ultra short acting in the brain due to the Redistribution phenomenon.
- When the drug Thiopentone is given it enters the brain immediately, then it enters the liver and kidney but enters the skeletal muscles very slowly and even slowly to the adipose tissues. The level of Thiopentone decreases in the blood vessels because it has gone everywhere.
- When the drug is decreased in the blood vessel, it immediately comes back from the brain again into circulation and gets distributed. Due to this phenomenon, the drug is very short-acting in the brain.
- It comes inside and goes outside so easily because of lipid solubility and the patient becomes conscious within 10 min.
- When it enters the adipose tissues, the drug does not come out of the adipose tissue. It remains there for 9 hours because the blood flow is less and is bound to the protein there. It comes out very slowly.

Clinical Questions

Q. Why is Thiopentone very short-acting?
Ans: Thiopentone is very short-acting due to the Redistribution Phenomenon.

Q. Why does the drug Thiopentone have a fast onset of action in the brain?
Ans: The drug Thiopentone has a fast onset of action in the brain because it is highly lipid soluble.

Q. What properties make high VD?
Ans: Properties that make high VD are

- Lipid soluble
- Non-ionized
- Small size or low molecular weight
- Protein-bound drug

Q. What is the formula for VD?
Ans: Volume of Distribution = Dose administered/PC

Q. What is Apparent VD?
Ans: When the VD is not real, it is apparent and known as Apparent VD.

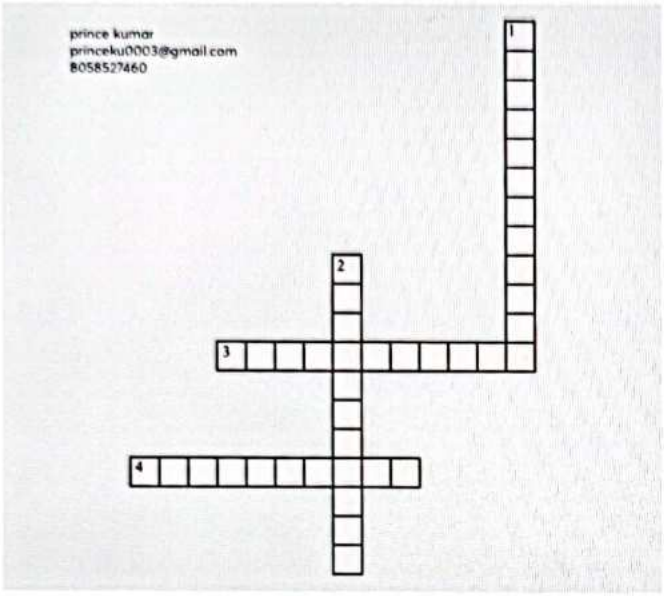
Q. How are the Loading dose and Maintenance dose given?
Ans: The loading dose is given depending on the VD and the Maintenance dose is given depending on the clearance of the drug.

Q. If a drug has to be chosen for a pregnant woman, what should be the properties of the drug?
Ans: Big size, water-soluble, and ionized.

Q. What are the two barriers of distribution?
Ans: 1) Blood-Brain Barrier and 2) Placental Barrier

CROSS WORD PUZZLES

Crossword Puzzle 1



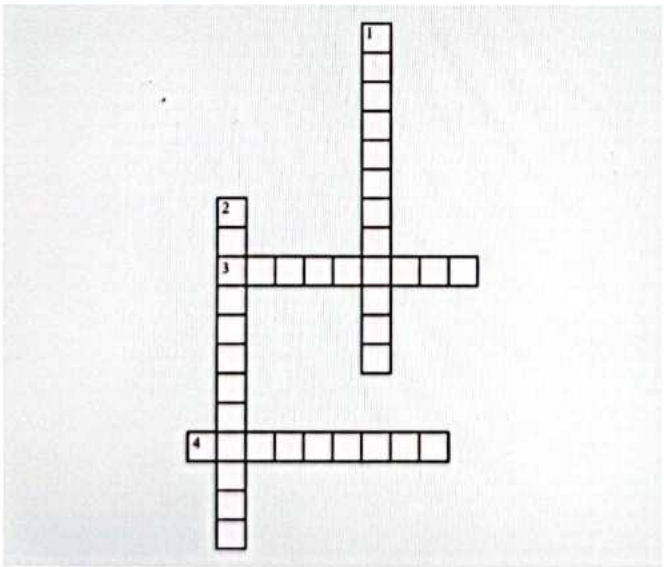
Across

3. _____ is an acidic drug.
4. _____ is a basic drug.

Down

1. _____ is also known as Jaundice.
2. _____ is an endogenous substance.

Crossword Puzzle 2



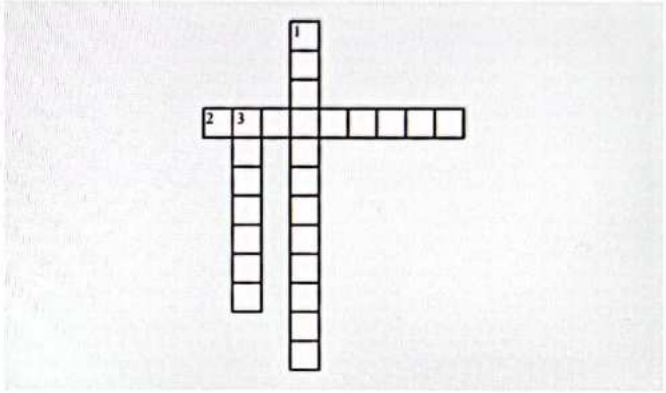
Across

3. _____ has the highest VD of 13000 L.
4. _____ is used in the treatment of Parkinson's disease.

Down

1. _____ is an inducing agent in anesthesia.
2. _____ is not used if a drug has high VD.

Crossword Puzzle 3



Across

2. _____ is an anticoagulant of choice in pregnancy.

Down

1. _____ is an antimicrobial drug.
3. _____ the blood flow is very very less.

4 PHARMACOKINETICS DRUG METABOLISM

Drug Elimination 00:00:55

- As the drug is foreign to the body, it will try to eliminate the drug. This elimination involves two processes:

Drug Metabolism

- In this process, the lipid-soluble drug is converted into water-soluble so that it can be easily thrown out of the body.
- Drug metabolism is also known as biotransformation.
- This biotransformation is mainly done by the liver and a little bit by the intestine and placenta.
- Liver: In the liver, there are two types of enzymes: microsomal and non-microsomal enzymes that metabolize drugs.
- Also, there are two phases of metabolism - phase I and phase II.

Drug Excretion

- There are some drugs that are eliminated without going through the process of metabolism. They are directly excreted.
- These are aminoglycosides and cetirizine.

Hoffman's Elimination

- This is a special type of elimination that doesn't go through the liver or kidney for elimination. Instead, the drug goes into spontaneous molecular rearrangement.
- This makes them safe for patients with liver or kidney diseases.
- Atracurium and cisatracurium are two drugs that go through Hoffman's elimination.

Biotransformation 00:07:30

Phase I Reactions

- These are also known as non-synthetic reactions. They are:
- **Oxidation**:
  - It is the most common reaction in phase I.
  - It can be of the following types –
    - → Hydroxylation: This can be of two types - Aliphatic and aromatic.
    - → Deamination
    - → Dealkylation
- **Reduction**: It involves adding hydrogen or removing oxygen.
- **Hydrolysis**
- **Cyclization**: In this, the structure of the drug is changed from a straight chain to a ring.
- **Decyclization**: The metabolism changes the structure of the drug from a ring to a straight chain.

Phase II Reactions

- These are also known as synthetic or conjugation reactions. (mnemonic - 3G SAM)
- Glucuronide conjugation:
  - It is the most common phase II reaction.
  - Examples of the drugs that undergo this reaction are (BIOCAMP)
    - → Benzodiazepines
    - → Irinotecan
    - → OCPs (Oral contraceptives)
    - → Chloramphenicol
    - → Atazanavir and Atorvastatin
    - → Morphine and Metronidazole
    - → PCT (Paracetamol)
- Glycine conjugation: Aspirin will undergo this process.
- Glutathione conjugation: The example is paracetamol.
- Sulfate conjugation: The example is paracetamol and methyldopa.
- Acetylation:
  - The enzymes that perform acetylation are called acetylators. These can be of two types depending on genetics: Slow and fast.
  - The examples of the drugs that undergo acetylation are: (SHIP)
    - → Sulfonamides, Dapsone
    - → Hydralazine
    - → Isoniazid
    - → Procainamide
- Methylation: The example of methylation is the process of converting noradrenaline into adrenaline or converting histamine into methylhistamine.

Enzymes 00:18:40

Microsomal Enzymes

- These are present in the smooth endoplasmic reticulum.
- Cytochrome P450 is the main microsomal enzyme.
- These enzymes are inducible and inhibitable.
- Phase I and glucuronidation (phase II) are done by these enzymes.

Non-Microsomal Enzymes

- These are present in the cytoplasm and mitochondria.
- Esterase and Amidase are examples of non-microsomal enzymes. Esterase can be of two types-
  - Plasma esterases: Usually the drugs metabolized by this enzyme are short-acting, for example, Esmolol and Remifentanyl.

- Pseudocholinesterase: These metabolize two important drugs - Succinylcholine and Mivacurium.
- These are non-inducible but inhibitable.
- They can do the phase I (like MAO and alcohol dehydrogenase) and phase II (except glucuronidation).

Cytochrome Enzymes 00:24:45

- Nomenclature of cytochrome enzymes:
- For example, in CYP3A4 -
  - 3 is the family.
  - A is the sub-family.
  - 4 is the isoenzyme.

Types of Cytochrome Enzymes

- **CYP 1A 1/2**: Theophylline, caffeine, and pro-carcinogens are metabolized.
- **CYP 3A 4/5:** >50% of the drugs are metabolized by this enzyme.
- **CYP2B6**: Nevirapine, efavirenz, and cyclophosphamide are metabolized.
- **CYP2C9**: Phenytoin and warfarin are metabolized.
- **CYP3C19**: Omeprazole and Clopidogrel are metabolized.
- **CYP2D6**: > 20% of the drugs are metabolized by this enzyme. For example, anti-arrhythmic drugs, beta-blockers (metoprolol), TCAs, SSRIs, conversion of codeine to morphine, and the conversion of Tamoxifen to Endoxifen are done by this enzyme.
- **CYP 2E1**: Paracetamol, Halothane and Alcohol are metabolized.

Microsomal Enzymes 00:31:20

Types

Induction

- A drug can increase enzyme synthesis, which will further increase drug metabolism. Thus, there will be a decrease in drug levels leading to drug failure.
- For example, rifampicin + OCPs will lead to contraceptive failure as Rifampicin induces the metabolism of OCPs.
- It is a slower process.

Inhibition

- The drugs can inhibit enzyme activity which will lead to decreased metabolism. This will cause failure in the elimination of the drug leading to its toxicity.
- For example, warfarin + ciprofloxacin (enzyme inhibitor) will lead to warfarin toxicity causing bleeding in the patient.
- It is a faster process.

Q. The drug ezogabine is given to a patient to treat partial seizures. The condition did not improve so the doctor gave phenytoin which is an enzyme inducer. On adding phenytoin, what changes should be done to the dosage of ezogabine?

Ans. Increase the dose of ezogabine.

Enzyme Inducers 00:39:52

- The mnemonic is New SCARP GPS. The drugs are:
  - Nevirapine: It is an auto-inducer which means it will increase its own metabolism.
  - Smoking: It stimulates the enzyme CYP 1A 1/2 which converts pro-carcinogens into carcinogens.
  - Carbamazepine: It is an auto-inducer.
  - Rifampicin
  - Alcohol: Chronic alcoholism causes enzyme induction.
  - Phenobarbital
  - Griseofulvin
  - Phenytoin
  - Saint John's wort: It is an herbal plant used as an antidepressant in western countries.

Microsomal Enzyme Inhibitors 00:43:15

- The mnemonic is I Am Eating Very Great Fresh Chocolate Pieces Only. They are:
  - Isoniazid
  - Azoles, acute alcohol, amiodarone.
  - Erythromycin
  - Verapamil, valproate
  - Grapefruit juice
  - Fluoxetine
  - Cimetidine, ciprofloxacin, clarithromycin
  - Protease inhibitors like Ritonavir
  - Omeprazole

Drug Metabolism 00:47:50

- In order to explain the pathway of drug metabolism, let's take paracetamol as an example.
- When paracetamol enters the body, 98% of it is made inactive by glucuronide and sulfate conjugation (phase II).
- The rest of the 1-2% first gets converted into N-acetyl Para benzoquinone imine (NAPQI) by the enzyme CYP2E1 (phase I).
- This NAPQI is hepatotoxic.
- However, glutathione (phase II) will block the toxicity of NAPQI and convert it into mercapto uric acid which will be excreted in the urine. So, there is no liver toxicity.
- **High dose intake:** If the patient takes 10 tablets of paracetamol, the 98% pathway will not work due to saturation.
- Now PCT will go through the second pathway. But, here also due to saturation, glutathione will not be able to convert all of the NAPQI into mercapto uric acid.
- So, the patient with a paracetamol overdose will have hepatotoxicity.
- **Management**: The antidote for paracetamol toxicity is N-acetyl cysteine. This replenishes the glutathione stores in the body.

- **Chronic alcoholic**: In case a chronic alcoholic takes a high dose of paracetamol, hepatotoxicity will be higher. This is because the liver of the alcoholic is already diseased and upon that chronic alcohol intake causes enzyme induction of CYP2E1 which in turn rapidly makes NAPQI.

Fate of Metabolism 00:54:45

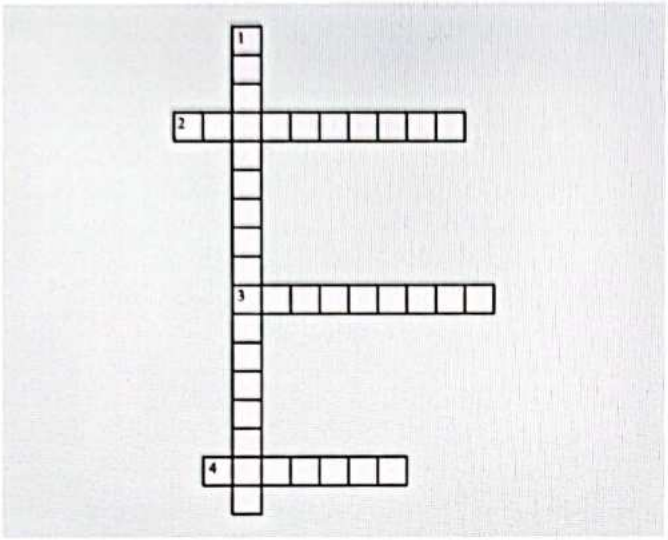
- An active drug will become inactive.
- An active drug can also become an active metabolite.
  - For example, the metabolism of diazepam will give rise to nordiazepam which is also active.
  - The metabolism of hydroxyzine will give cetirizine.
  - The metabolism of amitriptyline will give rise to nortriptyline.
- An inactive/pro-drug will metabolize into an active drug.
  - For example, Levodopa (pro-drug) is given to a Parkinson's disease patient. Levodopa can cross the blood brain barrier and enter the brain and there it can get metabolized into the active drug dopamine.
  - Clindamycin phosphate is a prodrug which gets metabolized to clindamycin as clindamycin has a very bad taste.
  - Methenamine is a urinary antiseptic which gets converted into formaldehyde in the acidic pH of the urine. This is given as the intake of formaldehyde causes stomach irritation and is toxic.
- An active drug will give rise to a toxic metabolite.
  - For example, the metabolism of paracetamol will give NAPQI.
  - Isoniazid metabolism gives rise to acetylhydrazine.

Disadvantages of Pro-Drug

- Pro-drugs are not useful in emergency cases.
- They are also not useful in liver disease as they will be metabolized slower.

CROSS WORD PUZZLES

Crossword Puzzle 1



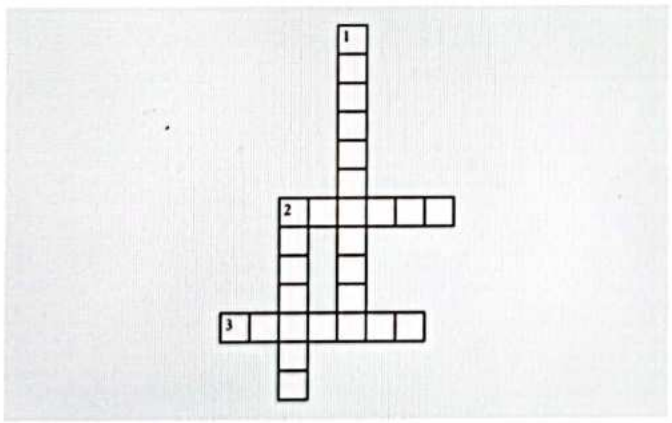
Across

2. Cetirizine is directly excreted from the body as it skips the _____ step.
3. _____ is the most common reaction in phase I.
4. Atracurium goes through _____ elimination.

Down

1. Drug metabolism is also known as _____.

Crossword Puzzle 2



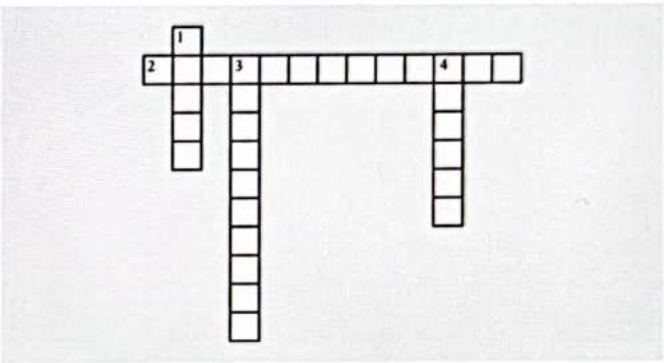
Across

2. Microsomal enzymes are present in the _____ endoplasmic reticulum.
3. Conjugation reactions are also _____ reactions.

Down

1. _____ conjugation is the most common phase II reaction.
2. Methyldopa goes through _____ conjugation.

Crossword Puzzle 3



Across

2. _____ inhibits warfarin.

Down

1. NAPQI causes toxicity to the _____
3. _____ + OCPs will lead to contraceptive failure.
4. >20% of the drugs are metabolized by _____ enzyme.

5 PHARMACOKINETICS DRUG EXCRETION

- The drugs can be excreted from the body by two routes Renal and Non-Renal routes.

Non-Renal Routes 00:01:00

- In the non-renal route, through the liver, the drug is thrown into bile, and from the bile, it is excreted through faeces.
- The drug can also be excreted through Sweat, Saliva, and Tears.
  - Lithium is a drug that undergoes excretion through sweat, saliva, and tears.
  - Lithium is given for conditions like Mania and Bipolar disorder.

- The drugs can also be eliminated through Breast Milk.
  - There is a risk in prescribing drugs to lactating mothers as most of the drugs are secreted in breast milk and there is a high chance that if the mother takes any medication the baby will also consume it through breast milk. So, if possible, drug prescribing should be avoided in lactating mothers.

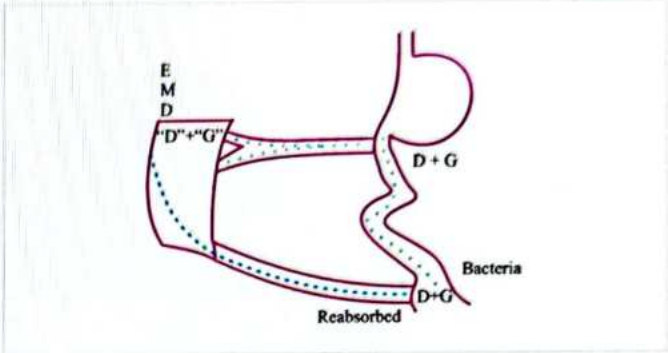
- The drug is also eliminated by the lungs through exhaled air.
  - Examples are alcohol, which came into the lungs in very minute quantities but can be detected by a Breathalyzer.
  - Another example of drug elimination by the lungs is general anaesthesia as they are also exhaled through the lungs.

Hepatic Clearance 00:04:56

- The drug excretion through the liver is called hepatic clearance.
- Hepatic clearance = Hepatic Blood flow × Hepatic Extraction Ratio
- If there is a question that,
  - Hepatic blood flow= 1500mL/min and Hepatic extraction ratio= 0.5
  - Hepatic clearance = 1500 x 0.5 = 750
- It is 750mL/min that is a hepatic clearance.
- In some cases, Hepatic extraction ratio is not given, and bioavailability (F) is given then suppose,
- Bioavailability of a drug is 0.4 (40%), so we can calculate hepatic extraction ratio by
- Hepatic extraction ratio = 1-F
  = 1-0.4
  = 0.6
- So, if Hepatic extraction ratio value is not given you can calculate it by the formula: **HER= 1-F**

Enterohepatic Recycling 00:07:14

- There are certain drugs that possess the property of recycling.



- The drug has undergone conjugation with glucuronide. So, the liver will excrete it by bile. Through the biliary tract, the drug goes. Now the drug will be eliminated as Drug + glucuronide and come into the faeces.
- In the intestine there are bacteria. Now, when the Drug + glucuronide comes into the intestine the bacteria remove glucuronide.
- The purpose of metabolism is to make lipid-soluble into water-soluble.
- That is the reason why we add glucuronide so it can be thrown out.
- Now when the glucuronide is removed by the bacteria the drug is also removed. Drugs being lipid-soluble are reabsorbed again and the drug enters circulation, again the drug goes for distribution, metabolism, and excretion and the cycle keeps on going.
- This is known as Enterohepatic recycling.

Importance of Knowing Enterohepatic Recycling 00:10:15

- Importance of knowing this is an example of Oral Contraceptive Pills (OCPs). OCPs are taken by women to prevent pregnancy.
- OCPs undergo glucuronide conjugation and the whole reabsorption process will occur.
- OCPs are longer acting.
- The problem comes when the patient on OCPs takes Tetracycline.
- Tetracycline is a broad-spectrum antimicrobial.
- So, when tetracycline reaches the intestine, it kills the bacteria and then the OCPs will become short-acting as the bacteria gets killed and OCPs will not undergo enterohepatic recycling.
- So due to this oral contraceptive pill will not be longer acting and there is a contraceptive failure.

Examples of Drugs Undergoing Enterohepatic Recycling

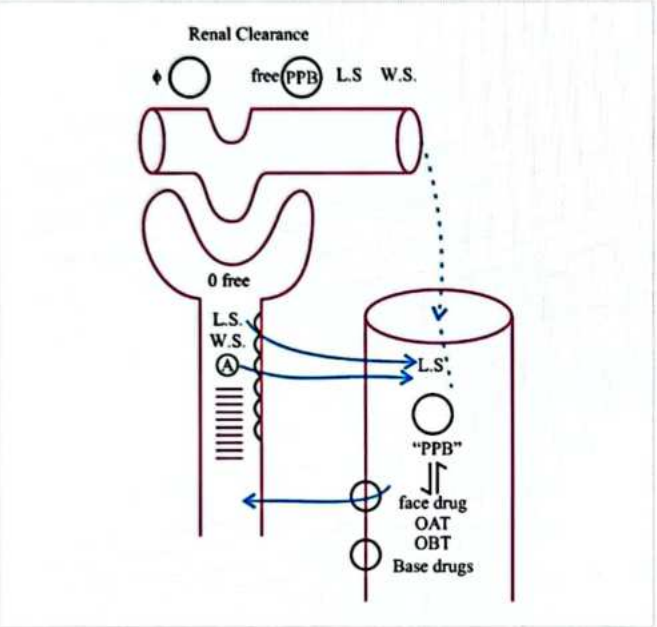
00:12:34

Mnemonic is A TOPPER

- Ampicillin
- Tetracyclines
- Oral Contraceptive Pills
- Piroxicam
- Phenylbutazone
- Erythromycin
- Rifampicin

Renal Clearance

00:13:38



Filtration

- Unit of kidney is nephron.
- First step when the drug enters the nephron is filtration.
- There are small gaps in the blood vessels and nephrons. Now the drugs have to go out in that small gap. So, drugs with smaller size can go easily.
- Lipid soluble, water soluble, small size and free drugs can get filtered easily.
- Plasma protein bound drugs and big in size drugs are not filtered

Reabsorption

- Lipid-soluble drugs can go back, and the process is known as reabsorption.
- The drug which escapes the filtration like a big-sized, plasma protein bound comes to the peritubular vessel.
- The bound drugs become the free drug. To throw them back there are transporters.
- Organic acid transporter and Organic basic transporter are the two transporters.
- Acid drugs take organic acid transporters and basic drugs take organic basic transporters.
- It is a two-way process. The drugs can either be secreted or reabsorbed by these transporters.

Secretion

- The free drugs are thrown into the lumen of the nephron and this process is called secretion

Aspirin Poisoning

00:20:22

- When the aspirin comes into the urine, it may get reabsorbed. So, to not let it reabsorb we can make the urine pH of aspirin from acidic to an alkaline medium.
- It becomes ionized so it will not be reabsorbed.
- Sodium bicarbonate is used to make the urine alkaline.

Phenobarbitone

- It is a basic drug.
- Phenobarbitone poisoning makes the urine pH alkaline.

Amphetamine Poisoning

00:22:32

- Amphetamine is a weakly basic drug. Urine should be made acidic by using ammonium chloride.
- We can also give Vit C to make the urine acidic.
- The basic drugs in an acidic medium become **ionized** and easily go out of the kidney.

Inhibition of Organic Acid Transporter

00:24:14

- There is a drug that inhibits organic acid transporter and that is Probenecid.
- But if given penicillin with probenecid penicillin will become longer acting.
- As penicillin is an acidic drug and probenecid inhibits organic acid transporter and penicillin is not thrown out and becomes longer acting.
- Thiazide diuretics are also acidic in nature.
- Thiazide and uric acid will go for organic acid transporter. Hence thiazide will take organic acid transporter and get secreted.
- Uric acid cannot take it because thiazide is stronger. So, the levels of uric acid increases

Important Information

- The adverse effect of Thiazide is Hyperuricemia.

- Renal Clearance = (F+S) – Reabsorbed
- If Glomerular filtration rate= 120mL/min,
- If Renal clearance of drug is 120mL/min then it is only filtered.

- If Renal clearance is more than 120mL/min that means drug is filtered + secreted.
- If Renal clearance is less than 120mL/min that means the drug is filtered – reabsorbed.

Clearance = Renal clearance + Hepatic clearance + other clearance

- Linagliptin undergoes bile elimination. This drug is safe to use in renal failure.

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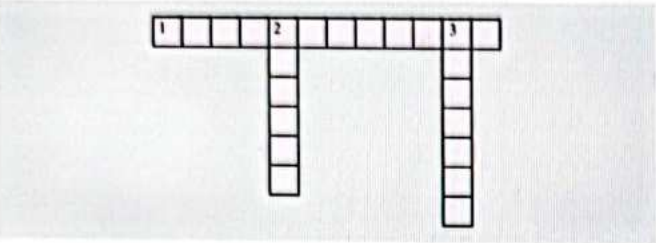
CROSS WORD PUZZLES

Crossword Puzzle 1



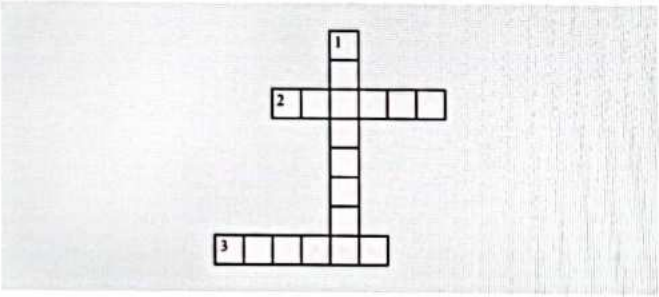
Across

1. Oral contraceptive pills should not be given with _____

Down

2. Penicillin is _____ in nature.
3. There are small gaps in the blood vessels and _____.

Crossword Puzzle 2



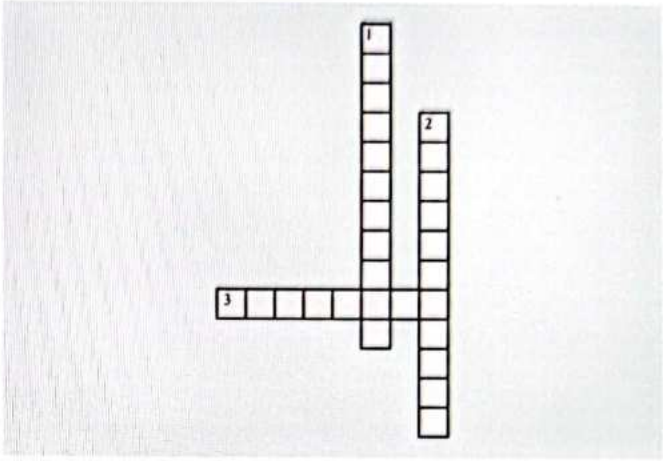
Across

2. Thiazide diuretics are _____ in nature.
3. Enterohepatic recycling makes the drug _____ acting

Down

1. Hyperuricemia is the adverse effect of _____

Crossword Puzzle 3



Across

3. Sodium bicarbonate is used to make the urine _____

Down

1. _____drug is safe for renal failure
2. Drug which inhibit organic acid transporter _____

6 HALF - LIFE, KINETICS OF ELIMINATION AND STEADY STATE PLASMA CONCENTRATION

Basic Concepts 00:00:22

Plasma Half Life

- Plasma half-life is defined as the time required to make the drug to its 50% of the original concentration.
- For example, a 500 mg drug is given and within 2 hours it becomes 250 mg that is half of its original concentration. So, the half-life will be 2 hours.
- Another example is if an 8 mg drug is given, and it becomes 6 mg in 2 hours and 4 mg in another 2 hours. So, the half-life would be 4 hours as the half-life is when the drug becomes 50% of its original concentration.

Elimination Rate

- Elimination rate is the amount of drug which is eliminated in unit time.
- Amount is expressed in milligram and time is expressed in hour. So, the elimination rate is expressed in mg/hr.

Clearance

- Drug clearance is the volume of plasma cleared of a drug in a unit of time.
- Volume is litre and the unit of time is an hour. So, clearance is expressed in L/hr.
- It is like GFR. GFR is written as ml/min, mL is the volume and min is the time.
- Clearance is also given by Elimination Rate divided by Plasma Concentration.
- Unit of Elimination Rate is mg/hr and the unit of Plasma Concentration is mg/L, mg gets cancelled, so the unit is L/hr.
- Clearance is the total of different clearances like renal clearance + hepatic clearance + other routes of clearance.

Kinetics of Elimination 00:05:12

- There are two types of elimination processes one is called First-order elimination and the other is called Zero-order elimination.
- To throw drugs out of the body we require metabolism and excretion.

First Order Elimination

- For Example, in the first order, if there are 100 drugs, then 100 enzymes are needed to metabolise them, if there are 200 drugs, then 200 enzymes are needed to metabolise them, and if there are 300 drugs, then 300 enzymes are needed, which means that the enzymes are present regardless of how much the drug concentration is increased.
- The constant fraction of drugs eliminated in unit time is called first order.
- The elimination rate is directly proportional to the plasma concentration which means if you increase the plasma concentration the elimination rate also increases.
- Half-life and clearance are the same in a first order.
- Most drugs follow first-order elimination.

Important Information

- In first-order elimination fraction is the same, the half-life is the same, and the clearance is the same.
- The elimination rate is variable because if plasma concentration increases elimination rate also increases.

Zero Order Elimination

- In zero order, if there are 80 medications, there are 80 enzymes to metabolise them; if there are 100 drugs, there are 100 enzymes to metabolise them; nevertheless, if the dose is increased further, let's say you provide 200 drugs, there are only 100 enzymes; if you give 300 drugs, there are still 100 enzymes.
- Due to the restricted availability of enzymes, they get saturated, which causes the drug level to rise and prevents the drug from being eliminated from the body.
- As a result, clearance drops, which is out of place.
- Zero order is also called Mixed order because initially, it was following first order but as the dose increases the metabolism and elimination shifts to zero order.

- It is also called saturation kinetics because the enzymes got saturated and that's the reason why a drug is not metabolized.
- The constant amount eliminated in unit time is called zero order.
- The elimination rate is constant in zero order.
- Half-life and clearance are variable in zero order.
- Half-life is directly proportional to plasma concentration, if plasma concentration is more the half-life of the drug is also more.
- Clearance is inversely proportional to plasma concentration. If plasma concentration increases clearance decreases.
- Only a few drugs follow zero order. (Mnemonic- WATT power)
  - Warfarin
  - Aspirin, alcohol
  - Theophylline
  - Tolbutamide
  - Phenytoin.
- In phenytoin, there is no problem in a normal dose as there are many enzymes but as the dose increases the phenytoin level increases, drug accumulates, and toxicity occurs. So, these drugs require special care when the doses are changing.

Important Information

- Elimination rate is constant.
- Half-life and clearance are variable.
- Plasma concentration and clearance are inversely proportional.
- WATT Power drugs follow this. These drugs if their dose increases there is a chance they can accumulate and cause toxicity.

Important Information

- Alcohol is the only drug which purely follows zero order kinetics.
- While other drugs follow mixed order kinetics.

Examples of First Order Elimination 00:13:15

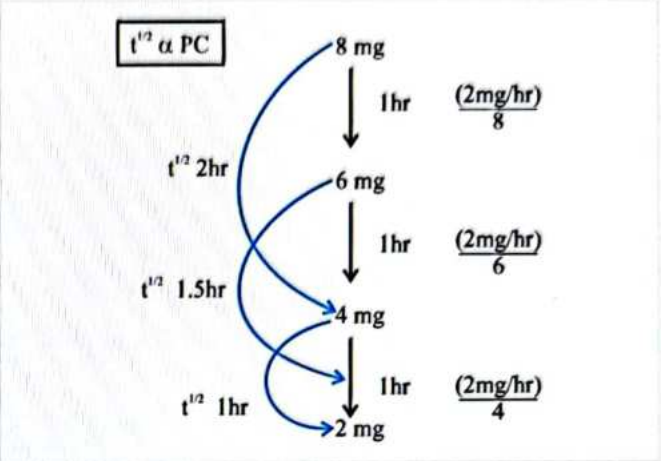
- An 8 mg drug is given, and it becomes 4 mg in 1 hour and 4 mg becomes 2 mg in 1 hour and 2 mg becomes 1 mg in 1 hour.
- The fraction is reduced by half every hour.
- So, the fraction of drugs eliminated is constant in the first order.
- Every hour 4 mg, 2 mg, and 1 mg are going out. The elimination rate is variable if the drug concentration is more the elimination of the drug is more and vice-versa.
- Clearance is the elimination rate divided by plasma concentration. So, if we divide, we get 0.5 in every hour which means clearance is the same in the first order.
- Half-life is also the same in the first order.

Examples of Zero Order Elimination 00:16:10

- 8 mg will become 6 mg in 1 hour and 6 mg will become 4 mg in 1 hour and 4 mg will become 2 mg in 1 hour.
- So, a constant amount is going out in zero order.
- The elimination rate remains the same.

	CL
8 mg	↓
↓ 1 hr $\frac{(2mg/hr)}{8} = \frac{1}{4} = 0.25$	
6 mg	
↓ 1 hr $\frac{(2mg/hr)}{6} = \frac{1}{3} = 0.3$	
4 mg	
↓ 1 hr $\frac{(2mg/hr)}{4} = \frac{1}{2} = 0.5$	
2 mg	

- Clearance is variable if the plasma concentration is more, the drug concentration is more, clearance is low, and if it is less clearance is high.
- Plasma concentration is inversely proportional to clearance. Clearance is variable that means if you give more and more drugs they will accumulate and will not go out.



- Half-life is also variable, if drug concentration is more, the half-life is more, and vice-versa.
- Half-life is directly proportional to plasma concentration.

Half-Life 00:19:50

- Half-life is written as t1/2 and is called plasma half-life. It is the time required to make the drug 50%. For example a 500 mg drug is given, it must be made 250 mg and it takes 2 hours for that.
- So, half-life is 2 hours.
- How many half-lives are required to eliminate the drug?
  - Suppose 100 molecules of the drug are given, 100 must become 50, and for that 1 half-life is required, 50 must become 25, require 2 half-lives, now 25 must become 12.5 is 3 half-lives, now 12.5 must become 6.25, require 4 half-lives, 6.25 will become 3.125 after 5 half-lives.
- Clinically we require 4 to 5 half-lives to eliminate the drug.
- Formula to calculate half-life:

$$t\frac{1}{2} = \frac{0.693}{K}$$ K = Elimination rate constant

K = 0.693

$$t\frac{1}{2} = 0.693 \times \frac{Vd}{CL}$$

  - Vd is the volume of distribution and Cl is the clearance.
- If the volume of distribution is high, half-life is also high if clearance is more half-life is less.

Importance of Half Life

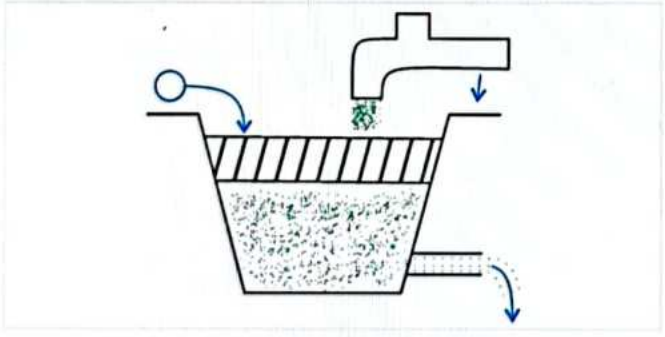
- Half-life will tell us about the dosing schedule like how many times a day we can give the drug.
- Half-life will also tell us about achieving steady state concentration.

Dosing Schedule 00:24:50

- Suppose the half-life of a drug is 5 minutes. If the half-life is very short as in the case of Oxytocin the drug will be given as an IV Infusion.
- Dopamine has a half-life of 2 minutes; it cannot be given repeatedly so it can also be given by IV Infusion.
- If the half-life of a drug is 2 hours for example half-life of paracetamol is 2 hours, if the half-life is between 2-4 hours, we try to increase the duration of action by increasing the dose, and the doses are doubled. So, by doing that the drugs can be given at 6 hourly means 4 times a day.
- In the case of paracetamol, we are adjusting the dosing in such a way that it is given 4 times a day as half-life being 2 hours you cannot be given it 12 times a day.
- If the half-life of a drug is 6 hours, it is given as four-times a day
- If the half-life is 8 hours, then it should be given three times a day.
- If half-life is 12 hours, then it should be given two times a day
- If the half-life is 24 hours, then it should be given once a day.
- Half-life will give a rough idea of the dosing schedule. It will not tell about the duration of the action.

Steady State Plasma Concentration 00:28:27

- Steady-state plasma concentration is the rate of drug entry that should be equal to the rate of drug exit. For example, if 100 drugs are given, there will be a point when hundred drugs are also going out.
- Levels of certain drugs should be maintained within that steady state range then only they'll work. For drugs, like Paracetamol, there is no problem but for drugs like lithium and digoxin, their level should be maintained within that steady state range as they are being given for a very long time.



- We can understand this by an example. There is a bucket on the terrace now you must fill the water in that bucket from the tap. The water is coming from the tap. Now the problem with the bucket is that the bucket has a hole. So, the purpose of keeping this bucket is to feed the birds in summer.
- What happens is when you put the water in, the water will fill up and after some time the water will not remain at that level. That level is kept so that the birds can sit and drink the water. But when you fill the water, the water will slowly go away from the hole i.e., eliminated.
- You should adjust that in such a way that the water should always remain at that level, how do we do that? We do that by adjusting the entry of water, for that you need to adjust the tap so that the entry from the tap is equal to the exit from the bucket.
- So, the rate of entry should be equal to the rate of exit and the water should remain at that level for the birds to drink.
- Suppose you fill the bucket in the beginning and close the tap. What will happen is the water will go away.
- If you adjust the water in such a way that the entry is equal to the exit, then the water level is always maintained. So, this is called a steady state.
- For the drugs, steady state is the rate of drug entry equal to the rate of drug exit.
- The rate of entry means the rate of infusion or infusion rate.
- The rate of drug exit is also called the Elimination rate.
- Clearance is equal to the elimination rate divided by plasma concentration.
- So, we can write that the elimination rate is equal to the clearance × plasma concentration.
- So, the rate of infusion is equal to Clearance × plasma concentration.

  Maintenance dose = Rate of Infusion × Dosing Interval

$$M.D = \frac{CL \times PC \times \text{dosing interval}}{F}$$

- The maintenance dose depends on clearance.
- In the dosing interval, if the question says to give the drug 8th hourly or give it thrice daily, in that case, we will put 8th hourly. If twice daily is given, you will put the 12th hourly. If four times daily, then 6 hourly will be written.

How to Achieve Steady State 00:35:38

- By giving the drug intermittent dosing.
- By giving the drug continuously dosing.

Intermittent Dosing

- In the X-axis time is written in hours. And plasma drug concentration on the Y-axis. We must achieve a steady state between maximum and minimum. To maintain the level, we can give the drug repeatedly so that the drug produces the effect. If a drug has a half-life of 2 hours, we give the drug every 2 hours to see how much time is required to achieve a steady state. To achieve a steady state between 200 and 100.

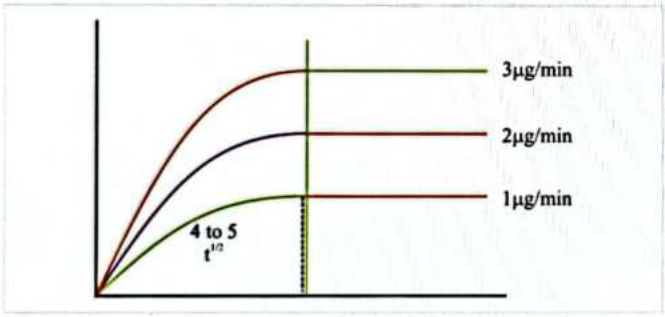
Refer Diagram 6.1

- So initially the drug given was 100. In the first half-life, the drug becomes 50 then another 100 is given now it becomes

150 after another half-life it becomes 50 that is 75 another 100 is added now it becomes 175. After one half-life, it becomes 87.5 more precisely 88; another 100 added now it becomes 188. Another half-life, it becomes 94.

- After 4 half-lives it has achieved 94 if we add 100 it becomes 194. At the end of 10 hours, it becomes 194 and again it comes down to 97. So, the drug is approximately between 97 and 197. This is a clinical steady state. It doesn't occur immediately and takes some time.
- Midline crossing is known as average, so it is called steady state average. The maximum is the steady state maximum, and the minimum is the steady state minimum called the trough.
- Trough means low level and peak means high level.
- Approximately 5 half-lives were required to achieve a steady state. 1 half-life is required to achieve a 50% steady state. 2 half-lives are required to achieve a 75% steady state. 3 half-lives are required to achieve an 87.5 steady state.
- The clinical steady state requires a 4 to 5 half-life to achieve a steady state. Mathematically more than 7 half-lives are required to achieve a steady state.
- Lithium has a half-life of 1 day. Lithium requires 1 day to achieve a 50% steady state, 2 days to achieve 75%, and 3.3 days to achieve a 90% steady state. 4-5 half-life is required to achieve a clinical steady state.

Continuous Dosing 00:44:10

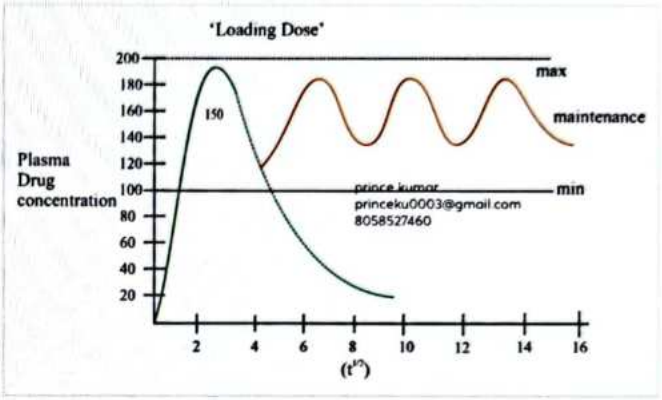


- If continuous IV infusion has been given, it takes 4 to 5 half-lives to achieve a steady state. For example, if infusing it at 1 microgram/min, now if the dose is further increased again it takes the same time to achieve a steady state.
- But now a new steady state will be achieved, the infusion may change to 2 micrograms/min but only the graph will go up. If again infused too fast it still takes the same time to achieve that, the infusion rate may increase to 3 micrograms/min, but it takes the same time. So, the time required to achieve a steady state is the same whether given faster or slower, the rate of infusion changes, and the steady-state level increases.
- To achieve a steady state 4 to 5 hours are required whether you give continuous or intermittent dosing it takes the same time.

  Rate of Infusion = CL × PC

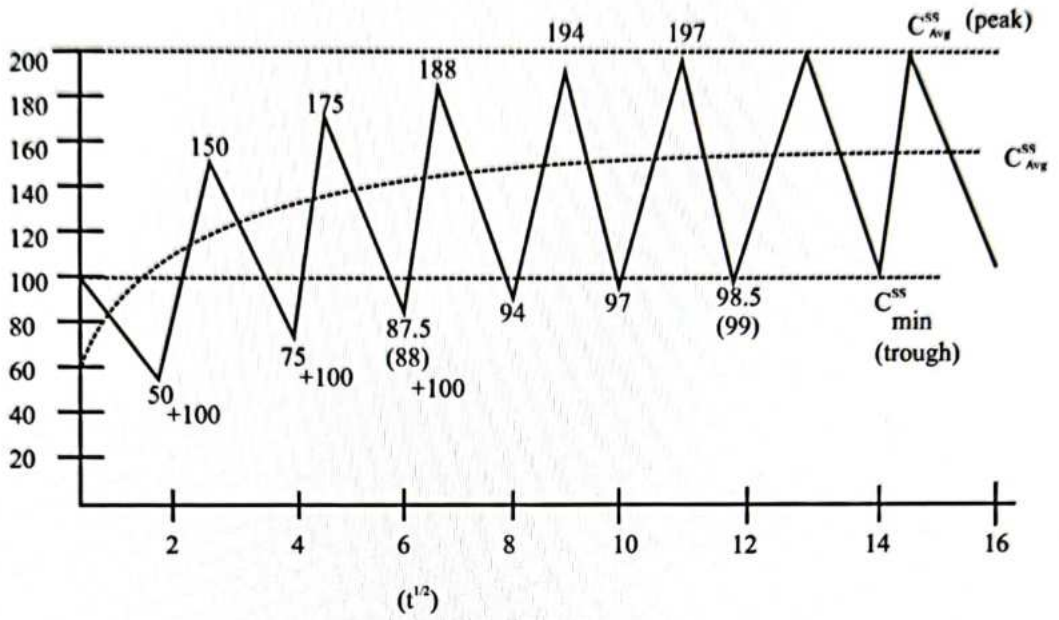
  Rate of Infusion = CL × Steady state PC

- To calculate the rate of infusion if plasma concentration is not given you can still calculate the infusion rate by multiplying it with steady state.
- Suppose the drug digoxin has a half-life of 40 hours. To achieve a steady state, we require 200 hours. In an emergency waiting for 200 hours is not possible.



- We must maintain the level. We give a high dose, called a loading dose. After giving the loading dose the drug will achieve the required level but after some time, it will fall, and no effect will be seen.
- Then the loading dose is given to get an immediate effect followed by the maintenance dose. This is another dosing strategy for drugs having a long half-life and a steady state is not achieved faster. We can give a loading dose followed by a maintenance dose.
- The formula for loading dose is target plasma concentration × volume of distribution divided by bioavailability.
- The formula for maintenance dose is target plasma concentration × clearance × dosing interval divided by bioavailability.

Diagram 6.1



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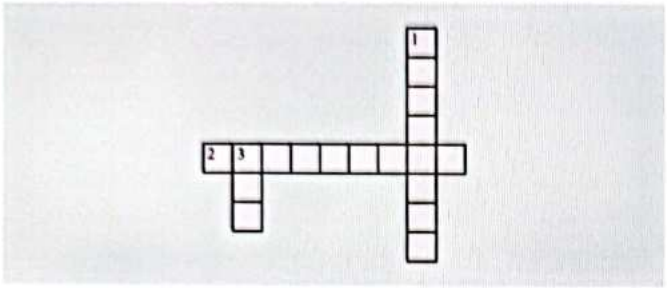
CROSS WORD PUZZLES

Crossword Puzzle 1



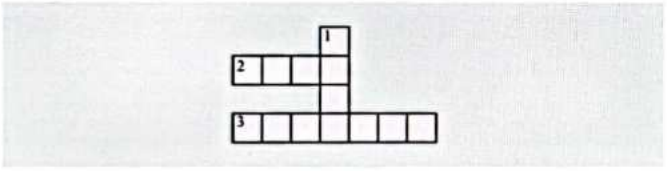
Across

2. Maintenance dose depends on _____

Down

1. Elimination rate is _____ proportional to plasma concentration.
3. Trough means _____ level.

Crossword Puzzle 2



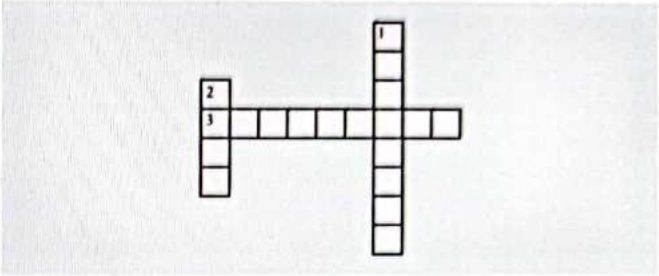
Across

2. Half-life and clearance is _____ in the first order.
3. _____ has a half-life of 40 hours.

Down

1. Elimination rate is constant in _____ order

Crossword Puzzle 3



Across

3. Clearance is _____ proportional to plasma concentration.

Down

1. The half-life is _____ proportional to plasma concentration.
2. Peak means ____ level.

7 pH AND pKA

Absorption of Weakly Acidic and Weakly Basic Drugs

00:00:21

- If a weakly acidic drug is placed in an acidic medium, the drug will be lipid soluble (LS), meaning it is non-ionized (NI), and will easily cross the cell membrane, increasing the absorption.
- If a weakly basic drug is placed in a basic medium or an alkaline medium, the drug will be lipid soluble (LS), meaning it is non-ionized (NI), and will easily cross the cell membrane. There will be an increase in the absorption.
- **Examples:** Aspirin is an acidic drug, and morphine is a basic drug. Aspirin is absorbed from the stomach because it is NI in the acidic medium of the stomach. Similarly, morphine is a basic drug, and the pH of the intestine is also alkaline, so it is absorbed easily from the intestine.

PH in Various Regions of The Body

00:02:24

- The stomach has a pH of 1-2.
- The intestine has a pH of 6 -7.4.
- Blood has a pH of 7.4 (neutral).
- The cell has a pH of 6.8 to 7.
- Urine has a pH of 4.5-7.8.
- Various body fluids have different pH.
- We don't know how much of the drug is ionized and how much is non-ionized (NI).
- Thus, to understand it, we have pka value.

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pKA Value

00:03:52

- The pka value is used to determine the amount of ionized (NI) value of a drug in the body.
- Example: The pka value of aspirin is 3.5.
- Pka is a pH at which 50% of the drug is ionized (I) and 50% NI.

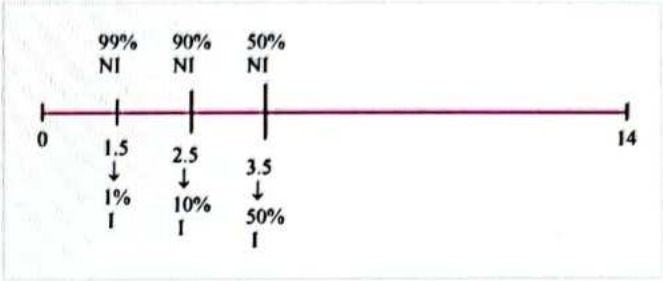
Henderson Hasselbalch Equation

00:06:00

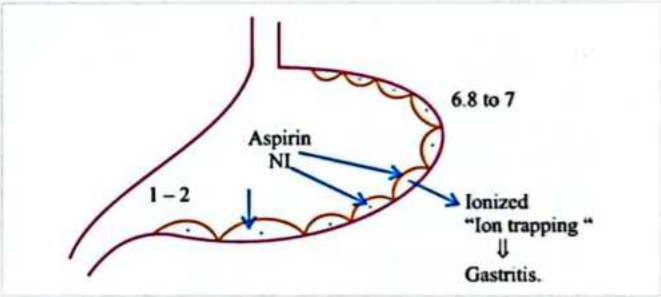
- According to the Henderson-Hasselbach equation, pH = pka + log [I]/[NI].
- To get the value of log [I]/[NI], we can use the formula log 50% [I]/50% [NI]. These get canceled out, giving the value log [1].
- The formula becomes pH= pka + log [1]. However, log [1] is 0.
- Thus, the formula becomes pH = Pka + 0.
- Thus, pH= pka. This is the Henderson-Hasselbach equation.

Aspirin has a PKA of 3.5

00:07:35



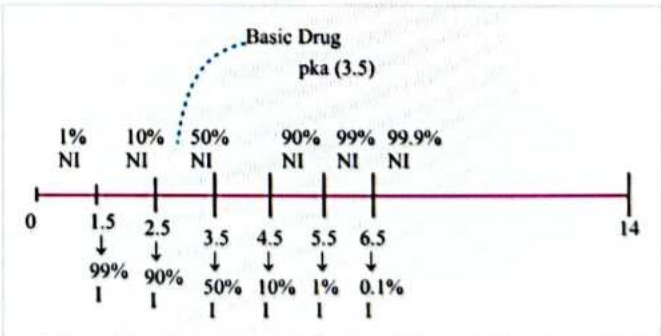
- On the pH scale for aspirin, the pH ranges from 0 to 3.5 is acidic, and from 3.5 to 14 is basic.
- Aspirin is 50% NI at pH 3.5.
- At a pH of 2.5, aspirin is 90% NI and 10% I.
- At a pH of 1.5, it is 99% NI and 1% I.
- At a pH of 0.5, it is 99.9% NI and 0.1% I.



- When aspirin is given to the patient, the stomach has a pH of 1-2. Thus, aspirin is most potent in NI form and moves easily into the cells.
- However, if aspirin is put in a pH of 4.5, then only 10% NI aspirin remains and 90% becomes I. This will increase with the increasing pH.
- The pH inside the cells is 6.8 to 7. Aspirin gets ionized inside the cells and cannot move out of the cells. This is called "ion trapping."
- Due to "Ion Trapping," the patient may experience gastritis.

Basic drug with a PKA of 3.5

00:13:21



- On the pH scale, pH values of 0 to 3.5 are acidic, and 3.5 to 14 are basic.
- For this drug, pka is 3.5, which means that at this pH, 50% of the drug is NI and 50% is I.
- At pH 2.5, 10% of the drug is NI and 90% is I.
- At pH 1.5, it is 1% NI and 99% I.
- At pH 4.5, the environment is basic for the drug. Thus, it is 90% NI and 10% I.
- At pH 5.5, it is 99% NI and 1% I.
- At pH 6.5, it is 99.9% NI and 0.1% I.

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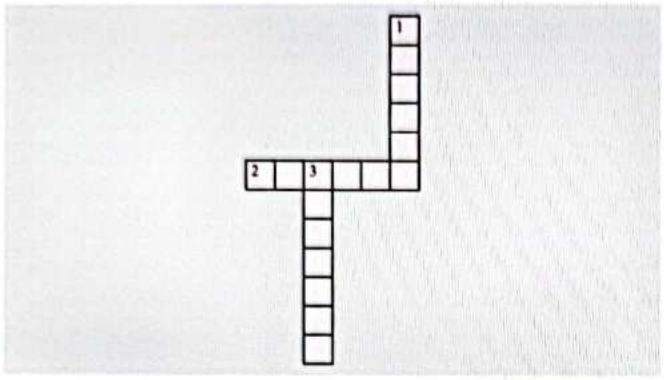
CROSS WORD PUZZLES

Crossword Puzzle 1



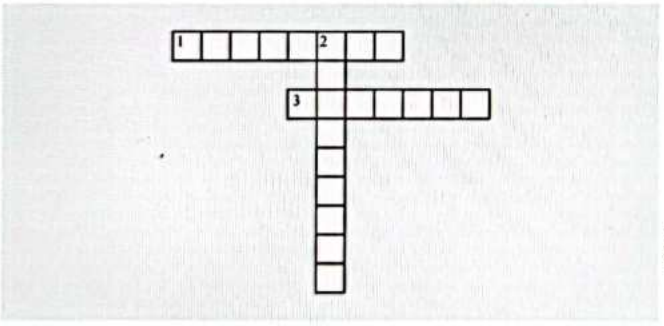
Across

2. _____ acidic drug, when placed in an acidic medium, will be lipid soluble (LS). It means that it is non-ionized (NI), and will easily cross the cell membrane, increasing its absorption.

Down

1. _____ basic drug, when placed in a basic medium or an alkaline medium will be lipid soluble (LS). It means that it is non-ionized (NI), and will easily cross the cell membrane, increasing its absorption.
3. _____ is an acidic drug.

Crossword Puzzle 2



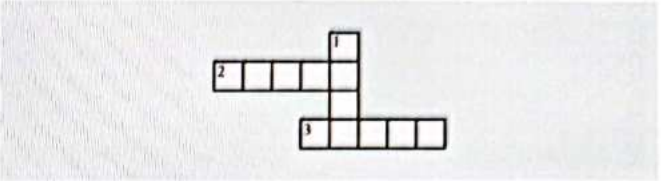
Across

1. _____ is a basic drug.
3. _____ has a pH of 1-2.

Down

2. _____ has a pH of 6.7–7.4.

Crossword Puzzle 3



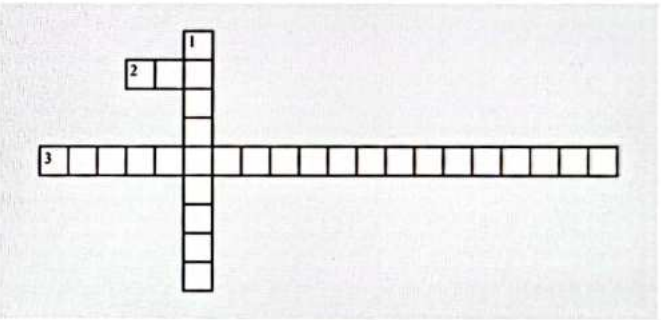
Across

2. _____ has a pH of 4.5-7.8.
3. _____ has a pH of 7.4 (neutral).

Down

1. _____ has a pH of 6.8 to 7.

Crossword Puzzle 4



Across

2. _____ is a pH at which 50% of the drug is ionized (I) and 50% non-ionized (NI).
3. _____ equation is pH = pka + log [I]/[NI].

Down

1. _____ is experienced due to "Ion Trapping".

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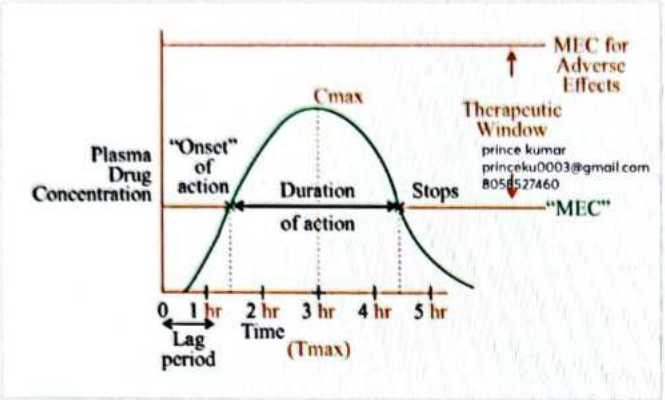
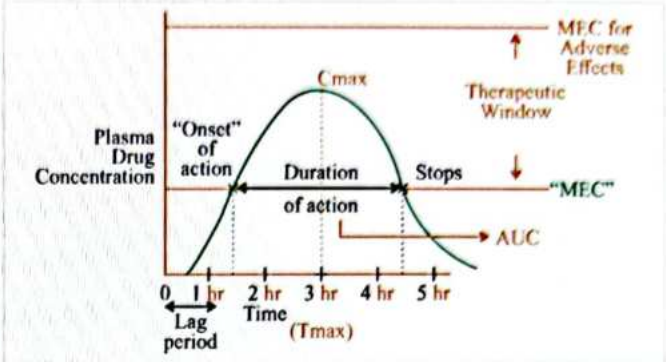
8 BIOAVAILABILITY

Bioavailability Graph

00:00:05



- When a drug is administered, it gets absorbed slowly, and the plasma concentration increases until it reaches a maximum level and then starts falling. If we plot a graph to show the plasma drug concentration, it is known as a "bioavailability graph."
- The y-axis shows the plasma drug concentration and the x-axis shows the time in hours.
- When a drug is administered, the plasma drug concentration reaches its peak gradually and then starts falling. The graph looks like a bell-shaped curve.
- The concentration where we see the maximum drug concentration is the Cmax. The time that it takes to reach the Cmax is called the Tmax.
- The minimum effective concentration (MEC) is the plasma drug concentration level at which the drug starts to be effective. This is called the "onset of action" of the drug.
- When the drug level falls below the MEC, it stops working. The point between the onset of action and when the drug stops working is called the "duration of action".
- The minimum effective concentration (MEC) for adverse effects (AE) is the minimum drug concentration at which adverse effects start occurring.
- The range between the MEC and the MEC for AE is called the therapeutic window.
- The drug should be given within this therapeutic window to remain effective without A/E.
- For example, the dosage of paracetamol in an adult is 500mg. If an adult takes only 100 mg, then it will not achieve the MEC and thus not work. If a higher dose of 2–3 gm of paracetamol is given, then it exceeds the MEC for AE and thus can lead to AE. Thus, the drug should be given within the therapeutic window.



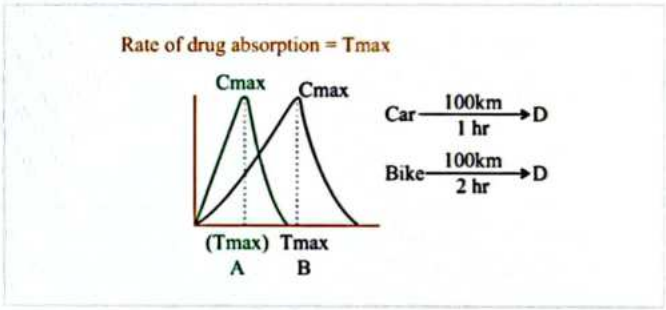
- The area under the bell curve is called the area under the curve (AEC).

Questions Asked Under Bioavailability

00:08:48

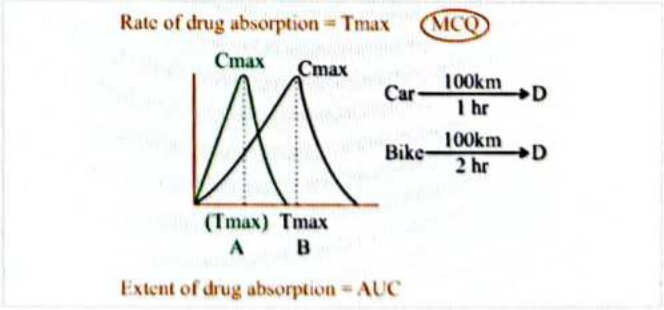
Q. What parameter in the bioavailability graph will give us the rate of drug absorption?

Ans.



- The rate of drug absorption is mainly given by Tmax.
- For example, drug "A" achieves a certain Cmax and Tmax, while drug "B" achieves a different Cmax and Tmax. The drug A absorbs fast since its Tmax is shorter.
- Another example is a car and a bike. A bike takes 1 hour to cover a distance of 100 km, while a bike takes 2 hours to cover the same distance of 100 km. Thus, the car is faster than the bike as it takes less time to cover the same distance.

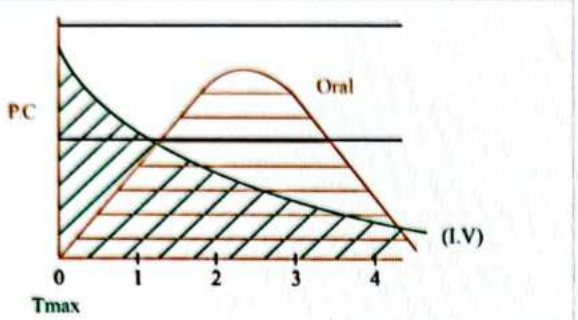
Q. What parameter in the bioavailability graph will give us the extent of drug absorption?



Ans.

- The extent of drug absorption is given by AUC.

Formula to calculate the bioavailability 00:11:38

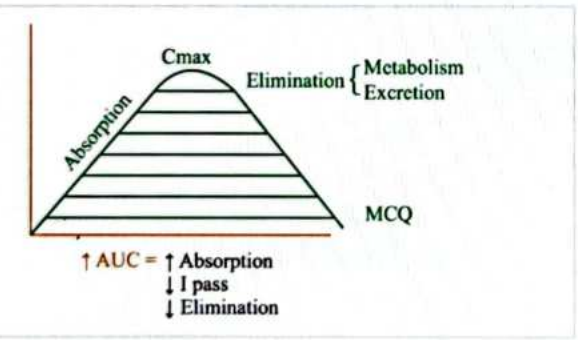


- When the drug is given via the IV route, the drug's plasma level falls below the maximum level. There's no bell curve because there's no absorption. This is the AUC of the IV route. The Tmax is zero as the drug works immediately.
- When the drug is given via the oral route, the drug concentrations increase, reach a peak, and then fall. This is the AUC for the oral route.
- Bioavailability (BA) is calculated as follows:

$$BA = \frac{\text{AUC [Oral/ any route]}}{\text{AUC [I.V]}} \times 10$$

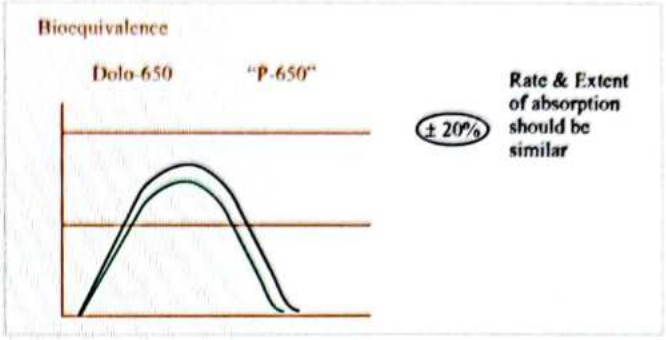
Q. How to increase the AUC? 00:14:05

Ans.



- When a drug is given orally, the graph goes up, reaches the Cmax, and then comes down. The bell curve shows the AUC.
- If the absorption is more, the drug concentration will be more. The graph comes down after reaching Cmax due to drug elimination via metabolism and excretion.
- To increase the AUC, either the absorption of the drug needs to be increased, the first-pass metabolism should be decreased, or the elimination of the drug should be decreased.

Bioequivalence 00:16:40



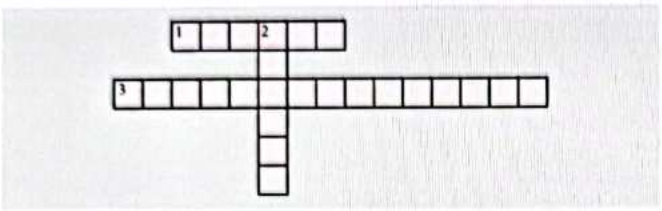
- Example: A company has a brand of paracetamol with the name Dolo-650. If another company wants to come up with the brand "P-650" for paracetamol, it should have a similar bioavailability as Dolo-650 to receive approval.
- The new drug should have an almost similar bioavailability of +/-20% as that of the comparator drug, i.e., the rate and extent of absorption of the drug should be similar. This is important to have a similar effect and avoid AE.

Summary 00:19:56

- The y-axis in a bioavailability graph shows the drug's plasma concentration, and the x-axis gives the time.
- The rate of absorption is given by Tmax.
- The extent of absorption is given by AUC.
- To increase the AUC, we need to increase the absorption, decrease the first pass, decrease the metabolism, or decrease the excretion of the drug.
- Bioequivalence: The new drug should have a similar bioavailability as the original drug with a variation of +/- 20% to get approved.
- The onset of action of the drug is the time when the drug reaches MEC. The drug stops being effective after it comes down below the MEC. The duration between the MEC and drug effect stoppage is the duration of action.
- The IV route has immediate onset of action since the Cmax can be achieved immediately.

CROSS WORD PUZZLES

Crossword Puzzle 1



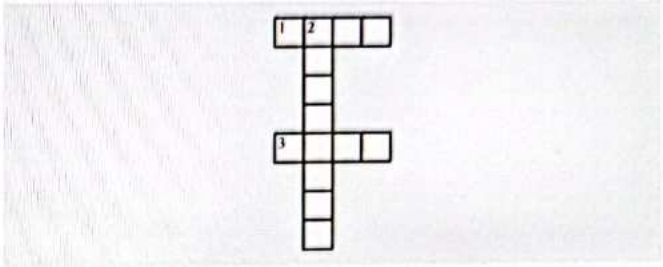
Across

1. _____ shows the plasma drug concentration.
3. _____ graph is the graph that is plotted to show the plasma drug concentration.

Down

2. _____ shows the time in hours.
3. _____ otalgia means the cause of pain is elsewhere.

Crossword Puzzle 2



Across

1. _____ is the maximum drug concentration.
3. _____ is the time taken by the drug to reach the Cmax.

Down

2. _____ effective concentration is the plasma drug concentration level at which the drug starts to be effective.

9 PHARMACODYNAMICS

00:01:00

- Pharmacodynamics is defined as the study of the effect of a drug or the mechanism of a drug's action.
- In other words, what a drug does to the body.
- Drugs can produce action in different ways- Stimulation, Depression, Replacement, Irritant, and Cytotoxic effects.
- Depression is defined as the reduction in the activity of CNS. For example- sedatives slow down brain activity.
- Replacement is the use of hormones in a state of deficiency. For example- Type-I diabetes where there is noinsulin in the body. So, insulin gives from an external source. In Hypothyroidism, levothyroxine is given from an external source.
- Irritants suppress the pain by producing inflammation when applied locally.
- Stimulation is the enhancement of the activity of cells.
- The cytotoxic effect is the killing of harmful cells. Drugs can kill human cells or microbes.
- Drugs can kill human cells (chemotherapy) in 2 situations- immunosuppression, and cancer cells.

Mechanism of Drug Action

00:05:00

- Drugs can act through receptors and non-receptor mechanisms.

Non-Receptor Mediated Action

00:05:43

Physical method

- When the drug does not produce any chemical reaction in the body.
- Example: Activated charcoal (universal antidote) + Poison = It adsorbs the poison.

Chemical method

- When the drug produces any chemical alteration in the body.
- When the stomach acid (HCL) is high, it causes gastritis. To neutralize this effect, antacids are used.
- Example: $HCL + Mg(OH)_2 \rightarrow MgCl_2 + H_2O$
- HCL is acidic, and Mg (OH)is basic→It produces a chemical reaction and neutralizes the effect.

Enzyme inhibition

- When the drug causes inhibition of the enzyme.
- Example- Paracetamol inhibits the enzyme cyclooxygenase (COX) in the hypothalamus. As a result, it lowers the body temperature or fever.
- Enzyme inhibition is divided into two types- Competitive and Non-competitive enzyme inhibition.

1. **Competitive enzyme inhibition:**
   - When the substrate binds to the enzyme, it gives the response.
   - If the drug and substrate bind to the same site, it is called competitive inhibition.

Important Information

- Example: Allopurinol inhibits the enzyme xanthine oxidase.
- Vmax remains the same and Km increases.

2. **Non-competitive enzyme inhibition:**
   - The enzyme has one more site called the allosteric site. When drugs bind to the allosteric site and substrates bind to the normal site. This is called Non-competitive inhibition.

Important Information

- Example: Acetazolamide inhibits the enzyme carbonic anhydrase.
- Vmax decreases and Km remains the same

Placebo effect

- Meaning of Placebo is "I shall please"
- It works through the psychodynamic effect. It works only when the doctor and patient have a good understanding.
- It increases the endorphin release in the brain. It is blocked by Naloxone.
- Example: Lactose tablet, For injections (distilled water), Sham surgery,
- Used in Clinical trials, Hospitals.

Nocebo effect

- It is a negative effect of a placebo. The patient does not believe the doctor regarding the treatment.

Inhibition of transport mechanism

- It inhibits the transport of adrenaline and serotonin.
- Example: Tricyclic antidepressants (TCA), Selective serotonin reuptake inhibitors (SSRIs).

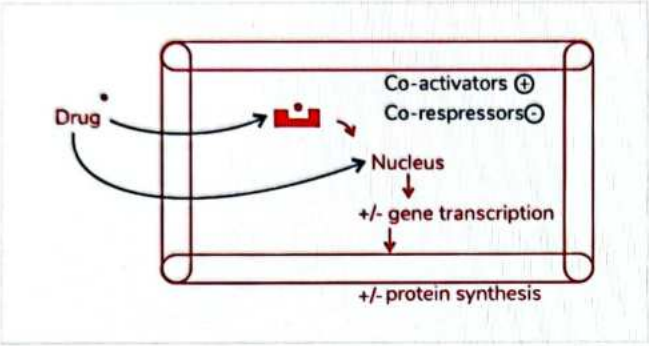
Receptor Mediated Action

00:20:21

- Receptor is a macromolecule that binds to a drug and causes a biological response in the body.
- Drug + Receptor Action (response)

- The drug commands the receptor to increase or decrease the action.
- For the signal to a receptor, a transducer mechanism is responsible for the action.
- Example: Adrenaline binds to the β1 receptor and increases the heart rate. To increase the heart rate, the signal is transmitted to the receptor to increase the heart rate.

Location and Function of Receptors

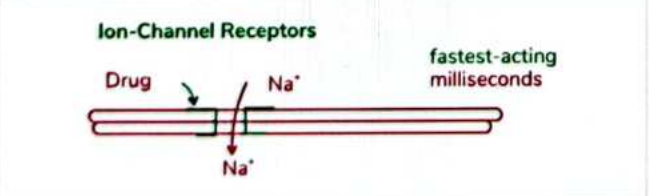


- The drug enters the cell membrane via the cytoplasm, binds to the receptor in the cytoplasm, and then enters the nucleus.
- It produces stimulation or inhibition of gene transcription (protein synthesis).
- Stimulator is called Co-activators and Inhibitor is called Co-repressors.
- Some drugs can directly go to the nucleus and then stimulate or inhibit gene transcription.
- Drugs that are lipid soluble can easily cross the cell membrane and the lipid-soluble hormones. These receptors are called nuclear receptor superfamily.
- These receptors are the slowest-acting receptors. Example: Testosterone.
- Examples are corticosteroids (mineralocorticoids, glucocorticoids), sex hormones (progesterone, estrogen, testosterone), thyroxine, vitamin A and D, and PPAR.

Cell membrane receptors

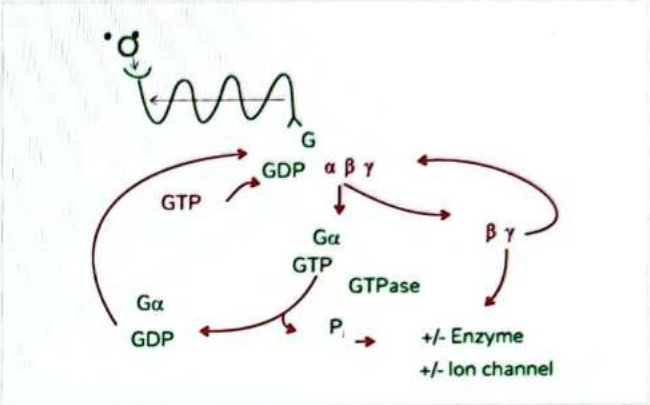
- Drugs that act through the outside of the cell are called cell membrane receptors. These receptors are located on the cell membrane.
- Examples: Ion channel receptors, G-protein coupled receptors (GPCR), and Transmembrane receptors.

Ion-Channel Receptors



- When a drug binds to the receptor, it opens the channel, and ions move inside. Example: Na+ ion.
- Ion channel receptors are the fastest-acting receptors. These receptors can act in milliseconds.
- Example: Nicotinic receptor (opens Na+ channel), Glutamate (opens Ca+/Na+ channel), GABAA (opens Cl channel), 5HT3, Glycine, Glutamate has 3 subtypes: NMDA, AMPA, and Kainate receptor.

G-protein coupled receptors (GPCR) 00:31:15



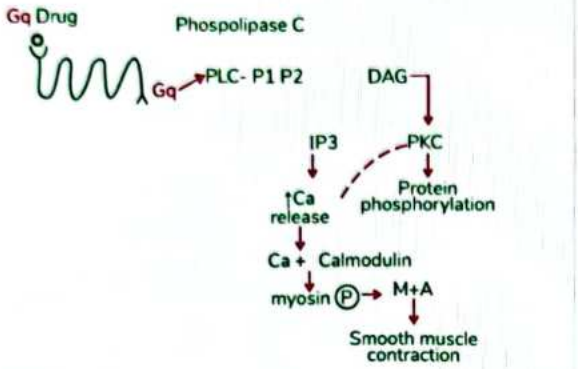
- G protein-coupled receptor (GPCR), also called Seven Transmembrane receptor/Serpentine receptor/ Metabotropic receptor.
- GPCRs are called G-proteins. Because they interact with G-proteins (GDP), and α,β,γ subunits present in the cell membrane.
- When the drug binds to the GPCR, it causes conformational change (Gα and GTP are separated).
- Gα has GTPase intrinsic activity, it releases phosphate (p). This phosphate utilizes to stimulate or inhibit the enzyme or ion channel.
- β,γ are also responsible for stimulating or inhibiting the ion channel.
- When the GTPase activity is completed, only GDP remains. As a result, GDP, β, γ again reconstitute to act.

Subtypes of GPCRs

- Gα determines the type of subtype. Gα is classified into 3 families (Gi, Gs, Gq).
- **Gs (stimulatory)**
  - When this receptor is stimulated, it activates the adenyl cyclase (AC) and converts the ATP into cAMP
  - cAMP activates protein kinase A (PKA). This PKA stimulates the heart (β1) to increase heart rate, conduction, and force of contraction. It also increases the Ca+ entry inside the cell.
  - When PKA acts on smooth muscle (β2), it relaxes the smooth muscle.
  - cAMP is also called a secondary messenger. Once cAMP

33

sends the signal then it terminates.
  - cAMP is terminated by phosphodiesterase enzyme (PDE) and produces 5'AMP.
- **G_i (inhibitory)-**
  - It inhibits the enzyme adenyl cyclase. As a result, it decreases the activity of cAMP and PKA.
  - G_i closes the Ca+ channel and opens the K+ channel.
- **Gq coupled receptor-**
  - When the drug activates Gq coupled receptor, it activates the enzyme phospholipase-C (PLC).



  - PLC converts into phosphatidylinositol 4,5-bisphosphate (PIP2). PIP2 is metabolized into inositol 1,4,5 triphosphate (IP3) and diacylglycerol (DAG).
  - As a result, IP3 increases Ca+ release from the sarcoplasmic reticulum and DAG activates PKC.
  - Ca+ also releases PKC and causes protein phosphorylation.

Important Information

- Ca+ combines withCalmodulin. As a result, it will activate myosin phosphorylation and cause smooth muscle contraction.
- Example: M3 receptor present in the bronchus, it causes broncho-constriction.
- Second messenger: IP3, cAMP, NO, cGMP, Ca+, and DAG is secondary messenger.

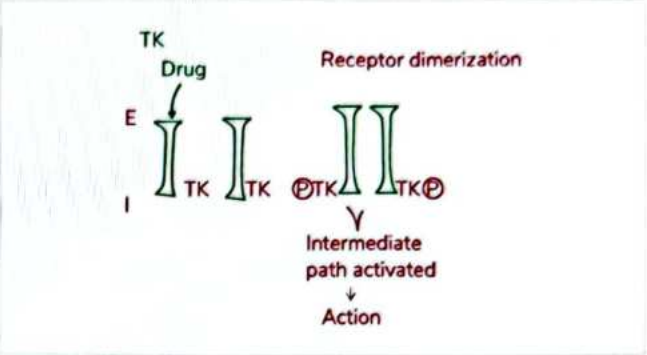
Cyclic GMP (CGMP) as a Secondary Messenger

- The Guanylyl cyclase (GC) enzyme is located at the cell membrane (membrane-bound guanylyl cyclase mGC) and inside the cytoplasm (soluble guanylyl cyclase, sGC).
- mGC is activated by the natriuretic peptide. Examples: brain natriuretic peptide (BNP), and atrial natriuretic peptide (ANP).
- sGC is activated by nitric oxide (NO).
- When GC is activated, it converts GTP into cGMP (secondary messenger).
- cGMP activates PKG. As a result, it causes smooth muscle relaxation.
- Second messenger – cGMP gets terminated by PDE to 5' GMP

Transmembrane Receptor 00:48:36

- Transmembrane are receptors that are embedded in the cell membrane.
- It is divided into 2 subtypes: Intrinsic tyrosine kinase activity, and JAK-STAT pathway.

1. Intrinsic tyrosine kinase activity

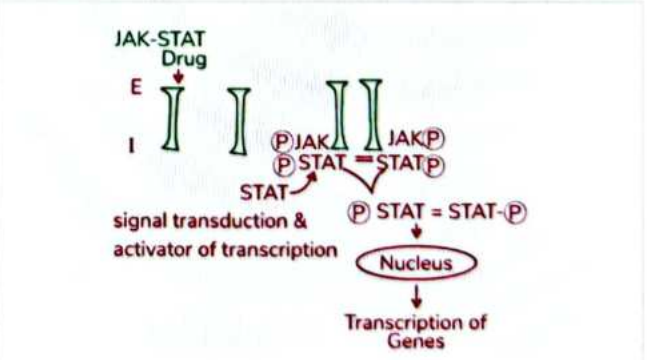


- Tyrosine kinase (TK) is located in the intracellular region. One more receptor is similar to TK present in the intracellular region.
- When the drug binds, receptors come into proximity and cause receptor dimerization.
- TK is phosphorylated by intrinsic tyrosine property. Then intermediate pathways are activated. As a result, action is performed.

Important Information

- Examples: insulin, Insulin-like growth factor (IGF-1), growth factor (vascular endothelium growth factor- VEGF, Epidermal growth factor- EGF, platelet-derived growth factor- PDGF).
- VEGF, EGF, and PDGF cause the cell to proliferate. Blocking TK stops the stimulus from these factors and stops the multiplication of cancerous cells.

2. JAK-STAT pathway



34

- JAK-STAT has no intrinsic tyrosine kinase activity. One more receptor is present there.
- When the drug binds, these receptors come into proximity.
- Janus kinase (JAK) enzyme is located near the receptor and binds to the receptor.
- JAK is then phosphorylated and activates the receptor. As a result, it causes stimulation of the signal transduction activator of transcription (STAT).
- STAT moves freely in the cytoplasm, STAT attaches to the receptor, gets phosphorylated, and forms the bond.
- Phosphorylated STAT enters the nucleus and causes the transcription of genes.
- Examples: Prolactin, Growth hormone, Cytokines, Interleukins.

IMPORTANT QUESTIONS

Q.1 Gα is classified into how many types-
Ans. Gα is classified into 3 types (Gα, Gβ, Gγ).

Q.2 What are the examples of secondary messenger-
Ans. cAMP, cGMP, NO, DAG, IP3, Ca+

Q.3 What are the principles of drug action-
Ans. Stimulation, Depression, Irritation, Replacement, and Cytotoxic action.

Q.4 Insulin is an example of-
Ans. Replacement mechanism of drug action.

Q.5 JAK-STAT pathway is the type of-
Ans. Transmembrane receptor.

Q.6 Gi (inhibitory) inhibits which enzyme-
Ans. Adenyl cyclase enzyme.

Q.7 Insulin-like growth factor is an example of the
Ans. Intrinsic transmembrane pathway.

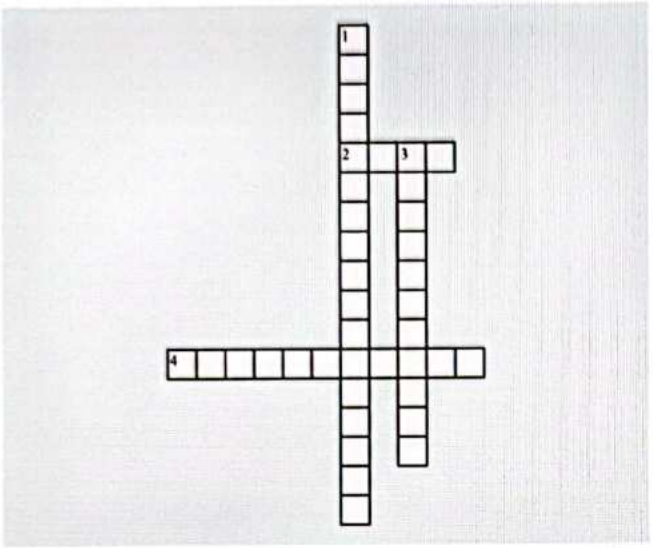
Q.8 Gq coupled receptor activates which enzyme-
Ans. Phospholipase-C (PLC).

Q.9 Paracetamol inhibits which enzyme-
Ans. Cyclo oxygenase enzyme (COX).

Q.10 Vmax decreases and Kmaxremains the same in
Ans. Competitive enzyme inhibition.

CROSS WORD PUZZLES

Crossword Puzzle 1



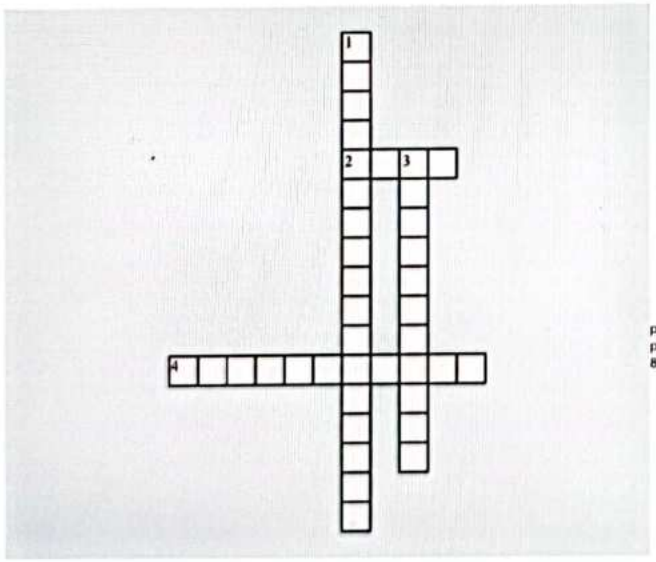
Across

1. ____ remains the same in the competitive enzyme inhibition.
4. ____ is the type of mechanism of drug action.

Down

1. ___ is the universal antidote.
2. ___ inhibits the enzyme xanthine oxidase.

Crossword Puzzle 2



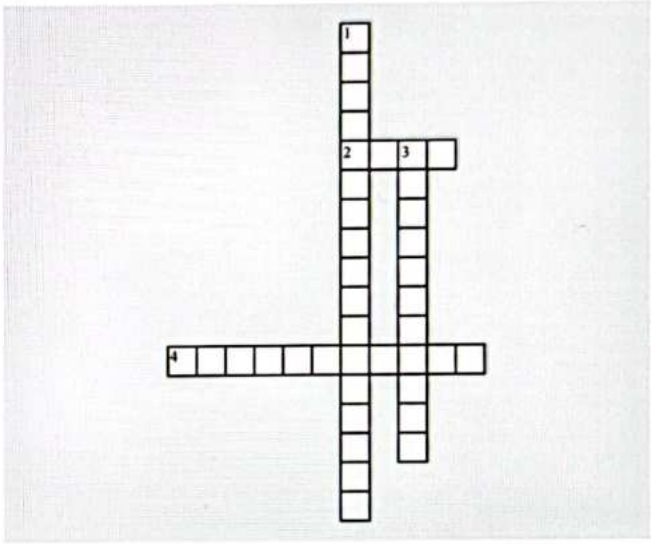
Across

3. _____ combines with Ca+. As a result, it activates myosin phosphorylation and causes smooth muscle contraction.
4. _____ is the type of glutamate receptor.

Down

1. _____ is the fastest-acting receptor.
2. _____ activates by Gq coupled receptor.

Crossword Puzzle 3



Across

3. ____ is the other name of the GPCR receptor.
4. ____ is an example of the JAK-STAT pathway.

Down

1. ____ causes bronchoconstriction.
2. ____ is the secondary messenger.

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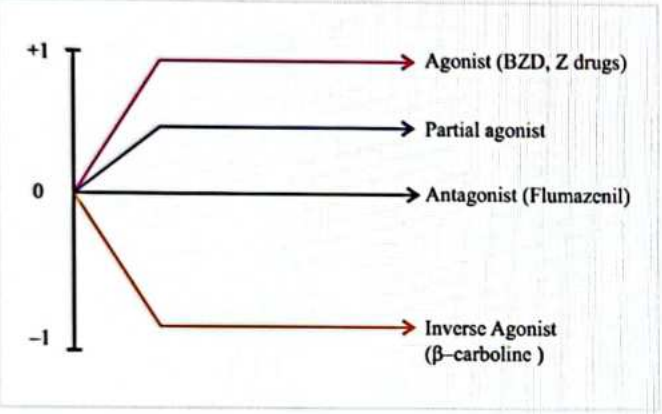
10 DOSE RESPONSE CURVE

Classification

- Drug + Receptor ⇒ Response
  - Ex. Adrenaline + ß ⇒ ↑ Heart Rate
- When the drug binds to the receptor, it should produce some response.
- Affinity is the ability to bind receptors. It should produce some response. So that response is also called intrinsic activity.

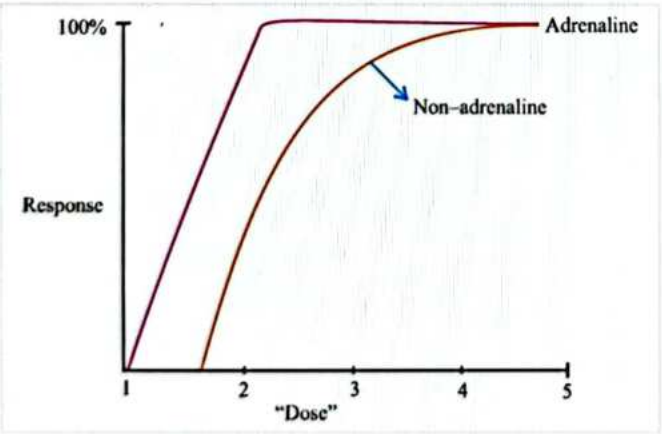
Refer Table 10.1



Dose-Response Curve

00:09:00

- The Dose-Response Curve describes the magnitude of the response of an organism as a function of exposure to a stimulus or stressor after a certain exposure time.
- The relationship between a dose's size and the response's extent to it.
- E.g. Adrenaline + ß1 = ↑ Heart Rate

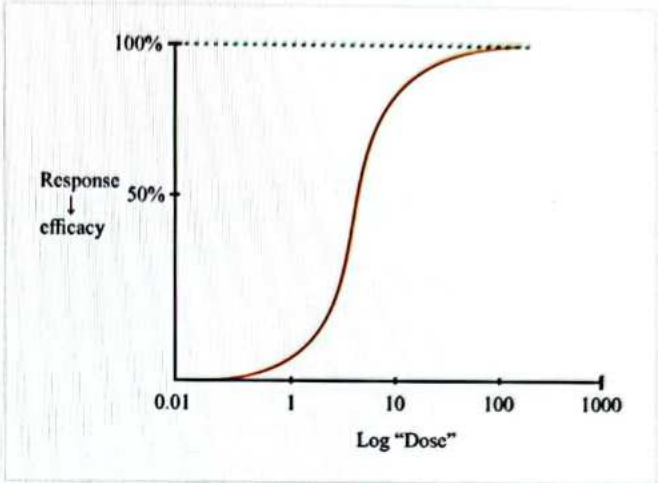


Drawback

- Cannot compare two different drugs since they can overlap
- Cannot compare large doses.

Log Dose-Response Curve

00:12:12



- A dose-response curve is a coordinate graph relating the magnitude of a dose (stimulus) to the response of a biological system.
- The graph looks like an S-Shape called a Sigmoid Curve.
- A Sigmoid Curve shows the highest response of 100 %.
- The response is called Efficacy.
- **Efficacy:** The ability to produce a desired or intended result.
- **Potency:** The relative amount of drug required to produce the desired response.
- The dose is correlated with the potency.
- The response is correlated with efficacy.
- The dose is inversely proportional to the Potency.
- When a drug is prescribed we have to worry about the efficacy of the drug.
- Ex. DMT2 ⇒ Metformin 500 mg (HbA1C ⇒ ↓ 1-2%)
  ⇒ Glimepiride 1 mg (HbA1C ⇒ ↓ 1-2%)

ED 50 (Effective Dose)

- ED 50 is the dose of a drug to produce 50 % of the response.

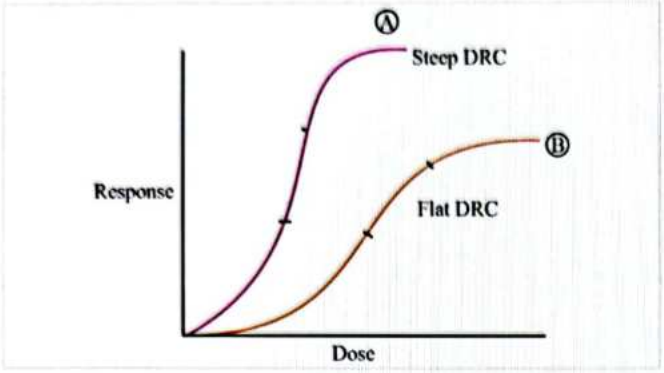
Q. ED 50 is a measure of?
Ans: Potency

- EC 50 (Effective concentration)
- Effective concentration of the drug to produce 50% of response

LD 50 (Lethal Dose)

- LD 50 is the dose of a drug that produces death in 50 % of the animals.

Slope of the Curve

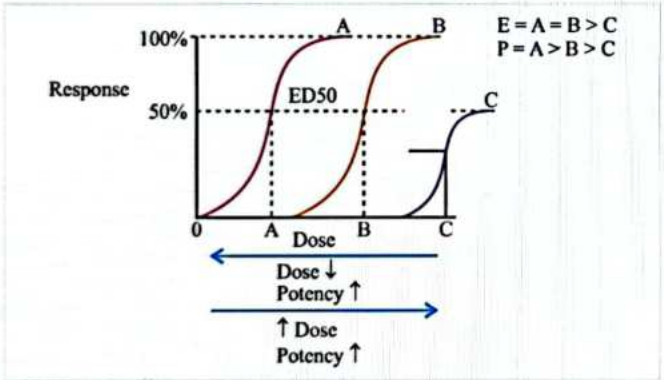


- Drugs A and B produce two different DRC.
- Drug A produces a steep DRC and is less safe. E.g. Barbiturates
- Drug B produces a flat DRC and indicates the drug is safe. E.g. Benzodiazepines

Efficacy and Potency

00:22:10

- When a drug is prescribed we have to worry about the efficacy of the drug.
- Ex. DMT2 ⇒ Metformin 500 mg (HbA1C ⇒ ↓ 1-2%)
  ⇒ Glimepiride 1 mg (HbA1C ⇒ ↓ 1-2%)



- The above graph shows the DRC of three different drugs.
- Based on the efficacy, A and B are equally efficacious and C is the least efficacious drug.
- Based on the potency, ED 50 of all the drugs are considered and lower the dose more potent and higher the dose less potent i.e A > B > C.
- E.g. A = Morphine, B = Pethidine and C = Aspirin.

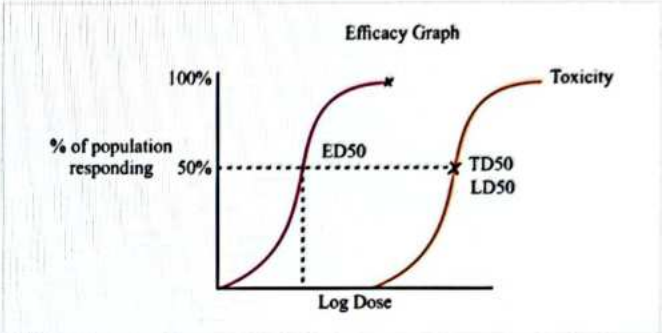
Difference Between Efficacy and Effectiveness

Efficacy	Effectiveness
↓	↓
Ideal Condition	Real life Situation
↓	↓
Response (Clinical Trial)	Response (Drugs prescribed in hospitals)

Types of Log Dose Response Curve

00:29:10

- **Graded Log DRC**
  - ↑The dose of drugs more and more causes the response of the drug
  - Give the drug to the individual patient and take responses related to the drug.
- **Quantal Log DRC**
  - Efficacy is fixed.
  - Give drugs to the population of patients.
  - It follows All or None phenomenon



  - The Y axis is the % of population responding and the X axis is Log dose.
  - In this graph, ED 50 represents in 50 % of the population what dose of the drug will give the response. This is efficacy graph.
  - TD 50 represents in the 50% population what dose of the drug will give the toxic response. This is Toxicity graph.

Therapeutic Index

00:35:02

- The therapeutic index is a quantitative measurement of the relative safety of a drug.
- It compares the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity.

$$\text{Therapeutic index} = \frac{TD50}{ED50} \text{ or } \frac{LD50}{Ed50}$$

- TD = Toxic dose, ED = Effective dose and LD = Lethal dose
- The drug A is safer to prescribe because the distance between the efficacy and the toxicity is more in the graph. This is known as the wide therapeutic index.
- The drug B has narrow therapeutic index and less safe to use
  - E.g. Digoxin, Lithium and TCA's.

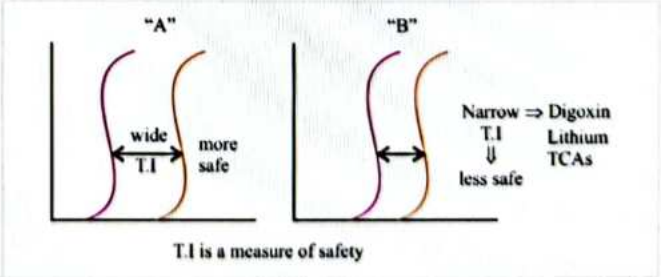
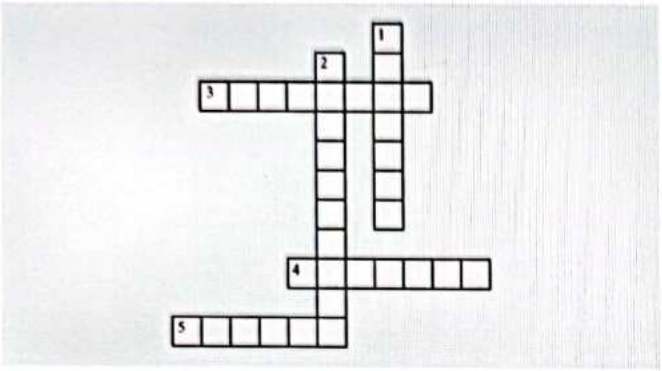


Table 10.1

Agonist	Partial Agonist	Antagonist	Inverse Agonist
• An agonist has affinity and produces an intrinsic activity of +1 (maximum) • Ex. Benzodiazepine	• Partial agonist has affinity and produce an intrinsic activity of 0-1 • Partial agonists with lower Intrinsic activity at receptors are full agonists.	• Antagonist have affinity but produce 0 intrinsic activity • In medicine, a substance stops the action or effect of another Substance. • Ex. Flumazenil	• Inverse agonists have affinity and produce -1 intrinsic activity (opposite response). • An inverse agonist is a ligand that binds to the same receptor-binding site as an agonist and not only antagonizes an agonist's effects but exerts • The opposite effect by suppressing spontaneous receptor signalling (when present). • Ex. β Carboline

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Is the ability
4. Graph look like an S-Shape called
5. The lesser the dose is more

Down

1. The dose is Inversely proportional to the
2. Substance stops the action or effect of another substance

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11 COMBINED EFFECTS OF DRUGS

Background Concept

- The interactions that occur when two or more drugs are taken simultaneously, leading to potentially unpredictable or harmful effects.
- The effects can range from mild to severe and may include increased side effects, altered drug metabolism, and increased risk of overdose.

Types of Combined Drug Effects 00:15:00

Refer Table 11.1

Side Note

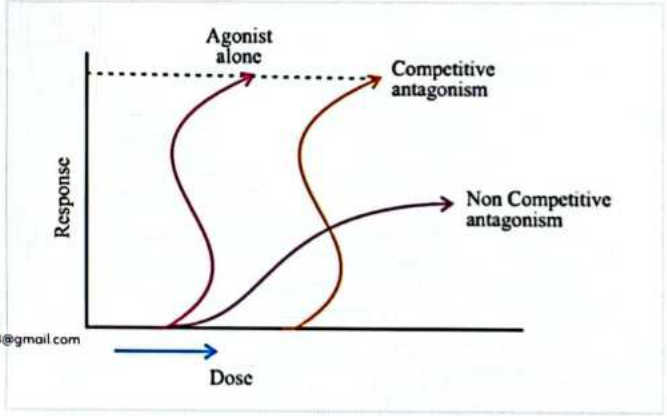
Parkinsonism management aims to increase the levels of dopamine in the brain.
↓
Levodopa is a precursor of dopamine used to treat the condition, as dopamine cannot cross the blood-brain barrier.
↓
Peripheral decarboxylase metabolizes levodopa before reaching the brain.
↓
Carbidopa inhibits peripheral decarboxylase.
↓
Increases the availability of levodopa in the brain
↓
Enhances the efficacy of levodopa

Types of Receptor Antagonism 00:14:30

Competitive receptor antagonism	Noncompetitive receptor antagonism
• Agonists and antagonists compete for the same active site. • The end effect depends on the relative concentration of the drugs. • The effect of an agonist can be enhanced by increasing the dose. • This is called Surmountable. The efficacy of the agonist remains the same while the potency decreases.	• The antagonist binds to a different site called allosteric site whereas the agonists binds at a different site. • The end effect does not depend on the relative concentration of the drugs. • The antagonist has the upper hand and reduces the sensitivity of the target receptor. • The efficacy of the drug decreases, but potency remains the same.
• Example 1. Acetylcholine (agonist) and atropine (antagonist) compete for the same active site on the muscarinic receptor. 2. Morphine (agonist) and Naloxone (antagonist) compete for the same active site on the μ receptor.	• Example: Benzodiazepine binds non-competitively to the GABA receptor and reduces the effect of Bicuculline.

Graphical Analysis of Drug Interactions 00:22:30

- Plots of drug response against doses in the absence and presence of an antagonist can be used to identify the type of antagonism.



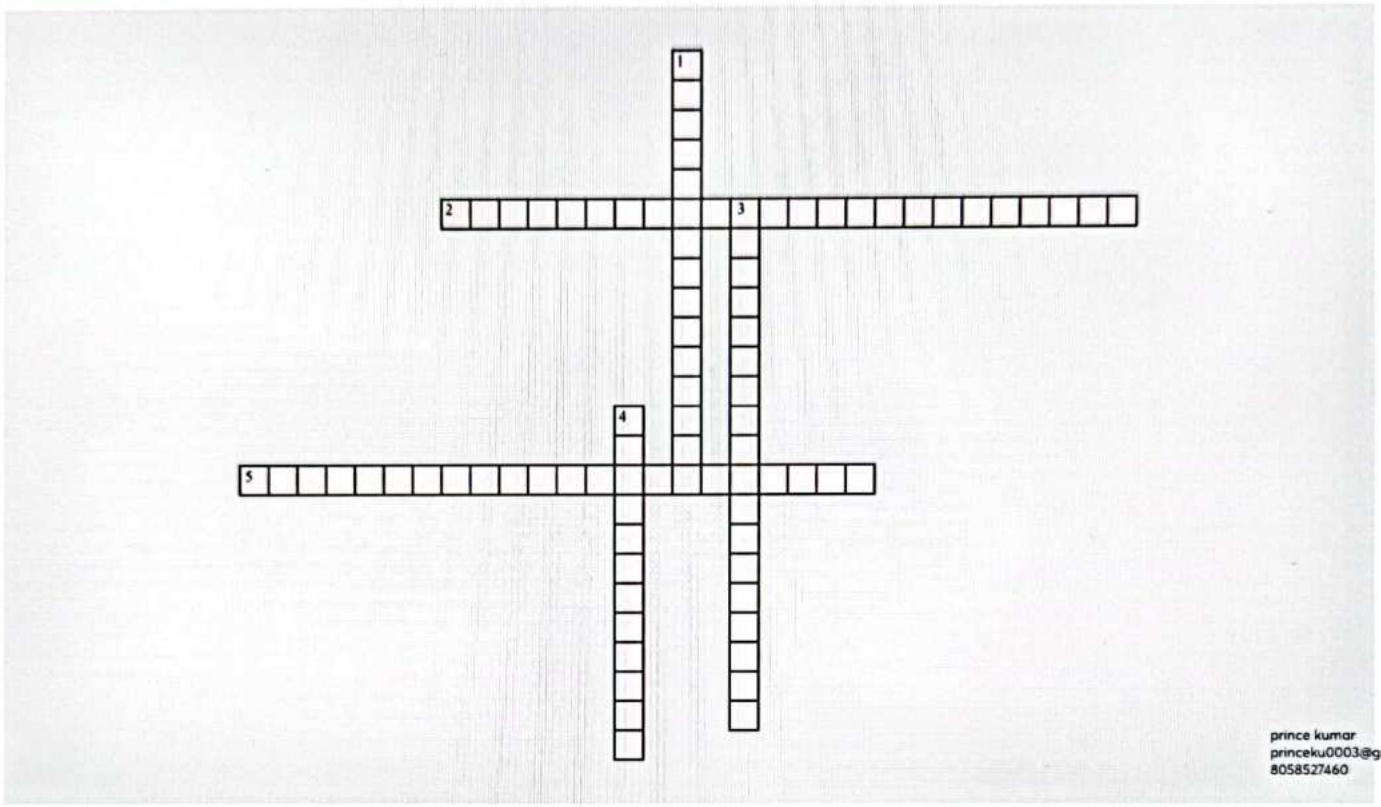
- The graph represents plots of drug response versus the dose.
- The response of drugs (agonists) in the absence of an antagonist increases with an increase in its dose, represented by the white curve.
- In the presence of a competitive antagonist, the pattern of increase in response with dose remains the same, but the plot shifts towards a higher level. It implies that it can achieve its maximum response at a higher concentration.
- In the presence of a noncompetitive antagonist, the response decresed with a dose up to a limit. It cannot achieve its original efficacy by increasing the concentration.

Table 11.1

Effect	Definition	Example
Permissive action	An interaction wherein a drug confers complete functionality to another drug.	Adrenaline and noradrenaline do not function in the absence of steroids.
Additive effect	Two or more drugs function independently and result in the sum of their effects.	The combination of paracetamol and diclofenac has an additive effect.
Synergistic effect	Two or more drugs act against the same disease or condition with a different mechanism, increasing the efficacy of the treatment.	• Antiplatelet drugs aspirin and clopidogrel act against platelet production and activation. • Cotrimoxazole is a combination of trimethoprim and sulfamethoxazole.
Potentiation	Increase the efficacy of a drug using another drug that does not have a direct pharmacological effect on the target disease.	Carbidopa is a drug that enhances the efficacy of levodopa used for the management of parkinsonism.
Antagonism	The effect decreases the efficacy of a drug as the other drug reduces its activity.	Estrogen receptor antagonist prevents the stimulating impact of estrogen on a tumor cell.
Physical antagonism	A drug physically restricts another drug from reaching the target by adsorption.	Charcoal adsorbs proteinaceous charcoal particles and prevents its adverse effects on the body.
Chemical antagonism	It refers to the negative effect of a drug on another drug through a chemical reaction.	• $Mg(OH)_2$ neutralizes the acidic effect of HCl in the stomach. • Protamine sulfate neutralizes the anticoagulant heparin, which is acidic.
Physiological antagonism	When two or more drugs cause opposite effects on a physiological process, the drugs are called physiologically antagonistic. The receptors should be different and the response should be opposite.	• Histamine causes bronchoconstriction leading to wheezing. → Adrenaline acts on beta (ß)2 receptors and causes bronchodilation. • Glucagon increases glucose level by GPCR and insulin decreases glucose levels by acting on tyrosine kinase receptors.
Receptor antagonism	Drugs acting on the same receptor but producing opposite effects are receptor antagonists.	• Ketamine is a quasi-antagonist at the NMDA-glutamate receptor, whereas naloxone is a competitive antagonist at all opioid receptors. • Salbutamol acts on beta (ß)2 receptors causing bronchodilation and Propranolol acts on beta (ß)2 receptors causing bronchoconstriction.

CROSS WORD PUZZLES

Crossword Puzzle



Across

2. Drugs that produce opposite effects on the same physiological process
5. Antagonism that can be overcome by increasing agonised concentration and getting same efficacy

Down

1. A drug that complements the effect of another drug to improve the efficacy
3. Relation between heparin and protamine sulfate
4. Interaction between carbidopa and levodopa

12 ADVERSE DRUG REACTIONS

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00:00:03

- Whenever any kind of drug is injected into the patient's body some affects can be witnessed.
- It can either be beneficial or harmful for the patient.
- Adverse drug effect means unintended or undesirable consequence of drug administration.

Side Effects

- Pheniramine is an antihistamine drug. It blocks histamine.
- It is used to treat an allergy.
- It can cross the blood bank barrier (BBB) and block histamine receptor inside brain causing sedation.
- Histamine is required for wakefulness in CNS of brain but when it is blocked by pheniramine, sedition becomes noticeable.
- It is used in normal dose.
- Side effects occurs due to the pharmacodynamic action of the drug.
- It is produced directly by the drug.
- Therefore, if the drug is used at a normal dose, the extension of pharmacodynamic action, produced directly by the drug, it is known as side effect of the drug.

Secondary Effect

- Corticosteroids produce immunosuppression which can lead to opportunistic infections.
- Corticosteroids by themselves do not cause infections.
- They have anti-inflammatory effects that hinders healing of a wound. Thus, when steroids are used, wounds do not heal at their normal pace.
- It is used in normal dose.
- It is caused the indirectly by the drug.
- Therefore, secondary effect of corticosteroids is noticed when the drug is used in normal dose cause opportunistic infections by causing immunosuppression.
- Corticosteroids do not directly lead to poor wound healing health but they possess anti-inflammatory properties that can lead to poor healing health.
- Tetracyclines are antimicrobials known as broad spectrum.
- They kill normal flora of intestine which leads to proliferation of pathological bacteria and patient suffers from diarrhoea.
- Hence, diarrhoea is a secondary effect of tetracycline.

Toxicity

- A drug can produce acute or chronic toxicity.
- High dose of paracetamol can cause toxicity of liver that is called hepatotoxicity.
- When chloroquine is used for long duration of time can damage the retina. It is known as Bull's eye maculopathy.
- Toxicity occurs either due to high dosage of drugs or when a drug is used for a long period of time.

Drug Poisoning

- Toxicity and poisoning are somewhat similar. Poisoning, however, can be an immediate threat to a patient's life.
- It is lethal if not treated properly.
- **Following are major principles used to manage poisoning:**
  - Always maintain air, breathing and circulation of the patient.
  - Remove all contacts of the poison from the patient immediately.
  - Use gastric lavage for oral drug intake to avoid further absorption of drug in the body. It should be done within six hours of drug infusion as drugs will be completely absorbed after six hours.
  - Search for an antidote to neutralise drug effects. For example – Atropine sulphate is an antidote for op poisoning; naloxone is an antidote for morphine.
  - In case of absence of antidote, drug should be excreted out of the patient's body.
  - There are two process to excrete the drug out of a patient's body:

a. Dialysis machines can be used to dialyse the poison and remove it.

b. Changing pH of urine can also help in extraction of the drug. If the poisoning is acidic in nature, pH of urine should be made alkaline and if the poisoning is alkaline or basic in nature, pH of urine should be transformed to acidic.

- **Following are some of the cases in which dialysis cannot be used:**

- **mnemonic – Better Care A-V-O-I-D.**
  - **Benzodiazepines- Diazepam** – It has high plasma protein bindings which makes dialysis useless.
  - **Chloroquine** – It is an antimalarial drug.
  - **Amphetamine** – It is a sympathetic drug.
  - **Verapamil** – It is a calcium channel blocker.
  - **OP** – Organophosphate poisoning and opioid poisoning.
  - **Imipramine** – It is a tricyclic anti-depressant.
  - **Digoxin**
- All the above-mentioned drugs have high volume of distribution (Vd). They stay outside the blood vessels which makes them difficult to remove through dialysis.

Drug Allergy 00:12:30

- When any kind of drug is injected into a patient's body, it may cause several allergies and hyper sensitivities.
- Following are some of the important hypersensitivity reactions (HR) that can be evident in several patients:
  - **Type 1 hypersensitivity reaction** – It is the most important hypersensitivity reaction that can cause anaphylaxis. Penicillin can cause anaphylaxis to certain people.
  - **Type 2 hypersensitivity reaction** – Halothane causing hepatitis is a hypersensitivity reaction.
  - **Type 3 hypersensitivity reaction** – Lamotrigine causing Stevens-Johnson syndrome (SJS) is a hypersensitivity reaction.
  - **Type 4 hypersensitivity reaction** – Clonidine applied as transdermal patch (TDP) can produce contact dermatitis is a delayed hypersensitivity reaction.
- Anaphylaxis is the most severe hypersensitivity reaction that can lead to person's death.
- A test dose is highly recommended before administration of this drug.

Photosensitivity 00:15:00

- When the patient is exposed to sunlight after the infusion of certain drugs, several rashes or skin irritation can be evident. This reaction of sunlight to drug elements is known as photosensitivity.
- Sparfloxacin and tetracycline are two major photosensitive drugs.
- Once patients consume one of these two drugs, they should not expose themselves to sunlight or else they might get rashes or various skin infections.

Idiosyncratic Reaction

- If a person becomes excited after taking sleeping pills instead of falling asleep, it is called idiosyncratic reaction.
- It is seen only in some people.
- It has genetic basis.
- Sleeping tablets such as benzodiazepine produce excitation in some people instead of drowsiness.
- Aplastic anaemia caused by chloramphenicol is also an idiosyncratic reaction.

Drug Induced or Physician Induced or Iatrogenic Effect

- A patient suffering from knee arthritis is prescribed NSAIDs by the doctor. NSAIDs can cause gastritis or peptic ulcer diseases.
- Thus, a patient intended for treatment of arthritis can suffer from gastritis or peptic ulcer diseases due to NSAIDs reaction.
- Therefore, PPI'S along with NSAIDs is recommended to avoid such harmful effects.
- When corticosteroids are used for long duration of time, they may cause osteoporosis.

Carcinogenecity

- It can cause cancer to the patient.
- Drug such as procarbazine can cause secondary leukaemia.

Teratogenecity

- When a drug is consumed by a pregnant woman, it crosses the placenta to reach the foetus.
- It can produce congenital malformation in the foetus. This is called teratogenicity.
- Human pregnancy shows three prominent trimesters.
- Organogenesis occurs in the first trimester.

Q. Which trimester is the most important when a drug is prescribed to a pregnant woman?

- First trimester is the most important as it involves organogenesis and most of the malformation can occur during this time.

Teratogenicity Risk

- **United States Food and Drug Administration (USFDA)** provides a list of teratogenicity risk category based on human and animal study.
- Pregnancy teratogenicity risk category-safety. They are:

CATEGORY	SAFETY
A	Very safe
B	Safe
C	Maybe safe
D	Not safe
X	High risk of teratogenicity.

Example of category A- folic acid, levothyroxine
Example of category B – paracetamol

Teratogenicity Risk Drug 00:23:03

Refer Table 12.1

Dependence

- Patient starts depending upon several drugs such as :
  - Opioids
  - Tobacco
  - Alcohol
  - Benzodiazepine

Pharmaco Vigilance 00:29:45

- Pharma means "drug" and vigilance means "to keep an eye on".
- Drugs should always be monitored as they can produce adverse effects.

- Aim of pharmaco vigilance is to monitor adverse effects of drugs.
- The Pharmacovigilance Programme of India (PvPI) is an important national programme.
- The program came into existence due to following reasons:

1. Thalidomide caused sealed limb deformity in most of the babies.
2. Rosiglitazone increased number of deaths due to cardiovascular. Due to this reason, rosiglitazone is not used anymore in India.

- Thus, Pharmacovigilance Programme is important because:

1. It can detect adverse drug effects.
2. It contributes to assessment of adverse drug reactions.
3. Understanding it's causes.
4. Preventing the adverse effects in future.

Adverse Drug Effects (ADE): Workflow

- Fill in the adverse drug effects reporting form. Anybody including the doctor, nurse or even the patient can fill this form.
- Regional ADR monitoring centre (AMC). Most of the medical colleges are AMC these days.
- Vigiflow (software) receives all the data and stores them in the form of vigibase database.
- The data proceeds to National Pharmaco Vigilance Centre located in Ghaziabad. It is Indian Pharmacopoeia Commission (IPC).
- Once data is received by national centre, it is forwarded to worldwide centre called Uppsala Monitoring Centre located in Sweden.
- Therefore, this workflow is very crucial for saving lives of millions of people all around the globe by detecting the adverse effects of all the drugs used and passing the information forward.

Other Vigilance 00:35:20

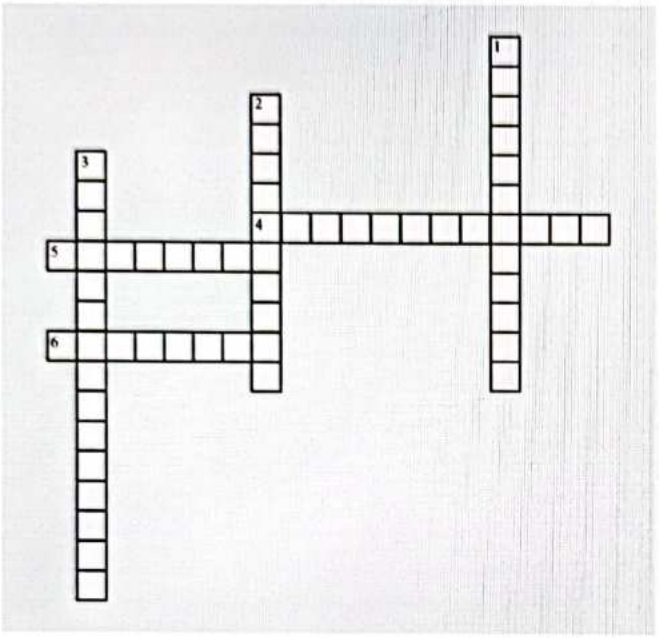
- **Materio Vigilance** – It is used to report stent failure.
- **Hemo Vigilance** – It is used to report any adverse effect during blood transfusion.
- **Herbal Vigilance** – It is used to report adverse effects of herbal drugs.

Table 12.1

Sr No.	DRUGS	DISEASES
1.	Thalidomide	Pocomelia or Sealed Limb Deformity
2.	Warfarin	Foetal Warfarin Syndrome or Contradict Syndrome.
3.	Anti-Epileptic drugs: a. Phenytoin b. Carbamazepine c. Valproate	a. Foetal Hydantoin Syndrome. b. Neural Tube Defects c. Neural Tube Defects
4.	Anti-microbials such drugs as: a. Aminoglycosides b. Fluoroquinolones c. Tetracyclines	a. Damage Ears b. Damage Cartilage c. Damage Bones and Teeth
5.	Lithium	Ebstein's anomaly.
6.	Misoprostol	Mobeius syndrome.
7.	Thioamides drugs such as : a. Carbimazole b. Methimazole	Scalp Defects
8.	Diethylstilbesterol	Vaginal Adenocarcinoma
9.	Isotretinoin	Avoid high dosage of Vitamin A
10.	Anti-cancer drugs	Stop cell multiplication
11.	Indomethacin	Premature closure of PDA
12.	ACE inhibitors or Angiotensin receptor blockers (ARBs)	Renal agenesis

CROSS WORD PUZZLES

Crossword Puzzle 1



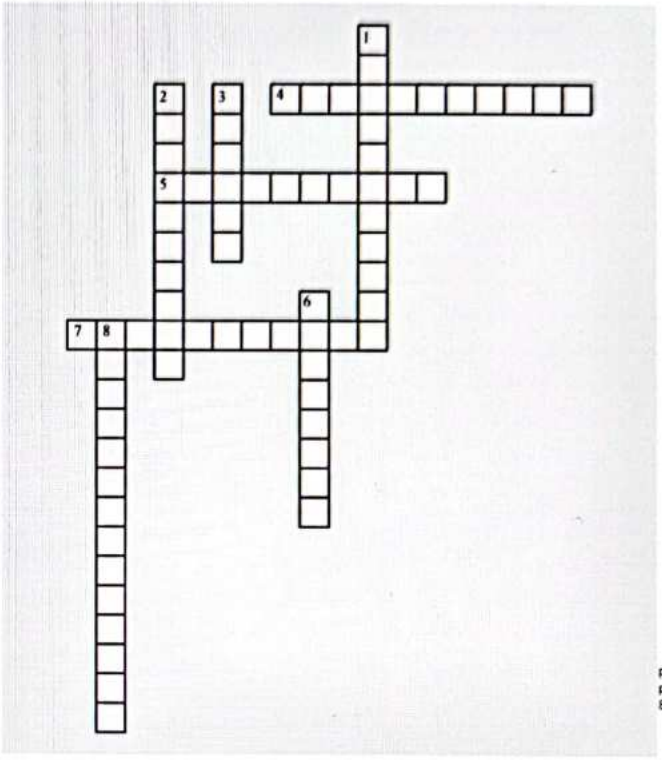
Across

4. Sparfloxacin and _____ are two major photosensitive drugs.
5. _____ sulphate is an antidote for op poisoning.
6. Naloxone is an antidote for _____.

Down

1. effects of drugs are produced _____ by the drugs.
2. Adverse drug effects are _____ consequence of drug administration.
3. _____ produce immunosuppression which can lead to opportunistic infections.

Crossword Puzzle 2



Across

4. _____ is the most severe hypersensitivity reaction that can lead to person's death.
5. Corticosteroids cause the infections _____.
7. Bull's eye maculopathy is caused due to long duration of usage of _____ drugs.

Down

1. _____ is a sympathetic drug.
2. Sleeping tablets such as benzodiazepine produce _____ in some people instead of drowsiness.
3. Uppsala Monitoring Centre located in _____.
6. Changing pH of urine and _____ can be used to excrete the drug out of a patient's body.
8. _____ is caused due to high dose of paracetamol can cause toxicity of liver.

13 NEW DRUG DEVELOPMENT

Three important steps of new drug development

The three important steps in new drug development are as follows:

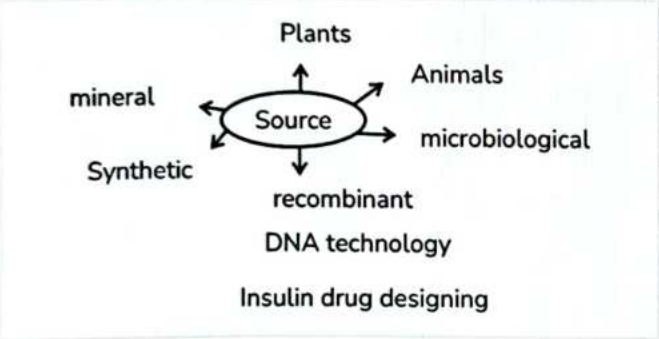
I. **Source:** The first step is to find out the source of the drug. Once this is done, we need to proceed to the next step, i.e., the animal study.

II. **Animal study or pre-clinical trial:** After checking the results of the animal study, we need to proceed with the human study.

III. **The human study, or clinical trials.**

Source of a drug

00:01:43



A drug can be obtained from various sources, as follows:

I. **Plant source.** In the earlier days, we could obtain drugs from the plant source, e.g., vinca alkaloids, digoxin, reserpine, etc.

II. **Animal source.** This is the second important source of drugs, e.g., heparin, insulin, etc.

III. **Microbiological source,** e.g., penicillin obtained from Penicillium notatum.

IV. **Mineral source,** e.g., calcium, Iron, etc.

V. **Synthetic source.** These are the drugs that are synthetized in the lab, e.g., aspirin.

VI. **Recombinant DNA technology.**

VII. **In-silico drug designing.** This is a recent development drug discovery, where computers are used to obtain the drugs binding to a particular receptor.

Animal study [Pre-Clinical Trial]

00:04:20

- Animals such as mice, rats, dogs, and rabbits are used in animal research. However, smaller animals like rats, rabbits, and guinea pigs are preferred.
- The major aim of the animal study is to find out the toxicity of the drug, since not all diseases occur in animals. Under toxicity, we check the following:
  - Acute toxicity.
  - Subacute toxicity.
  - Chronic toxicity.
  - Teratogenic effect.
  - Carcinogenic effect.
  - Mutagenic effect.
- The second major aspect of the animal study is to check the efficacy of the drug.
- Sometimes, tissue culture or organic cultures are used to check the efficacy and toxicity. This is done to avoid killing animals for the study.

The human study [Clinical Trial]

00:06:48

- This is the third aspect of new drug development.
- The first step in the human study is to file an investigational new drug (IND) application with the Central Drug Safety Control Organization (CDSCO).
- The head of CDSCO is called the Drug Controller General of India (DCGI).
- The DCGI will check whether the pre-clinical trials are conducted in the correct manner and will approve the human study only after satisfaction with the animal trials.
- Once the DCGI approves the human study or the clinical trial, then we must proceed with the Phase I, Phase II, and Phase III trials, respectively.
- After the completion of the Phase III trials, we need to apply for a new drug application (NDA) to CDSCO to obtain a marketing license. Once granted, then the drug can be made available on the market.
- After obtaining the marketing license, the Phase IV clinical trial (post-marketing surveillance) is conducted.

Important Information

- Ethics committee approval is required to conduct Phase I, Phase II and Phase III clinical trial.
- The ethics committee sees whether a trial is ethically required or not.

Clinical Trial Phases (Human Study)

Phase I trial [human safety pharmacology)

00:10:50

- The primary goal of a Phase I clinical trial is to evaluate a drug's safety in humans.
- The population involved in the Phase I study is called "human healthy volunteers." This is done because healthy humans volunteers are more likely to tolerate the adverse events compared to patients.
- The second goal is to determine the maximum tolerated dose. This is the maximum dose at which the first signs of an adverse event are noted.

- The third aim of the Phase I trial is to determine the "pharmacokinetics," i.e., absorption, distribution, metabolism, and excretion of the drug.
- Efficacy is rarely checked in the Phase I trial, but in cases of terminal illnesses like HIV and cancer, we can include these patients to check for efficacy.
- Around 10 to 100 volunteers are involved in the Phase I study in order to minimize the risk of adverse events.
- The Phase I trial is an "open label" type of study in which the healthy volunteer knows the type of drug administered to them.
- The duration of the Phase I trial is around 1 to 2 years.

Important Information

- Phase I trials involve healthy human volunteers and are done to check the safety of the drug.
- Efficacy is rarely assessed in Phase I trials; however, in cases of terminal illnesses such as HIV and cancer, we can include these patients to assess efficacy.

Phase II trial [Therapeutic exploratory trial) 00:15:12

- The major aim of the Phase II trial is to confirm the efficacy of the drug.
- If the drug is efficacious, then we check for dose ranging. This is the dose that works for the patient in treatment of the particular disease e.g. Paracetamol can be given from 500 mg to 1000 mg for fever.
- Around 300 to 500 patients are involved in the Phase II trial. However, for certain conditions, it's difficult to get the required population e.g. Myasthenia Gravis. In such conditions, we can conduct the study with less number of patients also.
- The type of study in Phase II is called "randomized control trial" (RCT).
  - In an RCT, 50% of the population receives the drug, and the remaining 50% receives a placebo.
  - The patients don't know whether they have received the drug or a placebo. Thus, it's a blinded trial.
- Since we don't know the efficacy of the drug at this stage, the Phase II trial has the highest failure rate.
- The duration of the study is usually 2 to 3 years.
- The number of centers involved is between 1 and 2.
- The duration of the Phase I trial is around 1 to 2 years.

Important Information

- Maximum failures occur in the Phase II trial since we don't know the efficacy of the drug at this stage.

Phase III trial [therapeutic confirmatory trial) 00:18:52

- The major aim of the Phase III trial is to confirm its efficacy in a large population.
- This phase investigates pharmacokinetics and safety.
- The population of this phase involves 3000–5000 patients.
- This phase is a multi-centric trial since pharmacogenomics may affect the results of the trial. Thus, the number of centers matters more than the number of patients.
- The type of study is an RCT. Here, a new drug is compared with an old drug.
- The duration of the Phase III trial is around 3–5 years.
- This phase is also called a "pivotal trial," since it is a very important step in new drug development.
- Once it's confirmed in this phase that the drug has good safety and efficacy, we can apply for the license, i.e., the marketing license (NDA).

Important Information

- Phase III is multi-centric since pharmacogenomics will affect the results of the trial. Thus, the number of centers matters more than the number of patients.

Phase IV trial [post-marketing surveillance) 00:22:16

- This phase is conducted after the NDA.
- **The main aim of the Phase IV study is as follows:**
  - To check for rare adverse events that did not occur during the first three phases.
  - Long-term adverse events: To determine the long-term risks of adverse events over time, such as bladder cancer over a 30-year period, this can help in prevention of these long-term adverse events.
  - Drug interaction.
  - Special populations: These involve pregnant women, children, lactating women, and elderly patients. These patients are not involved in the first three phases of the clinical trials. As a result, it is critical to monitor the drug's effect in these patients.
- The type of study is "observational." If any effects occur, then they are reported.
- The duration of the Phase IV study is "unlimited."
- The population isn't restricted and can be extended to any type.

Phase 0 trial (Micro-dosing trial) 00:25:12

- This phase is conducted before the Phase I trial.
- The dose used is usually 100 micrograms, or 1/100th of the dose used in animals.
- The aim of the Phase 0 trial is to check for "pharmacokinetics," i.e., absorption, distribution, metabolism, and excretion of the drug. This can help in

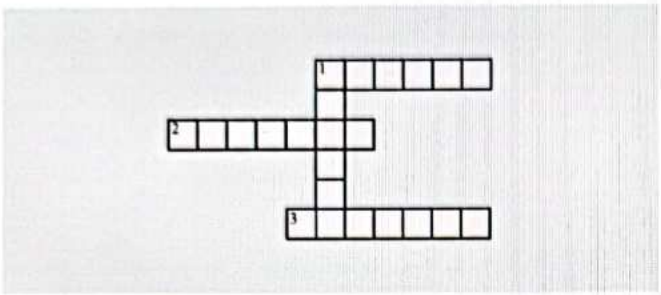
determining the appropriate route of the drug, e.g., the intramuscular route.

Summary

- The first step in the new drug development is to find out the source of the drug.
- The next step is the animal study. The main aim of the animal study is to check for toxicity rather than efficacy since most of the human diseases do not occur in all animals.
- Following the successful completion of the animal study, an IND is submitted to CDSCO.
- After the IND is filed, the Phase I trial is commenced, which is also called human safety pharmacology. Here, the main goal is to check the safety of the drug.
- The Phase II trial will be conducted in one or two centers to assess efficacy.
- The next step is the Phase III trial. This is done to confirm the efficacy of the drug.
- The last step is the Phase IV trial. This is conducted to check for rare adverse events, the long-term safety of the drug, drug interactions, and the effect of the drug in a special population.

CROSS WORD PUZZLES

Crossword Puzzle 1



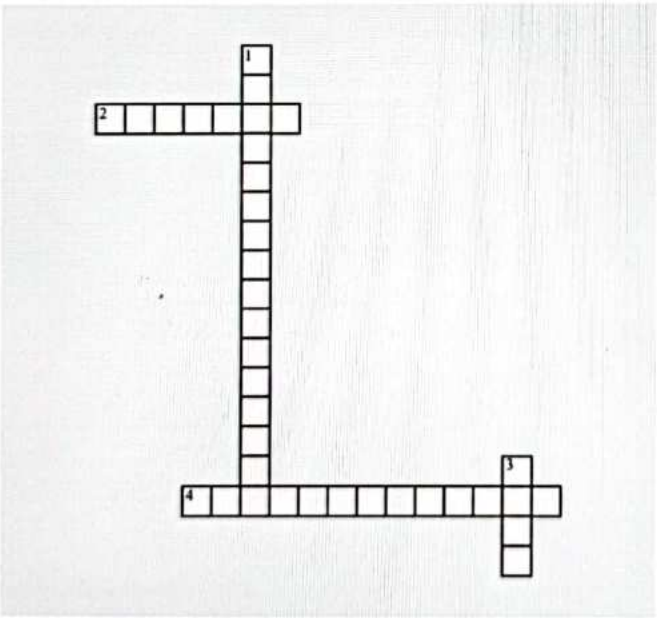
Across

1. _____ evaluation of the drug is the main aim of the Phase I trial.
2. _____ tolerated dose determination is the secondary aim of the Phase I trial.
3. _____ human volunteers are involved in the Phase I trial.

Down

1. _____ is the first step in the new drug development.

Crossword Puzzle 2



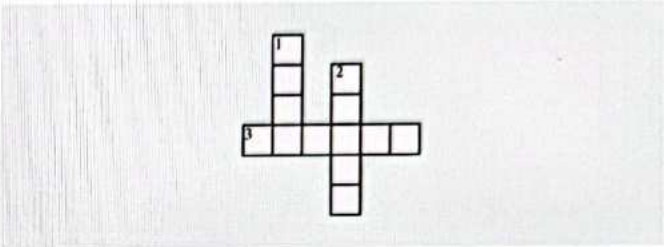
Across

2. _____ populations involve pregnant women, children, lactating women, and elderly patients.
4. _____ type is the study type of the Phase IV trial.

Down

1. _____ evaluation is the aim of the Phase 0 trial.
3. _____ adverse events that did not occur during the first three phases are checked during the Phase IV trial.

Crossword Puzzle 3



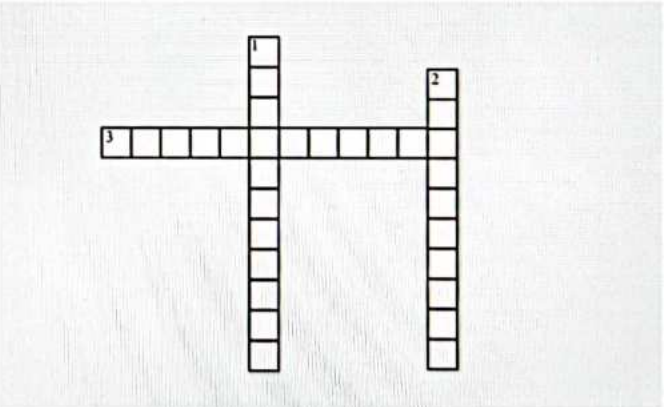
Across

3. _____ study is the second important step in new drug development.

Down

1. _____ label is the type of study in the Phase I trial.
3. _____ study is the third step in new drug development.

Crossword Puzzle 4



Across

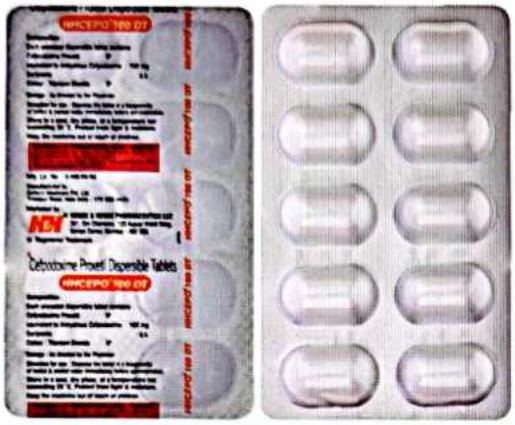
3. _____ of the efficacy of the drug is the main aim of the Phase II trial.

Down

1. _____ confirmatory trial is the synonym of the Phase III trial.
2. _____ control trial is the type of study in the Phase II and Phase III trials.

14 DRUG LABEL AND FDC

Drug Label 00:31:00



- Tells about the composition of the drug.
- Tells about the form- either in tablet, capsule, or syrup
- Generic name
- Side effects
- Red line over the packing of the drug indicates that it requires a prescription.
- Date of Manufacturing and expiry date. Expiry date indicates that the quality of the drug cannot be assured.

Pharmacopoeia

- IP: Indian pharmacopoeia
- BP: British pharmacopoeia
- USP: US pharmacopoeia
- JP: Japan Pharmacopoeia
- Suppose a company claims they are giving DOLO 650 mg but they would have packed Calcium carbonate.
- The testing conditions to test the identities of the drug, they will be given in these books called Pharmacopoeia.
- This is required for drug regulators, Pharma companies and the government.

National Formulary of India 00:06:25

- Important for doctors or prescribers
- Gives detail about drug uses
- Availability form of the drug
- Dosage level to adults, children, senior citizens
- Red line over the packing of the drug indicates that it requires a prescription.
- Date of Manufacturing and expiry date. Expiry date indicates that the quality of the drug cannot be assured.

Storage Condition of the Drug 00:07:36

- **Freezer temperature:** 20° Celsius to -10° Celsius.
- **Cold temperature:** 2° Celsius to 8° Celsius.
- **Cool temperature:** 8° Celsius to 25° Celsius.
- Example:
  - Insulin should be stored in 2° Celsius to 8° Celsius. If it is kept in the freezer, since insulin is a protein it denatures. Hence, patients should be educated while prescribing insulin.

Schedules of the Drug

Refer Table 14.1

Important Information

- NRx - Means New Prescription
- Suppose a cancer patient is prescribed Morphine and purchases it from a pharmacy. The patient cannot use the same prescription for purchase of morphine the second time. The doctor writes NRx indicating it is a new prescription.

Important Information

1. **Misbranded drugs:** Drugs having labelling errors.
2. **Spurious drugs:** These are fake drugs that are made that lack active ingredients.
3. **Adulterated drugs:** These are drugs containing filthy, harmful substances.

Nomenclature of Drugs 00:18:25

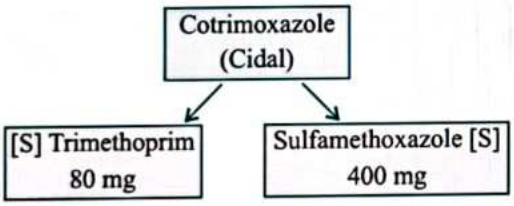
- It is classified into chemical, generic and brand names.
- Example:
  - The chemical name is acetylsalicylic acid; the generic name is aspirin. And the brand name is Ecosprin.

Fixed-Dose Drug Combination 00:20:58

- When two or more drugs are given in fixed dose ratios then it is called a fixed-dose drug combination.
- A single tablet contains two or more drugs.
- For example: in the image below single drug contains rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride

Advantages of FDC 00:22:56

- Giving one combination pill of two or more drugs reduces the pill burden.
- Combining the drugs will decrease the overall cost.
- As the burden of pills decreases, compliance increases.
- Increases efficacy. E.g.



- The adverse effects decrease. E.g.

$(Al(OH)_3$ + $Mg(OH)_2)$

↓ ↓

Constipation Diarrhea

- Decrease in resistance problem.

The disadvantage of FDC 00:25:47

- More drugs can be added unnecessarily.
- You cannot blame a single drug in combination with drugs for adverse effects and the whole tablet should be discontinued.
- The adverse effects of combined drugs need to be studied before prescribing.
- Cannot alter the dose.

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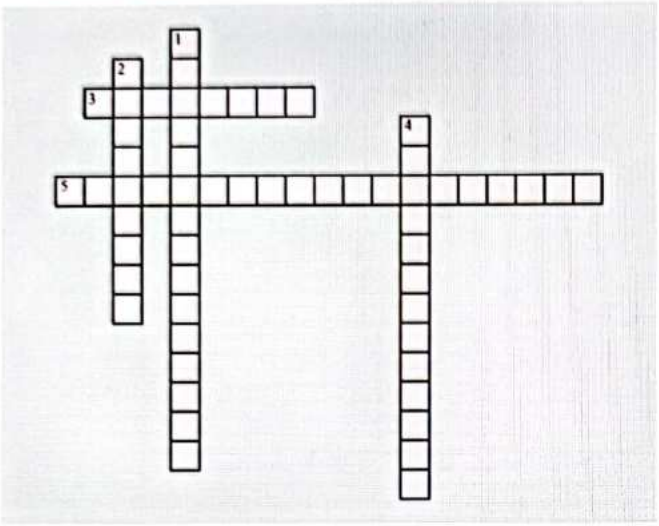
Table 14.1

Schedules	Description
Schedule A	Contains various forms and formats of letters for licensing applications, etc
Schedule B	Contains fee structure for government-run labs.
Schedule C	Contains various biological products and their regulation. Examples: Serums, Adrenaline Vitamins etc.
Schedule D	List of drugs exempted from the provision of import of drugs.
Schedule E	Contains various poisons and their regulation. Examples: Sarpa Visha (Snake venom), Parada (Mercury) etc.
Schedule F	This contains regulations and standards for running a blood bank. • Schedule F-I: This contains regulations and standards for vaccines. • Schedule F-II: This contains regulations and standards for surgical dressing. • Schedule F-III: This contains regulations and standards for umbilical tapes.
Schedule F-F	This contains regulations and standards for ophthalmic ointments and solutions.
Schedule G	List of drugs taken under registered medical practitioner supervision.
Schedule H	Contains prescription drugs under Drug and Cosmetic Act 1945.
Schedule K	Contains various drugs that can be taken over the counter.
Schedule M	Contains various regulations for manufacturing, premises, waste disposal and equipment.
Schedule N	Contains various regulations and requirements for a pharmacy.
Schedule O	Contains various regulations and requirements for disinfectant fluids.
Schedule P	Schedule P: Contains regulations regarding the life period and storage of drugs. • Schedule P-I: Contains regulations regarding the retail package size of various drugs.
Schedule Q	Contains various regulations and requirements for record-keeping
Schedule R	Contains various regulations and requirements for condoms and other mechanical contraceptives.
Schedule S	Lists various cosmetics and toiletries and directs cosmetics manufacturers to conform to the latest Bureau of Indian Standards requirements.
Schedule T	Contains various regulations and requirements for manufacturing Ayurvedic, Siddha and Unani products
Schedule U	Contains various regulations and requirements for record-keeping
Schedule V	Contains standards for drug patents.
Schedule W	Contains Generic Drugs List.
Schedule X	Contains a list of highly narcotic and Psychotropic. Example – Ketamine, Phencyclidine, Secobarbitone. These drugs should be given two prescriptions- one should be kept by the pharmacist in a locker for two years and it should be shown to the drug inspector when asked for.
Schedule Y	Contains requirements and guidelines for clinical trials.

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. The brand name of asprin.
5. Full form of IP

Down

1. Drugs having labelling errors
2. This schedule contains Drugs are taken under medical supervision
4. Schedule Q consist of this regulation

Answer key

1. Schedule G
2. Indian Pharmacopoeia
3. Recordkeeping
4. Misbranded Drugs
5. Ecosprin

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15 THERAPEUTIC DRUG MONITORING

- It is the monitoring of the drug for the use of therapy by measuring drug levels in a blood sample.

Why is TDM done? 00:00:26

Consider 4 different important cases: -

- **Case 1:** A patient with hypertension and BP=150/90 mmHg
  - Diagnose the patient with hypertension and put him on telmisartan 20mg
  - Ask the patient to return after 1 month/3 months and monitor the BP
    → If BP is high → dosage must be increased
    → If BP is maintained → Continue the same dose
    → We are not measuring the telmisartan levels
- **Case 2:** A patient has diabetes and HbA1c=7.1, FBS=150 mg/dl, PPBS=200 mg/dl
  - Diagnose the patient with type 2 and start with Metformin 500 mg tablet
  - After 3 months, measure lab parameters i.e., HbA1c, FBS, PPBS
  - We are not measuring the metformin levels
- **Case 3**: A patient has mania.
  - For prophylaxis, we start with lithium.
  - After 3 months, mania cannot be clinically measured.
  - So, we measure drug levels i.e., lithium.
- **Case 4:** A patient has a generalized tonic-clonic seizure.
  - The patient is put on Phenytoin
  - Since we cannot check for seizures.
  - We check drug levels i.e., phenytoin.

- However, this method of checking drug levels to measure progress cannot be adopted for every drug.
- It can only be done with certain drugs whose drug levels should correspond to clinical response.
- Eg:- When Phenytoin is used for a patient with seizure, the level should be between 10-20µg/ml.
  - If this level is less than 10µg/ml, the drug does not work and the patient will not have control over seizures.
  - If this level is more than 20µg/ml, the patient will develop toxicity.
- TDM is a costly procedure.

When is TDM done? 00:05:03

TDM is performed in the following cases: -

- **Plasma concentration of drug correlates with clinical response.**
  - Eg:- Phenytoin level must be maintained between 10-20µg/ml to control seizures.
  - Digoxin levels must be maintained between 0.5-1.4ng/ml to obtain an effect.
- **Drugs have a narrow therapeutic index**
  - Therapeutic index is a measure of safety, thus drugs with narrow therapeutic indexes are less safe.
  - Eg:- Digoxin(more than 2ng/ml will cause arrhythmia), Tricyclic Antidepressants(TCAs), Lithium
- **To check for patient compliance**
  - This means checking whether the patient is adhering to the drug regimens.
- **Inter-individual Pharmacokinetic Variability**
  - Pharmacokinetics include ADME i.e., Absorption, Distribution, Metabolism, and Excretion.
  - If there are pharmacokinetic variabilities i.e., differences in the given parameters in each person, the drug levels can be checked for these variabilities.

When not to do TDM? 00:08:42

TDM cannot be performed in the following cases:-

- **Plasma concentration of the drug doesn't correlate with the clinical response.**
- **Clinical response can be measured easily.**
  - EXAMPLES:
    → Diabetic patient → Blood glucose level
    → Hypertensive patient → Blood pressure
    → Dyslipidemia → Lipid profile
  - In such cases, the given parameters can be measured and there is no need to perform TDM.
- **Hit & Run Drugs**
  - These drugs remain in the body for a few hours, but their action lasts for a very long period. TDM will not be useful and judgement might be faulty.
  - Eg:- Aspirin, Omeprazole, Reserpine, MAO inhibitors.
- **Irreversible Blocking Drugs**

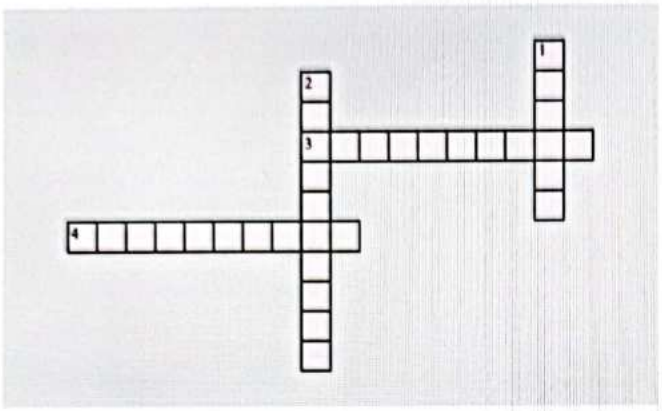
Drugs Requiring TDM

- **A mnemonic can be created as follows: -**

- **'Look at TDM concentration'**
  - **Look** → Lithium.
  - **At** → Anti-epileptic drugs, Aminoglycosides(antibiotics)
  - **T** → TCAs, Theophylline(methylxanthine)
  - **D** → Digoxin
  - **M** → Methotrexate (anti-cancer drugs)
  - **Concentration** → Calcineurin inhibitors Eg: - cyclosporine, Tacrolimus

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

3. pharmacokinetics include ADME i.e., Absorption, Distribution, _____ and Excretion.
4. More than 2ng/ml of digoxin will cause ___.

Down

1. TDM can be performed when _____ concentration of drug correlates with clinical response.
2. Patient ____ means checking whether the patient is adhering to the drug regimens.

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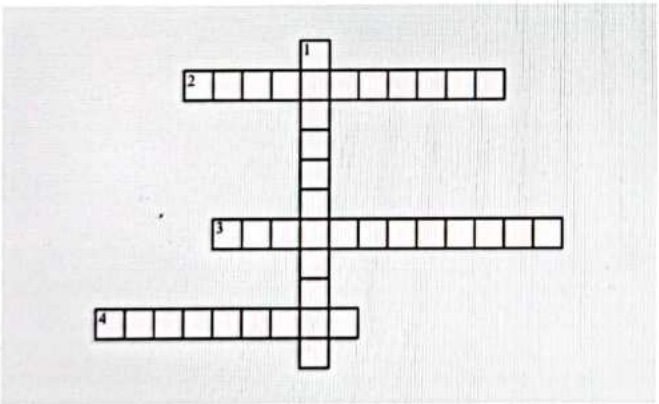
Crossword Puzzle 2



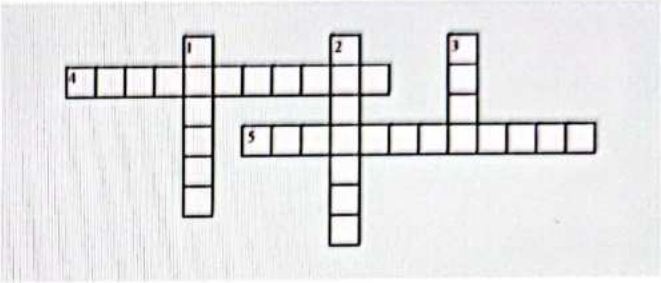
Across

2. digoxin is a drug that has a narrow _____ index.
3. Blood pressure is monitored in the case of _____ patients.
4. _____ is a drug usually used to control seizures.

Down

1. Tacrolimus is an example of _____ inhibitors.

Crossword Puzzle 3



Across

4. _____ index is a measure of the safety of drugs.
5. _____ is an anti-cancer drug.

Down

1. Drugs with _____ therapeutic indexes are less safe.
2. _____ levels are checked 10-12 hours post dosage i.e., when it is at peak level.
3. Clinically, we require ____ half-lives to achieve a steady state.

16 RATIONAL DRUG PRESCRIBING, ESSENTIAL MEDICINE & EBM

Rational Drug Prescribing 00:00:47

- It involves the process of prescribing right drugs as per the requirement of patients.
- The prescription should be rational.
- It should contain appropriate amount of dose required by the patient.
- It should be given at the right time for equitable duration.
- It should be properly documented to avoid legal issues.
- **For example:**
  - If a patient has fever, paracetamol is prescribed to him/her. Any other prescription may cause serious effects.
  - A teratogenic drug should not be prescribed to a pregnant lady.
  - If an adult man of about 40 years age old comes with a fever, 50 mg of paracetamol will not suffice him. He should be given dose according to an adult man, that is 500 to 650 mg. Similarly, a child of approximately 20 kg should not be given such a high dose. Therefore, appropriate amount of dosage is important.
  - Sleeping tablets should be taken at night-time and not during the day.
  - A person suffering from tuberculosis should be treated for at least six months if the treatment is positive. Similarly, an antibiotic should be taken for minimum five days.
  - Whatever medicine is prescribed, it should be written properly. It should depict right time and duration of consumption. Number of tablets to be taken before or after food intake should also be mentioned clearly.

P-Drug 00:03:26

- P-drug is also known as preferred or personalized drug.
- If a person suffers from typhoid caused by Salmonella typhi, he/she can be treated by one of the following ways:
  - **Ceftriaxone** (given intravenously- IV)
  - **Cefixime** (given orally)
  - **Ciprofloxacin** (given orally)

Refer Table 16.1

- Therefore, drug prescription changes depending upon the patient.

Parameters of P-Drug 00:08:43

- Following are the parameters that decide the selection of drug.

1. **Efficacy** – A drug with maximum efficacy is preferred. Cefixime has maximum efficacy.
2. **Safety** – Whether the drug to be prescribed has an adverse effect or not is also considered. Ciprofloxacin is avoided in case of children and pregnant women because they can cause cartilage damage.
3. **Affordability** – Paying capacity of the patient is also considered while prescribing a drug. Costly drugs can be avoided if a supplement is present.
4. **Suitability** – Whether the drug is suitable for the patient or not is also important.

Essential Medicines 00:10:45

- Essential medicines are the medicines that take care of priority health care needs.
  - **CASE 1** - Patient asks for body building drugs.
  - **CASE 2** - Patient is suffering from androgenic alopecia.
  - **CASE 3** - Patient is suffering from tuberculosis.
  - **CASE 4** - Patient is suffering from hypertension.
- Among all these cases the patients suffering from tuberculosis and hypertensions are considered as priority health care needs.
- Every country must have affordable medicines for communicable diseases such as TB, HIV, malaria and typhoid and non-communicable diseases such as diabetes or hypertension, etc. These are called essential medicines.
- Every country has its own prior healthcare medicines at a rate affordable for its citizens.
- World Health Organisation (WHO) has prepared a list of essential medicines.
- Every country has a different disease pattern.
  - For example – anti-snake venom essential medicine is rendered useless in a country which does not have snakes.
- Therefore, every country prepares its own list of essential medicines that is known as National List of Essential Medicines.
- According to National list of essential medicines of India of the year 2022, there are 384 essential medicines that are classified into 27 therapeutic categories.
- Different therapeutic categories such as anaesthesia, vitamins, and minerals, anti-infective, drugs for heart, etc are classified into distinct categories.

Refer Table 16.2

- Above pictures depict the National List of Essential Medicines, India (2022).
- It records name of the medicine, the level of healthcare (where it should be available) and form and strength of the medicine.
- For example – Diclofenac should be available in primary, secondary and tertiary health care centre with 20mg in tablet form and 25 mg/ml in the form of injection.
- Fentanyl should be available only in secondary and tertiary health care centres.
- Most of the time primary health care centres do not require certain medicines such as anaesthetics.

Evidence Based Medicine 00:16:50

- Suppose an intern witnessed his senior prescribing metoprolol tablets to a 50 years old female patient with blood pressure of 150/90 mmHg. So, he too prescribed the same tablets to a 50-year-old female patient with blood pressure of 150/90 mmHg. This practice of prescribing medicines by copying has no evidence.
- Systematic review of meta-analysis of several studies such as case-studies, case-control studies, cohort studies, randomized controlled trials (RCT), etc that are found in journals or on internet can be used as evidence.

Hypertension Guidelines 00:19:06

- The first line treatment of hypertension should be ACE inhibitors or ARB's.
- Calcium channel blockers should be used.
- Thiazide diuretics should be used.
- This is the guidelines that is used for the patient of hypertension.
- One should not copy the prescriptions from his or her seniors but use the guidelines provided for the disease.
- The appropriate time to use Metoprolol tablets can also be found in the guidelines.
- This is known as evidence-based medicine (EBM).
- Evidence based medicine is also known as bench to bed medicine. As it involves the doctor or the intern to sit on the bench, read the articles or guidelines of prescribing the medicines and then go to bed to the patient to prescribe them.
- This process makes the treatment effective, and the patient can receive maximum benefit from it.
- Thus, all the guidelines for various diseases such as diabetes, arthritis, hypertension, etc are based on these protocols that can provide maximum benefit to the patient.
- In case there are no guidelines provided for a particular medicine, evidence of medicine can be taken from:
  - **Systematic reviews**
  - **Meta-analysis**
  - **Randomized controlled trial.**
  - **Cohort study**
  - **Case-control study**
  - **Case-series** – It is seen in rare cases. For example – use of paracetamol causing cataract. Thus, one case does not determine the drug results.
- The probability or chance of authenticity of any medicine showing a particular result increase from below to above.
- This means that systematic reviews provide the best evidence.

Orphan Drug 00:22:10

- As the name suggest orphan drugs do not have anyone to care for them.
- Orphan drugs are used to treat, prevent, or diagnose rare diseases or conditions.
- **For example:**
  - Pitolisant – It is an H3 inverse agonist that is used to treat narcolepsy.
  - Fomivirsen – It is used to treat infection caused by cytomegalovirus.
- Pharma companies manufacture these drugs, but these drugs do not provide much profit to them.
- Drugs such as paracetamol, antibiotics or drugs for diabetes are manufactured in thousands of numbers and they can provide lots of profit to the firm.
- So, to continue the production of these drugs, government provides certain exclusive advantage such as tax exemption to the companies that can manufacture orphan drugs.
- Thus, the drugs used to treat or prevent rare diseases are called orphan drugs.

Me-Too Drugs 00:24:35

- Me-too drugs are the drugs that are not very special but are present in the market.
- Suppose a patient with severe gastritis asks for medical help and doctor prescribe him proton-pump inhibitors.
- Pantoprazole, rabeprazole, omeprazole, lansoprazole are some effective drugs that can be prescribed to this patient.
- All these drugs do not have any advantage over the other. They are almost same with little pharmacokinetic differences.
- These types of drugs are called me-too drugs.
- They do not have any therapeutic advantage and their efficacy is almost.
- They only add up to the list of available medicines.

Table 16.1

Case	Patient suffering from typhoid	Sickness level	Treatment	Avoid
1.	10 yrs. old boy	Very sick Sick	Ceftriaxone (I.V) Cefixime (oral)	Ciprofloxacin (can damage cartilage)
2.	32 yrs. old male	Very sick	Ceftriaxone (I.V)	
3.	40 yrs. old male	Sick	Cefixime (oral) can be sent home.	
4.	Pregnant woman	Sick	Ceftriaxone (I.V) or oral Cefixime (if she is not admitted)	Ciprofloxacin (can damage cartilage of foetus)
5.	Carrier (do not have the disease but carry the bacteria)		Ciprofloxacin	

Table 16.2

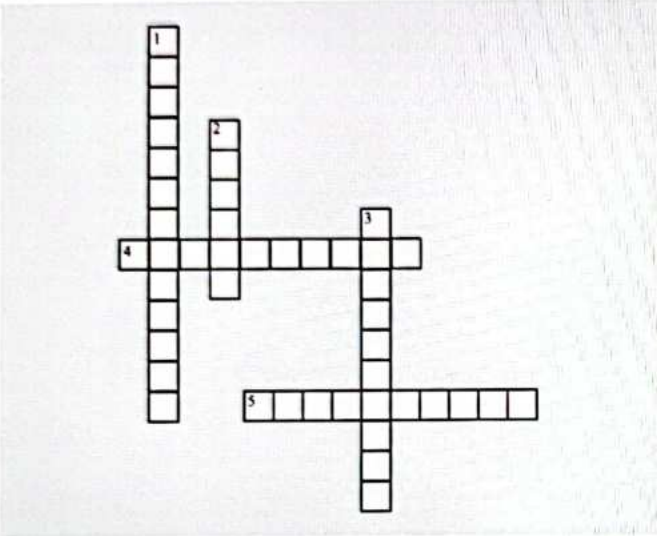
	Medicine	Level of Healthcare	Dosage form(s) and strength
2.1.2	Diclofenac	P,S,T	Tablet 50mg Injection 25 mg/mL
2.1.3	Ibuprofen*	P,S,T	Tablet 200mg Tablet 400mg Oral liquid 100mg/5 mL(p)
2.1.4	Mefenamic acid	P,S,T	Tablet 250mg Oral liquid 100mg/5 mL (p)
			Tablet 500 mg Tablet 650 mg Oral liquid 120mg Oral liquid 125 mg
2.2.1	Fentanyl	S,T	Injection 50mcg/mL

*Ibuprofen formulations are also listed in Section 5.2.2 - Medicines used in Neurological Disorders-Antimigraine Medicines
** Paracetamol formulations are also listed in

A. Section 5.2.3 - Medicines used in Neurological Disorders-Antimigraine Medicines
B. Section 27.4 - Medicines for COVID - 19 Management

CROSS WORD PUZZLES

Crossword Puzzle 1



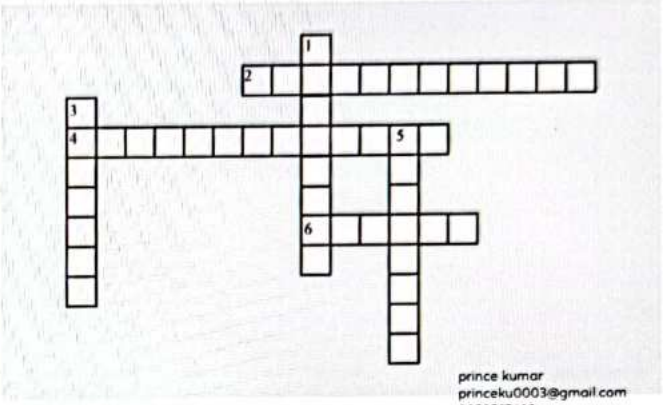
Across

4. Rational drug prescribing should be properly _____ to avoid legal issues.
5. Pitolisant is an H3 inverse agonist orphan drug that is used to treat _____.

Down

1. _____ is avoided in case of children and pregnant women as it can damage cartilage.
2. _____ is also known as preferred or personalized drug.
3. Evidence based medicine is also known as _____ medicine.

Crossword Puzzle 2



Across

2. National list of essential medicines of India of the year 2022 has a total of 384 medicines divided into _____ categories.
4. _____ of the drugs by the patient is the most important criteria taken under consideration while prescribing a drug.
6. _____ drugs do not have any therapeutic advantage over one another and their efficacy is almost.

Down

1. _____ has maximum efficacy for treatment of typhoid.
3. _____ channel blockers should be used while treating hypertension.
5. Fentanyl should be available only in secondary and _____ health care centres.

17 PHARMACOGENETICS

Pharmacogenetics

Case Study

A patient was planned for intubation and was given Succinylcholine. Usually, it acts for 5 minutes only, and apnea will not be prolonged. In this patient, apnea got prolonged for 2 hrs. after giving Succinylcholine, and was put on ventilator support.

- Succinylcholine is used during endotracheal intubation to relax the neck muscles to pass the ET tube easily.
- Sometimes it can relax the diaphragmatic muscles and cause apnea, in certain cases this can be prolonged and the patient had to be put on ventilatory support.
- Succinylcholine is called a Depolarizing skeletal muscle relaxant. It is mainly given for intubation.
- The drug acts for 5 minutes only. So, the duration of action is for 5-minute, and the drug is metabolized by an enzyme called pseudocholinesterase (Typical pseudocholinesterase).
- When Succinylcholine is given in a patient with atypical pseudocholinesterase, increase the duration of action of Succinylcholine leading to prolonged apnea. The patient is put on ventilatory support and a FFP or recombinant pseudocholinesterase is given.
- It is a study of drug response based on individuals' genetic makeup called pharmacogenetics.
- Atypical pseudocholinesterase condition occurs then we use testing called Dibucaine number

Dibucaine number

• Normal	• Heterozygous	• Homozygous
• 80 Number	• 50-60 Number	• 20-30 Number

- If these numbers are detected, there is a high chance of Succinylcholine apnea.
- So, Succinylcholine can be given according to the Dibucaine number.

Drug treatment

- If the dibucaine number is 50-60 and 20-30 (Rocuronium is also a skeletal muscle relaxant, which has a fast onset of action)
- Rocuronium can be used for intubation.
- Mivacurium (Shortest acting skeletal muscle relaxant)
- Mivacurium is not used because the enzyme pseudocholinesterase metabolizes it.

Q. If the patient has atypical pseudocholinesterase, what will be used for intubation?

Ans: Don't use Mivacurium. Use Rocuronium for intubation.

Pharmacogenomics

00:08:38

- A field of research that studies how a person's genes affect how they respond to medications.
- It will help to reach the right drug to the right patient. (Based on genetic makeup)

Pharmacogenetic problem

How G6PD works	In G6PD deficient patients
G6PD ↓ RBC ↓ NADPH ↓ Prevent Oxidative Stress in RBC ↓ No Hemolysis	Using Certain Drugs ↓ Produce oxidative stress ↓ Hemolysis (In G6PD deficient patients, the NADPH is not produced, and the oxidative stress is not blocked).

Drugs avoid in G6PD deficient patients

- Primaquine
- Tafenoquine
- Chloroquine
- Chloramphenicol
- Sulfonamides
- Methylene blue
- Nitrofurantoin

Metabolism

00:13:28

- The chemical changes that take place in a cell or an organism.
- The enzyme does metabolism in a human. Enzymes are nothing but proteins.
- Certain people don't produce metabolism adequately and are called poor metabolizers.

1. Cytochrome enzymes (CYP)

CYP2D6	CYP2C19	CYP2C9
Codeine ↓ Morphine ↓ Analgesic effect	Clopidogrel (Pro drug) ↓ Active drug	Warfarin Phenytoin (Decrease in Metabolism)

2. **Acetylation**
   Drugs:
   - INH
     → **Slow acetylation** (prone to peripheral neuropathy)
     → **Fast acetylation** (prone to Hepatotoxicity)
   - Hydralazine (drug-induced Lupus)
   - Procainamide (drug-induced Lupus)

3. **Glucuronidation:** UDP Glucuronosyltransferase
   - **E.g.** Irinotecan → treatment of colorectal cancer
     ↓ (UDP GT)
     Metabolized
   - The enzyme is not metabolized, causing diarrhea to become severe.

4. **Malignant Hyperthermia**
   Drugs
   - Succinylcholine
   - Volatile anesthetics (Halothane) → Muscle rigidity, increase in temperature, Rhabdomyolysis (Leads To renal failure).

Q. What is the problem with ryanodine receptors being defective?

Ans:

- The sarcoplasmic reticulum releases calcium, and calcium is required for muscle contraction.
- There is increased release in Calcium in patients with ryanodine receptors when Succinylcholine/ Halothane is given, leading to muscle contraction increasing the temperature, and Rhabdomyolysis occurs.
- So, the drug of choice for this condition is Dantrolene sodium.

Warfarin

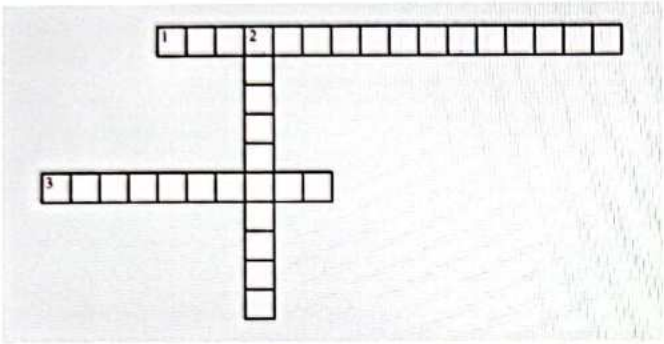
- It is a Vitamin K antagonist
- Warfarin Causes the metabolism of 2, 7, 9, 10 and proteins C and S into the active form.
- To make them active Vitamin K reduce will become vitamin K oxidized and the cycle continues. This is done by an enzyme called vitamin K epoxide.
- Deficiency of vitamin K epoxide prevents this cycle.
- Due to that, they are prone to bleeding.
- If Warfarin is given in this patient it will increase the risk of bleeding.

Association of HLA

- HLA makeup is 5701 → Abacavir can lead to hypersensitivity.
- HLA makeup is 5701 → Flucloxacillin can lead to liver toxicity.
- HLA makeup is 5801 → Allopurinol can lead to skin allergy.
- HLA makeup is 1502 → Carbamazepine can lead to Steven Johnson syndrome.

CROSS WORD PUZZLES

Crossword Puzzle



Across

1. Genetic makeup drug response called
3. The diabolical number is 20-30 then

Down

2. Patient has typical pseudocholinesterase

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18 PHARMACOKINETIC PROBLEMS

Formulas Related to Pharmacokinetics

00:00:20

- $t^{1/2} = \frac{0.693}{k}$ k = Elimination rate constant
- $t^{1/2} = \frac{CL}{Vd}$
- $M.D = \frac{\text{Target PC} \times \text{"CL"} \times \text{Dosing interval}}{\text{"F"}}$
- $L.D = \frac{\text{Target PC} \times Vd}{F}$

C_{ss}

$C_{PSS} = \frac{\text{rate of infusion}}{\text{clearance}}$

$CL = \frac{\text{"ER"}}{PC}$

rate of infusion = rate of elimination

rate of infusion = CL × PC

- Hepatic CL = HBF × HER
- HER = 1 − "F" = 1 − 0.5 = 0.5 (50%, F = 0.5)
- $CL = \frac{Dose}{AUC}$
- $BA = \frac{AUC(oral)}{AUC(I.V)} \times 100$

Problems

00:05:35

Q. A drug X has elimination rate constant of 0.693/hour. What is the half life of the drug in hours.

A. 2
B. 3
C. 1
D. 30

Solution:

$t_{1/2} = \frac{0.693}{K}$

$\frac{0.693}{0.693/hr} = 1\ hr$

Q. The percentage of drug remaining in the plasma after 3 half life is

A. 6.25%
B. 12%
C. 6%
D. 12.5%

Solution:

If there is 100 milligram of the drug it gets reduced to 50% in one half:
After the First half-life 50
After the Second half-life 25
After the Third half-life 12.5
Suppose there is the question that how much drug is eliminated after 3 $t_{1/2}$ then
100-12.5=87.5 %

Important Information

- Half-life is the time required by the drug to get reduced to half of its concentration.

Q. Calculate hepatic clearance of a drug with hepatic blood flow of 2000ml/min and hepatic extraction ratio of 0.5

A. 1000ml/min
B. 1500ml/min
C. 1125ml/min
D. 750ml/min

Solution:

Given, HBF = 2000 ml/min
HER = 0.5
We know, Hepatic Clearance = HBF × HER
= 2000 × 0.5
= 1000 ml/min

Q. Calculate the maintenance dose of a drug X, if it has a clearance of 1L/h and you need to achieve to plasma concentration of 15microgram/L and drug given four times a day

A. 600mcg
B. 60 mcg
C. 900 mcg
D. 90 mcg

Solution:

Given, CL = 1L/hr
PC = 15 mcg/L

Dose Interval = $\frac{24}{4} = 6^{\text{th}}$ hourly

If bioavailability is not given take it as 1, F = 1

Maintenance dose = $\frac{\text{Target PC} \times \text{Clearance} \times \text{Dose Interval}}{F}$

$$= \frac{15\text{mcg/L} \times 1\ \text{l/hr} \times 6}{1}$$

$$= 90 \text{ micrograms}$$

Q. After starting continuous IV infusion of a drug X, 75% of the drug steady-state concentration is reached after

A. 1 half life of drug X
B. 2 half life of drug X
C. 3 half life of drug X
D. 4 half life of drug X

Solution:

Steady state is the state where the rate of entry is equal to ready drug exit, to achieve a steady state 4 to 5 $t_{1/2}$ are required.
To achieve 50% of steady state 1 $t_{1/2}$ is required.
For 75% of the steady state, 2 $t_{1/2}$ is required.
For 89% = 3 $t_{1/2}$
For 90% = 3.3 $t_{1/2}$
So, 2 half-life are required for 75% of the drug's steady state.
Ans.

Q. Hepatic extraction ratio is given by

A. Hepatic blood flow multiple by Vd
B. Hepatic blood flow multiple by hepatic clearance
C. Hepatic clearance divided by hepatic blood flow
D. Hepatic blood flow multiple by bioavailability

Solution:

We know, HC = HBF × HER

$$\text{HER} = \frac{\text{HC}}{\text{HBF}}$$

So, hepatic extraction is equal to hepatic clearance divided by hepatic blood flow.

Q. "18" mg drug was administered to a patient, in that 6 mg of drug excreted in 2hrs. The given drug follows first order kinetics, how much drug will remain after 4 hrs?

A. 6 mg
B. 12 mg
C. 8 mg
D. 3 mg

Solution:

If the drug follows first-order kinetics, that means half-life remains the same, clearance remains the same, the elimination rate is directly proportional to plasma concentration, and the constant fraction of the drug is eliminated in unit time.
Given that patient is given 18 milligrams of the drug and after 2 hours 6 milligrams of the drug are eliminated that means the elimination rate is 6 mg/2hrs.

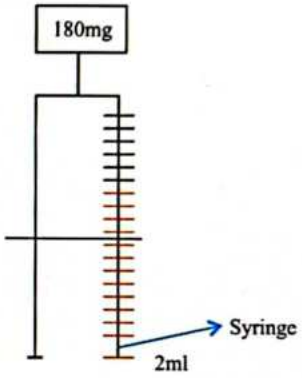
After 2 hrs, 12 milligrams are remaining, and 1/3rd is lost
After another 2 hrs,4 milligrams are lost i.e., 1/3rd, 8 milligrams are remaining.

Q. 500mg/5ml ceftriaxone is available. 180mg of the drug is to be administer using 2ml syringe with each ml having 10 divisions. How many divisions would be needed to administer 180mg of drug.

A. 1.8
B. 9
C. 18
D. 6

Solution:

Given, 5 ml contains 500 mg of ceftriaxone,



If 5 ml contains 500 mg drug,
Then 1 ml = 10 mg
0.1 = 100mg
and, 1 division = 0.1 ml
So, 1 division = 10 mg

To achieve 180 mg, $= \frac{1 \times 180}{1}$ 18 divisions

Q. A patient comes 6 hours after consuming morphine and present with pinpoint pupils and respiratory depression. t1/2 is 3 hours and Vd is 200L. Plasma concentration is 0.5 microgram/ml. Calculate the initial morphine dose consumed?

A. 100 mg]
B. 400 mg
C. 10 mg
D. 50 mg

Solution:

Given, the volume of distribution= 200 L
$t_{1/2}$ = 3 hrs
Plasma concentration = 0.5 microgram/ml
Plasma concentration 6 hours earlier = 2 microgram/ml

Converting it into litres= 2 = 2×10^{3} milligrams/ 10^{3} = 2 milligrams/liters.

$$\text{Loading dose} = \frac{\text{Target PC} \times \text{Vd}}{\text{F}} = \frac{2 \times 200}{1} = 400\,\text{mg}$$

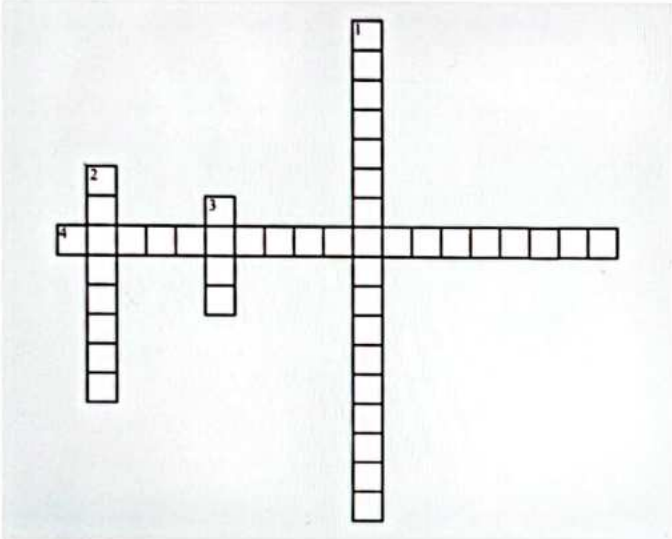
Q. A drug Y takes 6 hours to reach its 50% steady state plasma concentration when given IV. What is the half-life of the drug Y?

A. 4 h
B. 6 h
C. 12 h
D. 24 h

Solution:
50% = 1 $t_{1/2}$ = 6 hours

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

4. In the first order of kinetics, the elimination rate is directly proportional to_____.

Down

1. _____is equal to hepatic clearance divided by hepatic blood flow.
2. _____is the time required by the drug to get reduced to half of its concentration
3. If the drug follows first-order kinetics, the half-life of the drug remains the_____.

19 INTRODUCTION TO ANS AND CHOLINERGIC DRUGS

Relevance

- A patient whose heart rate is 40 bpm.
- A patient has a BP of 80/40 mm of Hg.
- A 32-year-old female has wheezing.

Classification

- The nervous system is divided into the Central and Peripheral nervous system
- In the central, there is the brain and spinal cord. And in the peripheral, there are the Autonomic nervous system and the somatic nervous system.
- The autonomic nervous system is divided into parasympathetic, sympathetic, and enteric.

ANS Introduction

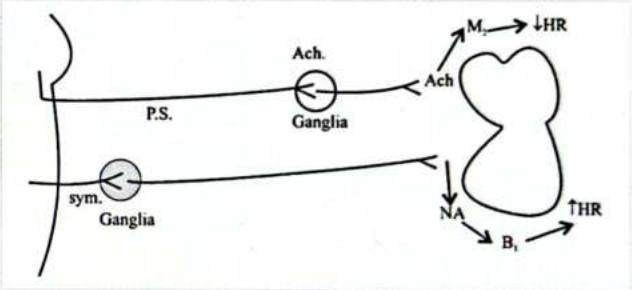
00:03:51

Parasympathetic	Sympathetic
• Relaxation and digestion. • Causes Secretion. • Causes evacuation of bowel and bladder. • Miosis in the eye. • **Heart-** It decreases the heart rate and conduction. • **Lungs-** There is Bronchoconstriction. • Responsible for learning and memory. • Responsible for erection. • **Receptors-** Muscarinic (M) and Nicotinic (N). • **Neurotransmitter-** Acetylcholine (Ach). • This is cranial sacral output.	• Fight, flight, freight, and anxiety are examples of sympathetic actions. • They decrease secretions. • Decrease evacuation of bowel and bladder. • Mydriasis in the eye. • **Heart-** Increases the heart rate, increases conduction and force of contraction. • **Lungs-** Bronchodilation. • Responsible for ejaculation. • **Receptors-** α and β receptors • **Neurotransmitter-** Noradrenaline (NA) • Thoracolumbar output.

Mechanism of Action

00:08:48

- As parasympathetic nerves come from the cranial nerves, the nerve comes out and forms a synapse. The nerve making a synapse with another nerve is called the ganglia. In the ganglia neurotransmitter is acetylcholine. This acetylcholine is released at the junction where the nerve is going and meeting the target organs. For example, if the target organ is the heart, M2 receptors of the heart are activated and the heart rate comes down.
- In the sympathetic system, ganglia are closer to the spinal cord, so, presynaptic fibres are shorter and postsynaptic fibres are longer. In the sympathetic system also the neurotransmitter in the ganglia is acetylcholine. But the target organ neurotransmitter which is released is noradrenaline. In the heart, noradrenaline receptors act on the heart's β_1 receptor, increasing the heart rate.
- This is how things are balanced.



- **Exceptions:** Even the fibres are sympathetic in certain places they are cholinergic, for example-
  - In sweat glands neurotransmitter is acetylcholine, it acts on a receptor called M_3 and this acts on the sweat gland called the thermoregulatory sweat gland. Even if the origin is sympathetic, they are called sympathetic cholinergic fibres.
  - Dopamine acts on a receptor called D_1 it is mainly present in renal blood vessels.

Important Information

- In the adrenal medulla, a neurotransmitter that is released at the ganglia is acetylcholine (as at any ganglia there is the release of acetylcholine neurotransmitter), when they stimulate the adrenal medulla there is the release of catecholamines i.e. adrenaline, and noradrenaline.

Drug Action

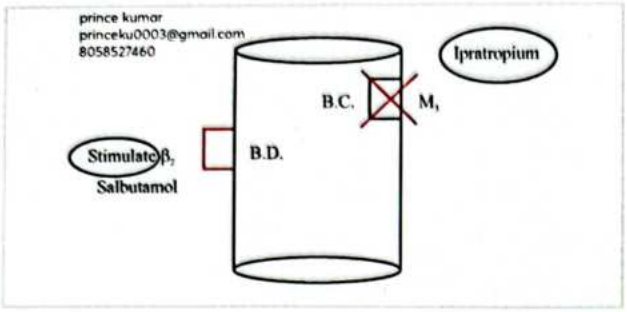
00:14:50

β_1 & β_2 Agonist

- Isoprenaline stimulates the β_1 receptor and increases heart rate.
- Salbutamol stimulates the β_2 receptor and causes bronchodilation.

M_1 & M_3 Antagonist

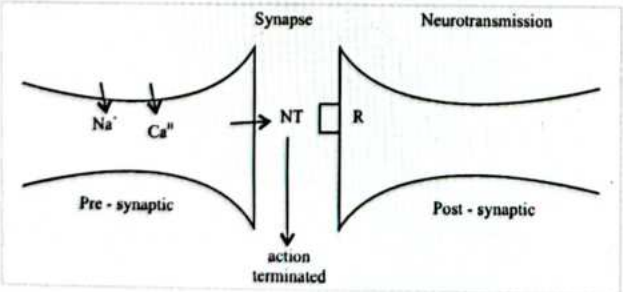
- Atropine blocks the M_2 receptor and the heart rate is increased.
- Ipratropium blocks the M_3 receptor and decreases bronchoconstriction action.



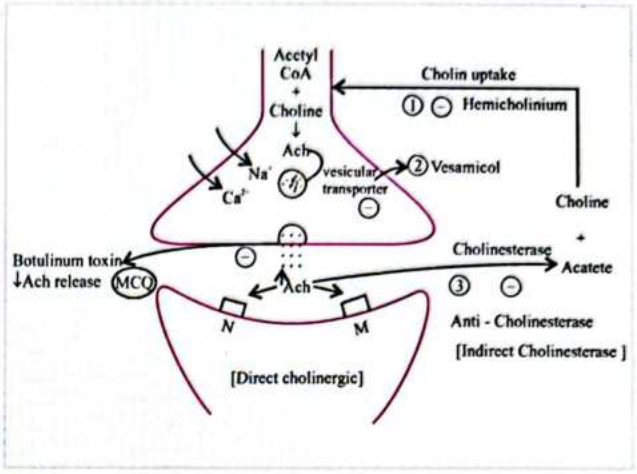
Parasympathetic or Cholinergic System 00:18:44

- Two important receptors are Muscarinic(M) and Nicotinic(N)
- Muscarinic receptors are called G protein coupled receptors (GPCR) and Nicotinic receptors are ion channel receptors.
- In the ion channel receptor, there is the nerve-nerve junction. These are present in Ganglia and modified ganglia are adrenal medulla. The neurotransmitter is acetylcholine and the receptor is NN.
- One more important place in the ion channel is NM, it is present in the neuromuscular junction. Here also the neurotransmitter is acetylcholine and the receptor is the NM receptor.
- Ion channel receptors are the fastest acting.
- The muscarinic receptors have M_1 M_2 M_3 M_4 M_5
- M_2 and M_4 are Gi coupled receptors.
- M_1, M_3 and M_5 are Gq coupled receptors.
- M_1 receptors are present in CNS and gastric glands.
- M_2 receptors are present in the heart.
- M_3 receptors are present in smooth muscles and the eye, two important muscles of the eye where it is present are sphincter pupils and ciliary muscles. This receptor is also present in the exocrine gland (increases secretions).

Neurotransmission



- During an action potential, Sodium and Calcium enter and there is the release of neurotransmitters from the presynaptic nerve, the junction between two nerves is a synapse.
- Neurotransmitters will act on receptors present on the postsynaptic nerve. The receptor will be stimulated and the neurotransmitter action is terminated. This is neurotransmission.



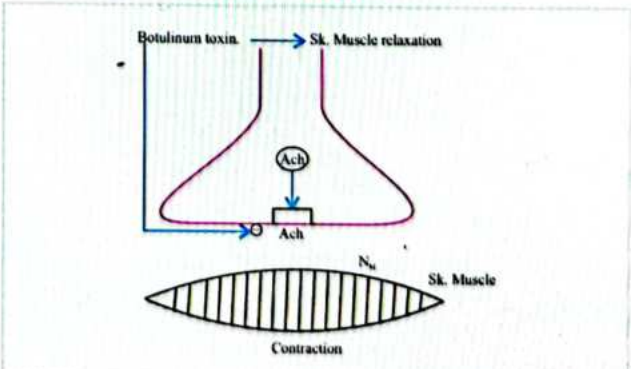
- Acetyl CoA combines with choline to form the neurotransmitter acetylcholine. It will be stored in a vesicle with the help of a vesicular transporter.
- Whenever the signal comes, Na^+ and Ca^{2+} enter the presynaptic terminal. Calcium gives a command to release acetylcholine. Vesicles will fuse with the presynaptic membrane and there will be the release of acetylcholine.
- Acetylcholine acts on receptor nicotinic and muscarinic depending on the target organ.
- Acetylcholine is terminated with the help of an enzyme called cholinesterase. It breaks down Acetylcholine into acetate and choline. Choline again goes back and this is called choline uptake.

Blocking the Steps

- Choline uptake is blocked by the drug Hemicholinium.
- VESAMICOL is an inhibitor of vesicular transporter.
- Cholinesterase enzymes can be inhibited by anticholinesterase drugs. These drugs indirectly act on receptors that's why they are called indirect cholinergic.
- Botulinum toxin blocks the release of acetylcholine.

Botulinum toxin

- Botulinum toxin will block release of acetylcholine and this will lead to skeletal muscle relaxation.



- **Uses:**
  - Botulinum toxin is used locally for cosmetic purposes such as glabellar lines and wrinkles.
  - Botulinum toxin is used in strabismus, blepharospasm, cervical muscle spasm and achalasia cardia.
  - Onabotulinum toxin A is used in migraine prophylaxis and overactive bladder.

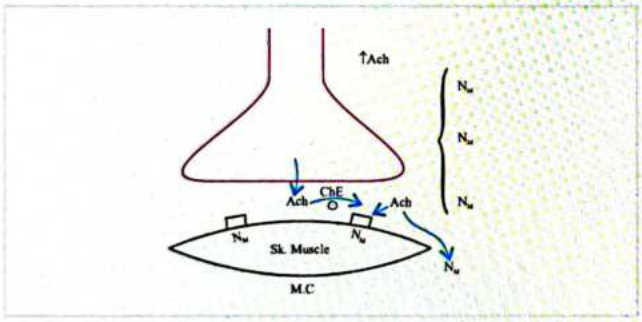
Important Information

- Cobra toxin also blocks NM receptors, this causes neurotoxicity and muscle relaxation.
- That is why in cobra bite, along with anti-snake venom **Neostigmine** is given.

Concepts 00:41:15

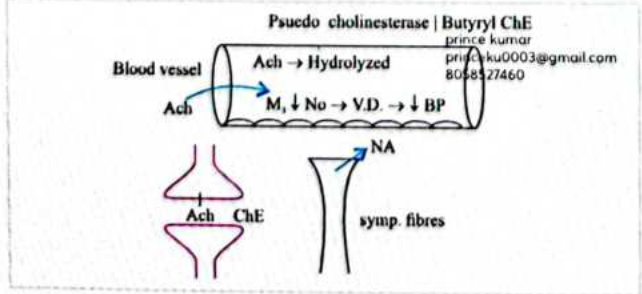
Refer Table 19.1

Skeletal Muscle:



- Drugs are used to increase the activity of the NM junction.
- Conditions affecting NM receptors
  - D-Tubocurarine, nondepolarizing skeletal muscle relaxants, is used to block the NM receptors before the surgery to relax the muscles.
  - Myasthenia gravis produces auto antibodies against NM receptors.
  - Cobra toxin blocks the NM receptors
- Ach is increased by inhibiting cholinesterase called as Anticholinesterase.
- If the NM receptors are stimulated repeatedly, they undergo desensitization leading to flaccid paralysis

Blood vessels:



- Blood vessels are innervated by sympathetic fibres. Stimulation of these fibres leads to release of NA causing vasodilation or vasoconstriction.
- When Ach is given IV, it acts on the m3 receptors on the endothelium of the blood vessels which releases NO causing vasodilation (reduces BP).
- The enzyme Pseudocholinesterase/ Butyryl cholinesterase present in the blood vessels hydrolyses Ach. Here it is metabolised slowly.
- Since Ach is very short and metabolized rapidly, it is not used in therapy

Adverse effects: MUSCARINIC EFFECTS (Mnemonic- DUMBELS)

- D- Diarrhoea
- U- Urination
- — Miosis
- B- Bronchoconstriction and Bradycardia
- E- Emesis
- L- Lacrimation
- S- secretions (Salivation, sweating and lung secretions)

Cholinergic Drugs 01:05:00

Direct Cholinergic

- They directly stimulate the receptors.
- They are two types:
  - **Plant alkaloids-** Arecoline, Muscarine, Pilocarpine. Pilocarpine is used in eye drops to cause active miosis and it is also used in glaucoma. Pilocarpine is also given as an oral drug to manage Sjogren's syndrome.
  - **Choline esters-**
    - → Ach: Shorter acting, nonspecific action, used for experimental purposes only.
    - → Methacholine (M_2>>>M_1): Used in tachycardia, used to diagnose bronchial hyperactivity.
    - → Carbachol: Used to treat glaucoma.
    - → Bethanechol: Used in postoperative paralytic ileus, postoperative urine retention, and atonic bladder.
    - → Cevimeline: M_3 agonist, used in Sjogren's syndrome.

Indirect Cholinergic 01:14:45

- They are anticholinesterase, and act on both receptors N and M.
- These drugs are of two types: reversible and irreversible.
- Reversible drugs are used in treatments.

Reversible Anticholinesterase

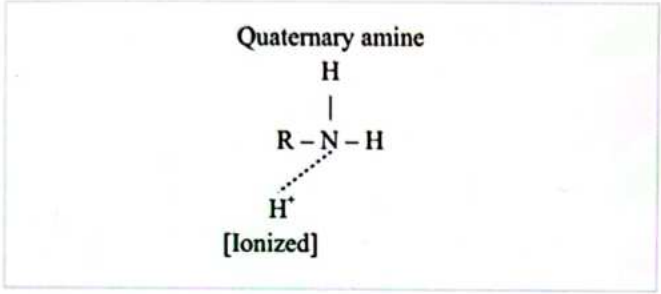
Physostigmine

Tertiary Amine	H
$R-NH_2$	$R-\underset{\displaystyle R}{\overset{\displaystyle H}{\underset{\displaystyle |}{N}}}-H$

- It is a tertiary amine. [NI]

- It is a non-ionised drug which can easily cross the membranes and blood brain barrier.
- Uses:
  - It is a drug of choice for Atropine/ Belladonna/ Datura poisoning
  - It is also used in Glaucoma.

Pyridostigmine and neostigmine



- These are called quaternary amines.
- These are ionised and will not be able to enter the brain.
- **Uses:**
  - **In NM junction-** Cobra bite (Anti-snake venom + Neostigmine/Physostigmine), To reverse non-depolarising skeletal muscle relaxants and Myasthenia gravis.
  - **In M receptors-** Post OP paralytic ileus, Urinary retention and Atonic bladder (NOT USED).
- **Adverse effects:** Muscarinic symptoms are the adverse effects and they are managed by antimuscarinic drugs.

Edrophonium

- It is a shorter-acting drug.
- Used to diagnose myasthenia gravis (Tensilon test).
- Used to differentiate cholinergic versus myasthenic crisis.

Rivastigmine, Donepezil, and Gallantamine

- These drugs are used in Alzheimer's disease.

Tacrine

- Causes Hepatotoxicity (banned).

Important Information

- Other drugs used in Alzheimer's disease:

1. Memantine- NMDA antagonist, used in moderate-severe disease, Mono/combined therapy, Dose-5-20 mg/day
2. Aducanumab- Monoclonal antibody against β-amyloid

Irreversible Anti-cholinesterase 01:32:10

- They are not used in therapy since they cause toxicity.
- There are two types- Organophosphates and Carbamates.
  - **Organophosphates:**

Insecticide/ pesticides	Nerve gases
• MALATHION • Parathion • Dyflos • Diazinon	• Tabun • Sarin • Soman

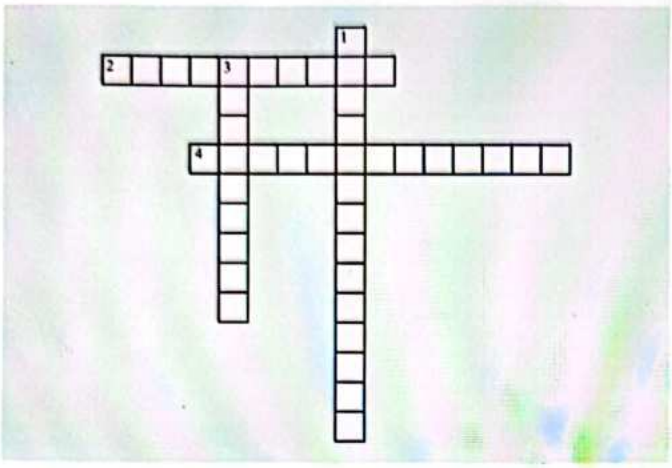
  - **Carbamates:**
    → Carbaryl
    → Propoxur
- Drug of choice for OP poisoning- Atropine + Oximes.
- Drug of choice for Carbamate poisoning- Atropine, Oximes are contraindicated.
- **Chronic OP poisoning:**
  - Due to prolonged exposure to OP compounds.
  - Symptoms similar to Multiple sclerosis.
  - No treatment.

Table 19.1

	Actions	Uses	Adverse effects
CNS (M_1)	Increase in Learning and memory	Alzheimer's disease	-
Eye (M_3)	Sphincter pupillae leads to miosis and ciliary muscle spasm, (Spasm of accommodation)	Glaucoma, To counteract mydriasis	Eyebrow pain
Mouth (M_3)	Increase in lacrimation and Salivation	Sjogren's syndrome	Increase in lacrimation and Salivation
Heart (M_2)	**Atria-** Increases heart rate, conduction and decreases FOC. **Ventricle-** decreases heart rate and conduction.	Tachycardia	Bradycardia Decrease in conduction
Lungs (M_3)	Bronchoconstriction Increase secretions	-	Bronchoconstriction Increase secretions
Stomach (M_1)	Gastric secretion and increase in HCl	-	Gastritis
Intestine (M_3)	Increase motility and Open sphincter	Constipation and Post OP paralytic ileus	Diarrhoea
Urinary bladder (M_3)	Increases detrusor contraction	Postoperative urine retention and Atonic bladder	Increases Urination
Penis	Erection	-	-

CROSS WORD PUZZLES

Crossword Puzzle 1



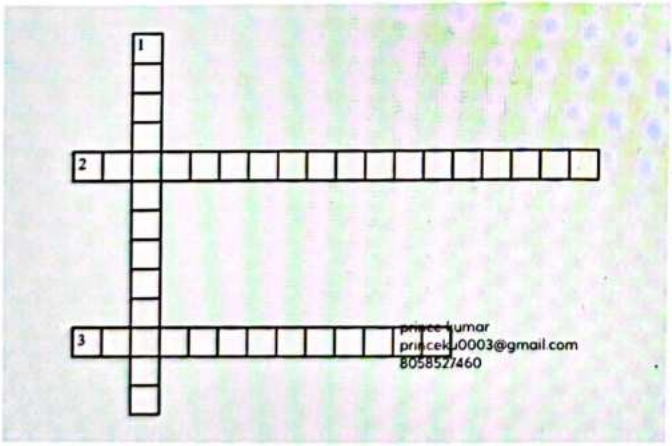
Across

2. _____ is an inhibitor of the vesicular transporter.
4. Acetyl CoA combines with choline to form the neurotransmitter_____.

Down

1. _____ blocks the release of acetylcholine.
3. _____ is a plant alkaloid.

Crossword Puzzle 2



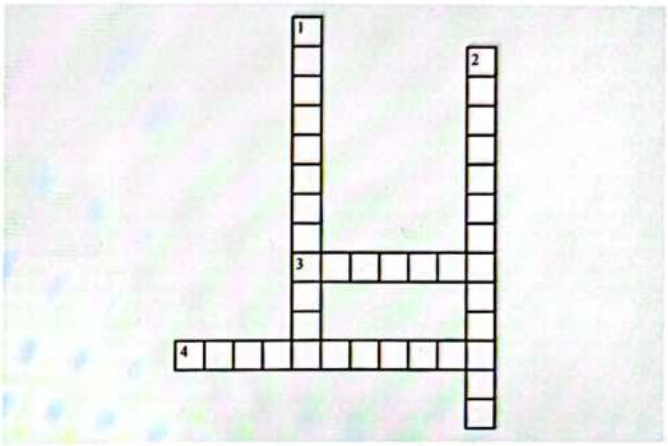
Across

2. Cholinesterase enzymes can be inhibited by_____.
3. _____ is used as a calcium channel activator.

Down

1. M3 receptors are present in_____.

Crossword Puzzle 3



Across

3. _____ causes hepatotoxicity.
4. _____ is given along with anti-snake Venom in cobra bite.

Down

1. Test which is done in myasthenia gravis is_____.
2. _____ are used for experimental purposes only.

20 MANAGEMENT OF OP AND CARBAMATES POISONING

Introduction

- The OP compounds and carbamates are irreversible anticholinesterases.
- These are enzyme inhibitors.
- Poisons where the pupil is miotic
  - OP poisoning
  - Carbamate poisoning
  - Phenol poisoning
  - Pontine haemorrhage.
  - Opioid poisoning.

Organophosphates (OP) Poisoning 00:03:20

- OP Poisoning occurs due to the direct or indirect consumption of organophosphates.
- Acetylcholine is split into acetate and Choline by cholinesterase.
- When Cholinesterase is inhibited by OP compounds there is increase in activity of Acetylcholine at the synapse which acts on muscarinic and nicotinic receptors. This leads to OP compound poisoning.
- OP compounds are Highly lipid soluble: they can absorb on skin.
- They are:

Insecticides / Pesticides	Nerve Gases
Malathion (Prodrug)	Tabun
Parathion (Prodrug)	Sarin
Dyflos	Soman
Diazion	-

- Farmers can take OP to kill insects or use it on the farm for killing pests/insects.
- Sometimes they can be used for committing Suicide by consuming these OP.

Muscarinic (M) Causes Adverse Effects 00:06:00

- **Mnemonic: DUMBELS**
  - D - Diarrhoea
  - U - Urination
  - M - Miosis
  - B - Bradycardia, Bronchial Constriction
  - E - Emesis
  - L - Lacrimation
  - S - Salivation

MOA of Nicotinic Receptors

Nicotinic (N)(Nm)
↓
Rapid Desensitization
↓
Paralysis of Skeletal Muscle
↓
Flaccid Paralysis
↓
Respiratory Failure → Mechanical Ventilation

Management of OP Poisoning 00:09:08

- Airway, Breathing, Circulation
- Gastric Lavage
  - Remove excess poisoning.
  - No use of gastric lavage after 6 hrs of poisoning
- Wash the skin
  - Antidote for OP poisoning- Atropine, blocks muscarinic activity

Signs of Atropinization

- How do I know if the Atropine dose I have given is correct? Should I repeat the dose?
  - Pupil size (dilation) (most common)
  - ↑HR
  - ↓Secretion → ↓Pulmonary Secretion (most specific)

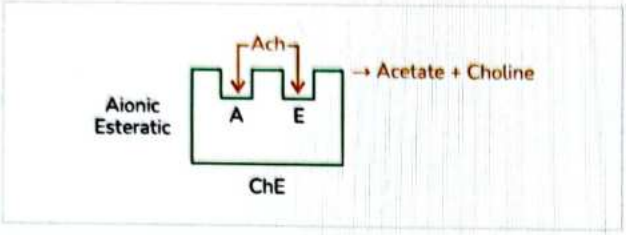
Important Information

- Do not confuse Organophosphate poisoning with Organochlorine poisoning.
- Organochlorine poisoning does not have an antidote and Atropine does not work. It is treated symptomatically.

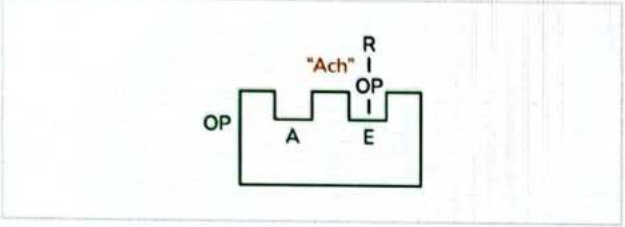
Enzyme Reactivators

- Since OP Compounds Increase Acetylcholinesterase due to decreased cholinesterase, Enzyme Reactivators [Oximes] are used in the treatment of OP poisoning. They are:
  - Pralidoxime
  - Obidoxime (Most potent)
  - Diacetyl monoxime → Cross BBB

- MOA of Oximes
  - Normal mechanism

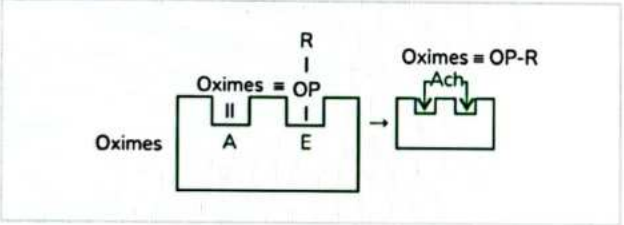


  - OP poisoning mechanism



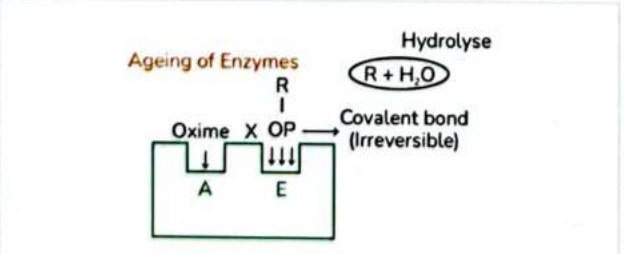
→ When we give OP compounds, they bind at the E site. They have an R Group attachment.
→ When they bind on these, Ach cannot bind because it requires both sites for binding.
→ OP compounds are competitive and irreversible

  - **Oximes mechanism**



→ When we give oximes, they will come and bind on the anionic site; they form a bond with OP.
→ Oximes bond with the OP and R groups; they will be released from the enzyme.
→ Once the released enzyme becomes free, then Ach can attach and reactivate the enzyme.

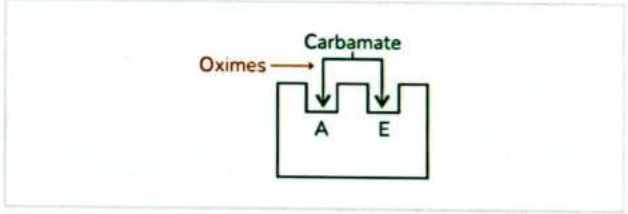
Ageing of Enzymes 00:18:35



- OP compound binds on the E site with the R group.
- When we delay the treatment with oximes, R group is released from the enzyme combines with water and undergoes hydrolysis.
- Then the OP compound is alone. OP forms a strong covalent bond, and the enzyme becomes irreversible.
- Due to irreversibility, even giving oxime, they cannot remove OP from the site.
- Formation of the covalent bond and making the enzyme irreversible is called Ageing of the enzyme.
- It occurs within 6-8 hrs.
- Ageing of enzymes varies for different OP compounds
- This is the reason Atropine is used as an antidote in OP poisoning.

Carbamates Poisoning 00:21:05

- Carbamates are responsible for carbamates poisoning are
  - Carbaryl
  - Propoxur
- Drug of Choice → Atropine
- Oximes are not used.



- Carbamate binds to both sites because there is no binding site available for oxime that is not used.
- Oximes are contraindicated.
  - In carbamate poisoning, the carbamate will block cholinesterase enzyme receptors and a small amount of the receptors which are not blocked will convert Ach
  - When Oximes are given, they bind to the anionic site. Ach requires both the sites for metabolization. Since Oximes have already been binded to anionic site, Ach cannot be metabolized. Thus, Oximes prevent the remaining metabolization of Ach.
  - This is the reason the Oximes are contraindicated in the Carbamate poisoning. They have weak Anti-cholinesterase properties.

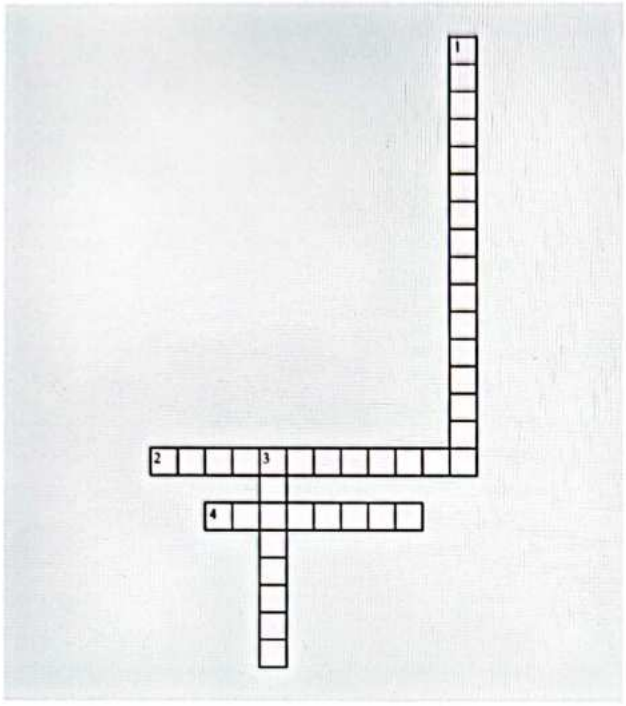
Clinical Case 00:25:01

Q. A 55-year-old farmer was brought to casualty with symptoms of severe abdominal cramps with vomiting and diarrhoea and profuse Lacrimation, and salivation. Pupillary constriction is marked. The drug used in the management of the above poisoning is

A. Malathion
B. Physostigmine
C. Pilocarpine
D. Atropine

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

2. Organophosphate Poisoning causes_____.
4. Antidotes for OP poisoning is _____.

Down

1. _____ Irreversible and Competitive
3. Carbamates poisoning causes _____.

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21 DRUGS USED IN MYASTHENIA GRAVIS

Introduction

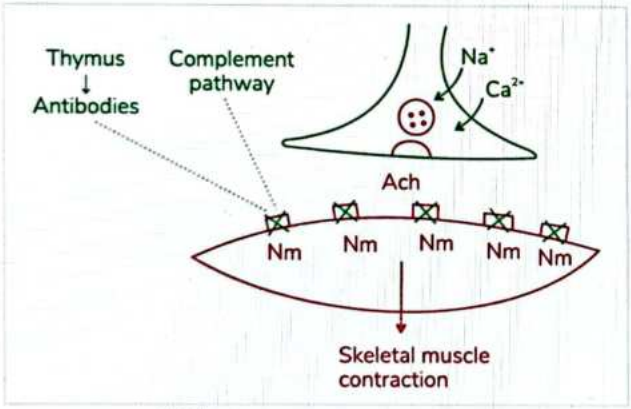
- Myasthenia gravis is an autoimmune disorder. One in every 10,000 people is affected by this.
- Antibodies are produced against the Nm receptor. It is a nicotinic receptor present at neuromuscular junctions. The function of Acetylcholine gets limited in this condition. The muscles are unable to work effectively and efficiently.
- In particular, the eyelids, facial muscles, and pharyngeal muscles are affected. As the disease progresses, other muscles get involved.

Case Based Approach (MCQ) 00:01:00

Question: A Mr. Swamy, aged 38 years, comes to the OPD with complaints of drooping of eyelids, difficulty while chewing food, and weakness of upper and lower limbs, which fluctuates in intensity over time. He was diagnosed with a case of myasthenia gravis. The drug used to diagnose this condition is

A. Rivastigmine
B. Edrophonium
C. Physostigmine
D. Malathion

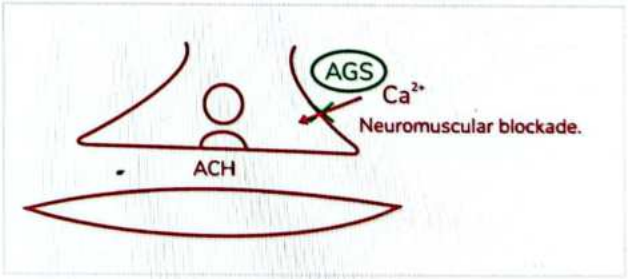
- The antibodies produced in myasthenia gravis are called autoantibodies against the Nm type of receptors.



- As shown above, let's understand the disease in detail via a schematic diagram of the neuromuscular junction. As the action potential comes, Na+ and Ca+ enter the cell; there's a release of Acetylcholine from the cell into the junction and acts on the Nm receptors present in the skeletal muscle. This Nm receptor is responsible for skeletal muscle contraction.
- In the case of myasthenia gravis, the thymus in certain people is active and contains muscle cells with Nm receptors. It starts producing antibodies against the Nm receptors present in its muscle cells. There's the activation of the complement pathway as well. Thus, Nm receptors get killed and are not able to work.
- Certain receptors are not attacked, and they keep working.
- Acetylcholine is metabolised by the enzyme cholinesterase (ChE) and broken down into choline and acetyl.
- There are a few ways to deal with the situation in the case of myasthenia gravis:
  - Increase the stay of acetylcholine to ensure all the receptors are activated and the muscle functions normally. Acetylcholine cannot be administered as a drug as it is short-acting. So, Acetylcholine activity can be increased by limiting the activity of the enzyme cholinesterase. Anticholinesterase drugs are used to inhibit the activity of the enzyme cholinesterase.
  - In young patients with thymoma, surgery can be done to remove the thymus.
  - Another way to deal with the problem is by removing antibodies through a process called plasmapheresis.
  - Immunosuppressants, specifically corticosteroids, can be used. The most commonly prescribed one is Prednisolone. Azathioprine and cyclosporine are also available. Rituximab is a monoclonal antibody that targets CD20.
- A complement pathway can be suppressed by the use of a new drug called Eculizumab. It inhibits the cleavage of C5.

Anti-Cholinesterase 00:08:45

- The drugs in this category include Neostigmine and Pyridostigmine. The latter one is longer acting as compared to the former drug.
- The action of an Acetylcholine is needed in the neuromuscular junction. Many a time, it may work on muscarinic receptors and cause adverse effects. Atropine or atropine substitutes are administered to block the muscarinic receptors if a patient has adverse muscarinic effects.



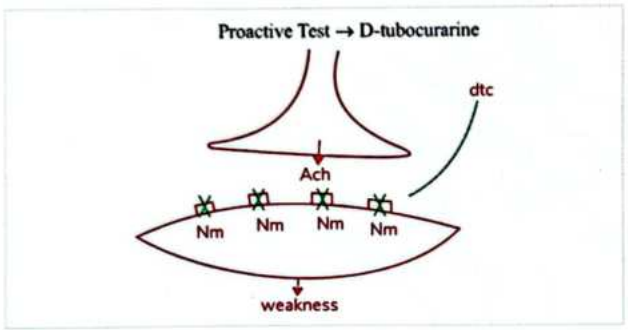
- Suppose aminoglycosides are given if a patient with myasthenia gravis develops some gram-negative infection. These are antimicrobials particularly used for gram-negative infections. Muscle weakness will worsen in this case. Ca++ entry into the muscle cells is blocked by aminoglycosides,

thereby causing weak contractions. There's a neuromuscular blockade. That's why aminoglycosides are contraindicated in myasthenia gravis.

Diagnosis of Myasthenia Gravis 00:12:04

- **Tensilon Test:**
  - 2mg of Edrophonium is given intravenously to check whether the muscle weakness improves. If there's no improvement after 30 to 60 seconds, another 8 mg of Edrophonium is given. If the muscle weakness improves, myasthenia gravis is diagnosed. It's because Edrophonium is an anti-cholinesterase. So, it allows maximum expression of muscle receptors. A patient should be able to open their eyelids after this drug is given. This test is called the Tensilon test. It is because the brand name of Edrophonium was Tensilon upon its release to the market.

- **Proactive Test:**



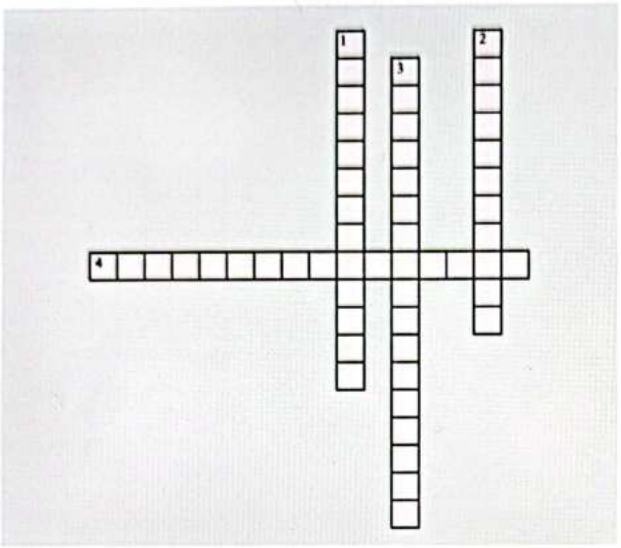
  - D-tubocurarine is the drug used in this test. D-tubocurarine is a competitive blocker. Since antibodies have already blocked most of the receptors responsible for muscle contraction, this drug is given to block the remaining ones. So, there's sudden weakness in patients. This test should only be done in an ICU or with ventilator support.

- Nowadays, anti-NR antibodies are being used to check for myasthenia gravis.
- Another problem in this is how to detect a variation in doses. When the acetylcholine is less, it is unable to act on Nm receptors, and weakness occurs. When the acetylcholine is more, repeated stimulation of Nm receptors occurs, and they undergo rapid desensitisation. There's a weakness of muscle as well. If the dose is less, there's less acetylcholine, and it is called myasthenic crisis, and if the dose is higher, it's called cholinergic crisis.
- The differentiation between the two crises is made by giving the drug Edrophonium intravenously. It increases acetylcholine activity. In the case of a myasthenic crisis, muscle weakness improves, and in the case of a cholinergic crisis, muscle weakness worsens. The dosage of a drug can be increased or decreased based on the results of this test.

Pyridostigmine
↓
Edrophonium
- Muscle weakness Improves = ↑ dose
- Muscle weakness Worse = ↓ dose

CROSS WORD PUZZLES

Crossword Puzzle 1



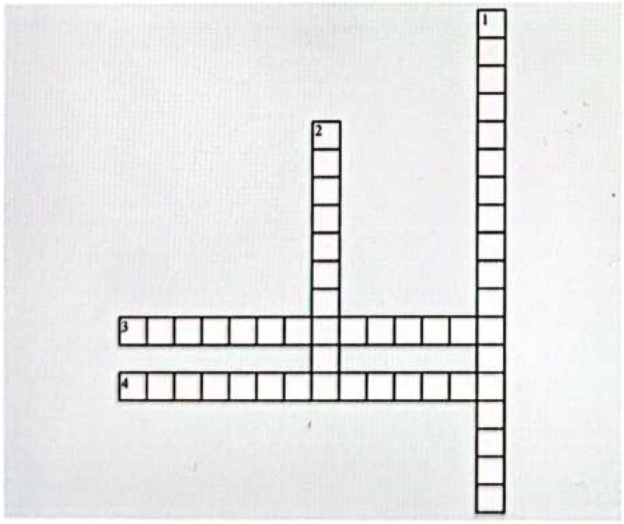
Across

4. There's a weakness of muscle as well. If the dose is less, there's less acetylcholine, and it is called a _____, and if the dose is higher, it's called a cholinergic crisis.

Down

1. The action of an anti-cholinesterase is needed in _____ the junction
2. Another test is the _____ test. D-tubocurarine is the drug used in this test.
3. There's a weakness of muscle as well. If the dose is less, there's less acetylcholine, and it is called myasthenic crisis, and if the dose is higher, it's called _____.

Crossword Puzzle 2



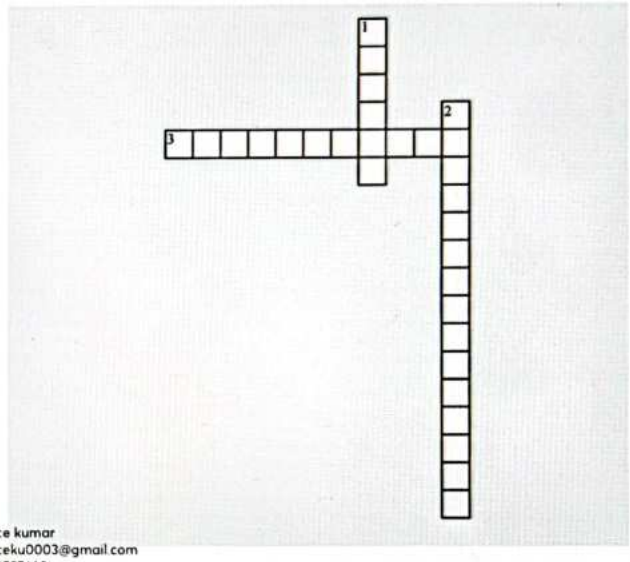
Across

3. The antibodies produced in myasthenia gravis are called_____.
4. Acetylcholine is metabolized by the enzyme _____ (ChE) and broken down into choline and acetyl.

Down

1. _____drugs are used to inhibit the activity of the enzyme choline esterase.
2. In myasthenia gravis, _____are produced against the Nm receptors.

Crossword Puzzle 3



Across

3. Certain drugs are used for the diagnosis of myasthenia gravis. 2mg of _____ is given intravenously to check whether the muscle weakness improves.

Down

1. Nowadays, _____ antibodies are being used to check for myasthenia gravis.
2. _____ are contraindicated in myasthenia gravis.

22 ANTI CHOLINERGIC DRUGS

Introduction

- A substance or drug that reduces the activity of this system is called an anticholinergic drug.
- Also known as the Parasympatholytics.
- Acetylcholine is the main neurotransmitter in the cholinergic system.
- The cholinergic system has two important receptors; muscarinic receptor and nicotinic receptor.
- Nicotine receptors have two important subtypes; NN and NM receptors.
- NN is present in the ganglia, and NM in the neuromuscular Junction.
- Drugs blocking NN receptors are called ganglionic blockers.
- Drugs blocking NM receptors are called peripheral-acting skeletal muscle relaxants (SKMR), also known as non-depolarizing skeletal muscle relaxants, e.g., d-tubocurarine (d-TC).

Antimuscarinic Drugs / Anticholinergic Drugs 00:02:05

- These drugs block the muscarinic receptors.
- Atropine blocks M1, M2, M3, M4, and M5 receptors.
- The problem with Atropine is that all the muscarinic receptors are blocked.
- The source of Atropine is Atropa belladonna and Datura.

Anticholinergics their Targets, Effects, and Uses 00:04:10

- Different anticholinergic drugs, their affecting organs/systems, effects, and uses are discussed in the given table.

Refer Table 22.1

Important Information

- In COPD, the larger bronchioles are affected, and anticholinergic drugs better direct them.
- Trospium is preferred for an Alzheimer's disease patient with an overactive bladder.
- Fesoterodine is a pro-drug that gives rise to Tolterodine.

Problem Questions

Q. Why can Atropine not be used in treating COPD?

Ans. Firstly, Atropine is nonspecific and acts on all the receptors. The drug has to be receptor specific for COPD. Secondly, Atropine interferes with ciliary Motility. And it will not allow the secretion to clear properly. Therefore, specific drugs are used in the management of COPD and Asthma.

Q. A patient is given hyoscine for treating abdominal colic and spasms. After some time, he comes back with the problem that he cannot see things properly. What would be your diagnosis?

Ans. Hyoscine is an anticholinergic drug that causes temporary blurring of vision. The patient would be fine after some time.

Central anticholinergics

- For treating Parkinson's disease, Drug induced Parkinson's.
  - Benzhexol (Trihexyphenidyl)
  - Benztropine
  - Biperiden
  - Procyclidine

Glycopyrrolate

- Used as a Preanesthetic medication
- It is a quaternary compound that does not cross Blood Brain Barrier (BBB)

Use

- Decreases secretions from the stomach, salivary glands, and lungs.

Advantage

- Decreases the chance of aspiration pneumonia.
- Decreases reflex bradycardia (due to vagus stimulation)

Important Information

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Q. Why is Atropine not given as preanesthetic medication?
Ans: Atropine can cross the blood-brain barrier and causes delirium confusion-hallucination.

Atropine 00:33:30

Uses

- Heart: Manage bradycardia and AV Block.
- Poison: OP poisoning, carbamate poisoning, early mushroom poisoning.
- Eye:
  - Refractive error testing in children less than 5 yrs. The tone of ciliary muscles in children is very high, for which the most efficacious drug is required. Therefore, Atropine is preferred for refractive error testing.
  - As an eyedrop for fungal corneal ulcers to relieve ciliary spasm.

Important Information

- Atropine is not used in Organochlorine poisoning

Atropine Poisoning/Anticholinergic Overdose 00:36:40

- In atropine poisoning, patients may have the following conditions
  - Constipation
  - Urine retention
  - Mydriasis
  - Bronchodilation
  - Tachycardia
  - Decrease in secretions
  - Atropine fever
  - No sweating
  - Vasodilation causing flushing
  - 3 Cs (Convulsion, cardiotoxic, coma)

Atropine Fever

- Sympathetic fibres are cholinergic for sweat glands that release acetylcholine which acts on the M3 receptor and causes sweat. These are thermoregulatory sweat glands that increase sweating to bring the body temperature down.
- In atropine poisoning, the M3 receptor is blocked, and no sweating occurs. Furthermore, flushing occurs due to vasodilation to maintain the body temperature, which causes the patient to turn red and indicates fever.

Atropine Toxidrome

- Blind as Bat: Mydriasis and cycloplegia,
- Hot as Desert: Atropine fever,
- Mad as Hatter: Hallucination and confusion
- Dry as Bone: No secretions
- Red as Beet: Flushing

Important Information

- The antidote for atropine poisoning and Datura Poisoning is Physostigmine.

Anticholinergic Adverse Effect 00:43:20

- Dry mouth
- Blurring of vision
- Constipation
- Urinary retention
- Tachycardia

Contraindications of Atropine/Anticholinergics 00:44:10

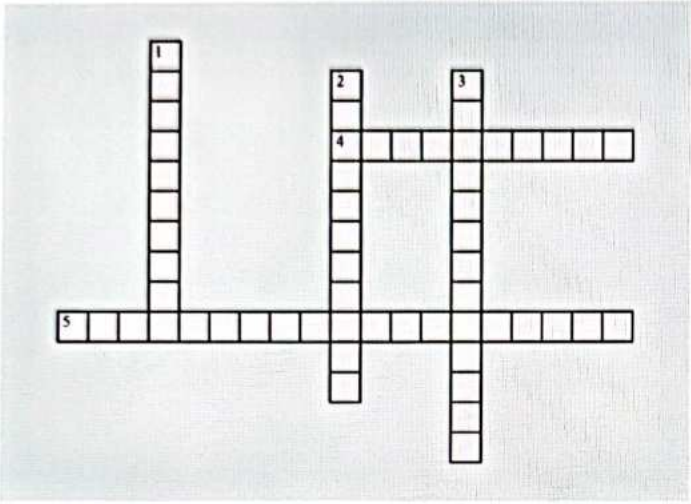
- **Elderly patients:** Occurrence of benign hypertropia of the prostate (BHP) in an elderly male patient causes urine to not come out due to a large prostate. These drugs cause further urine retention. Anticholinergics also cross BBB in the elderly and cause confusion or hallucination.
- **BHP**
- **Angle Closure Glaucoma (ACG):** The mydriatic drugs further close the angle between the iris and cornea, which may trigger (ACG).

Table 22.1

Target	Drug	Effect	Use
Central Nervous System	Atropine (atropine poisoning)	Excitement, Hallucination, and Delirium	
	Hyoscine (Scopolamine)	Sedation, confusion, and amnesia	Narco Analysis as a Truth serum in combination with Thiopentone.
Eye	Atropine (longest acting drug; 7-10 days), Homatropine (1-3 days), Cyclopentolate (24 hrs), Tropicamide (shortest acting drug 4-6 hrs)	Passive mydriasis, paralysis of accommodation (cycloplegia)	Refractive error testing and Fundoscopy
Mouth		Dryness of mouth	
Ear (Vestibular Apparatus)	Hyoscine (tab or patch)		Prevent motion sickness
Heart	Atropine	Increased heart rate and conduction (Adverse effect- Tachycardia)	Bradycardia and AV Block
Lungs	Ipratropium Bromide, Tiotropium bromide	Bronchodilation	Management of COPD (chronic obstructive pulmonary disease), Bronchial asthma
Stomach (M1 receptor is blocked)	Pirenzepine, Telenzepine	Decrease in HCl secretion	Gastritis or Peptic Ulcer Disease (PUD)
Intestine	Hyoscine, Clidinium, *Dicyclomine	Decrease in Motility, closure of sphincters	Abdominal colic/spasm Biliary colic/spasm *Dysmenorrhea (painful menstruation condition)
Urinary Bladder	Flavoxate, Fesoterodine **Mnemonic Friend DOST** • D - Darifenacin • O - Oxybutynin • S - Solifenacin • T - Trospium (quaternary compound) Tolterodine [fenacins (D, S) are Vesico-selective]	Urine retention	Overactive bladder (OAB)
	Valethamate Bromide		Cervical ripening (induction of labour)

CROSS WORD PUZZLES

Crossword Puzzle



Across

4. Anticholinergic drugs used to treat overactive bladder
5. Potential danger associated with anticholinergic drug use in the elderly

Down

1. Primary function of anticholinergic drugs.
2. Preferred anticholinergic drug when the objective is sedation
3. Common side effect of anticholinergic drugs

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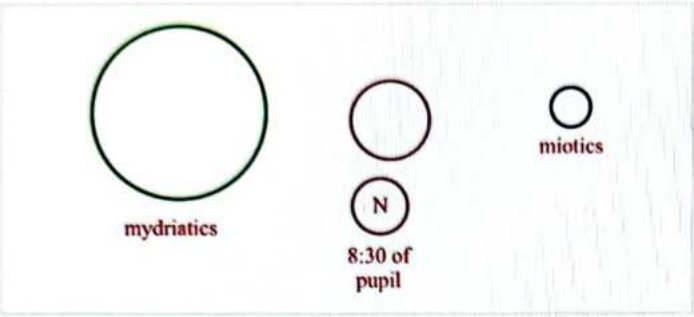
23 DRUGS ACTING ON EYE

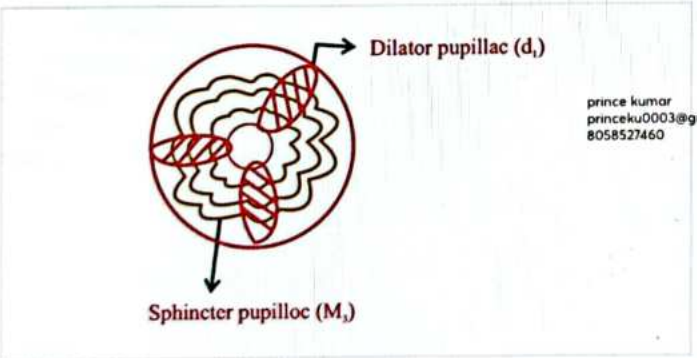
- Suppose this is the normal size of the pupil.



- If the drug increases the diameter of the pupil, we call it Mydriatics.
- If the drug decreases the diameter of the pupil, we call it Miotics.

Mydriatics & Miotics 00:01:05

- Consider the pupil of the eye which consists of two important muscles: -
  - The muscle that looks like the radial of a tire is known as Dilator Pupillae or radial muscles. They have a receptor called α_1.
  - The circular muscles present in the pupil are called Sphincter Pupilliae. They have a receptor called M_3.



- The constrictor pupillae tries to constrict while the dilator pupillae tries to dilate, resulting in a balance between them.
- For dilation, the dilator pupillae must be stronger and this can be achieved through the stimulation of the corresponding receptor. α_1 agonists such as Phenylephrine is used for this stimulation, and these are called Active mydriatics.
- M3 antagonist produces mydriasis this is called passive mydriasis
  - Any drugs that are mydriatics are contraindicated in Angle Closure Glaucoma, particularly those that have anticholinergic properties. Eg:- TCAs
- For constriction, we can use M_3 agonists such as Pilocarpine to produce active miosis.
  - M_3 receptor is also present in the ciliary muscle of the eye, which is responsible for accommodation. Thus, Pilocarpine also produces spasms of accommodation since it increases the tone of ciliary muscle.

Passive Mydriatics 00:03:43

- M_3 antagonists can be used as they block the action of sphincter pupillae. Thus, the dilator pupillae passively takes over and causes passive mydriasis.
  - When M_3 antagonists block M_3 in the ciliary muscle, paralysis of accommodation occurs, and it is called Cycloplegia (near objects are clear whereas far objects are blurred).
  - α_1 has no role on ciliary muscles.
  - M_3 antagonists that cause passive mydriasis are:
    - → Atropine → duration of action = 7-10 days (longest acting)
    - → Homatropine → Duration of action = 1-3 days
    - → Cyclopentolate → Duration of action = 24 hours/1 day
    - → Tropicamide → Duration of action = 4-6 hours (shortest acting)

Uses of Mydriatics 00:07:22

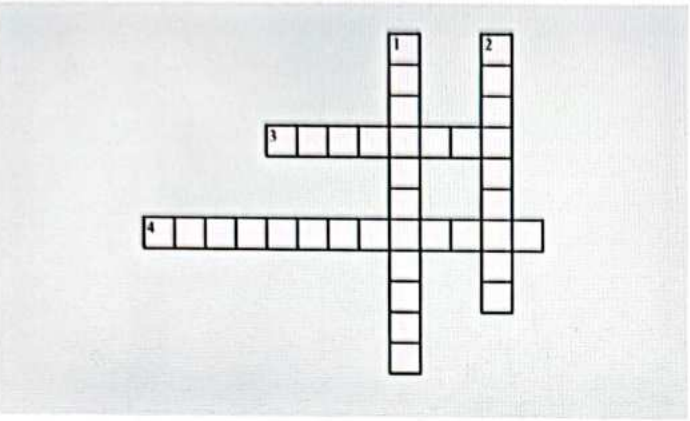
- They are used in 2 conditions: -
  - Fundoscopy
  - Refractive Error Testing
- Atropine is used as:-
  - Ointment in children < 5 years of age - This is because the ciliary tone is very strong at this age.
  - Eyedrops in case of Fungal corneal ulcer - it causes ciliary spasms, which are relaxed when given atropine and thereby reducing pain.
- Phenylephrine is used for Fundoscopy.
- Pilocarpine is used as:-
  - Eyedrops in cases of glaucoma
  - To break adhesions between the iris and cornea or iris and lens. Adhesions break when mydriatic and miotic are given alternatively.

Passive Miotics 00:10:21

- If the α_1 is blocked, the α-blockers produce passive miosis.
- For example, α-blockers such as Prazosin, Tamsulosin, etc.

CROSS WORD PUZZLES

Crossword Puzzle 1



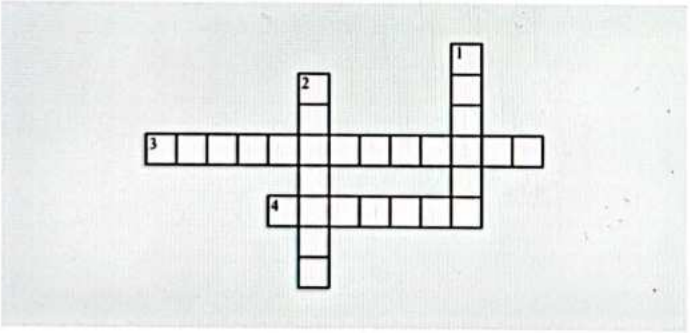
Across

3. Longest acting mydriatic is ____.
4. When M3 antagonists block M3 in the ciliary muscle, paralysis of _____ occurs.

Down

1. Shortest acting mydriatic is ____.
2. _____ break when mydriatic and miotic are given alternatively.

Crossword Puzzle 2



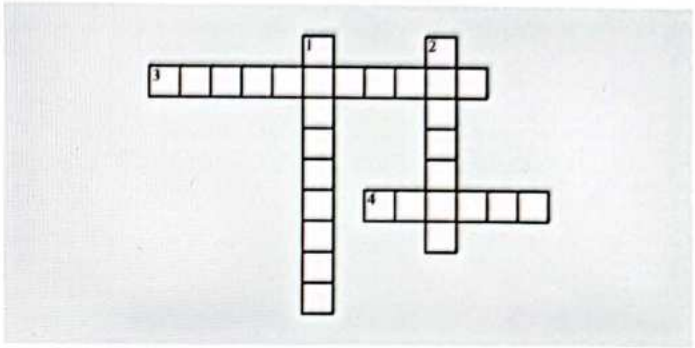
Across

3. _____ is used for Fundoscopy.
4. Antagonist producers cause ____ mydriasis.

Down

1. Agonist producers cause _____ mydriasis.
2. α 1 has no role on ____ muscles.

Crossword Puzzle 3



Across

3. paralysis of the accommodation is called _____.
4. The α -blockers produce passive ____ when α 1 is blocked.

Down

1. _____ Pupilliae have a receptor called M3.
2. The muscle that looks like the radial of a tire is known as _____ Pupillae.

24 DRUGS ACTING ON BLADDER AND BOWEL

Urinary Incontinence 00:01:05

- Patients with urinary incontinence (UI) cannot voluntarily control the urine.
- There are three types of UI:
  - Urge incontinence.
  - stress urinary incontinence.
  - Overflow urinary incontinence.

Urge Incontinence 00:02:00

- In urge incontinence, the problem is in the bladder because the detrusor is irritated. So, even if a small amount of urine is collected, there's a sudden urge to pass the urine.
- This condition is called an overactive bladder.

Treatment of Overactive Bladder (General Mechanism)

- The α1 receptors are present in the prostate and in the trigone of the bladder.
- The detrusor is supplied by β2 and β3 receptors, which are sympathetic. It is also supplied by the M3 receptor.
- When the detrusor is activated by β3, it relaxes. However, M3 causes its contraction.
- If α1 receptors are activated, then they cause constriction.
- Thus, when α1, β2, and β3 receptors are activated, it causes urinary retention.
- The M3 receptor (cholinergic) causes evacuation of the urine.
- To manage the overactive bladder, we can either give β2, and β3 receptor agonists or M3 antagonists.
- Thus, we can either use anticholinergic drugs (causing urinary retention) or β2 or β3 agonists.
- We should not use α1 agonists as it will block the urine completely.

Drugs for Overactive Bladder (OAB) 00:06:18

- The mnemonic that can be used to remember the drugs is "My friend DOST."
- **My**- Mirabegron and Vibegron (β3 agonists).
- **Friend**- Fesoterodine (prodrug of tolterodine) and Flavoxate.
- **D**- Darifenacin.
- **O**- Oxybutynin.
- **S**- Solifenacin.
- **T**- Trospium (It doesn't cross the blood brain barrier and doesn't cause anticholinergic side effects in the brain unlike the other drugs) and tolterodine
- All the above drugs are anticholinergics.
- Onabotulinum toxin A is another drug that is given locally to treat OAB. It acts by decreasing presynaptic acetylcholine release.

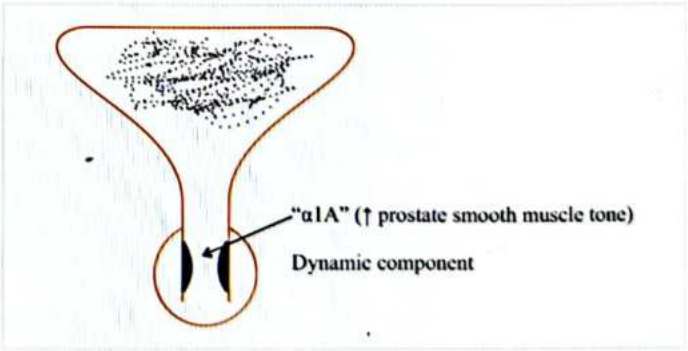
Stress Urinary Incontinence 00:09:37

- Whenever there's an increase in intra-abdominal pressure (due to coughing, sneezing, etc.), the sphincter won't be able to hold the urine, and it will pass through the urethra. This is called stress urinary incontinence.
- Sometimes, it also happens due to weak muscles of the pelvic floor.
- Treatment involves surgery and pelvic floor exercises.
- Drugs aren't very useful. However, Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI) that has additional muscarinic blocking properties, is used. Blocking the muscarinic receptor causes urine retention.

Overflow Incontinence 00:11:56

- The prostate enlarges in older men, which is called benign prostate hyperplasia (BPH).
- This closes the urine outlet. The urine accumulates, and there's an overflow.
- The patient cannot pass the urine completely.
- In cases of "atonic bladder," too, overflow incontinence occurs.
- Anticholinergics and atropine are contraindicated in overflow incontinence and BPH.

Treatment of BPH 00:13:48



- In BPH, there's an increase in the prostate's smooth muscle tone. This is maintained by the α1A receptor. This is known as the "dynamic component." Thus, α1 blockers like prazosin, terazosin, doxazosin, alfuzosin, and bunazosin are used to block the dynamic component. If the patient has both BPH and hypertension, then these are preferred, as they block both α1 and α2 receptors, except for alfuzosin, which is approved only for BPH.

- Another category of drugs to treat the dynamic component of BPH include α1A selective blockers like tamsulosin and silodosin. These are approved for BPH only, as they don't have an effect on the blood vessels. One of the adverse effects of tamsulosin is "intraoperative floppy iris syndrome" Most elderly patients have cataracts, and if they are already using tamsulosin, then this complication can occur. Thus, it needs to be stopped at least 15–20 days prior to cataract surgery.
- All of the above are the fastest-acting drugs for BPH.
- Also, when the prostate is enlarged, it is known as the "static component."
- In cases of prostate enlargement, surgery is the best option. However, sometimes the patient cannot go for surgery.
- In such cases, we can reduce the prostate's size with drugs like finasteride and dutasteride. These drugs prevent the conversion of testosterone to dihydrotestosterone (DTH), which is responsible for the enlargement of the prostate, by blocking the enzyme 5 α reductase. However, these take time to decrease the prostate's size and are slower-acting drugs.
- Terazosin and doxazosin have quinazoline moieties that have been shown to produce prostate smooth muscle apoptosis.

Atonic Bladder 00:21:42

- An atonic bladder is due to the nerves not working properly and preventing the contraction of the bladder.
- The drugs used to treat an atonic bladder include M3 receptor agonists.
- Examples of drugs used to treat atonic bladder are as follows:
  - Bethanechol.
  - Neostigmine (Anti-Cholinesterase).
  - Pyridostigmine.

Post-Operative Issues 00:22:58

- There are two post-operative issues: post-operative urine retention and post-operative paralytic ileus.
- The patient is given anesthesia during the surgery. This reduces the GIT and bladder motility.
- Usually, after some time, the patient passes the urine. If it isn't passed, then the patient has postoperative urinary retention. The drugs used in these conditions are bethanechol, neostigmine, and pyridostigmine.
- **Case 1:** The patient had a history of bronchial asthma and post-operative retention. What would be the treatment given to the patient, bethanechol or tamsulosin?
  - **Answer:** Bethanechol is a cholinergic drug and can cause bronchoconstriction. This can worsen asthma. Thus, tamsulosin is used as an off-label drug in postoperative urine retention as it blocks the α1 receptor.

Summary 00:26:42

- For the urge or OAB, the treatment drugs can be remembered by the mnemonic "My friend DOST."
- For stress urinary continence, treatment includes surgery, pelvic floor exercise, and duloxetine.
- Any drug that causes urinary retention should not be used in overflow incontinence because there's already urinary retention. Thus, bethanechol, neostigmine, and pyridostigmine are used.
- For BPH, treatment includes α1 blockers and α1A selective blockers. The slow-acting drugs are 5 α reductase inhibitors.
- In postoperative urine retention and paralytic ileus, we can use bethanechol, neostigmine, and pyridostigmine.
- If the patient has asthma and postoperative urine retention, then we can use tamsulosin because it is an α1 receptor blocker and is an off-label treatment.

MCQ 00:27:37

Q. A 30-year-old male had an UTI and complained of a frequent and sudden urge to urinate that was difficult to control. His treating physician gave him antibiotics and wanted to control this symptom, so he started following therapy for his symptoms. Which drug was given?

a. Bethanechol.
b. Flavoxate.
c. Finasteride.
d. Flutamide.

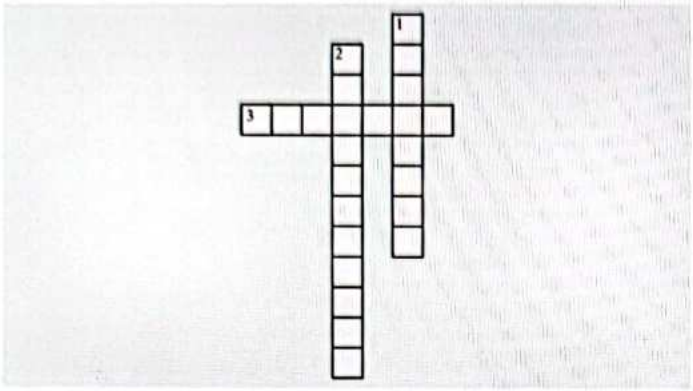
Ans: B. flavoxate.

Explanation:

- It is a case of OAB. He was given antibiotics to control the symptoms. Bethanechol is an M3 agonist and increases the urine evacuation, so it cannot be used. Flavoxate is a M3 receptor antagonist and is used to treat OAB. Finasteride is a 5 α reductase inhibitor used to treat BPH. Flutamide is an androgen receptor blocker used to treat prostate cancer.

CROSS WORD PUZZLES

Crossword Puzzle 1



prince kumar
princeku0003@gmail.com
8058527460

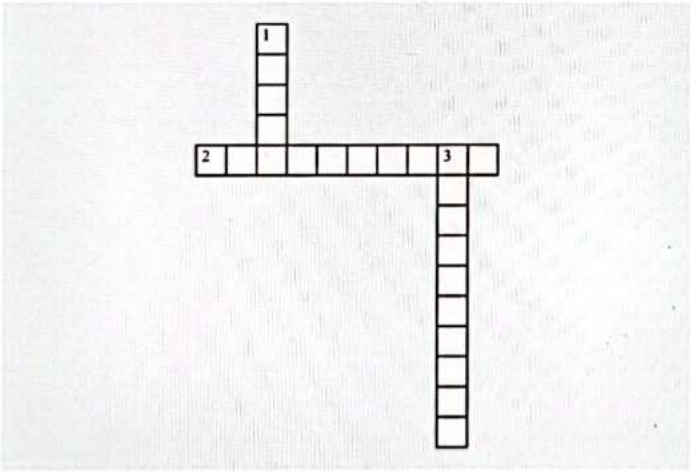
Across

3. _____ incontinence (UI) means the patient cannot voluntarily control the urine.

Down

1. _____ is irritated in the urge incontinence.
2. _____ of detrusor occurs via M3 receptor activation.

Crossword Puzzle 2



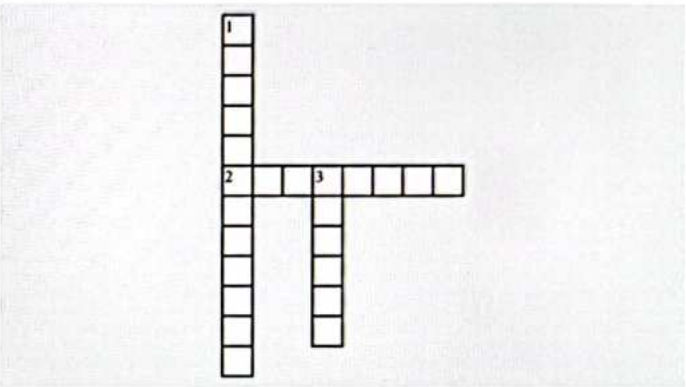
Across

2. _____ of the urine is caused by the M3 receptors.

Down

1. _____ 1 agonist are not used in overactive bladder as they will block the urine completely.
3. _____ bladder can be managed either by β2, and β3 receptor agonists or M3 antagonists.

Crossword Puzzle 3



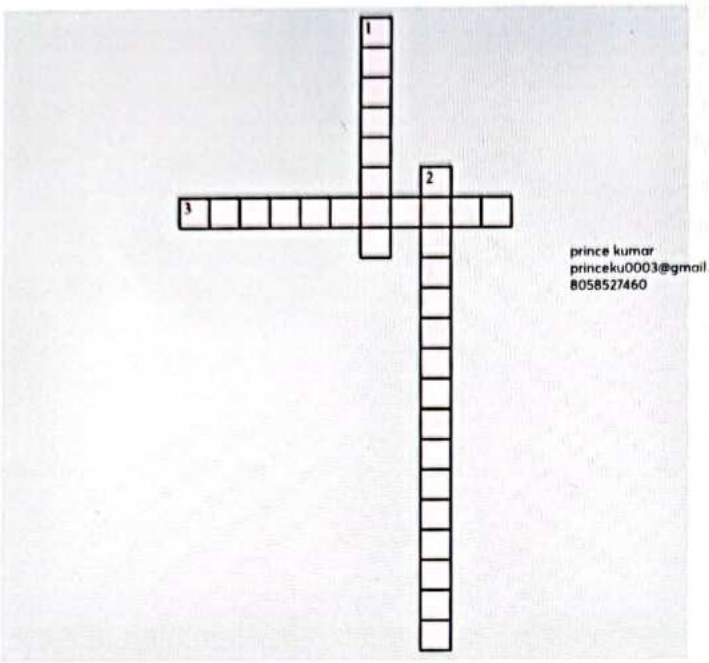
Across

2. _____ doesn't cross the blood brain barrier and doesn't cause anti-cholinergic side effects in the brain unlike the other drugs.

Down

1. _____ toxin A is another drug that is given locally to treat OAB.
3. _____ urinary incontinence treatment involves surgery and pelvic floor exercises.

Crossword Puzzle 4



Across

3. _____ a selective serotonin reuptake inhibitor (SSRI) that has additional muscarinic blocking properties, is used in stress urinary incontinence treatment.

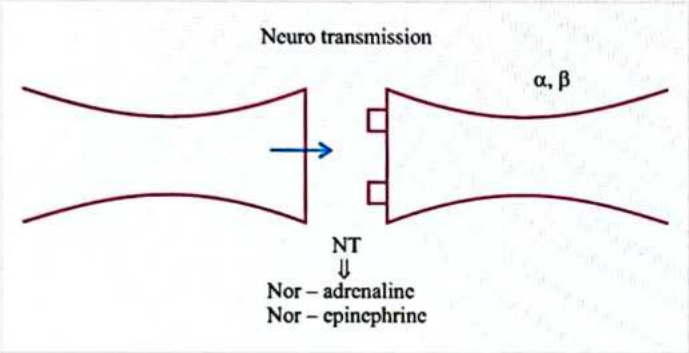
Down

1. _____ enlarges in older men, which is called benign prostate hyperplasia.
2. _____ and atropine are contraindicated in overflow incontinence and BPH.

25 INTRODUCTION TO ADRENERGIC DRUGS

- Adrenergic drugs are also known as sympathetic drugs.
- The sympathetic system is for emergency situations.
- It is responsible for fight, flight and freight response and also induces anxiety.
- In the heart it increases HR, conduction and force of contraction.
- In the eye it causes mydriasis.
- In the bowel and the bladder, it decreases evacuation.
- In Penis, it is responsible for ejaculation.

Neurotransmission 00:02:40



- The major neurotransmitter in the sympathetic system is nor-adrenaline which acts on alpha and beta receptors.
- In renal and mesenteric blood vessels, the neurotransmitter is dopamine, which acts on D1 receptors.
- The adrenal medulla is modified ganglia with acetylcholine as a neurotransmitter.
- Thermo-regulatory sweat glands the neurotransmitter is acetylcholine.

Receptors in the Sympathetic System 00:05:10

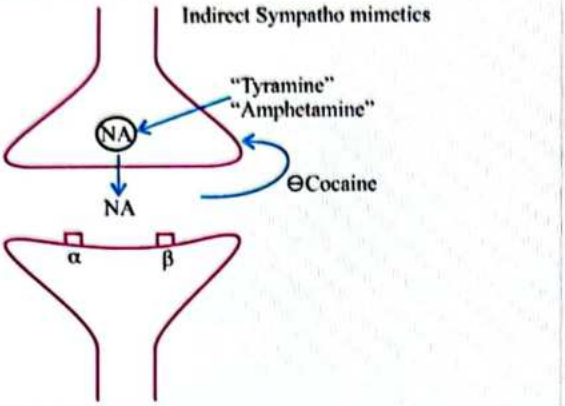
- α1
- α2
- β1
- β2
- β3
- D1
- D2

Neurotransmission in Sympathetic System 00:05:45

Refer Diagram 25.1

- In the presynaptic terminal,
- Tyrosine is obtained from phenylalanine.
- The enzyme hydroxylase converts tyrosine into DOPA, and the enzyme decarboxylase converts DOPA into dopamine.
- Vesicular monoamino transporter 2 (VMAT 2) transports dopamine into the vesicles.
- Dopamine inside the vesicle will get converted to NA with help of hydroxylase.
- Entry of Na+ and Ca2+ will fuse with the vesicle and signal the release of NA.
- NA acts on the receptors Alpha and Beta on the postsynaptic terminal and will not stay for a long period.
- The action of NA is terminated by uptake.
- The process of uptake is done by a transporter known as nor-adrenaline transport (NAT).
- The NA is again stored inside the vesicles with the help of VMAT 2.
- The NA put inside the presynaptic membrane can be metabolized by the enzyme monoaminoxidase (MAO), and its level can be depleted.
- Some of the NA can leak and get metabolized by the COMT enzyme.
- When NA is given through the blood vessels, the enzyme COMT metabolizes it faster than MAO.
- In synapse, the majority of NA is taken up by uptake and remaining is metabolized by MAO.
- The rate limiting step here is the conversion of tyrosine into DOPA.
- If this is slow, the synthesis of NA is affected.
- Pheochromocytoma is a tumor of adrenal gland where there is excessive synthesis of NA and adrenaline.
- This can be prevented by giving a drug Metyrosine that inhibits the enzyme Tyrosine hydroxylase.
- Carbidopa and Benserazide inhibit the decarboxylase and used in the treatment of Parkinson's disease
- Reserpine is a VMAT 2 inhibitor used in the treatment of hypertension.
- It leads to the depletion of NA by MAO, which causes depression. This leads to the risk of suicide.
- MAO inhibitors are used to treat depression by decreasing the depletion of NA
- NAT inhibitors
  - TCA: Tricyclic antidepressants.
  - SNRIs: Serotonin nor-adrenaline reuptake inhibitors
  - Cocaine is abused as it increases sympathetic activity, and the individual always wants to party.
- Bretylium and Guanethidine inhibit the release of nor-adrenaline, that is these do not allow the release of NA from pre-synaptic terminal.

Indirect Sympathomimetics 00:18:10



- Tyramine and amphetamine, and cocaine are not acting directly on alpha and beta receptors.
- These drugs increase NA, which acts on alpha and beta receptors. These are called indirect sympathomimetics.

Receptors in the Sympathetic System 00:19:50

- α1 = Gq coupled receptor- Acts through IP3/DAG
- α2 = Gi- Decreases cAMP
- β1 = Gs- Increases cAMP
- β2= Gs- Increases cAMP
- β3= Gs- Increases cAMP
- D1= Gs- Increases cAMP
- D2= Gi- Decreases cAMP
- All the receptors are mainly G protein coupled receptors.
- Alpha 1 causes contraction.
- Alpha 2 is inhibitory in nature.
- D1 is in CVS
- D2 is in CNS

Alpha Receptors 00:22:30

- Alpha receptors have two types: alpha 1 and alpha 2

Alpha 1 Receptors

Eye

- It is present in the eye.
- Alpha 1 agonists cause active mydriasis by acting on the Dilator pupillae, which is required in a fundoscopic or retinoscopic examination.
- Alpha 1 agonists cause vasoconstriction of the ciliary blood vessels and decrease aqueous humor production. Hence, it is used in the treatment of glaucoma.

Blood vessels

- In the blood vessels, Alpha is responsible for vasoconstriction and beta 2 is for vasodilation.
- Alpha 1>>> Alpha 2>>> Beta 2
- Alpha 1 is major in control while Beta 2 is minor in the blood vessels.
- When the action is on alpha 1 and alpha 2 the total peripheral resistance increases, resulting in an increased BP.
- So, the drugs that stimulate alpha receptors (mainly alpha 1) are used to treat hypotension.
- The role of beta 2 in blood vessels is not significant clinically. Its actions come into play during emergencies.

Bladder

- Alpha receptors also play an important role in the trigone of bladder and male prostate.
- The trigone of the bladder and the sphincters are controlled by alpha 1.
- When alpha 1 constricts, it leads to urine retention.
- The detrusor muscle of the bladder has beta 2 and beta 3 receptors, causing relaxation of the detrusor muscle and resulting in urine retention.

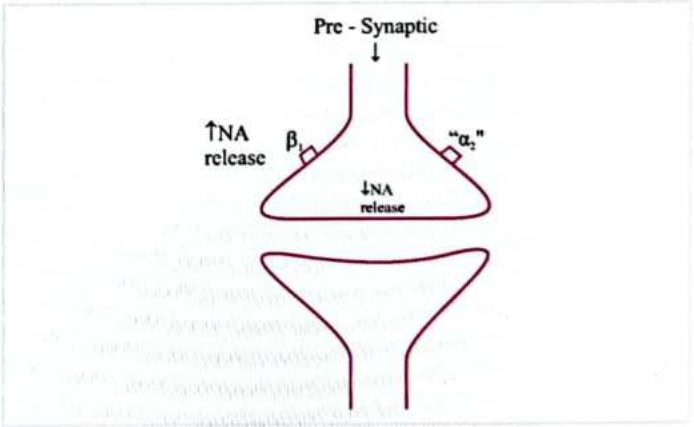
Male reproductive system

- Seminal vesicles and the vas deferens are also supplied by alpha 1 and are responsible for ejaculation.

Alpha 2 Receptors 00:29:17

Presynaptically

- The role of alpha 2 is to decrease the release of NA.
- Presynaptically beta 1 increases the NA release.



Post synaptically

- Alpha 2 is present in the following:
  - Blood vessels causing vasoconstriction
  - Pancreases causing decreased insulin release.
  - Kidney causing decreased renin release. (Beta 1 modulates the release of Renin).
  - Ciliary epithelium in the eye causing decrease in cAMP and reduced aqueous humour production

Beta Receptor 00:33:25

Beta 1 receptors

- The major location is in the Heart.
  - When nodal tissue is stimulated, it causes an increase in HR and conduction.

- When the cardiac muscle is stimulated, it causes an increase in the force of contraction.
- It can act on both atria and ventricles.

- In the kidney
  - Located in JG cells
  - When there is a fall in BP and decrease in renal blood follow. Beta receptors in JG cells are activated and cause an increase in Renin release.
- In CNS
  - It causes anxiety, increases attention, increases alertness and anorexia.
- In ciliary epithelium of eye
  - Increases cAMP and increases aqueous humour production
  - Beta blockers are used to treat glaucoma to reduce aqueous humour production.

Beta 2 receptors 00:38:20

- In smooth muscle
  - Beta 2 causes relaxation of smooth muscles by increasing cAMP.
  - Bronchus- Bronchodilation
  - Blood vessels- Vasodilation
  - Intestines- Relaxation leading to constipation
  - Detrusor muscle- Relaxation leading to urine retention
  - Uterus- Relaxation during preterm delivery
- In liver
  - They cause glycogenolysis leading to increased glucose

- In Pancreases
  - Cause mild increase in the insulin. The penultimate action of sympathetic is to cause hyperglycemia.
- In skeletal muscles
  - Increases blood flow and increases exercising capacity
  - Cause tremors
- Sympathetic drugs push the potassium ions into the cells, resulting in hypokalemia. Example, adrenaline.
- In ciliary epithelium of eye
  - Increases cAMP and increases aqueous humour production

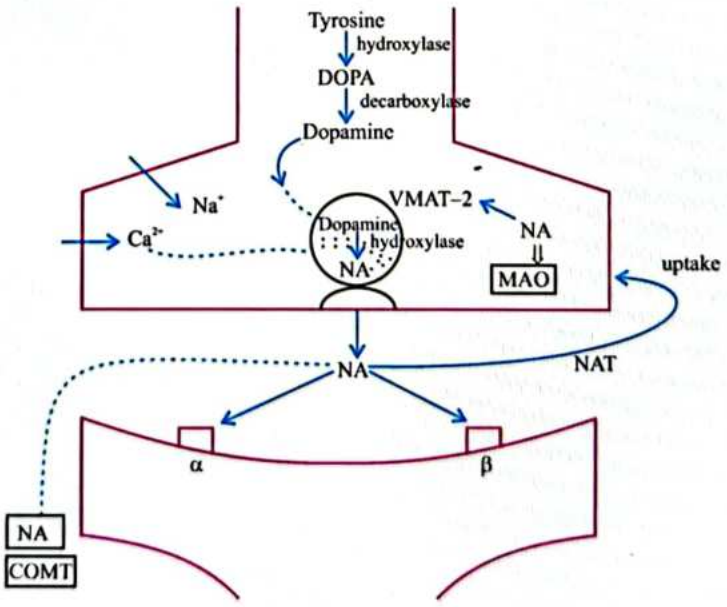
Important Information

- Beta 1 causes cardiac muscle contraction by increasing cAMP.

Beta 3 receptor 00:46:00

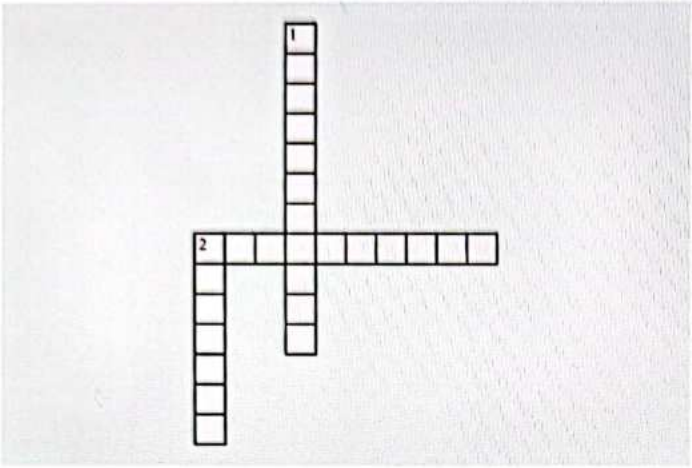
- It is mainly located in the adipose tissue
  - It causes lipolysis and increases the FFA (free fatty acids).
- The lipolysis is more significant in brown fat (adipose tissue).
- As the person becomes an adult, the brown pad is less, so beta 3 agonists are not successful in treating obesity in adults.
- In the detrusor, it can relax the bladder.

Diagram 25.1



CROSS WORD PUZZLES

Crossword Puzzle 1



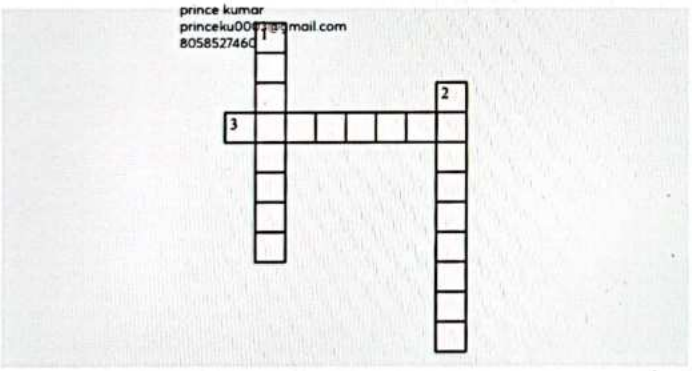
Across

2. _____ drugs are also known as sympathetic drugs.

Down

1. _____ system is for emergency situations.
2. _____ medulla is modified ganglia with acetylcholine as neurotransmitter

Crossword Puzzle 2



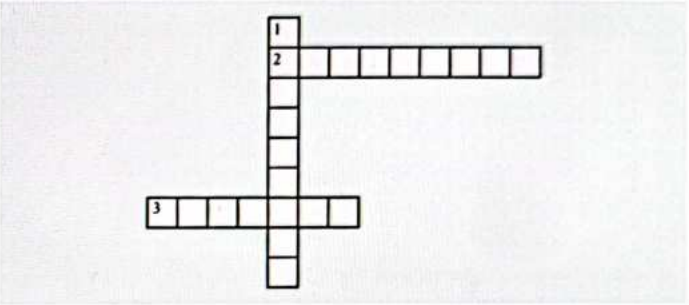
Across

3. _____ is the neurotransmitter in mesenteric blood vessels.

Down

1. _____ is obtained from phenylalanine.
2. _____ monoamino transporter 2 (VMAT 2) transports dopamine into the vesicles.

Crossword Puzzle 3



Across

2. _____ is a VMAT 2 inhibitor used in the treatment of hypertension.
3. _____ is abused as it increases sympathetic activity.

Down

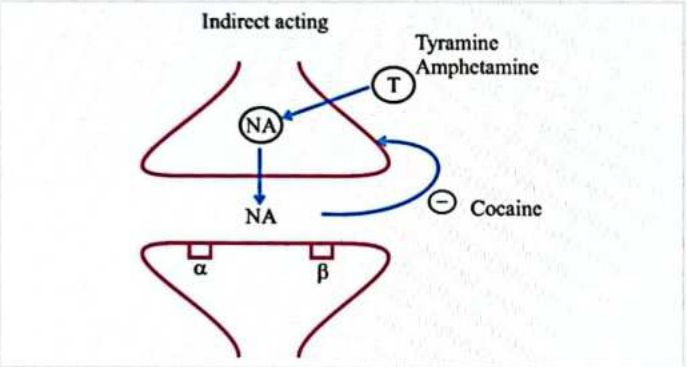
1. _____ and Guanethidine inhibit the release of noradrenaline

26 ADRENERGIC DRUGS AND CATECHOLAMINES

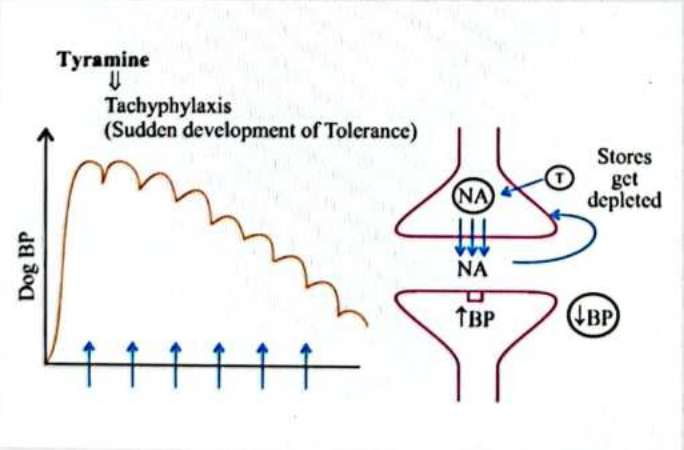
- Adrenergic drugs are those drugs that mimic or interfere with the functioning of the sympathetic nervous system by affecting the release or action of norepinephrine and epinephrine.
- Adrenergic drugs are classified into three types:
  - Direct acting
  - Indirect acting
  - Mixed acting drugs or sympathomimetics.

Indirect Acting Sympathomimetics 00:02:00

- Examples- Tyramine, Amphetamine, Cocaine.
- Indirect-acting drugs not directly acting on the α and β receptors.



- When Tyramine, Amphetamine is given, enters inside the presynaptic terminal releases nor-adrenaline from the synaptic vesicles, and acts on the α and β receptors.
- Tyramine causes tachyphylaxis (sudden development of tolerance).



- One experiment was conducted on a dog to evaluate the effect of tyramine on a dog's heart.
- Initially, tyramine increased the BP with an increase in the dose because of indirect-acting sympathomimetic.
- After multiple doses of tyramine, BP fell down because of rapid tolerance and nor-adrenaline stores were depleted and nor-adrenaline was not able to release from the vesicles. As a result, the BP fell down. This is an example of Tachyphylaxis.
- Cocaine inhibits the uptake of nor-adrenaline.
- Tachyphylaxis means rapid development of Tolerance.

Mixed-Acting Sympathomimetics 00:06:20

- These drugs can either act directly on α and β receptors or by the release of nor-adrenaline.
- Examples- Ephedrine obtained from plants, Pseudoephedrine, and Mephenteramine.
- These drugs are mainly used in the treatment of hypotension.
- Pseudoephedrine is used as the nasal decongestant.

Direct Acting Sympathomimetics

- These drugs are divided into two categories- Catecholamines and Non-catecholamines.
- Catecholamines are further divided into endogenous and synthetic or exogenous drugs.
- Endogenous drugs- Dopamine, Adrenaline, Nor-adrenaline.
- Synthetic or exogenous drugs- Fenoldopam, Dobutamine, Isoprenaline, Dopexamine.

Catecholamines

- Catecholamines are metabolized by the enzyme COMT and MAO.
- Catecholamines cannot be administered in oral form and can't enter the brain because of metabolism by COMT.
- Catecholamines are short-acting and used in the parenteral form for emergency conditions.

Fenoldopam 00:12:15

- Fenoldopam is D1 and α2 agonists.
- D1 receptors are located in the kidney and mesenteric blood vessels.
- Fenoldopam stimulates the D1 receptor and causes vasodilation in the kidneys which increases renal blood flow and glomerular filtration rate.
- In hypertension, the peripheral blood vessels are constricted which increases the pressure. If mesenteric blood vessels are dilated, the pressure from the periphery comes to the mesenteric that results in decrease in BP.
- α2 agonist decreases the BP because α2 receptor decreases the nor-adrenaline release.
- **Uses**

- Fenoldopam is used in the management of hypertension emergencies and hypertension emergencies with oliguria.

Dobutamine 00:14:50

- Dobutamine mainly acts on β1 receptors (mainly stimulates muscles than nodes).
- Dobutamine is also α1 and β2 agonists.
- Dobutamine is known to mildly decrease total peripheral resistance and blood pressure because of β2 action.
- It increases the cardiac output which results in an increase in BP.
- **Uses**
  - Dobutamine is used in the management of cardiogenic shock with BP maintained.
  - Acute CHF
  - Dobutamine in low doses causes an increase in CO and ejection fraction (EF) but not heart rate.
  - Used in cardiac stress testing (stress test that shows how the heart works during physical activity. Exercise makes the heart pump harder and faster. A stress test can show problems with blood flow within the heart) in high doses.
- **Adverse effects**
  - Risk of arrhythmia because it increases the heart rate.

Dopamine

- In the low dose, 1-2 μg/kg/min acts on the D1 receptor that can increase RBF and GFR but decrease BP.
- In the intermediate dose, 2-10 μg/kg/min acts on the β1 receptor and D1 receptor.
- Due to β1 action, increases CO and EF and systolic BP.
- Dopamine does not cause tachycardia because it majorly acts on muscle tissues more than nodal tissue.
- **Uses**
  - Cardiogenic shock with oliguria because it increases GFR to correct oliguria and force of contraction.
- If dopamine is used in a dose of more than 10 μg/kg/min, acts on α1 which increases the BP.
- If dopamine is used in a dose of more than 10 μg/kg/min, it acts on the D1 receptor which increases GFR and decreases BP and on the β1 receptor it increases CO and Systolic BP.
- **Uses**
  - Cardiogenic shock or septic shock with hypotension.
- Risk of arrhythmia increases in high doses.

Dopexamine 00:25:10

- Dopexamine is D1, D2, and β2 agonists.
- Inhibits catecholamine uptake which increases nor-adrenaline activity.
- **Uses**
  - Used in CHF with low cardiac output.
  - It increases stroke volume and decreases systemic vascular resistance because of β2 action.

Isoprenaline or Isoproterenol

- It acts only on β1 and β2 receptors. No α action.
- When it acts on the β1 receptor, it increases heart rate, conduction, and force of contraction.
- **Uses**
  - Management of bradycardia, and heart block.
- When it acts on the β2 receptors, it causes vasodilation and bronchodilation.
- It is not used in the treatment of asthma because it increases heart rate.
- It causes vasodilation. So, it cannot be used in patients with hypotension.

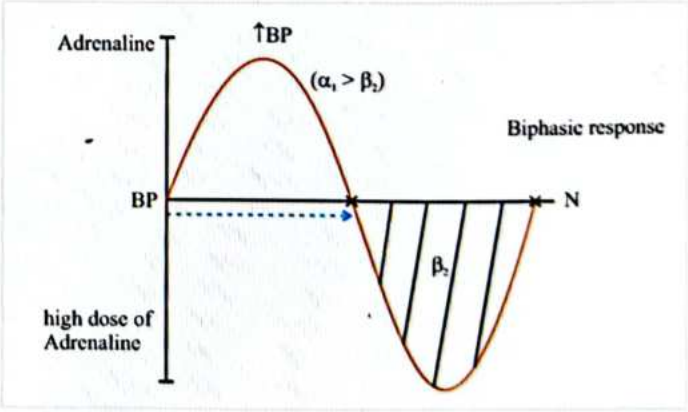
Adrenaline or Epinephrine 00:29:00

- It acts α1, α2, β1, β2 but weak β3 action.

- **Adverse effects**
  - Increases BP
  - Increased risk of arrhythmias
  - Stroke
  - Vasoconstriction

- When adrenaline is used in high doses, stimulates the α1 receptor (less sensitive to adrenaline) and causes vasoconstriction which increases peripheral resistance and diastolic blood pressure.

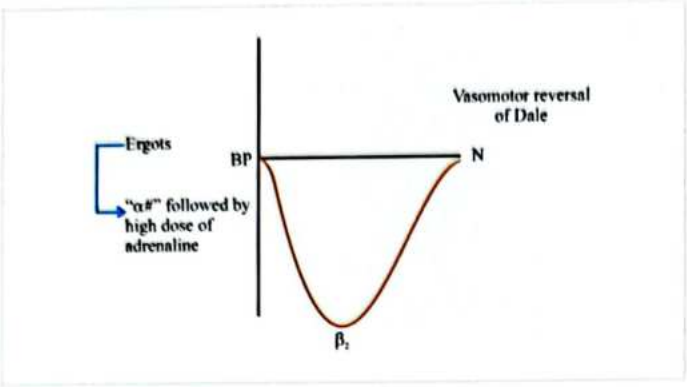
- When adrenaline is used in low doses, stimulates the β2 receptor (more sensitive to adrenaline) and causes vasodilation which decreases peripheral resistance and diastolic blood pressure.



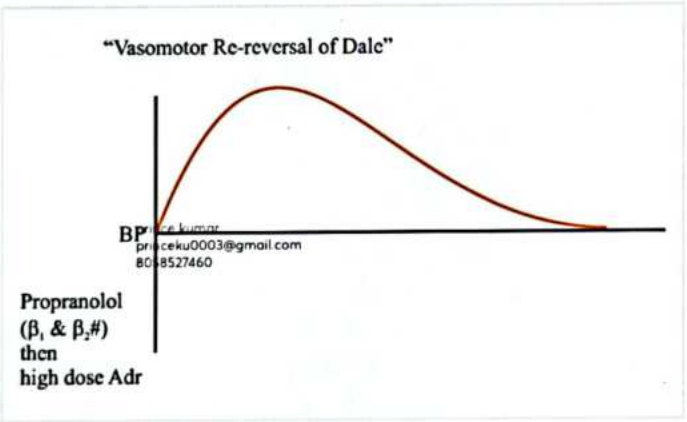
- When a high dose of adrenaline is administered to the animals, increases BP initially (adrenaline acts on the α1 receptor more than β2) but after some time BP decreases. This response is called a Biphasic response.

- As time passes, adrenaline passes out from the body and α1

can't be activated. As a result, β2 shows action by decreasing BP.



- Sir Henry Dale performed the same experiment by giving α blocker followed by a high dose of adrenaline.
- In this case, blood pressure suddenly falls down because the α receptor is blocked.
- From this theory, he found that there are certain receptors that are responsible for decreasing the BP which lead to the discovery of β receptor.
- He used ergot because they had α blocker property.



- Vasomotor Reversal of Dale- In this experiment, propranolol (β1+ β2 blocker) is used before high dose of adrenaline given to animals. It does not cause a decrease in BP, BP will shoot up.
- It is used in the treatment of Pheochromocytoma (tumour of the adrenal gland, high level of adrenaline), and BP is high in these patients.
- In this condition, BP is first managed by α blocker followed by β blocker.
- If β blocker is used first, it shoots up the BP and α receptor can get activated which may result in a stroke. So, α blocker is used first for seven days then followed by β blockers.
- α blocker (phenoxybenzamine) followed by propranolol.

Uses

- Adrenaline acts on all the receptors, it is used in diluted form.
- Ratio- 1:1000 (1-gram adrenaline in 1000 ml of water)- used in anaphylactic shock.
- The intramuscular route is preferred because, in shock condition, blood flow is decreased to the periphery.
- Subcutaneous route has less blood flow than the intramuscular route.
- If the patient does not respond to the IM route in anaphylactic shock then IV route can be preferred.
- Blood vessel is constricted and no bleeding will occur.
- 0.3-0.5mg drug is used and vastus lateralis muscle is used because of good absorption.
- Dose of adrenaline in a child <10 kg is 0.01ml/kg.
- 10-25 kg is 0.15 mg, 25-50 kg is 0.3 mg, and >50 kg is 0.5 mg.
- Histamine causes bronchospasm.
- Physiological antagonist for histamine is adrenaline.
- It is used as nebulization in croup and bronchospasm due to anaphylaxis.
- DOC for anaphylactic shock is adrenaline.
- 1:10000 dilution, IV/Intra-osseous/Endotracheal, is used in CPR (Cardiac arrest), Anaphylactic shock.
- 1:50000 dilution to 1:200000 dilution is used for local anaesthesia (lignocaine + adrenaline).
- When adrenaline is given locally, constricts the blood vessel and lignocaine is not absorbed.
- **Adverse effects**
  - Increases BP because it acts on all the receptors
  - Risk of increase in arrhythmia
  - Stroke
  - Vasoconstriction

Nor-Adrenaline or Nor-Epinephrine 00:51:45

↑V.C → ↓ → ↑TPR → ↓ → ↑DBP

Cardiac Muscle → ↓ → ↑CO → ↓ → ↑SBP

Nodal ⟶ Initially ↑HR

$MAP = \frac{2}{3}DBP + \frac{1}{3}\uparrow$ MAP → Tissue perfusion

↑

Monitor

- It acts on α1, α2, and β1 receptors (no/weak action on β2 receptor).
- It is not used in anaphylactic shock because it has no action on the β2 receptor.
- It causes vasoconstriction which increases total peripheral resistance and diastolic blood pressure.
- B1 increases cardiac output and systolic blood pressure in cardiac muscles.
- When diastolic and systolic pressure is increased, causes mean arterial pressure

- ⅔ of diastolic blood pressure and ⅓ of systolic blood pressure increases mean arterial pressure.
- Monitoring of mean arterial pressure (MAP) is important. If the mean arterial pressure is improved, it indicates the drug is working.
- MAP indicates tissue perfusion.
- Infusion of nor-adrenaline initially increases the heart rate in nodal tissue.
- When the BP is too high or MAP increases too much, the carotid and aortic body senses this change, transfers this signal to the brain.
- Vasomotor centres work into this and stimulate parasympathetic fibres.
- Parasympathetic fibres release acetylcholine that will act on M2 on the heart resulting in decrease in heart rate. This mechanism is called reflex bradycardia.

Golden point

- If atropine is given to the patient first then nor-adrenaline is given. It will only result in tachycardia because atropine is an M2 blocker.
- If nor- adrenaline is given to a transplanted heart patient, the reflex mechanism will not occur because parasympathetic nerves are not there in transplanted heart. As a result, only tachycardia will be seen.
- **Uses**
  - Drug of choice in cardiogenic shock, neurogenic and septic shock (vasopressor)
  - Drug of choice for shock with hypotension.
  - Acute CHF

Blood Pressure

- Stimulation of Beta 1 receptors increases HR and CO which causes increase in systolic BP.
- Diastolic BP depends on blood vessels.
- Alpha 1 in BV causes vasoconstriction, leads to increase in total peripheral resistance and causes increased Diastolic BP.
- Beta 2 receptors cause vasodilation and decrease in total peripheral resistance and cause decreased diastolic BP.
- When diastolic BP raises, there's activation of parasympathetic releasing Ach acting M2 and reduces HR
- When diastolic BP falls, there is activation of sympathetic releasing Noradrenaline acting on beta 1 and increases HR.

$$MAP = \frac{2}{3} DBP + \frac{1}{3} SBP$$

↓

Tissue perfusion

Pulse pressure = SBP-DBP

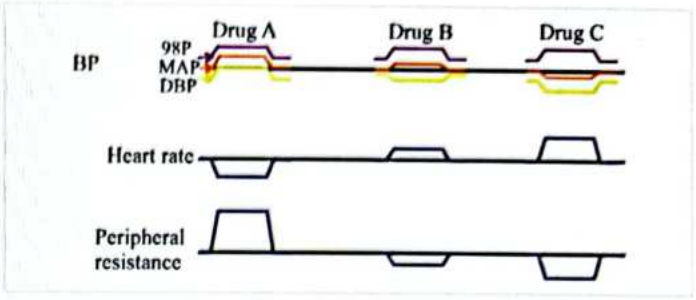
Effects of NA, Dobutamine and Isoprenaline 01:06:50

Adrenaline

Refer Table 26.1

Important Questions 01:14:40

Q. Identify the graph.



Ans:

- Drug A is noradrenaline, which raises the overall pressure.
- Isoprenaline is drug C because it has a greater effect on the beta-2 receptor (lower DBP is extremely high) and decreases peripheral resistance.
- Drug B is adrenaline because it increases MAP more than isoprenaline, isoprenaline cannot increase MAP.

Q. Catecholamines are metabolized by the enzyme

Ans: COMT and MAO.

Q. Catecholamines cannot be administered in oral form and can't enter the brain because of

Ans: Metabolism

Q. Tyramine causes

Ans: Tachyphylaxis (sudden development of tolerance).

Q. Fenoldopam stimulates the D1 receptor and causes vasodilation in the kidneys, which increases

Ans: Renal blood flow and glomerular filtration rate.

Q. Dobutamine mainly acts on

Ans: β-1 receptors (which mainly stimulate Cardiac muscles rather than nodes).

Q. Fenoldopam is used in the management of

Ans: Hypertension emergencies and hypertension emergencies with oliguria.

Q. Identify the drug

V.C = ↑TRP = ↑DBP

↑

High dose = α_1 [less sensitive]

Low dose = β_2 [more sensitive]

↓

V.D = ↓TPR = ↓DBP

Ans: Adrenaline

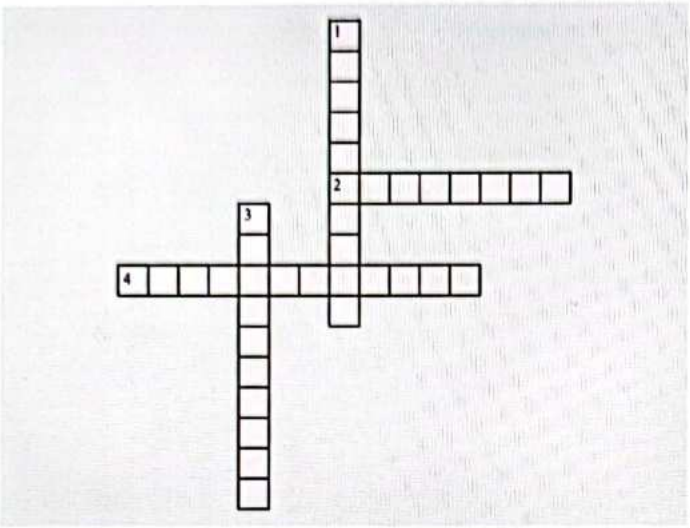
Q. DOC for anaphylactic shock is
Ans: Adrenaline.

Table 26.1

Adrenaline		SBP	DBP	MAP	Direct [HR]	Indirect [HR]	Result
High dose [b_1 & a_1]	NA [$a_1a_2b_1$]	↑SBP	↑DBP	↑MAP	↑HR	↓↓HR	↓↓HR
[medium dose] b_1,a_1=↑DBP b_2=↓DBP	Dobutamine [b_1, weak b_2]	↑SBP	↓DBP [mild]	No	↑HR	-↑[mild]	↑HR
Low dose [b_1,b_2]	Isoprenaline [b_1=b_2]	↑SBP	↓DBP	↓MAP	↑HR	↑HR	↑↑HR

CROSS WORD PUZZLES

Crossword Puzzle 1



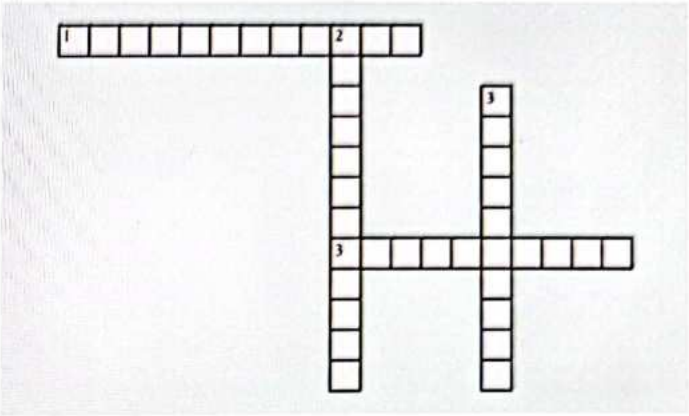
Across

2. _____ is used in cardiac stress testing.
4. _____ is a type of synthetic sympathomimetics.

Down

1. _____ is a D1 agonist as well as a D2 agonist.
3. _____ is the DOC for anaphylactic shock.

Crossword Puzzle 2



Across

1. _____ acts only on β-1 and β-2 receptors.
4. _____ is used in the treatment of pheochromocytoma.

Down

2. _____ is used in the management of bradycardia, and heart block.
3. _____ is used in CHF with low cardiac output.

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27 ADRENERGIC DRUGS AND NON CATECHOLAMINES

- Non-catecholamines fall under the category of direct acting drugs.

Non-Catecholamines 00:00:08

β1 Agonist

Prenalterol

- Prenalterol is an investigational drug.
- It is not still approved, it is being investigated for β-blocker toxicity and other conditions.
- Now it is investigated for β-blocker toxicity.

Dobutamine

- Another drug is Dobutamine.
- It is β1-agonist and is catecholamine.
- β1-action only, it does not have an action on the Dopamine receptor.

β2-Agonist Drugs

- β2 agonists can cause bronchodilation.
- These drugs are used in bronchial asthma and COPD.
- Drugs include
  - Salbutamol
  - Terbutaline
  - Salmeterol (Longer acting drugs)
  - Formoterol (Longer acting drugs)
  - Uterine relaxants
    - → These are also called Tocolytics.
    - → In the case of preterm delivery that means the delivery occurs before the term the baby is not matured, the lungs are not matured (or) While doing obstetric procedure or threatened abortions, uterine relaxants are used.
    - → Drugs used as uterine relaxants also include
      a. Salbutamol
      b. Terbutaline
      c. Specific drugs
      d. Ritodrine
      e. Isoxsuprine

Clenbuterol

- It is an anabolic agent.
- It is mainly to build the body.
- Athletics can take this drug and they can run. But it is banned for use in athletics.
- It is a β2-agonist but it has anabolic property.

β3-Agonist

- Mirabegron
- Vibegron
- β3 is located in adipose tissue and in Detrusor.
  - When β3 stimulation occurs, Detrusor will relax then urine will get retained.
  - Such a condition was known as overactive bladder.
  - These β3-agonists are used.

α1-Agonist 00:04:56

Phenylephrine

- Phenylephrine is a α1 agonist.
- It can be used as eye drops and produces active mydriasis.
  - Mydriasis is useful for fundoscopy and during adhesions.
  - If they are adhesions inside the eye, then miotic and mydriatic will be used alternatively, then mydriatic can also be used (phenylephrine).
- It is used intravenously in the management of hypotension.
  - It is one of the drugs for hypotension because it acts on α1 and increase the B.P.
- It is given orally. Orally the drug is used as a nasal decongestant.
  - Nasal decongestant means in the nose, when blood vessels are dilated, the water will come, the condition is running nose.
  - By using vasoconstrictor that will constrict the blood vessels, the running nose stops.

Hypotension Drugs 00:07:03

- In hypotension,
  - The direct acting drugs are
    a. Phenylephrine (α1-agonist)
    b. Methoxamine
  - Mixed acting drugs
    a. Ephedrine
    b. Mephenteramine
  - Severe hypotension drugs (non-specific drugs)
    a. Nor-adrenaline
    → Used in shock with hypotension
    b. Dopamine
    → Use of dopamine may have a risk of arrhythmia
- Nor-adrenaline and dopamine drugs are used only for severe hypotension.
- Commonly used for hypotension is phenylephrine.

Orthostatic Hypotension (or) Dysautonomia 00:09:11

- The drugs which act on α which are used for a condition called orthostatic hypotension.
- Dysautonomia means the autonomic nervous system is not working properly.

- When the people are lying down and suddenly get up.
  - → When they suddenly get up, the reflex mechanism is to constrict the blood vessels i.e. veins and blood comes to the heart and B.P is maintained.
- But in some people that phenomenon does not work properly.
  - → When they suddenly get up the veins will not constrict. The B.P falls and they have hypotension i.e called orthostatic or postural hypotension.

- Drugs for orthostatic hypotension
  - Midodrine
  - Droxidopa
  - Both midodrine and droxidopa are prodrugs.
    - → Midodrine will become active i.e., called desglymidodrine, and it acts on α1 and increase the B.P.
    - → Droxidropa will become nor-adrenaline and it act on α1 and increases the B.P.

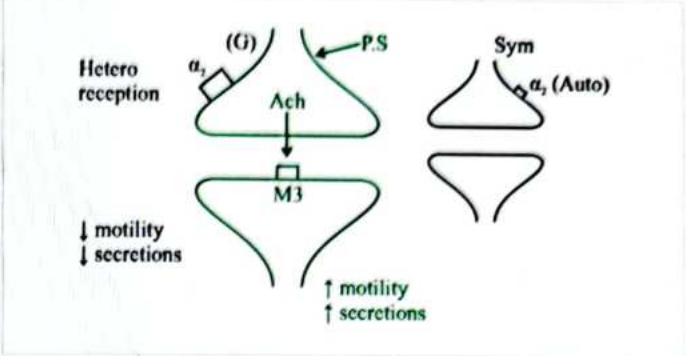
Nasal Decongestants 00:11:55

- Nasal decongestants are the drugs used for common cold. (means running nose)
- Drugs used as nasal decongestants. These can be given in two ways either it can be given topically or systemic.
  - Topical drugs are:
    - → Oxymetazoline
    - → Xylometazoline
    - → Naphazoline
  - Systemic drugs are:
    - → Phenylephrine
    - a. Usually it is given in pediatric formulation as nasal decongestant.
    - b. Usually given as drops or syrups in children.
    - → Pseudoephedrine - It is given as a tablet along with cetirizine.
  - Earlier the drug phenylpropanolamine that leads to stroke, but now it is banned, because it enters the brain and causes vasoconstriction and it may lead to stroke.

- Many times, these drugs are abused by people.
  - If the topical drugs are used repeatedly again they will cause Atrophic rhinitis, because these are vasoconstrictors, they constrict the mucosa so the nasal mucosa will become atrophic and this problem is called rhinitis medicamentosa.
  - These drugs should not be used regularly.
  - While prescribing these drugs should be used whenever necessary.
- All these nasal decongestants act on α1 and α2 receptors present in nasal mucosa.

α2-Agonist 00:15:28

- α2 is located mainly in presynaptic neuron.
- It decreases the noradrenaline and decreases the B.P.



- In synapse, when α2 receptor is stimulated by α2 agonist, α2 agonist decreases nor-adrenaline release that means it decreases the sympathetic outflow and BP decrease, then the patient will be having sedation.

Dexmedetomidine

- It is used in ICU-Sedation.
- It is also used as preanesthetic medication. (to calm down the patient).

Clonidine

- It decreases nor-adrenaline release. So, it is used to treat hypertension.
- It is also used in menopausal hot flush and also used in Diarrhea in diabetic patients (DMT2).
- Used in TICS disorder (it is also called Gilles de la Tourette syndrome).
  - So, the impulses coming from the CNS can be suppressed by the use of clonidine.
  - When clonidine is given to the patients there is initial increase in B.P followed by decrease in B.P. The reason is explained below
    - → α2 receptors are of two types α2A and α2B.
    - a. α2A is the one which is present in the presynaptic terminal.
    - b. α2B is the one which is present periphery.
    - c. When clonidine is given to the patient it will reach to the blood vessel, then the major action is on the α2B, that causes vasoconstriction there is increase in B.P, which was mild.
    - d. Later from the blood vessels it reaches the CNS, and it acts on α2A and decreases the noradrenaline release that will lead to decrease in BP that is major effect.

  - When it is used for diarrhea
    - → In the parasympathetic nerve, acetylcholine gets released and acts on the postsynaptic terminal i.e. M3 receptors and increase the motility of the intestine and

it also increases secretion (parasympathetic means secretion).

→ Acetylcholine release is also controlled by α2; this is called a Heteroreceptor. (It means which is present in other systems).

a. For example, in sympathetic system, α2 is present it is called auto receptor. If it is present in other systems i.e. parasympathetic then it is called heteroreceptor.

b. α2 is a Gi coupled receptor.

i) It will not allow acetylcholine to get released. So, there is decreased motility and decreased secretion. That was the reason, clonidine is used in patients with Diabetes diarrhea. Because In diarrhea there is increased motility and increased secretions.

α-Methyldopa 00:21:20

- α-methyl dopa is converted into α-methyl dopamine by an enzyme decarboxylase.
- α-methyl dopamine is converted into α-methyl noradrenaline by an enzyme hydroxylase.
- α-methyl noradrenaline is the active form of α-methyl dopa which is a prodrug.
- It acts on α2 agonist and decrease the B.P.
  - α-methyl dopa is safe
  - It is used for hypertension in pregnancy.
  - Simply, it is called methyldopa.

Guanfacine 00:22:41

- Guanfacine, now used in a condition called TICs disorder along with the patient has ADHD.
- Clonidine and Guanfacin can be used for patients with Tics disorder along with ADHD.
- Similar drugs are Guanabenz, it is also α2 agonist.
  - Used in patients with Tics disorder along with ADHD.

Lofexidine

- It is used to treat opioid withdrawal symptoms.
  - When opioids are used, the sympathetic system is blocked.
  - Sympathetic surge decreases.
  - When opioids are suddenly stopped, a sympathetic surge will come out.

Tizanidine

- It is used as a centrally acting skeletal muscle relaxant.
- They are used in muscle spasm.

Apraclonidine and Brimonidine

- These are α2 agonist, it acts in the eye and they decrease aqueous humor.
- They are used locally as eye drops in the management of glaucoma.

Other Drugs 00:26:00

Drugs for ADHD (Attention Deficit Hyperactivity Disorder)

- Drugs used are
  - Methylphenidate (derivative of amphetamine, it is a first choice of the drug)
  - Pemoline
  - Atomoxetine (inhibits the reuptake of nor-adrenaline)
- All these drugs are used to increase sympathetic activity, and the attention span increases.
- Amphetamine groups examples
  - Lisdexamfetamine
  - Dextroamphetamine

Amphetamine 00:27:48

- It is usually avoided in therapeutic use because it is a drug of abuse.
- A derivative of amphetamine is called MDMA.
  - It is called ecstasy, used in rave parties.
- So, these drugs have high abuse potential so it is not used in the treatment.

Modafinil 00:28:22

- It is used to treat narcolepsy.
  - Narcolepsy means excessive daytime sleepiness.
  - People may fall asleep suddenly, when they are driving a car they may fall asleep.
  - To make them alert the drug modafinil is used.
- It is an adjunctive drug for a condition called obstructive sleep apnea.
  - The patients with obstructive sleep apnea, always have the tongue may fall back and they will keep on getting up in the night.
  - Due to that in the morning they have so much sleepingness.
- Modafinil is also used when there is jet-lag.
- For narcolepsy, other drugs used are Tiprolisant.
  - Tiprolisant is not a sympathetic drug.
  - It is a H3 inverse agonist.
  - It is also called pitolisant.
- Recently one more drug is used for narcolepsy.i.e, Solriamfetol.
  - It is called NDRI (Noradrenaline and dopamine reuptake inhibitor).
- Modafinil is the drug of choice for narcolepsy.
- Recently another drug is used named dextroamphetamine.
  - It is used for ADHD as well as Narcolepsy.
- These are the drugs which are used for CNS conditions.
- To increase the attention span and to make the patient alert.
- Sympathetic stimulation can cause anorexia.

Anorectic Drugs

00:31:50

- Sympathetic drugs are called anorectic agents.
- They are also used to treat obesity. Drugs under this category includes,

Sibutramine

- The drug which increases both serotonin (5HT) and noradrenaline activity.

Fenfluramine

- The drug which increases only serotonin 5HT activity.

Phentermine

- The drug which increases only noradrenaline activity.

> **Important Information**
>
> - Sibutramine and fenfluramine drugs are banned because they are shown to increase cardiovascular deaths.

Drugs Used for Obesity

- Cooking medium for people with obesity can be Olestra.
- The inhibitor of lipase is called orlistat.
- **Points to Remember**
  - If the drugs end with stat they are enzyme inhibitors.
  - If the drugs end with ase themselves they are enzymes. E.g Asparaginase.
- If the lipase enzyme is inhibited in the gut, the fat is not metabolized.
- The patient will have adverse effects ie., loss of fat in stool that is steatorrhoea.

Rimonabant

- It was a stimulator of cannabinoid receptors, but now it has been banned.
- Older drug was cannabinoid 1 receptor antagonist.
  - Cannabinoids are going to increase the appetite.
  - Rimonabant is used to block cannabinoid 1 receptors, then it decreases the appetite.

Endogenous Slimming Peptide

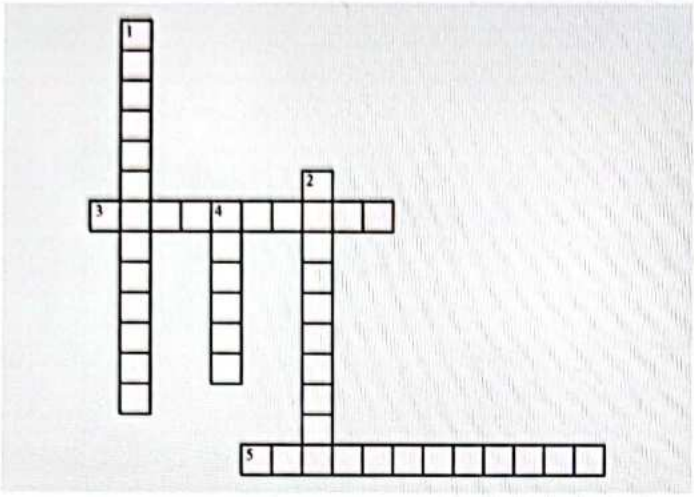
- It is called Leptin and is still under research.
- Diabetic drug that is GLP-1 receptor agonist.
  - Liraglutide
  - Semaglutide
- The 5HT2C agonist is called Lorcaserin.
  - Hint L for lorcaserin, O for obesity and SER for serotonin.
  - It is also banned for the reason of higher chances of cancers.

Combination Drugs for Obesity

- Bupropion + Naltrexone
- Bupropion+zonisamide
- Phentermine+Topiramate.

CROSS WORD PUZZLES

Crossword Puzzle 1



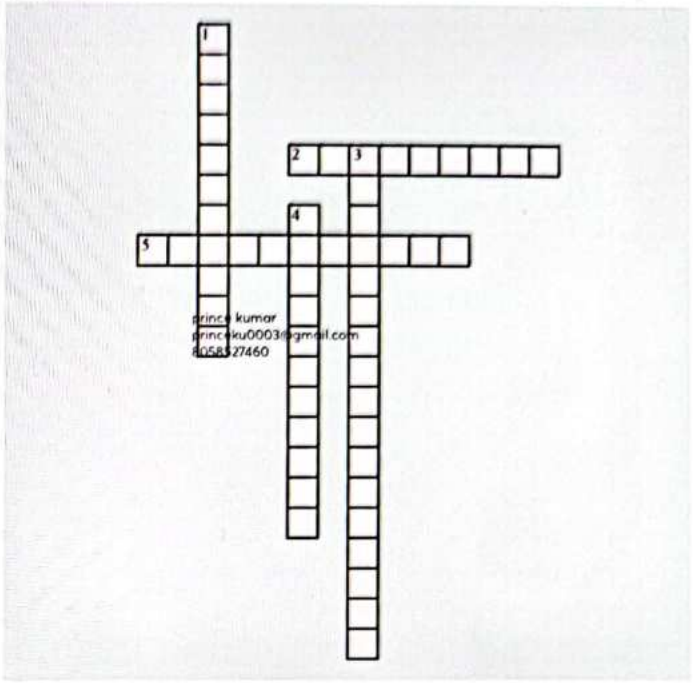
Down

1. _____ enzyme converts α-methyldopa to α-methyl dopamine.
2. _____ drug is a beta3 agonist used in overactive bladder.
4. _____ an endogenous slimming peptide.

Across

3. _____ are also known as uterine relaxants.
5. _____ drug increases only 5HT.

Crossword Puzzle 2



Down

1. _____ increases both 5HT and noradrenaline.
3. _____ is a drug which is used for ADHD as well as narcolepsy.
4. _____ is an anabolic agent which is banned for use in athletics.

Across

2. _____ is an adjunctive drug for obstructive sleep apnea.
5. _____ is a diabetic drug and is a GLP-1 receptor.

28 ALPHA BLOCKERS

- Alpha-blockers are a type of blood pressure medication.
- They lower blood pressure by preventing a hormone called norepinephrine from constricting the muscles in the walls of smaller arteries and veins.
- As a result, the blood vessels remain open and relaxed.
- This improves blood flow and lowers blood pressure.

Types of Alpha Receptor

α1	α2
Location: • Eye • Blood vessels • Intestine • Prostate • Seminal vesicles	**Location:** • Presynaptic terminal

Alpha 1

Effects of Blocking Alpha 1

- Block alpha in the eye causes miosis (passive).
- Vasodilation of blood vessels causes BP decreases (Hypotension).
- Vasodilation in the nose causes nasal stuffiness.
- Blocking alpha in the intestines will cause diarrhoea.
- Block alpha in the prostate; the sphincter holding the urine will relax and allow easy flow of urine.
- Block alpha in Seminal vesicles causes inhibition of Ejaculation.

Adverse Effects:

- Hypotension
- Stuffiness (Nasal Stuffiness)
- Diarrhoea
- Inhibits Ejaculation

Uses:

- To Treat hypertension.
- To treat Benign hypertrophy of Prostate

Alpha 2

- Blocking alpha 2 pre-synaptically causes an increase in Noradrenaline release.

Drugs for Alpha-Blockers 00:09:25

Non-Selective Alpha Blockers

- **Phenoxybenzamine (Irreversible)**
  - It is Longer acting.
  - Uses in Pheochromocytoma.
- **Phentolamine (Reversible)**
  - Systemic uses:
    - → In Pheochromocytoma (surgery).
    - → In Clonidine withdrawal reaction.
    - → In Cheese reaction.
  - Local uses:
    - → Erectile dysfunction.
    - → To reverse soft-tissue local anaesthesia.
    - → To reverse dermal necrosis due to vasoconstriction.
- **Tolazoline (Reversible)**
  - It is used in pulmonary hypertension.

Problem in Non-Selective Alpha-Blockers 00:17:25

- α1 present in post-synaptically
- α2 present in pre-synaptically

- When given a non-selective alpha blocker, they block both α1 and α2.
- Blocking α2 causes a increase in nor-adrenaline. They act on β1 chance to increase in Heart rate.

Alpha 1 Blockers Selective 00:18:35

- They only block α1.
- The Drugs are:
  - Prazosin
  - Terazosin
  - Doxazosin
  - Alfuzosin
  - Bunazosin
  - Indoramin
  - Urapidil

Uses of Prazosin

- To treat Hypertension. (Not a First line drug)
- To Treat If the patient has Hypertension + Benign Hypertrophy of the prostate.

- Used in conditions like Scorpion sting. There is an increase in sympathetic activity leading to high BP, myocarditis and Pulmonary edema. Prazosin will decrease sympathetic activity.
- Used in Peripheral Vascular Disease. (Raynaud's disease)

Important Information

- Terazosin and Doxazosin have quinazoline moiety which causes Prostate smooth muscle apoptosis.

Adverse Effect of Prazosin 00:24:03

- Hypotension (Postural) (First dose phenomenon). This is prevented by starting prazosin at night time and start with a low dose
- Inhibition of Ejaculation

Subtypes of Alpha 1 00:26:59

α1A	α2B
• Located in Prostate • Located in Trigone	• Located in Blood vessel

α1A Blockers

Tamsulosin

- It can Block α1A and α1D.
- It is used to treat benign hypertrophy only.
- **Adverse effect**
  - Floppy Iris Syndrome.

Silodosin

- It is used to treat benign hypertrophy only.

α2 Blockers

Yohimbine (Selective)

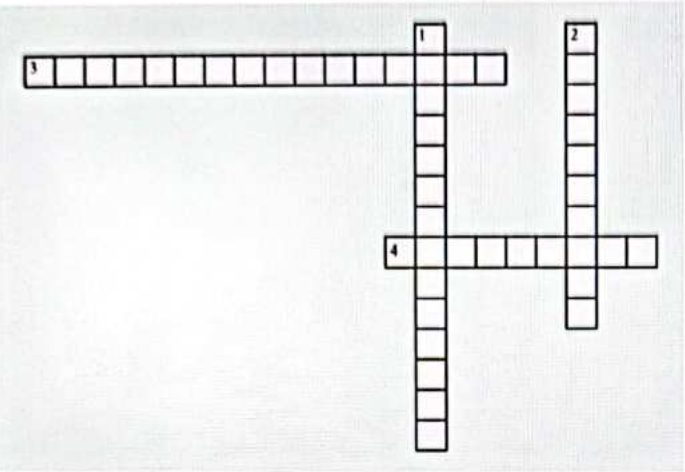
- Not used in any treatment.

Non-Selective Alpha Blockers

- Ergot
- Tricyclic Antidepressant
- Typical antipsychotic (Chlorpromazine)

CROSS WORD PUZZLES

Crossword Puzzle



Across:

3. Non-selective alpha blockers Uses in
4. Vasodilation of blood vessels causes BP

Down:

1. Lower blood pressure by preventing a hormone called
2. A drug shows Floppy Iris Syndrome is

Answer Key:

1. Norepinephrine
2. Tamsulosin
3. Pheochromocytoma
4. Decrease

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29 BETA BLOCKERS

Classification 00:00:35

- There are three types:
  - β1
  - β2
  - β3

β1 00:00:50

Location and action:

- It is located in the heart.
- It increases the heart rate.
- It increases conduction.
- It also increases the force of contraction.
- It is also located in the JG cells, where it increases renin. Renin activates angiotensin which activates aldosterone. In case of increased renin activity beta blockers can be used.

What happens when β1 is blocked?

- Decrease in heart rate.
- Decrease in conduction
- Decrease in force of conduction.

Uses of β1 blockers:

- Tachycardia (used to reduce the heart rate).
- Arrhythmias (used to block AV conduction).
- Stable angina (used to reduce the heart rate).
- Hypertension (in case of decreased renin activity).
- Chronic CHF (in which aldosterone levels are high which can cause mortality in CHF patients).

Contraindications of β1 Blocker: cannot be used.

- Bradycardia, as heart rate is already low.
- AV block.
- Acute CHF (congestive heart failure).

β2 00:04:51

Location and action:

- The Role of Beta 2 in blood vessels is Vasodilation.
- When β2 blockers are used there is Vasoconstriction because alpha 1 will take over causing Vasoconstriction.
- It is also present in the bronchus, where it is responsible for bronchial dilation.
- Present in the liver where they increase glycogenolysis and gluconeogenesis which ultimately increase glucose.
- β2 is present in the skeletal muscle, it increases tremors and also exercise capacity.

Contraindications β2 blockers:

- Vasospastic Angina: The coronary artery has a spasm.
- Peripheral vascular disease such as Raynaud's disease.
- COPD (Chronic obstructive pulmonary disease)
- Bronchial asthma (BA).

Diabetes Mellitus:

- For most diabetic type two patients, when taking insulin, the most common complication of insulin is patients developing hypoglycaemia to compensate that there should be an increase in glucose. Beta 2 will activate the liver to increase glucose. This compensatory mechanism is not seen in diabetic patients if they are on drugs that block beta 2.
- Decreases exercise capacity and tremors.

β3 00:12:05

- The adipose tissue causes lipolysis.

Impact of Beta blockers:

- When β blockers are used it will not allow the adipose tissue to cause lipolysis and which will lead to dyslipidemia.
- B blockers will enter the blood-brain barrier and the patients will have depression, but it will decrease performance anxiety and the patient may have nightmares.
- Sexual dysfunction is called erectile dysfunction.

Beta Blocker Drugs 00:15:19

Non-Selective Beta Blockers.

- When the drugs block both β1 and β2 they are called non-selective beta blockers.
- All the beta blockers end with "lol"
- **Propranolol:**
  - It causes depression, sedation, reduces performance anxiety, nightmares and Erectile dysfunction.
- **Nadolol:** Longest acting β blocker
- Sotalol
- Timolol

Contraindications of non-selective β blockers.

- Mnemonics: Please Don't allow β blockers in acute CHF
  - **P**: Peripheral Vascular disease and Prinzmetal angina.

- D: Diabetic patients
- A: AV block
- β: Bronchial Asthma and COPD
- B: Bradycardia
- Acute CHF

- In the case of a diabetic patient, the β blocker is contraindicated because the diabetic patient is already on insulin.
- Major complications on insulin is hypoglycemia and when a patient is in hypoglycemic state, the body responds by activating the sympathetic system which in turn stimulates β1 and β2 receptors.
- There are Sympathetic Cholinergic fibres that release acetylcholine and which act on m3 receptors and patients will have sweat due to thermoregulatory sweat glands.
- The β1 receptor is present in the heart and when it is stimulated the patient will feel tachycardia.
- And activation of β2 will cause tremors and tachycardia.
- The warning signs of Hypoglycemia:
  - Tachycardia
  - Tremors
  - Sweating
- When β2 is activated results in an increase in glucose. The practical aspect of a diabetic patient who is on insulin, they are given propranolol for managing various disease. The patient will only have the symptom of sweating which is very hard for the patient to distinguish between hypoglycaemia and normal sweating. This is called Hypoglycemic unawareness. This is why non-selective β blockers are not given to diabetic patients.

Cardio Selective B Blockers 00:22:45

- Also known as beta 1 selective blockers. The word selective specifically means that they will block the beta 1 receptor more than beta 2.
- They can be used in patients with:
  - Preferred in Diabetes.
  - Bronchial Asthma and COPD.
  - Peripheral vascular disease.
- Contraindications:
  - AV blocks.
  - Bradycardia.
  - Prinzmetal angina.
  - Acute CHF.

Cardio selective β blockers

- Mnemonics: ABC of every man's need
  - **A**: Atenolol for hypertension and acebutolol.
  - **B**: Bisoprolol for HTN and chronic CHF, Betaxolol is used in the treatment of glaucoma.
  - **C**: Celiprolol increases HDL level
  - **E**: Esmolol (shortest-acting beta blocker, Given IV because it is metabolised by an enzyme called Esterases). This drug is used for hypertension emergencies and arrhythmia.
  - **M**: Metoprolol used for hypertension, chronic CHF, MI Myocardial infarction and arrhythmia.
  - **N**: Nebivolol releases Nitric oxide used to treat hypertension.

Uses of cardio selective β blockers

- **Cardiac Uses:**
  - **Hypertension:** It decreases heart rate, Cardiac output and stroke volume, which will result in decrease of systolic BP. It also decreases the release of renin.
  - **Stable angina:** The drug decreases oxygen demand by decreasing the heart rate.
  - **Myocardial infarction:** Decreases the risk of arrhythmia, and also reduces the infarct size.
  - **Arrhythmia:** They belong to the class II antiarrhythmic.
  - **Chronic CHF:** It decreases the renin which reduces the aldosterone, decrease mortality.
  - **Dissection of aortic aneurysm**: A combination of esmolol + sodium nitroprusside.
  - **HOCM (Hypertrophic obstructive cardiomyopathy):** Reduces the force of contraction.
- **Non-Cardiac Uses:** Mnemonics GAME PIT
  - **G**: Glaucoma. For cardio-selective Betaxolol is used and for non-selective Timolol, Levobunolol and Carteolol are used.
  - **A**: Akathasia
  - **M**: Migraine Prophylaxis, decreases anxiety.
  - **E**: Essential Tremors.
  - **P**: Performance anxiety, Portal Hypertension Prophylaxis and Pheochromocytoma. (Pheochromocytoma is a type of adranal gland tumour. First alpha blockers are given and then Beta blockers are given).
  - **I**: Infantile Haemangioma.
  - **T**: Thyrotoxicosis.
  - Except for glaucoma, the choice of drug is Propranolol. It inhibits the conversion of T4 to T3.
  - As propranolol has a property called membrane stabilising property also called local anaesthetic property, is the reason propranolol is not used in glaucoma.

Adverse effects of Beta Blockers

- Sedation.
- Depression and bad dreams.
- Erectile dysfunction.
- Fatigue and exercise intolerance.
- Cold hands and feet.
- Dyslipidemia.
- Hypoglycemic unawareness.

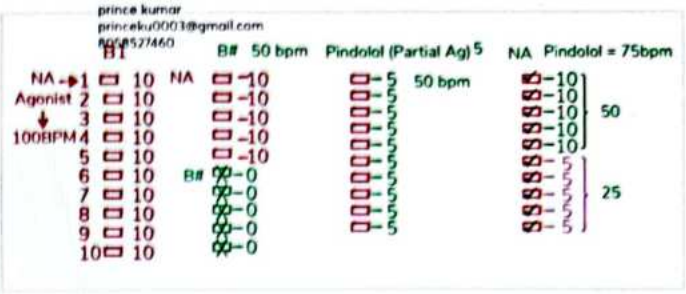
Important Information

- If the patient is on propranolol for the long term there will be a receptor upregulation and when the drug is suddenly stopped the patient will have an increase in BP increase in angina which may lead to death, don't stop drug abruptly.

- In case of beta-blocker toxicity, the patient will present with:
  - Decrease in heart rate.
  - Decrease in conduction.
  - Decrease in force of contraction.
- Antidote for Beta-blocker toxicity is Glucagon.
  - As it acts through its G protein-coupled receptors in the heart. And by acting on that it reverses everything.
  - It increases the Heart rate, Increases the conduction and increases the Force of contraction.
  - Atropine is not used as an antidote because it will increase the heart Rate, ↑ conduction.

Properties of Beta-Blockers 00:46:45

- The longest-acting Beta Blocker is Nadolol.
- The shortest-acting beta blocker is Esmolol.
- Tilisolol opens K+ channel.
- Sotalol closes the K+ channel. It is placed under class III antiarrhythmic.
- Beta-blocker when given orally it is 100% Bioavailability it is Pindolol.
- Low lipid solubility beta blockers.
  - Less absorption, less 1st pass and eliminated in Kidney unchanged. These are long-acting.
  - They don't cross BBB which results in no depression and other symptoms.
  - Examples: Mnemonics ABS Car: **A**- Atenolol, **B**- Bisoprolol, **S**- Sotalol and **Car**- Celiprolol.
- Local Anaesthetic property or membrane stabilizing property: (Mnemonics: Please make a lovely beta-blocker)
  - **P**: Propranolol, Pindolol.
  - **M**: Metoprolol.
  - **A**: Acebutolol.
  - **L**: Labetalol.
  - **Beta Blocker**: Betaxolol, has sodium channel-blocking properties. It can be used as an eye drop because of its less membrane-stabilizing properties, neuroprotection.
- Partial Agonistic / Intrinsic sympathomimetic property: Suppose a patient is diagnosed with HTN and also has bradycardia. If this patient is given a beta blocker the heart rate will decrease. For this patient the beta blockers used are Pindolol and acebutolol since they have Intrinsic sympathomimetic properties which means they bind to the receptor and stimulate it. For example, Pindolol will not lower the heart rate, it will increase it instead of lowering it.



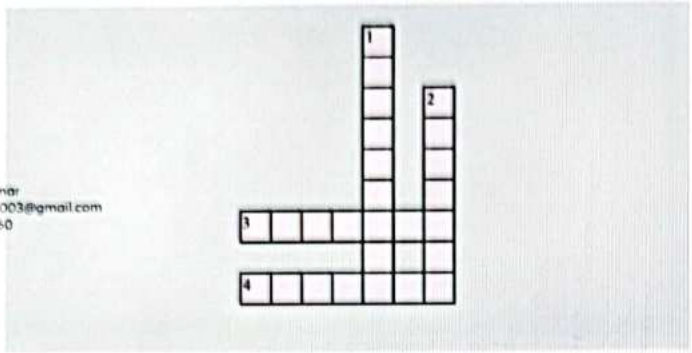
- **Explanation:** For example, let's take 10 beta 1 receptors. And it is known that the beta 1 receptor increases the heart rate. Let us assume whenever one of the receptors is stimulated the heart rate will increase by 10 and the heart rate will be 100 bpm, this is a natural phenomenon.
- But in a situation where a beta blocker is used, it will block 5 receptors so the response is zero. So, in a normal patient, the heart rate will become 50 bpm.
- In the case of pindolol, a partial agonist which has a sub-response. So pindolol will produce half response which means it will lead to 50 bpm.
- But in real-life situations, the heart has seen both pindolol and NA. NA is already present and pindolol is given externally. The heart rate will be 50 for NA and 25 for pindolol so the patient's heart won't go down. It will be 75 bpm.
- Intrinsic sympathomimetic property drugs are not used in Ischemic heart disease, Anxiety and migraine.
- Another advantage of Intrinsic sympathomimetic drugs is, they will not interfere with lipids.
- Beta blocker drugs with Intrinsic sympathomimetic: (Mnemonics: COPAL)
  - **C**: Celiproplol, Carteolol
  - **O**: Oxprenolol
  - **P**: Pindolol
  - **A**: Acebutolol
  - **L**: Labetalol

Generations of Beta-Blockers 01:02:35

- I Gen: Non-selective beta blockers.
- II Gen Cardio selective beta blocker.
- III Gen:
  - Cardio selective beta-blocker: Celiprolol, Bisoprolol and Nebivolol.
  - Non-selective beta blockers: Carvedilol, Labetalol, bucindolol and carteolol.
- α + β blockers:
  - Carvedilol - CCBs, Anti-oxidant and anti-mitogenic properties. It is used in chronic CHF and hypertension.
  - Labetalol- Used to treat hypertension. It is Drug of choice for Hypertension in pregnancy and hypertension emergencies in pregnancy.

CROSS WORD PUZZLES

Crossword Puzzle 1



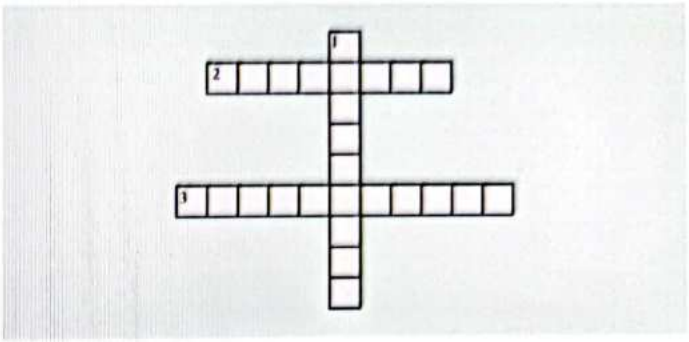
Across

3. _____ closes K+ channel.
4. Longest Acting Beta Blocker is _____.

Down

1. _____ opens the K+ channel.
2. Shortest acting beta blocker is _____.

Crossword Puzzle 2



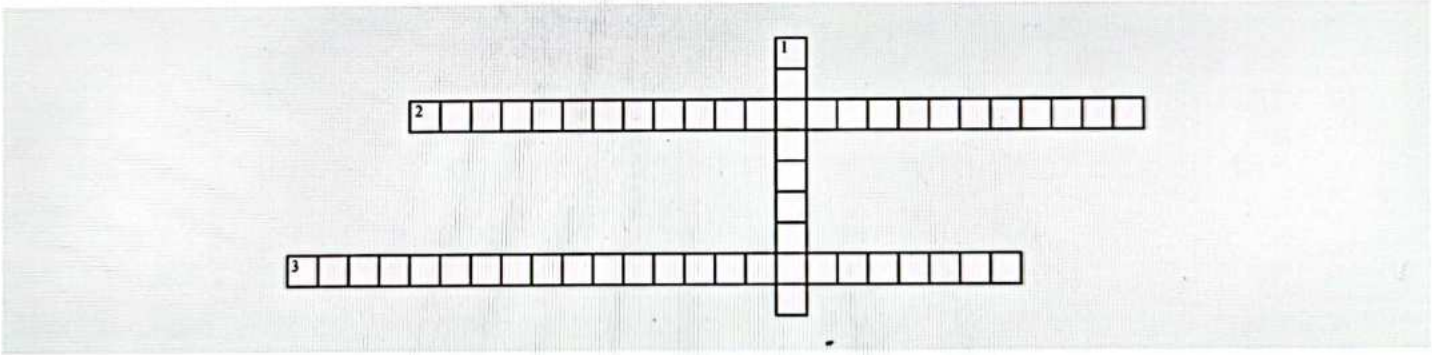
Across

2. An antidote for Beta-blocker toxicity is _____.
3. _____ is not used in glaucoma.

Down

1. _____is used to treat hypertension in pregnancy and hypertension emergency in pregnancy.

Crossword Puzzle 3



Across

2. When the drugs block both β1 and β2 they are called _____.
3. _____property drugs not used in Ischemic heart disease, Anxiety and migraine.

Down

1. _____ releases nitrous oxide used to cure hypertension.

30 PHARMACOTHERAPY OF GLAUCOMA

Introduction 00:00:10

- In the case of Glaucoma, the intraocular pressure increases, which in turn increases the pressure on the retina and damages it.
- It leads to tubular vision in the patients.
- If not managed, the patient may go blind.
- Intraocular pressure is due to aqueous humor produced by the ciliary body.
- The normal function of aqueous humor is to provide nutrition to the lens and cornea.
- After being produced by the ciliary body, aqueous humor moves from the posterior to the anterior chamber and is drained.
- There are two drainage outflow channels:
  - Trabecular outflow
  - Uveoscleral outflow
- The problem of Glaucoma can be explained with the help of an example. Suppose a person is taking a shower, their drainage gets blocked, and the door is locked. The person will ultimately drown unless a water outlet is available or the shower is turned off. The same is the case with Glaucoma.
- Either the aqueous humor production has to be increased, or the outflow of aqueous humor is to be decreased.

Decrease aqueous humor production 00:04:00

- The receptors, namely α1, α2, β2, and an enzyme, carbonic anhydrase, play an important role in producing aqueous humor.
- These can be classified as the following targets having respective agonist drugs:
  - Target a: α1- α1 agonist
  - Target b: α2- α2 agonist
  - Target c: β2-blockers
  - Target d: Carbonic anhydrase- Carbonic anhydrase inhibitors

α1 Agonist

- The name of the drug is Dipivefrine.
- It is a prodrug that gets converted to adrenaline after its metabolism.
- Adrenaline cannot be administered directly as an eye drop because it cannot cross the conjunctival barrier or corneal barrier.
- Adrenaline acts on α1 and causes vasoconstriction, which causes a reduction in aqueous humor production. This is the major mechanism of action.
- The minor mechanism of action is the increase in trabecular and uveoscleral outflows.
- Sometimes adrenaline becomes a pigment called adrenochrome on the conjunctiva. So, its adverse effect is Conjunctival Black Pigmentation.
- Another adverse effect that can be seen is Cystoid Macular Oedema.

α2 Agonist 00:08:00

- α2 agonist is a Gi-coupled receptor. It decreases cAMP and thereby decreases aqueous humor production.
- α2 is also present pre-synaptically. α2 agonist decreases norepinephrine and other neurotransmitters, causing a decrease in intraocular tension.
- The drugs, in this case, are Apraclonidine and Brimonidine.
- Apraclonidine can cause an adverse effect which is lid retraction.
- Brimonidine can cause anterior uveitis. It can cross the blood-brain barrier and suppress CNS, thus having the potential to cause CNS depression. It is not advisable for children.

β - Blockers

- These block B receptors, particularly β2, in the ciliary body.
- These also decrease cAMP, which in turn decreases aqueous humor production.
- Betaxolol is one of the blocking agents in this case. It is cardio selective, meaning it blocks β1 more than β2. It also blocks Na+ channels producing a neuroprotection effect.
- Timolol, Carteolol, and Levobunolol are non-selective beta blockers.
- If a patient comes with bronchial asthma and glaucoma, the preferred drug is Betaxolol because of its cardio selective property. Otherwise, Timolol is preferred.
- Eye Drops also get systemically absorbed; that's why there's a risk of bronchial complications.
- Corneal hypoesthesia is an adverse effect of beta blockers. It means decreased sensation in the conjunctiva.
- Blepharoconjunctivitis is another problem with beta-blockers.

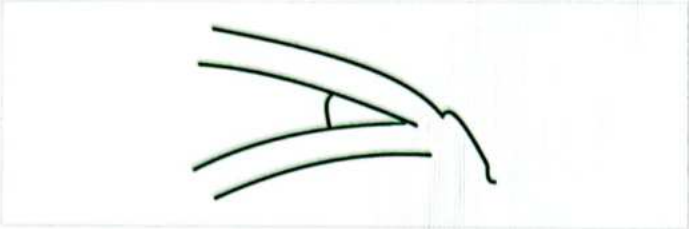
Carbonic Anhydrase Inhibitors

- Their role is to decrease aqueous humor as well.
- Acetazolamide is an oral drug in this category.
- Dorzolamide and Brinzolamide are available as eye drops.
- The adverse effects of carbonic anhydrase inhibitors include **Corneal Oedema and Bitter Taste.**

Increase the outflow of aqueous humor 00:00:10

Miotics

- Miotics are drugs that cause excessive constriction of the pupil of an eye.
- These drugs include trabecular outflow and are used in angle closure glaucoma.



- In angle closure glaucoma, the iridocorneal angle is closed. Miosis causes the angle to open up.
- Mydriatic drugs are contraindicated in this condition.
- The drugs used are Pilocarpine, Physostigmine, and Echothiophates.

Increase the uveoscleral outflow 00:17:45

- The drugs used are prostaglandins, and they're PGF2α analogues.
  - Latanoprost.
  - Bimatoprost.
  - Travoprost.
- Prostaglandins are the first-choice drugs for open-angle glaucoma.
- "MIG" is the pneumonic to remember the adverse effects of these drugs.
  - **M**- Macular Oedema
  - **I**- Iris pigmentation
  - **G**- Increased growth of eyelashes.
  - They can also produce Orbital Fat Atrophy.
- Prostaglandins are inflammatory mediators. That's the reason they're contraindicated in inflammatory glaucoma.

Newer Drugs 00:20:50

Netarsudil

- It inhibits an enzyme called Rho Kinase. It leads to vasodilation in the trabecular area, thereby increasing the outflow.
- Its adverse effect is Cornea Verticillata.

Latanoprostene Bunod

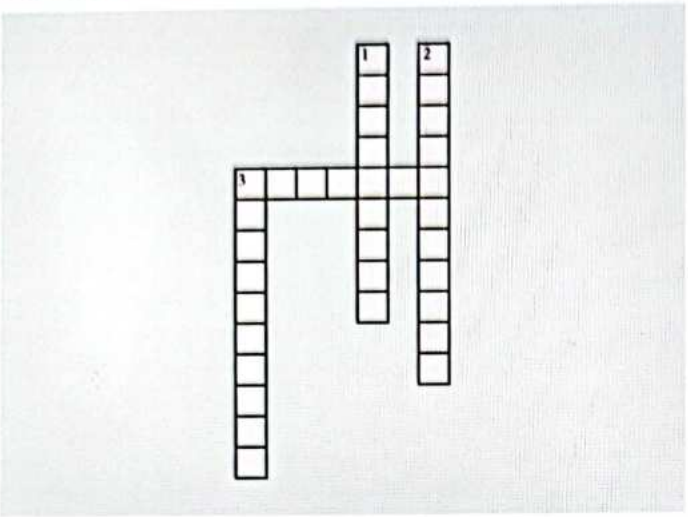
- It has two components, namely Latanoprost and Mononitrate.
- Latanoprost increases uveoscleral outflow.
- Mononitrate Causes vasodilation in the trabecular area, increasing the trabecular outflow.
- The advantage of this new drug is that it can increase both outflows.

Drug of choices

- The first choice of drugs for open-angle glaucoma is PGF2α analogues.
- For closed-angle glaucoma, the drugs used are Miotics.
- For acute congestive glaucoma, Mannitol is used intravenously. If unavailable, Acetazolamide can be used.
- One contraindication for closed-angle glaucoma is the use of Mydriatics. Anticholinergic drugs and tricyclic antidepressants should not be used either, like Imipramine.

CROSS WORD PUZZLES

Crossword Puzzle 1



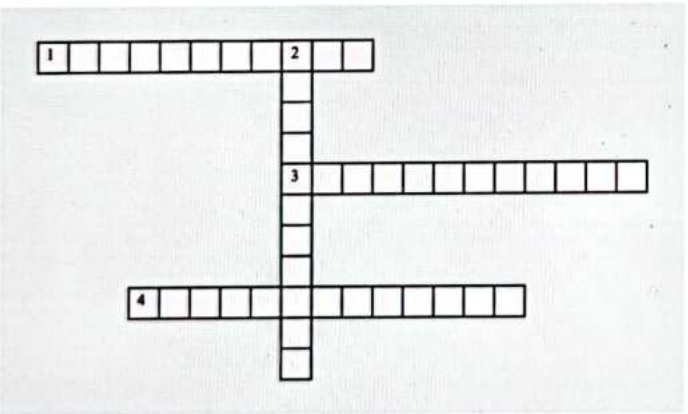
Across

3. For closed-angle glaucoma, the drugs used are _____.

Down

1. Netarsudil is one of the newer drugs. It inhibits an enzyme called_____.
2. Latanoprost increases _____ outflow.
3. One contraindication for closed-angle glaucoma is the use of_____.

Crossword Puzzle 2



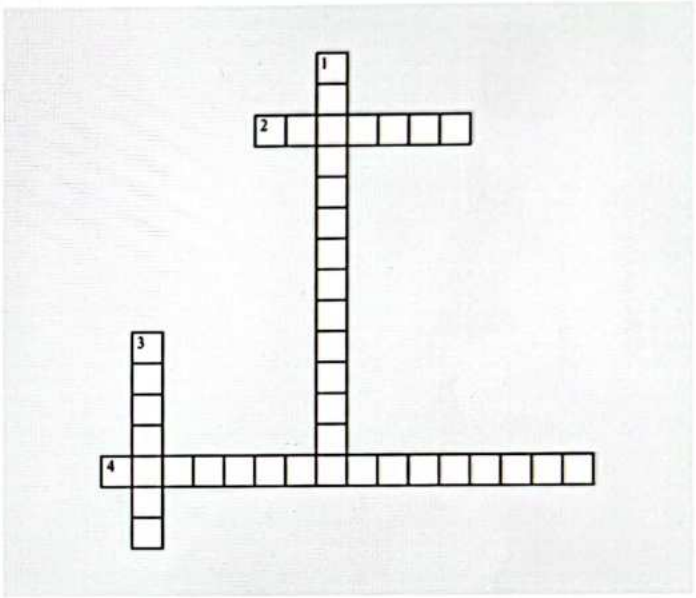
Across

1. _____is a prodrug that gets converted to adrenaline after its metabolism.
3. Intraocular pressure is due to _____ produced by the ciliary body.
4. _____ can cause an adverse effect which is lid retraction.

Down

2. In the case of Glaucoma, the _____ pressure increases, putting pressure on the retina and damaging it.

Crossword Puzzle 3



Across

2. _____are drugs that cause excessive constriction of the pupil of an eye.
4. Adrenaline acts on α1 and causes_____, which causes a reduction in aqueous humor production.

Down

1. _____are the first-choice drugs for open-angle glaucoma.
3. These block B receptors, particularly B2, in the _____ body.

31 DRUGS ACTING ON GANGLIA AND ANTI SMOKING DRUGS

- When discussing the concept of Ganglia, two important ganglia are to be considered: parasympathetic and sympathetic.
- Another more modified ganglia is also present, called the adrenal medulla.
- Acetylcholine (ACh) is the neurotransmitter that is present in the ganglia.
- Nn receptor is the receptor on which acetylcholine works.
- There is a predominance of the parasympathetic in every organ. For example, in the heart, there is a predominance of the parasympathetic. In the blood vessels, there is a predominance of the sympathetic.
- If the ganglia are stimulated, the predominance will increase.

Iris	Cholinergic (miosis)
Ciliary muscle	Cholinergic (ciliary contraction)
Salivary glands	Cholinergic (salivation) increased
Heart	Cholinergic (bradycardia)
Sweat gland	Sympathetic cholinergic (sweating)
Arterioles and veins	Sympathetic (vasoconstriction)
GIT	Cholinergic (motility increased)
Urinary bladder	Cholinergic (evacuation)
Penile	Erection Ejaculation

Important Information

- Blood vessels and sweat glands are the two places where the sympathetic is predominant.

Ganglionic Stimulants 00:02:52

Nicotinic Agonist ↓ Nicotine Lobeline Varenicline	Non - selective [N & m] ↓ • Ach • Pilocarpine • Carbachol • Anti – cholinesterase

Drugs can be classified as follows:

1. Nicotinic Agonists

These stimulate only the nicotinic receptors.

Drugs include:

- Nicotine
- Lobeline
- Varenicline

2. Non-Selective

They act on both nicotinic as well as muscarinic.

Drugs include:

- Ach
- Pilocarpine
- Carbachol
- Anti-cholinesterases

These drugs inhibit the enzyme cholinesterase and can increase the activity of acetylcholine. So, they can stimulate both N and M receptors. These are called Ganglionic Stimulants.

Ganglionic Blockers 00:04:36

Refer Table 31.1

Important Information

- Important use of ganglionic blockers was in the treatment of hypertension.

Drugs include:

- **Trimethapham** - They were used to treat hypertension, not used nowadays.
- **Hexamethaonium** - It was used for smoking cessation but is not used nowadays due to a lot of adverse effects.

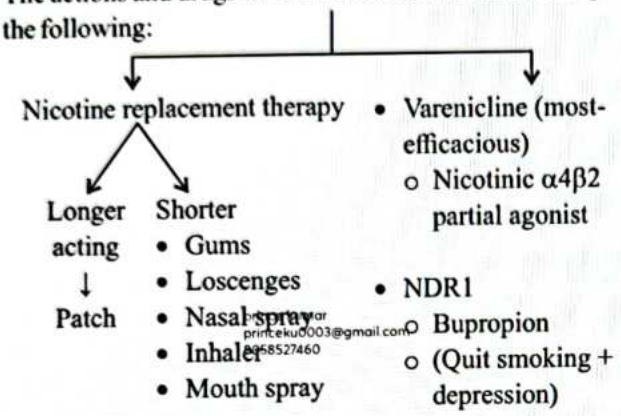
Drugs for smoking cessation 00:08:18

Tobacco
↓
Nicotine
↓
$\alpha_4\beta_2$
↓
Release of Dopamine = ↑ Reward function
= Relaxation

- Patients that are taking nicotine continuously, if asked to stop abruptly, will develop withdrawal symptoms.

- They get an immediate effect while smoking or chewing tobacco because while smoking, the nicotine immediately enters the lungs, and the surface area of the lungs is large, causing the absorption to happen faster. The nicotine will enter the brain, causing the patients to feel happy.
- When they chew tobacco, it is sublingually absorbed, causing the action to be faster again.
- That is why nicotine is given but in a slow form.

The actions and drugs used for the cessation of smoking include the following:



Other drugs for smoking cessation

- Not FDA approved.

a. Cytisine

- It is a plant alkaloid that has the same mechanism of action as Varenicline (Nicotine $\alpha_4\beta_2$ partial agonist).
- Clonidine

Table 31.1

Organ	Predominant tone	Effect of ganglion blockage
Iris	Cholinergic (miosis)	Mydriasis
Ciliary muscle	Cholinergic (ciliary contraction)	Ciliary muscle relax
Salivary glands	Cholinergic (salivation) increased	Dry mouth
Heart	Cholinergic (bradycardia)	Tachycardia
Seat gland	Sympathetic cholinergic (sweating)	↓ Sweating
Arterioles and veins	Sympathetic (vasoconstriction)	V.D= ↓BP
GIT	Cholinergic (motility increased)	Constipation
Urinary bladder	Cholinergic (evacuation)	Urinary retention
Penile	Erection Ejaculation	Impotence

CROSS WORD PUZZLES

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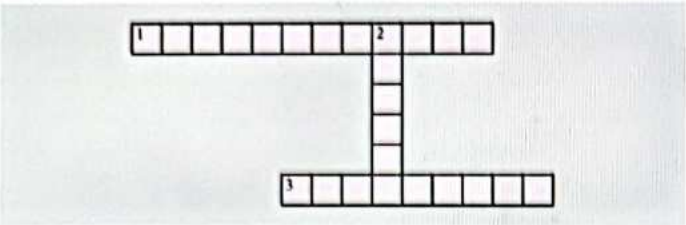

Across

1. Most effective therapy for quitting smoking _____.
3. _____ has anti-depressant properties.

Down

2. A transdermal patch is a _____ acting preparation.

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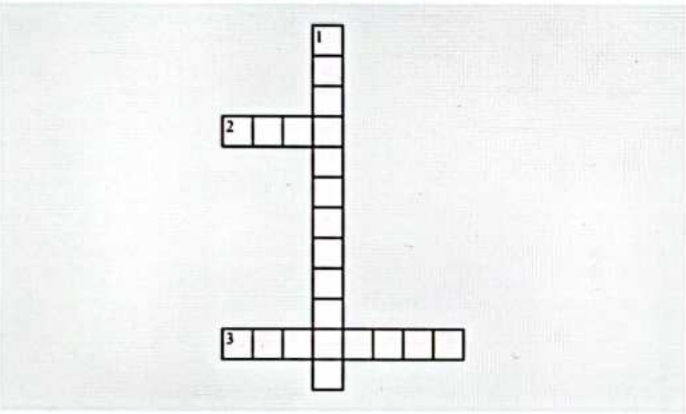
Crossword Puzzle 2



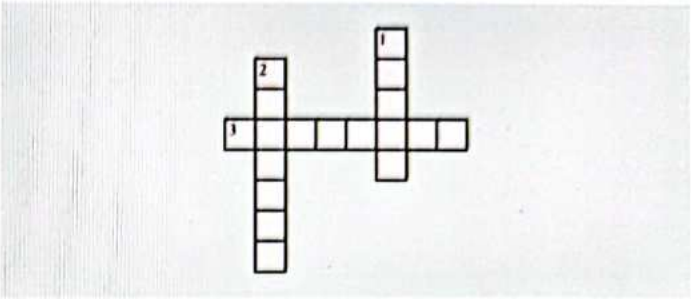
Across

2. Ganglionic blockers depend on the _____.
3. Tobacco mainly contains _____.

Down

1. The major use of Ganglionic blockers was to treat _____.

Crossword Puzzle 3



Across

3. The adrenal medulla is the _____ ganglia.

Down

1. Nicotine is a _____ drug.
2. Gums are _____ acting preparation.

33 SEROTONIN PHARMACOLOGY AND DRUGS FOR MIGRAINE

00:00:29

- Serotonin is also known as 5-hydroxytryptamine (5-HT).
- Carcinoid syndrome is also caused by the excess of serotonin in the bloodstream.
- It acts on 7 different types of receptors: 5HT1 to 7
- All are G-protein coupled receptors, except for 5HT3 (ion channel receptor).

Serotonin Receptors: Targets, Drugs, Action, and Uses

00:01:43

Refer Table 33.1

Important Information

- Buspirone does not work for acute anxiety disorder because the drug takes 2-3 weeks to start working.
- Bupropion is used for smoking cessation.
- Sumatriptan* is one of the most important 5H1TB/1D agonists given as oral, subcutaneous, and nasal routes. In oral bioavailability is less.

Mechanism of Action of Drugs

5HT1A partial agonists (Buspirone)

00:01:55

- 5HT1A receptor is present on the presynaptic neuron, and its partial stimulation decreases serotonin resulting in decreased anxiety.
- **Advantage** - No sedation, dependence, and tolerance.

5HT1B/1D Agonists (Triptans)

00:05:02

- They cause vasoconstriction and decreased neurogenic inflammation resulting in decreased activity of calcitonin gene-related peptide (CGRP) and decreased nausea and vomiting.
- 5HT1B/1D agonists are contraindicated in ischemic heart diseases, coronary artery spasms, and pregnancy.
- **Drug Interaction-** Ergots and sumatriptan cannot be combined as both are vasoconstrictors. They should be given in a gap of 24 hours.

Important Information

- Triptans should not be given in combination with SSRIs and SNRIs as the risk of serotonin syndrome increases as all of them increase serotonin levels.
- Lorcaserin was used for lowering obesity but is now banned due to developing cancer risk.

Ergots

- Derived from the fungus Claviceps purpura.
- They have multiple actions on 5HT, alpha, and dopamine receptors.

Refer Table 1.2

Important Information

- Ergotamine's are contraindicated in ischemic heart disease, coronary artery spasms, and uncontrolled hypertension.
- Ergotamine causing Vasoconstriction can be reversed before gangrene by treating with vasodilators such as sodium nitroprusside, an equal dilator of arteries and veins.
- Ergometrines are not used for labour induction as they constrict the upper and lower segments of the uterus, leading to foetal distress.

Q. Which is better for an acute migraine attack, triptans or ergotamine?

Ans: Triptans are better because ergotamine's only cause vasoconstriction and do not decrease nausea and vomiting neurogenic inflammation.

Treatment of Migraine

There are two theories of migraine:

- Vascular theory- Vasodilation of extracranial blood vessels.
- Neurogenic theory- Inflammation of the trigeminal nerve increases the release of CGRP.

Pharmacotherapy of Migraine

Acute Attack of Migraine-

- **NSAIDs-** Diclofenac and Aceclofenac
- **Antiemetics-** Ondansetron and metoclopramide for vomiting sensation and nausea
- **Triptans:** Sumatriptan (drug of choice)
- **Ergots-** Ergotamine and dihydroergotamine
- **CGRP Antagonists-** Ubrogepant and Rimegepant
- **5HT1F Agonist-** Lasmiditan

Prophylaxis

- **Tricyclic antidepressants (TCAs)-** Amitriptyline.
- **Ona botulinum toxin A**
- **Anti-Epileptics-** Gabapentin, sodium valproate, and Topiramate.

- **Beta-blockers-** propranolol, timolol, and metoprolol
- **Candesartan and calcium channel blockers (CCB)**
  - T-type CCB- Flunarizine
  - L-type CCB- Verapamil
- **CGRP Antagonist-** Erenumab, Galcanezumab, Fremanezumab, and Eptinezumab

Important Information

- The triggering factor for migraine is vasoconstriction, followed by vasodilation. In this condition, verapamil can be used as a vasodilator to prevent migraine triggering factor i.e., vasoconstriction.

Table 33.1

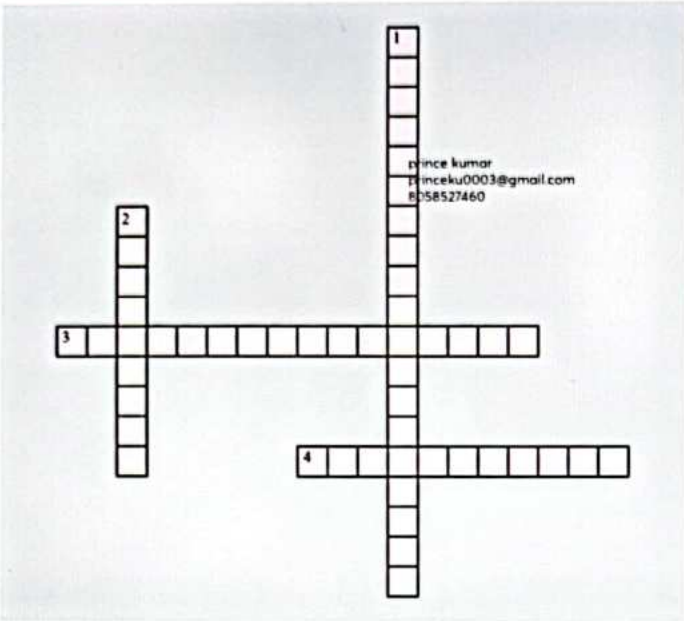
RECEPTORS	TARGET	DRUGS	USES
5HT1	**5HT1A partial agonists**	Buspirone, Gepirone, Ipsapirone	• Chronic anxiety and General Anxiety Disorder (GAD)
	5HT1B/1D agonists	**Triptans:** Sumatriptan Zolmitriptan (nasal) Frovatriptan (long acting) Rizatriptan (fast onset) Eletriptan Narotriptan Almotriptan	• An acute attack of a migraine
	5HT1F Agonists	Lasmiditan (advantage: no vasoconstriction and decrease CGRP)	• An acute attack of migraine with cardiovascular risk patients
5HT2	**5HT2 Antagonists [Atypical antipsychotics]**	Clozapine Olanzapine Risperidone	• Psychosis
	5HT2C Agonist	Lorcaserin	• Lowers obesity (banned because of increase cancer risk)
	5HT2 Antagonist and 5HT1 Agonist	Flibanserin	• Female hypoactive sexual desire disorder
	5HT2 Antagonist	Cyproheptadine (histamine agonist)	• Serotonin syndrome, carcinoid syndrome, and off-label to gain weight in children (not FDA approved)
5HT3 (ion channel receptor)	**5HT3 antagonists**	Ondansetron Alosetron	• Early chemotherapy-induced nausea and vomiting • Irritable bowel syndrome (IBS), Diarrhea predominant case
5HT4	**5HT4 Agonists**	Cisapride Mosapride	• GERD (Gastroesophageal reflux disorder) Presently banned due to increased cardiovascular deaths
		Tegaserod	• Constipation (banned)
		Prucalopride	• Constipation

Table 33.2

Drugs	Effects	Used in
Ergotamine Dihydroergotamine	• Vasoconstrictions and alpha blockage • **Adverse effects;** Fibrosis and gangrene (vasoconstriction)	• An acute attack of migraine
Ergometrine Methyl ergometrine	• Less vasoconstriction and no alpha blocking along with uterine stimulation and sustained uterine contraction	• Post-partum haemorrhage
Ergot-derived drugs: a. LSD (lysergic acid diethylamide) b. Methysergide c. Bromocriptine d. Cabergoline	• Hallucinogen • 5HT2 Blockage	• Migraine prophylaxis (not recommended now)

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Source of ergots
4. Used in acute attacks of migraine

Down

1. Another name for serotonin
2. Targets 5HT2

34 PROSTAGLANDINS

- Prostaglandins are responsible for fever, pain, inflammation, bronchoconstriction, bronchodilation, cervix softening, cervical dilation, and uterine contractions.

Prostaglandin Sources 00:00:45

- Membrane phospholipids get converted into arachidonic acid with the help of phospholipase A2.
- Arachidonic acid is enacted by cox (cyclooxygenase) and lipoxygenase (lox).
- Lox gives leukotrienes; LT C4, D4, and B4
- Cox gives prostaglandins (PG); PG G2, PG H2

PG H2-Derived Prostaglandins 00:02:00

Refer Table 34.1

- Prostaglandins cause inflammation, pain and fever.

Important Information

- Prostaglandins are contraindicated in inflammatory bowel disease (IBD) and inflammatory glaucoma, such as in the anterior uveitis patient with glaucoma.

Adverse Effects of PGS

- Nausea, vomiting, and diarrhoea
- Uterine cramps.
- Abdominal pain
- Fever
- Pain on injection
- Headache and flushing

Prostaglandins: Preparation/Drugs and Uses 00:08:00

Refer Table 34.2

Important Information

- PG F2α causes bronchoconstriction and is contraindicated in a patient with bronchial asthma.

PG F2α DRUGS

- These drugs increase uveoscleral outflow in the eye and are used to treat open-angle glaucoma. For example, Latanoprost, Bimatoprost, Travoprost, Unoprostone.

Q. Can PG F2α drugs be used with bronchial and open-angle asthma patients?

Ans. Yes, the given drugs are safer for a glaucoma patient to use as an eye drop without causing bronchoconstriction.

Cases

Q. A pregnant lady has come with peptic ulcer disease (PUD) and was given misoprostol. Is this condition rational or not?

Ans. Misoprostol is not suggested to treat PUD in pregnant women because it can cause abortion. Hence, this is not rational.

Q. A full-term primigravida comes with labour pains, 8 hours of labour pain, and the cervix is fine but not dilated. What drugs would you suggest?

Ans. Gemeprost or misoprostol can lead to softening of the cervix and dilation.

Q. After the baby's delivery, the same lady developed postpartum hemorrhage. Which drugs can be used in this condition?

Ans. Dinoprostone, dinoprost, carboprost, or misoprostol can be preferred for this condition.

Q. Babies born have transposition of great arteries (TGH). What should be done in this condition?

Ans. Patent ductus arteriosus (PDA) should be kept open until the surgery using the Alprostadil drug.

Q. Baby has developed pulmonary hypertension due to late diagnosis. Which drug is suggested for this condition?

Ans. PG I2 drugs such as Epoprostenol, Treprostinil and Iloprost can be given for this condition.

Table 34.1

Enzyme	Prostaglandins	Use	Effect
Thromboxane synthase	Thromboxane A2	Platelet aggregation	Vasoconstriction and bronchoconstriction
Prostacyclin synthase	PG I2	Inhibits platelet aggregation	Vasodilation
Isomerase	PG E2,	Maintaining gastric epithelium, platelet function, and kidney function	Vasodilator, bronchodilator, and uterine stimulant
	D2,	-	Vasodilator, and bronchoconstrictor
	F2α	Increases Uveoscleral Outflow	Bronchoconstrictor, and uterine stimulation

Table 34.2

Prostaglandins	Preparation/Drugs	Uses
PG E1	Misoprostol	Peptic ulcer disease, Cervical priming, Post-portal haemorrhage, Medical termination of pregnancy
	Alprostadil	Open patent ductus arteriosus, erectile dysfunction
	Gemeprost	Cervical priming
PG E2	Dinoprostone	Induction of labour, mid-trimester abortion, post-partum haemorrhage
PG F2α	Dinoprost	Mid-trimester abortion and post-partum haemorrhage
	Carboprost (15 methyl PG F2α)	
PG I2	Epoprostenol Treprostinil Iloprost	Pulmonary hypertension

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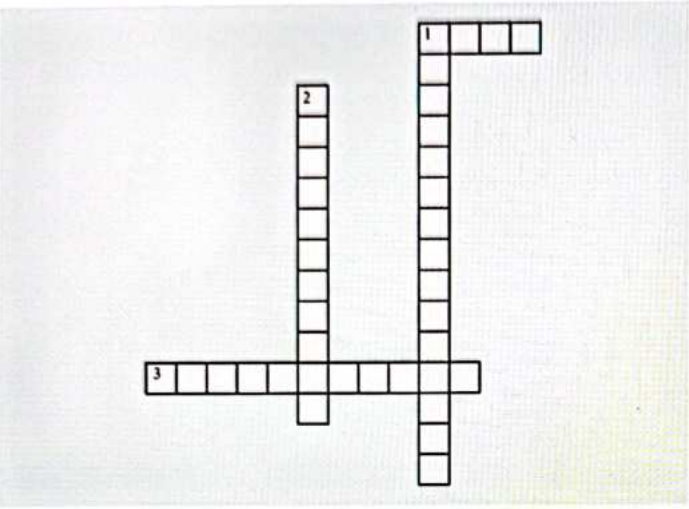
CROSS WORD PUZZLES

Crossword Puzzle



Across

1. Inhibits platelet aggregation
2. PG F2a Drugs

Down

1. Conversion of membrane phospholipids into arachidonic acid
2. Used to treat peptic ulcer disease

35 NSAIDs

- NSAIDs are Non-Steroidal Anti-Inflammatory Drugs.
- NSAIDs are commonly used as Analgesics.

Types of pain and their treatment

- Musculoskeletal pain – NSAIDS
- Cancer – Opioids
- Neuropathy pain - Pregabalin, Gabapentin, Carbamazepine and Amitriptylline

NSAIDS 00:02:12

Mechanism of NSAIDS

Cyclooxygenase (COX)
↓
Prostaglandin synthesis
↓
This prostaglandin synthesis is responsible for fever, inflammation, and pain.
↓
NSAIDs inhibit cyclooxygenase enzymes.
↓
Which in turn reduces the pain.

- There are two types of COX enzymes, COX 1 and COX 2.
- Inhibition of COX 1 by NSAIDS may cause Gastritis, Bleeding, and Analgesic Nephropathy if NSAIDS are used longer.
- Inhibition of COX 2 is for treating Pain, fever, and Inflammation.

Classification of NSAIDS 00:05:56

- Non- selective COX inhibitors.
- Preferential COX 2 inhibitors.
- Selective COX 2 inhibitors.

Non-selective COX inhibitors 00:06:45

- These inhibitors inhibit COX 1 and 2.
- COX enzymes can be inhibited either by reversible or irreversible processes.
  - Irreversible process - Aspirin
  - Reversible process - Other drugs

Non-selective irreversible COX inhibitors 00:07:48

Aspirin	Properties
A	• Aspirin has antiplatelet properties. When a low dose of Aspirin is given, it inhibits the COX enzyme in platelets. • This leads to a decrease in thromboxane A2 as the inhibition is irreversible. • A Decrease in Thromboxane A2 eventually decreases platelet aggregation • Aspirin is the drug of choice for Rheumatic Fever. • Aspirin has antipyretic, anti-inflammatory, and anti-analgesic properties.
S	• S refers to Saturation Kinetics/ Salicylate Poisoning • When a normal dose of Aspirin is given, it follows the first order. • When a high dose of Aspirin is given, it follows zero order.
P	• Prevents colon cancer and Pre-eclampsia. • It prolongs bleeding time.
I	• Irreversible COX inhibitor. • It increases uric acid when less than 2 grams is used.
R	• Reye's syndrome • This syndrome causes Encephalopathy and Liver Damage. • This syndrome is common among children less than 12 years who are under Aspirin medication for viral fever like Influenza.
I	• Ion tapping. • Aspirin is an acidic drug. When it moves into a cell with a pH of 6.8-7, aspirin gets ionized following which aspirin is trapped inside the cell. • This leads to gastritis
N	• Nephropathy • It can cause analgesic Nephropathy and papillary necrosis.

Important Information

- As platelets lack nuclei, they cannot produce new enzymes. The dose of Aspirin should be 162-325 mg during Myocardial Infarction.
- Aspirin is used to treat Niacin-induced flushing.

Non-selective reversible COX inhibitors 00:20:37

Drugs	Properties
Indomethacin	• Decreases Neutrophil Chemotaxis. • Additional anti-inflammatory property • It is used to treat osteoarthritis, rheumatoid arthritis and Gout. • It is used to close Patent Ductus Arteriosus. • **Adverse effects:** Severe Frontal Headache, Psychosis, Hallucinations and Suicidal tendencies. • **Contradictions:** Patients with Epilepsy, Depression, and Psychotic problems.
Ibuprofen	• It is used as an Analgesic in children • It is used to close Patent Ductus Arteriosus • **Adverse effect:** Aseptic Meningitis
Mefenamic Acid	• It gets concentrated in the uterus and decreases the prostaglandin activity • It has antipyretic properties. • It is used to treat dysmenorrhoea.
Paracetamol	• It is called Acetaminophen • Good analgesic and antipyretic drug (Proposed MOA is it inhibits COX 3 in hypothalamus) • However, it is a poor anti-inflammatory drug. (The proposed theory is called peroxide theory. Peroxides in the body will not allow the drug to inhibit COX) • It is preferred in children, Bronchial asthma, safest analgesic in CKD, analgesic of choice in Osteoarthritis, safe in pregnancy and lactating mother • In PCT overdose the NABQI is not metabolised by glutathione leading to hepatotoxicity. • N-acetyl cysteine is the antidote in PCT overdose. It replenishes Glutathione.
Ketorolac	• It is given intravenously and is used for treating post-operative conditions. • It is available as eye drops in markets.
Nabumetone	• It is a pro-drug used for osteoarthritis.
Piroxicam	• It is the longest-acting NSAIDS • It undergoes a process called Enterohepatic recycling, which is why it is considered as longest acting NSAID
Phenylbutazone	• Bone Marrow suppression

Preferential COX 2 Inhibitors 00:34:43

- These Inhibitors block COX 2 preferentially than COX 1.
- The advantage of these Inhibitors is they may lower the risk of gastritis in patients.
- Nimesulide Drug is one of the preferential COX2 inhibitors. The Adverse effect is Hepatotoxic (It harms the hepatic cells).
- Aceclofenac, Diclofenac, Meloxicam, diclofenac and Etodolac are a few of the preferential COX 2 inhibitors.

Selective COX 2 Inhibitors 00:36:43

- These Inhibitors selectively inhibit COX 2. The chances of gastritis are minimal.
- PareCOXib is given intravenously.
- CeleCOXib is given orally.
- RofeCOXib and ValdeCOXib are banned as they increase patients' risk of myocardial infarction.
- Etoricoxib given oral

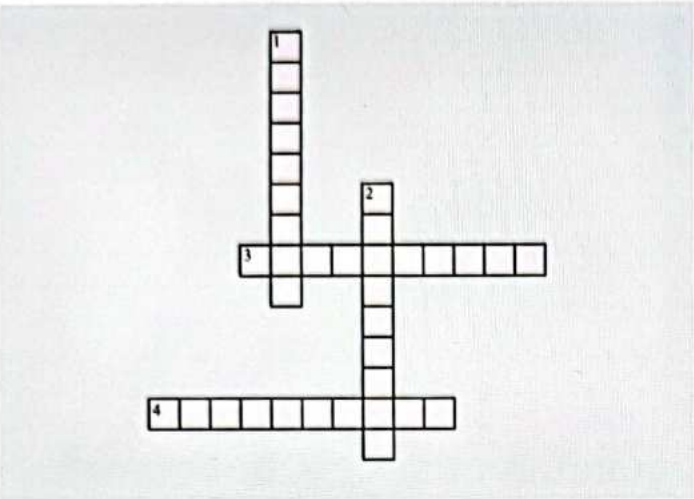
Clinical Questions:

What is Salicylate Poisoning?

- Salicylate Poisoning is known as Aspirin Poisoning, which is very common. The patient's airway breathing circulation and gastric lavage must be maintained; since Aspirin is an acid, no antidote can be given. Hence, Sodium Bicarbonate can be given to treat metabolic acidosis. At last, haemodialysis can be done to remove the Salicylate from the body,

CROSS WORD PUZZLES

Crossword Puzzle 1



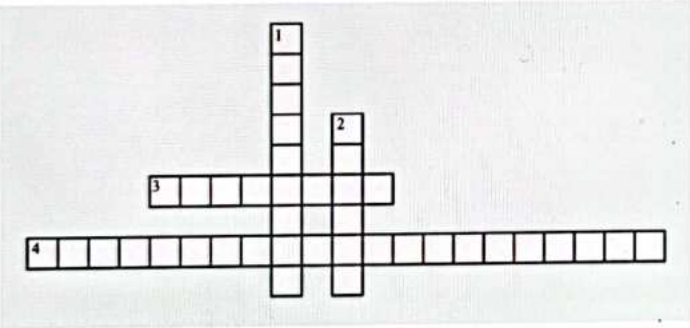
Across

3. _____ drug is one of the preferential COX2 inhibitors.
4. _____ is the other name for NSAIDS

Down

1. _____ causes Myocardial Infarction in patients
2. _____ is minimal due selective to Cox2 Inhibitors

Crossword Puzzle 2



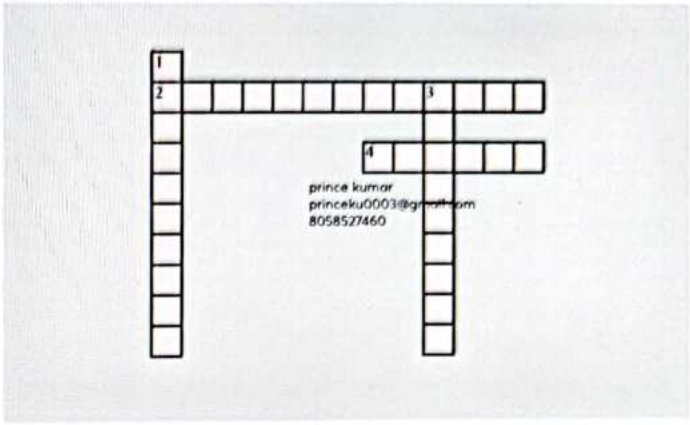
Across

3. _____ is a Non-selective Irreversible Cox Inhibitors
4. _____ arises from cyclooxygenase

Down

1. _____ undergoes a process called Enterohepatic recycling
2. _____ are used in the treatment of cancer pain.

Crossword Puzzle 3



Across

2. _____ is the other name of Paracetamol
4. _____ inhibit cyclooxygenase enzymes

Down

1. _____ is used for in the treatment of osteoarthritis
3. _____ lack nuclei and cannot produce new enzymes

36 GOUT

- Gout is a condition of increased uric acid crystals in joints. The metatarsophalangeal joint is most affected and known as the acute effect of gout.
- Gout can be managed in two ways:
  - Manage the attack
  - Prophylaxis

Pathophysiology of Gout 00:00:40

- Source for uric acid

Purine
↓
Xanthine
↓ Xanthine oxidase
Uric acid
↓
Gets deposited in joints
↓
Inflammation
↓
Neutrophil chemotaxis
↓
Pain (acute gout)

Drugs For Acute Gout 00:02:55

Refer Table 36.1

Important Information

- Aspirin is contraindicated in Gout, which increases uric acid.

Drugs For Chronic Gout 00:05:50

Refer Table 36.2

Allopurinol 00:08:40

- Gives rise to Oxypurinol, which also inhibits xanthine oxidase.
- Oxypurinol is not commonly available (orphan status). It is given when the patient is allergic to allopurinol.

Uses

- Chronic gout (DOC is Allopurinol)
- Tumour lysis syndrome (hyperuricemia)
- Lesch Nyhan Syndrome (rare use)
- Chagas disease
- Secondary hyperuricemia

Contraindication:

- Allopurinol and Febuxostat are contraindicated in acute gout.
- Allopurinol decreases uric acid in circulation by inhibiting xanthine oxidase. Now, uric acid will be stored in tissues (acute gout).
- When used in acute gout, uric acid from tissues decreases and enters the circulation (increased uric acid), which results in the precipitation of acute gout.

Avoid this Problem

- At the start, combine allopurinol/febuxostat with NSAIDs/Colchicine for 3 months. Then continue allopurinol/febuxostat for a longer period and stop NSAIDs/Colchicine.

Drug Interaction

- 6-mercaptopurine (An anticancer drug inactivated by xanthine oxidase) in combination with allopurinol is used to treat tumour lysis syndrome.
- In this combination, allopurinol inhibits xanthine oxidase.

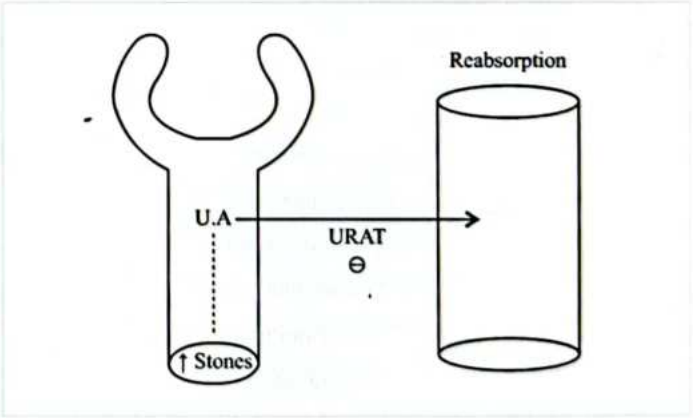
Q. What should be the dose of 6-mercaptopurine in this condition?

Ans. The dose of 6-mercaptopurine level has to be decreased because normal doses can lead to 6-mercaptopurine toxicity.

Uricosuric Drugs 00:16:35

- Probenecid, Sulfinpyrazone, Benzbromarone, Lesinurad, and Losartan (Angiotensin receptor blocker).

Mechanism of Action



- **URAT (uric acid transporter)** helps in the reabsorption of uric acid in blood vessels.
- Uricosuric drugs inhibit URAT to block reabsorption.

Complication

- Uric acid stone risk is increased due to the excess uric acid in urine.
- Proper hydration is recommended.

Important Information

Aspirin

- More than a 5gm/day dose of aspirin decreases uric acid.
  - **Reason-** inhibits the reabsorption of uric acid
- A dose of 2-5gm/day shows no effect on the uric acid level.
- A dose less than 2gm/day increases uric acid.
  - **Reason-** inhibits the secretion of uric acid.
- Loop diuretics and thiazide diuretics also increases uric acid by inhibiting the secretion of uric acid.

Uricase Substitutes 00:22:45

- In bird's uric acid, it is converted into allantoin by uricase and easily excreted in through kidneys.
- Humans lack uricase enzymes and recombinant technology is used to produce these drugs. They are:
  - Rasburicase and Pegloticase are substitutes for uricase which is not produced in humans.
  - Rasburicase is used in Tumour lysis syndrome (Hyperuricemia).
  - Pegloticase is used to treat Refractory Chronic Gout

Table 36.1

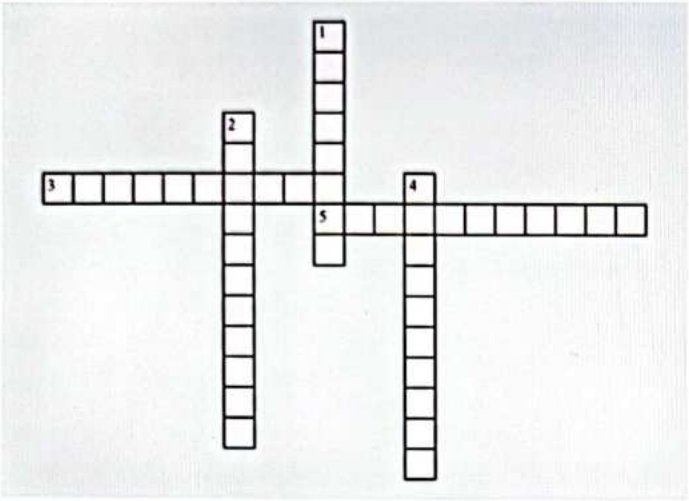
Target	Drugs	Use
NSAIDs (non-steroidal anti-inflammatory drugs)	Diclofenac Indomethacin	Relieve pain
Neutrophil chemotaxis inhibitor	Colchicine • Inhibits microtubules and mitosis. **Adverse effect-** Diarrhoea	Inhibits neutrophil chemotaxis
Inflammation	Steroids (intra-articular)	Decrease inflammation

Table 36.2

Target	Drugs	Use
Xanthine Oxidase	Xanthine oxidase inhibitors • Non-purine- Febuxostat (no-allergy) • Purine- Allopurinol (cause allergy)	Hyperuricemia Gout
Uric acid elimination	Uricosuric drugs: Probenecid, Sulfinpyrazone, Benzbromarone, Lesinurad, and Losartan.	Eliminating uric acid through urine

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Non-purine xanthine oxidase inhibitor
5. Xanthine oxidase inhibitor

Down

1. Uricosuric drug
2. Used in tumor lysis syndrome
4. Inhibits neutrophil chemotaxis

Answer Key

1. Losartan
2. Rasburicase
3. Febuxostat
4. Colchicine
5. Allopurinol

37 RHEUMATOID ARTHRITIS

Rheumatoid Arthritis 00:00:24

- Rheumatoid Arthritis is an Autoimmune Disorder and chronic inflammatory disorder that mainly affects to the joints of human beings, including in the phalanges of the hands and feet.
- Rheumatoid Arthritis mainly affects females.

Symptoms

- Joints destruction
- Joint stiffness
- Chronic pain in joints
- Inflammation in joints

Goals of therapy for Rheumatoid Arthritis 00:01:24

To take care of

- Pain
- Stiffness
- Deformity

NSAIDs 00:03:30

- NSAIDs stand for Non-steroidal Anti-inflammatory Drugs, also called Analgesics.
- NSAIDs are used in the treatment of pain. Commonly used Analgesics are Diclofenac, Aceclofenac, Ibuprofen.

Corticosteroids

- Rheumatoid Arthritis A is an autoimmune disorder, and corticosteroids have autoimmune suppressant properties.
- Corticosteroids have anti-inflammatory properties.
- Here, one major negative point is NSAIDs and Corticosteroids don't modify the disease and don't inhibit the progression of Rheumatoid Arthritis.
- Corticosteroids are used as Bridge Therapy in Rheumatoid Arthritis.
- Here, Bridge Therapy indicates temporary therapy.

DMARDS 00:04:57

- DMARDs stand for Disease Modifying Anti-Rheumatoid Drugs. DMARDs don't act rapidly.
- Therefore, DMARDs are also called SAARDs (Slow Acting Anti-Rheumatoid Drugs).
- **DMARDs are two types:**

1. Non-Biological agents are also known as conventional drugs
2. Biological agents

Conventional and Non-Biological DMARDs

Methotrexate 00:07:00

- Methotrexate is the Drug of Choice of Rheumatoid Arthritis
- **Mechanism of action of Methotrexate is:**
  - Methotrexates inhibit the enzyme, Dihydrofolate Reductase (DHF Reductase).
- Methotrexate has anti-inflammatory and immunosuppressant properties.

Important Information

- Methotrexate is an anti-cancer drug. It suppresses T and B cells. Therefore, methotrexate is used as an Immunosuppressant.

Adverse effect of Methotrexate

- Methotrexate decreases folate, so it produces Megaloblastic Anemia.
- Use Folic acid Supplementation with methotrexate to overcome Megaloblastic Anemia.
- Methotrexate also produces hepatotoxicity, so we regularly need to check L.F.T. (Liver Function Test).

Sulfasalazine 00:08:20

- Sulfasalazine is splitting to 5-ASA (5-amino salicylic acid) and Sulfapyridine.
- Sulfapyridine contains anti-inflammatory properties. Therefore, it is used in the treatment of RA.
- 5-ASA used in the treatment of Ulcerative Colitis (U.C.)
- Contraindication of Sulfasalazine is, don't give a prescription to a patient who has sulfa allergies.

Leflunomide 00:09:11

- **Mechanism of action of Leflunomide is:**
  - Leflunomide inhibits the enzyme, Name is Dehydro Orotate Dehydrogenase.
  - This enzyme is responsible for de-novo pyrimidine synthesis.
  - If inhibition is done, the result is a decrease in T and B cell proliferation.

Important Information

- Methotrexates, sulfasalazine and Leflunomide are the three most important drugs used in the treatment of RA.

Hydroxychloroquine 00:11:15

- Hydroxychloroquine contains lower efficacy in comparison to other DMARDs.
- But it also has anti-inflammatory effects.

- **Adverse effects of Hydroxychloroquine are**
  - In the Eye: If the patient used Hydroxychloroquine for a long period. It produces Bull's eye maculopathy and Corneal Deposits.
  - IN ECG: it produces QT prolongation.
  - It also produces pigmentation in nails and mucous membranes.
- Anti-cancer drug (Azathioprine) is also used in the treatment of RA, but it is not first-line treatment of RA.
- Immunosuppressant (Cyclosporine) is also used in the treatment of RA, and it inhibits Calcineurin.

Older Conventional drugs 00:12:00
- Gold salts and penicillamine.
- Gold salts were used earlier, but currently, they are not used. It is because gold salts were showing too many adverse effects.

Biological Drugs 00:13:10

TNF alpha antagonists
- **Adverse effect:**
  - Increase risk of cancer
  - Increase infections: TB, HBV

Important Information
- **TNF alpha antagonists (Tumour Necrosis Factor).**
  - TNF alpha antagonists increase the risk of cancer during treatment. Because of TNF alpha antagonist, there's necrosis of the tumour. Cancer increases and leads to infection.
  - But we should be very careful in the case of TB and HBV. If the patient has TB and HBV, so the patient will flare up and the condition will be chronic.

Drugs: 00:14:30
- Infliximab
- Certolizumab
- Adalimumab
- Golimumab
- At the end of all drug mab word is present. MAbs word represents Monoclonal Antibodies.
- Etanercept is Non-MAbs (Non-Monoclonal Antibodies)

IL-1 Antagonist 00:15:05
- IL-1 Antagonist represents to Interleukin 1.

Drugs:
- Anakinra
- Rilonacept
- Canakinumab

Janus kinase Inhibitors 00:16:21
- Tofacitinib is a Janus kinase inhibitor. It inhibits JAK 1 and 3.
- Barcitinib is also a Janus kinase inhibitor. It inhibits JAK 1 and 2.
- Upadacitinib is also a Janus kinase inhibitor, but it is not specific for JAK 1, 2 and 3.

IL-6 Antagonis 00:17:05
- IL-6 Antagonist represents Interleukin-6.
- Tocilizumab and Sarilumab are IL-6 antagonists used in the management of RA.
- There is the term SAT 60. In which SA represents Sarilumab and T represents Tocilizumab.
- Tocilizumab was used in the management of Cytokine Storm during Covid-19.

CD 80/86 Inhibitors (Co-stimulation inhibitors) 00:18:10
- Abatacept and Belatacept are co-stimulation 80/86 inhibitors in the management of RA.

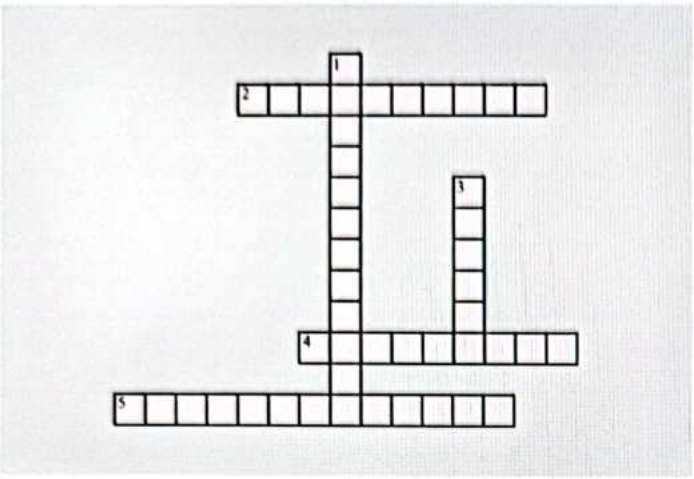
Against CD 20
- Rituximab is a monoclonal antibody used against CD-20 in the treatment of RA.

Important Information
- Biological drugs are highly effective in the management of Rheumatoid Arthritis, But here, one drawback is biological drugs are expensive for patients.
- Everyone can't afford biological drug treatment to cure Rheumatoid arthritis.

For Rheumatoid Arthritis Treatment guidelines: 00:19:35
- If a patient is diagnosed with RA, the use of Methotrexate should be started.
- If the patient is not getting Symptom remission, add leflunomide/Sulfasalazine with methotrexate.
- Still, if the patient is not getting symptom remission, add Biological DMARDs.

CROSS WORD PUZZLES

Crossword Puzzle 1



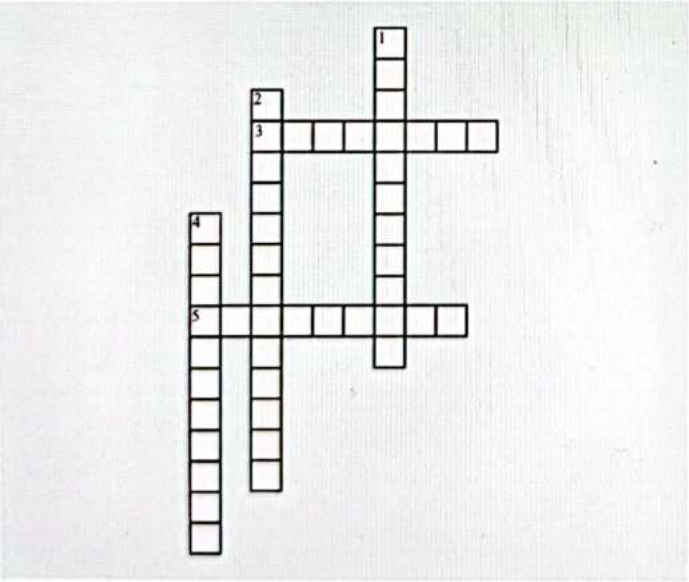
Down

1. Non-biological agents also know_____drugs
3. Corticosteroids used as_____therapy in Rheumatoid Arthritis

Across

2. Rheumatoid Arthritis is the_____ and chronic inflammatory disorder
4. NSAIDs stand for Non-steroidal Anti-inflammatory Drugs, also called_____
5. Methotrexate decreases folate, so it produce _____ anemia.

Crossword Puzzle 2



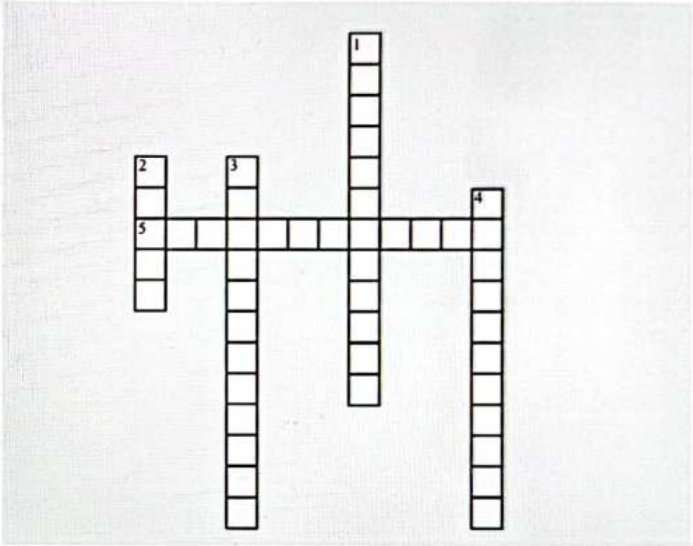
Across

3. Hydroxychloroquine contains lower_____ in the comparison of other DMARDs
5. Contraindication of Sulfasalazine is, Don't give a prescription to a patient who has sulfa_____

Down

1. Immunosuppressant (Cyclosporine) is also used in the treatment of RA, and it inhibits_____
2. Older Conventional drugs are gold salts and _____
4. _____is a Janus kinase inhibitor, it inhibits JAK 1 and 3.

Crossword Puzzle 3



Across

5. Anti-cancer_____ drug is also used in the treatment of RA

Down

1. Immunosuppressant_____ is also used in the treatment of RA
2. _____used in the treatment of Ulcerative Colitis (U.C.)
3. Use Folic acid Supplementation with_____ to overcome Megaloblastic Anemia
4. _____inhibits the enzyme, Name is Dehydro Orotate Dehydrogenase.

38 DIURETIC DRUGS

- Diuretics are drugs that increase Sodium and water excretion in the urine.
- Diuretics are used when sodium and water retention is more in conditions like edema, hypertension, and congestive heart failure.

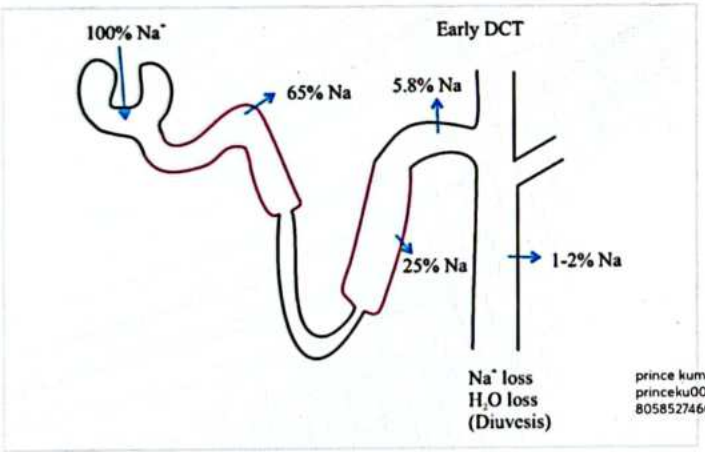
What are diuretics?

- They are drugs that increase the sodium and water excretion in urine.

What is the basic use of diuretics?

- It is used in edema when there is water and sodium retention.
  - Cardiac reasons: congestive heart failure, pulmonary edema.
  - In head injury: cerebral edema.
  - Cirrhotic edema.
  - Kidney reasons: CKD and nephrotic syndrome.
- Another condition where sodium is unwanted is in case of hypertension.

Elimination of Sodium and Water from body



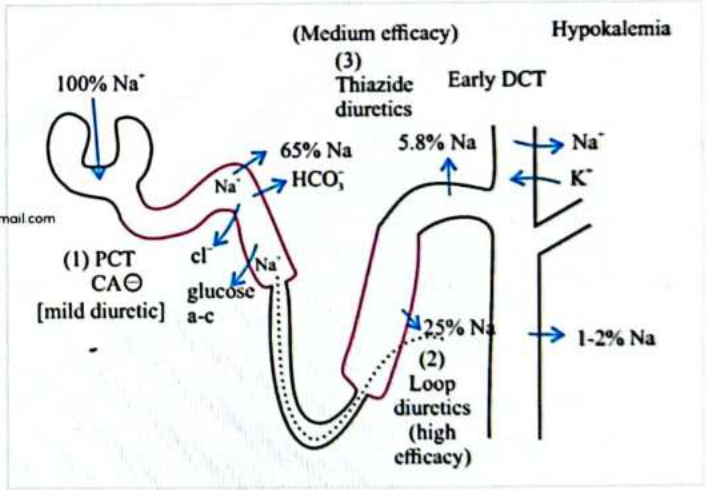
- The elimination is mainly done by nephrons.
- 100% of sodium is filtered at the glomerulus.
- In that 100%,
  - 65% of sodium is reabsorbed into the proximal convoluted tubule.
  - 25% of the sodium is reabsorbed in the thick ascending loop of Henle.
  - Around 5-8% is reabsorbed in the early part of the DCT.
  - 1 to 2% of the sodium is reabsorbed in the collecting ducts.
- If the reabsorption of sodium is stopped it will go into the urine and water will follow. But wherever water goes, sodium will not follow. If sodium is lost water will also be lost and this condition is known as Diuresis. The drug which does this is called diuretics.

The Drugs that Prevent Sodium Reabsorption

- The drugs that act on the proximal convoluted tubule are called carbonic anhydrase inhibitors. They inhibit the enzyme carbonic anhydrase. Their major site of action is PCT.
- The drugs that prevent sodium reabsorption in the thick ascending loop of Henle are called loop diuretics.
- Drugs that prevent sodium reabsorption into the early DCT are called thiazide diuretics.

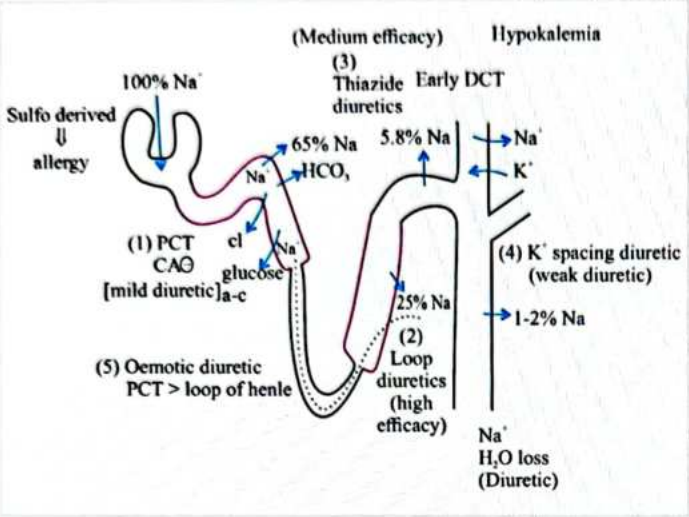
Among these which has more efficacy?

- Carbonic anhydrase is going to inhibit sodium reabsorption with bicarbonate reabsorption.
  - Sodium is reabsorbed along with bicarbonate, chloride, amino acids, and glucose. The sodium reabsorption is continuous with chloride reabsorption and glucose reabsorption.
  - If a carbonic anhydrase inhibitor is used, there is a chance that sodium is getting reabsorbed in the loop of Henle.
  - This is why carbonic anhydrase inhibitors are mild diuretics because it is interfering with one pathway which is sodium and bicarbonate reabsorption. Sodium is still reabsorbed along with the rest of the constituents.
- Loop diuretics lose 25% of sodium reabsorption.



  - 8% of sodium may still be reabsorbed into the early DCT. 2% is reabsorbed into the collecting duct.
  - Even if 10% is reabsorbed we are losing 10% of sodium. This is why loop diuretics are called high-efficacy diuretics.
- In the third case of thiazide, it can be seen that there is a loss of sodium of about 5 to 8%.
  - The efficacy of thiazide diuretic is medium efficacy.

- The carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics are Sulfa derivatives. Patients will have allergic manifestation.
- These drugs tends to lose sodium when there is loss of sodium, the aldosterone helps in reabsorption of the sodium into collecting duct to compensate the sodium entry, the potassium goes out.
- All these three drugs can cause hypokalemia.



Compensation of Hypokalemia

- Hypokalemia is compensated by potassium-sparing diuretics that act at the level of collecting ducts. These will spare the potassium and not allow it to get lost by interfering with the reabsorption of only one to two percent of sodium. These are very weak diuretics.
- Osmotic diuretics that can act throughout the nephron. These have high efficacy.

Q: What is the major site of their action of osmotic diuretics?

Ans: The major site of action of osmotic diuretics is proximal convoluted tubules and the loop of Henle.

Targets of the Drugs 00:10:06

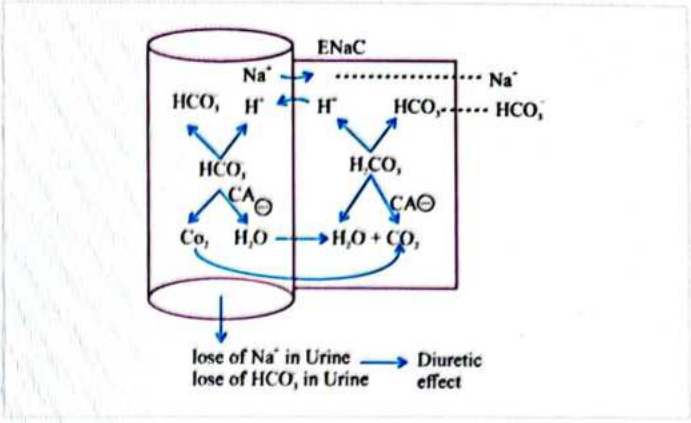
Carbonic Anhydrase Inhibitors

- Drugs:
  - Acetazolamide
  - Brinzolamide
  - Dorzolamide
  - Dichlorphenamide
- They inhibit carbonic anhydrase enzymes.
- The inhibition of the carbonic anhydrase inhibitor is non-competitive enzyme inhibition.

Q. What happens to the V max and KM if it is a non-competitive inhibition?

Ans: V max decreases and KM remains the same.

Mechanism Action of Carbonic Anhydrase inhibitor



- Sodium has to get reabsorbed, on which there is an out coming of H^+.
- The bicarbonate HCO_3^- combines along with the H^+ to form H_2CO_3.
- The H_2CO_3 will split up into H_2O and CO_2 with the help of carbonic anhydrase.
- This water and carbon dioxide can diffuse inside the cell and will combine to form H_2CO_3, again. This is also mediated by carbonic anhydrase. H+ and bicarbonate are again obtained.
- This way, sodium, and bicarbonate are again reabsorbed. This is normal physiology.

- Acetazolamide inhibits carbonic anhydrase. When it is inhibited, one will not get H^+ to exchange with sodium. H^+, thus, cannot combine with bicarbonate. Sodium and bicarbonate are therefore not reabsorbed. This causes a loss of sodium and bicarbonate in urine. This is responsible for diuretic effect.

Loss of Bicarbonate in the Urine

- On the loss of bicarbonate in urine, urine will become alkaline. This increases the chance of calcium and phosphate stones.
- Loss of bicarbonate cause metabolic acidosis. When the bicarbonate is lost, the proximal convoluted tubule will increase reabsorption of chloride. The patient will have hyperchloremia. This condition is called hyperchloremic metabolic acidosis.

Uses

- Acetazolamide is a drug of choice for acute mountain sickness or high-altitude sickness.
  - When a person ascends to a high altitude there is hypoxia causing the patient to breathe faster and lose carbon dioxide. This will lead to respiratory alkalosis. This drug compensates for that by producing metabolic acidosis.
  - A patient at a high altitude develops pulmonary edema, and this being a diuretic can take care of it.

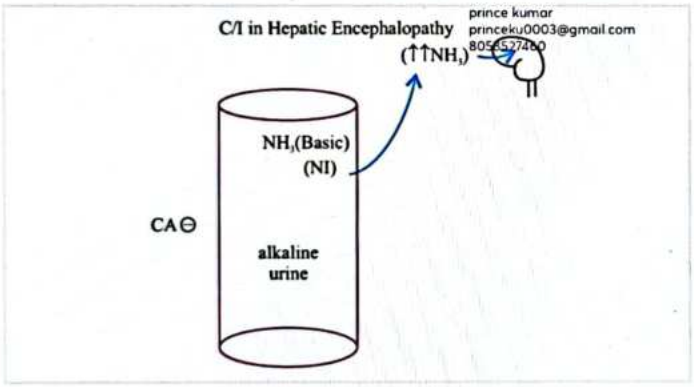
- Acute congestive glaucoma
- Glaucoma.
- Metabolic alkalosis
  - It corrects metabolic alkalosis because acetazolamide produces adverse effect metabolic acidosis.
- Decrease epilepsy (seizures).
- Dorzolamide and brinzolamide are used for glaucoma.
- Dichlorphenamide has been shown to have effect in case of familial periodic paralysis.

Adverse Effects

- Allergy- this happens because these drugs are sulfa derivatives.
- Hyperchloremic metabolic acidosis.
- Alkaline urine- this can lead to renal stones.
- Hypokalaemia
- Somnolence
- Paraesthesia

Contraindication

- Contraindicated in hepatic encephalopathy.
  - Hepatic encephalopathy, a condition where ammonia levels are high, the liver is not working properly and this will cause ammonia to enter the brain and cause encephalopathy. Excessive ammonia in circulation is causing encephalopathy.



  - Ammonia is basic. Ammonia needs to be thrown out, but it can get reabsorbed and well worsen hepatic encephalopathy. When carbonate anhydrase inhibitors are used, they will make the urine alkaline. In this environment, ammonia will become non-ionized, that is lipid soluble and reabsorbed. The ammonia levels will increase causing hepatic encephalopathy to worsen. Carbonic anhydrase inhibitors are contraindicated in hepatic encephalopathy patients.

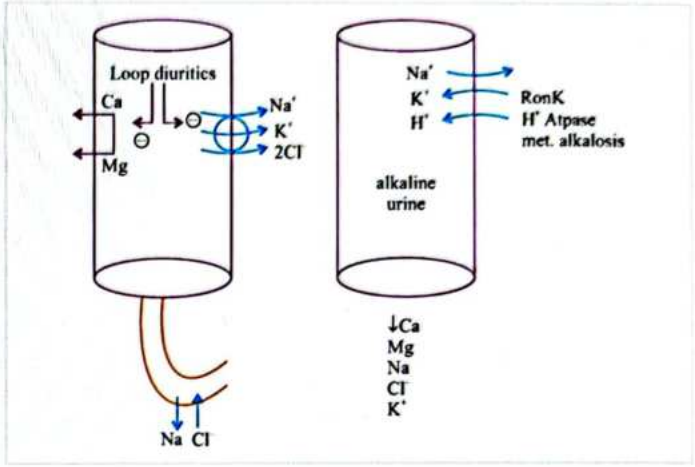
Loop Diuretics (high efficacy diuretics)

- The site of action of these is the thick ascending part of the loop of Henle. In that, they inhibit the transporter called Sodium Potassium 2 Chloride cotransport.

Drugs

- **Furosemide:** The brand name is Lasix, the drug that was lost for 6 hours.
- **Torsemide:** This is long-acting.
- **Bumetanide:** This is most potent and is used in low doses.
- All these drugs are derived from sulfa, and hence cause allergy.
- **Ethacrynic acid** is a non sulfa drug. When a person has sulfa allergy and prefers loop diuretics this drug can be used.

Mechanisms



- Loop diuretics are known to inhibit sodium, potassium, and the two chlorides. It will also prevent the reabsorption of calcium and magnesium.
- From the loop, they come to the DCT where some sodium and chloride are reabsorbed.
- When they come to the collecting duct, sodium goes out, and potassium compensates along with H+. The pump is called renal outer medullary potassium channel (ROMK), and for H+, it is known as the ATPase pump.
- A loop diuretic patient will have hypokalaemia and metabolic alkalosis.
- All the ions will decrease and eliminate sodium, potassium, magnesium, calcium, and chloride in the urine.

Adverse Effects

- **Electrolyte abnormalities**
  - Decrease in potassium that is hypokalaemia. Decrease in sodium that is hyponatremia.
  - Decreasing chloride, magnesium, and calcium. Losing calcium in the urine can cause renal stones.
- **Other side effects**
  - These drugs can produce metabolic alkalosis.
  - There can be a decrease of extracellular fluid.
  - They can cause allergies.
  - There is ototoxicity, toxicity of the ear. This is seen maximum with Ethacrynic acid.
  - Increase uric acid.

Uses

- Pulmonary oedema - Diuretic of choice is furosemide.
  - Furosemide releases vasodilatory prostaglandins which dilates the veins in the periphery. This will cause the fluid to be more in the vein and less in the lungs. This will shift the blood from pulmonary to the systemic circulation. This will help the patient to breathe easily.

- Can loop diuretics be used with NSAIDs?
  - When combined, vasodilatory prostaglandins will not be able to work and will not be able to provide the vasodilatory effect. That is why this combination is irrational.

2. Edema
- Cirrhotic edema
- CKD
- Nephrotic Syndrome

3. Hypercalcemia

4. Hypertension (GFR < 30ml/min)
It can also used in hypertensive emergencies

5. CHF
- Acute
- Chronic
- These are high-efficacy diuretics that cause high urine and are not preferred for chronic therapy. When used for a long period there is a chance of developing resistance and are only given for a shorter period.

Thiazide Diuretics 00:34:28

Thiazide diuretics include:
- Chlorothiazide,
- Hydrochlorothiazide.

Thiazide-like diuretics include:
- Chlorthalidone (longer acting),
- Indapamide,
- Metolazone
  - Thiazide are not effective in CKD patients except metolazone Metolazone even effective when the GFR is 15 ml/min.

Mechanism of Action
- It will inhibit the sodium chloride symport in the early DCT.
- It stimulates the activity of PTH and increases calcium reabsorption.
- These have mild carbonic anhydrase inhibitor properties.
- These are all derived from sulphonamides and have certain properties like acetazolamide.

Uses
- These are the first-choice drugs for hypertension. These are mild anti-hypertensive and can decrease the blood pressure by 5 to 10 mm/Hg.
- Edema:
  - CHF
  - Cirrhotic edema
- Osteoporosis:
  - Because it will helps in the calcium reabsorption.
- These are used to decrease renal calcium stones. If the patient is prone to renal stones again and again then thiazide can be used.
- Diabetes insipidus: both central and peripheral

Adverse Effects
- **Electrolyte adverse effects**
  - There is decreasing potassium, sodium, chloride, and magnesium. But there is an increase in calcium.

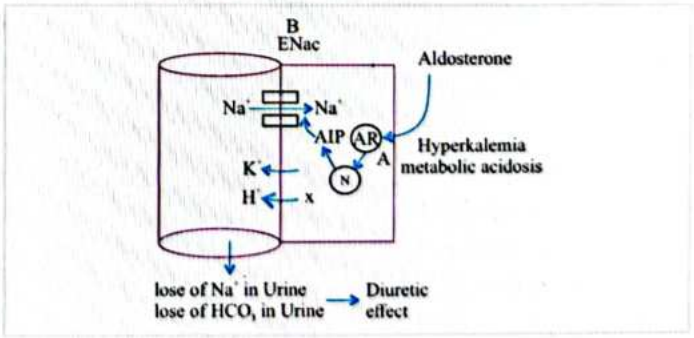
- **Metabolic adverse effects**
  - Increased uric acid (should not be used in a gout patient)
  - Increases glucose.
  - Increases LDL (dyslipidemia)
  - Risk is high when high doses of thiazide is used, and risk is low when a low dose of thiazide is used.

- **Others**
  - Allergy because these are sulfa derived.
  - Metabolic alkalosis.
  - These are medium-efficacy diuretics and can decrease ECF.
  - Erectile dysfunction.

Drug Interaction

Can we give Thiazide and lithium together?
- Whenever a loop diuretic is used, both cause hyponatremia.
- When sodium is lost, the PCT starts reabsorbing more and more sodium, when sodium is reabsorbed lithium is also reabsorbed, and this leads to lithium toxicity. This combination is contraindicated. Thiazides will do this more than loop diuretics.

Potassium Sparing Diuretics 00:45:45



- The main site of action for these drugs is the collecting duct.
- Sodium enters through the epithelial sodium channel. This is potentiated by a drug called aldosterone which acts through the nuclear receptor.
- Aldosterone enters the nucleus through the aldosterone receptor. Aldosterone-induced protein is produced in the nucleus which increases sodium reabsorption. The potassium and H+ will be thrown out.

How to spare the potassium?

- The aldosterone receptor is blocked.
- The epithelial sodium channel can be blocked.
- This will block the sodium from entering. Potassium stays inside leading to hyperkalaemia. H+ also stays inside causing metabolic acidosis.

When is a loop diuretic or Thiazide Given?

- Sodium enters and potassium comes out. Because potassium is not in circulation, to compensate for that, H+ will also come out. When loop diuretic or Thiazide is given, hyperkalaemia occurs along with metabolic alkalosis.

For acetazolamide,

- Sodium is again delivered to the collecting ducts, but it can only lose potassium. Acetazolamide will not lose H+. K+ will be the only Ion to compensate for sodium loss. This is called maximum potassium loss or Kaliuresis.

Aldosterone Receptor Antagonist/ mineralocorticoids receptor antagonist

00:49:07

- This is in potassium-sparing diuretic and is also called mineralocorticoid receptor antagonist (MRA) because mineralocorticoid is aldosterone.
- The main drug here is spironolactone which after metabolism is converted into canrenone. Both, spironolactone and canrenone, are active.
- Another drug is Eplerenone.
- These drugs can increase potassium and produce metabolic acidosis.
  - Aldosterone receptor antagonists act through the interstitial side of the nephron.
- All other diuretics work from the luminal side.

Spironolactone

- It blocks the Aldosterone receptor and the androgen receptor.

Uses

- Corrects hypokalaemia due to diuretics.
- Conn's syndrome or hyperaldosteronism.
- Resistant hypertension which is caused because aldosterone levels are very high.
- Cirrhotic edema, the diuretic of choice.
- Chronic CHF, it will decrease mortality.
- Spironolactone blocks the effect of aldosterone and prevent these effects.
- Hirsutism and PCOD patients because it has androgen blocking property.

Adverse Effects

- Increasing potassium levels.
- Metabolic acidosis.
- Gynaecomastia. (Because it blocks androgen.)
- Loss of libido. (It is an androgen blockade.)
- Menstrual irregularities in females. (Blocks progesterone receptors.)

Eplerenone

- Adverse effect of this drug is the same as above, except for androgen or progesterone blockade.

Epithelial Sodium Channel Blockers

00:55:33

- Amiloride.

Amiloride

- **Uses:**
  - Cystic fibrosis.
  - Used in Liddle's syndrome. ENac channels are hyperactive and will retain more and more sodium and water.
  - Lithium-induced diabetes insipidus in which case it is a drug of choice.
    - → There is a channel (epithelial sodium channel) through which lithium and sodium both enter. Entering lithium decreases the activity of ADH (anti-diuretic hormone). This will lead to the patient having diabetes insipidus.
    - → Amiloride blocks the entry of lithium and thereby blocks diabetes insipidus.
- Hyperkalaemia and metabolic acidosis also occur in this case.

Triamterine

- Adverse effect is that this can cause megaloblastic anaemia.

Osmotic Diuretics

00:58:10

These include:

- Mannitol.
- Glycerol.
- Urea.
- Isosorbide.

Mannitol

Refer Diagram 38.1

- This acts on the tissue.
- When a patient is suffering from cerebral oedema. Mannitol is given, it enters the blood vessel. It is an osmotic agent and will pull the excess from the oedema water into the blood vessel. When water increases inside the blood vessel there is a decrease in pressure in the tissue.
- This causes an increase in blood volume (ECF). The volume will be carried onto the heart and the heart must work more. When the heart pumps, it reaches the nephron. It can act through the entire nephron, but its major place of action is the PCT. Since it is an osmotic agent, it will not allow water to go out of the lumen.
- This will cause massive diuresis along with electrolyte abnormalities.
- This drug is used in cerebral oedema due to decrease blood pressure.
- It is used in acute congestive glaucoma.
- When there is pulmonary edema, the left ventricle has failed. There is back pressure on the lung.
- Mannitol is not used in pulmonary edema.
- Because this drug increases the blood volume, an increased workload is there on the heart. Since the left ventricle has already failed now, if it fails more and more, pulmonary edema worsens.
- In case of head injury and bleeding, blood vessels inside the brain tissue are damaged, and there is bleeding. If mannitol is given to such a patient, it will leave out from the blood vessel, causing more water to be drawn and the intracranial pressure to increase. If there is no active bleeding, mannitol can be used.

Uses

- It is a drug of choice for cerebral edema.
- It is a drug of choice for acute congestive glaucoma.
- It is used in poisoning so that the poison can easily be eliminated through diuresis.
- It is used in impending renal failure. There is a decrease in functioning in such a case and little urine is coming out (oliguria). Mannitol will increase blood volume and urine formation through vasodilation. More urine falls out. It increases the ECF volume, blood volume, and renal blood flow increases, GFR increases, and urine output increases, helping with oliguria.

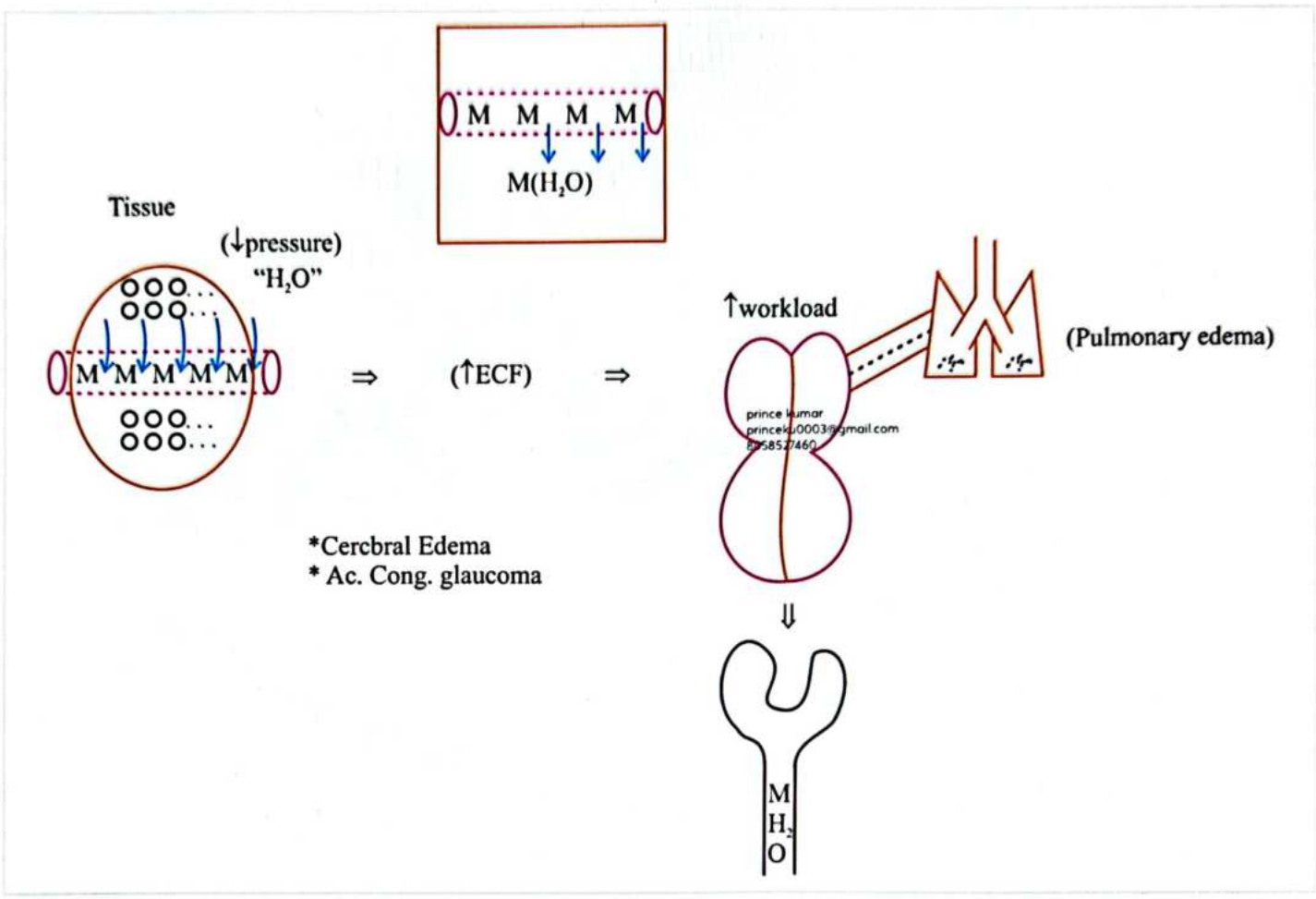
Contraindication

- If there is cerebral hemorrhage (active bleeding) this drug is contraindicated.
- In case of pulmonary edema/left ventricular failure this is not used.
- In case of renal failure/Anuria this is not used. (Blood volume increases and edema worsens if this drug is used.)

Other diuretic drugs are

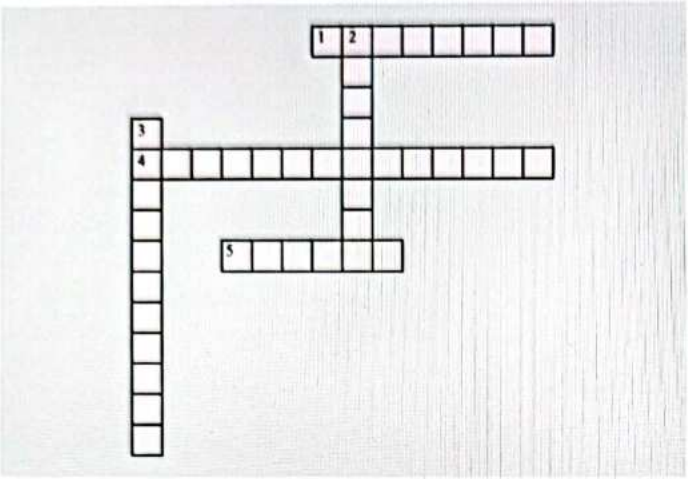
- **Nesritide:** it is a BNP analogue having diuretic property.
- **SGLT - 2 (sodium-glucose transporter) inhibitors:** Empagliflozin and dapagliflozin.

Diagram 38.1


M M M M
M(H2O)
Tissue
(↓pressure)
"H2O"
M M M M M
⇒
(↑ECF)
⇒
↑workload
(Pulmonary edema)
prince kumar
princeku0003@gmail.com
8958527460
*Cercbral Edema
* Ac. Cong. glaucoma
⇓
M
H2
O

CROSS WORD PUZZLES

Crossword Puzzle 1



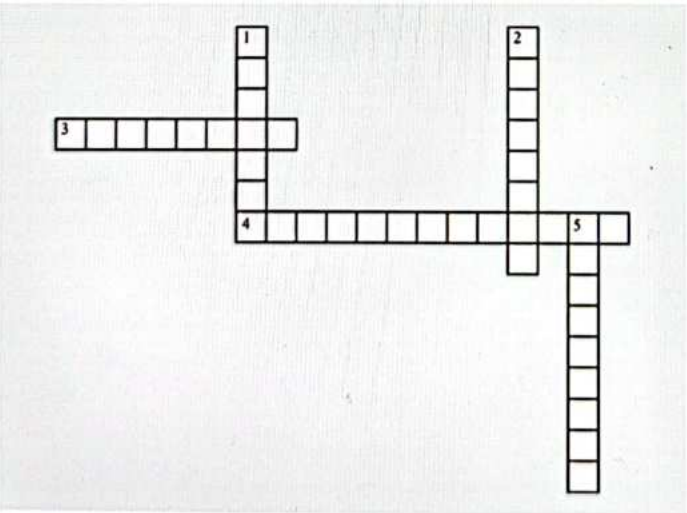
Across

1. If there is cerebral haemorrhage (active bleeding) the drug _____ is contraindicated.
4. A condition where ammonia levels are high and enters the brain is called _____.
5. If urine becomes alkaline, it increases the chance of calcium and phosphate _____.

Down

2. On the loss of bicarbonate in urine, it becomes _____.
3. Mannitol is not used for the case of pulmonary edema/ left _____ failure.

Crossword Puzzle 2



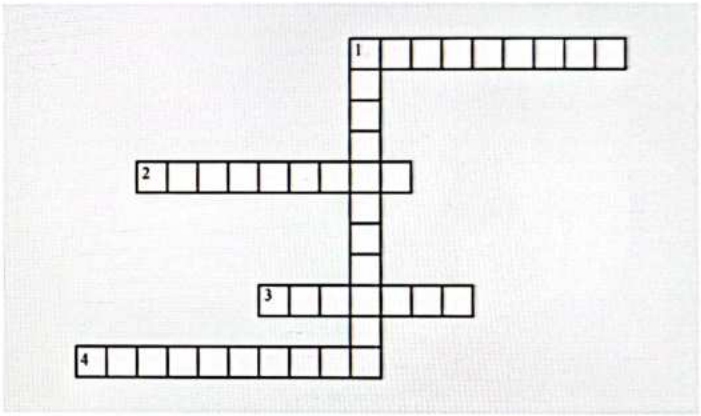
Across

3. In case of renal failure/Anuria, _____ is not used because blood volume increases and edema worsens if this drug is used.
4. The drug _____ is used as a drug of choice in case of acute mountain sickness or high-altitude sickness.

Down

1. When a person ascends to high altitude there is _____ causing the patient to breathe faster and lose carbon dioxide.
2. Mannitol is a drug of choice for cerebral edema and for acute congestive _____.
5. _____ are drugs that increase the sodium and water excretion in urine.

Crossword Puzzle 3



Across

1. In the case of respiratory _____, acetazolamide compensates by producing metabolic acidosis.
2. When carbonate _____ inhibitors are used, they will make the urine alkaline.
3. The major sites of action of _____ diuretics are proximal convoluted tubules and the loop of Henle.
4. Thiazide will normally not work in CKD patients with the exception of _____.

Down

1. When there is loss of sodium, _____ comes into the picture and tries to take up sodium inside the collecting ducts.

39 ANTI DIURETICS

- Antidiuretic drugs are analogs of the antidiuretic hormone, also known as Vasopressin.
- The name consists of two terms "vaso," which means "blood vessels," and "pressin," which means "to constrict. There are two receptors for these drugs; V1 and V2.
  - **V1 selective Drugs-** Terlipressin is used in the treatment of esophageal varices.
  - **V2 selective Drugs-** Desmopressin; used in Central Diabetes Insipidus (CDI), Nocturnal Enuresis, Bed-wetting, Hemophilia, and Von Willebrand Disease.

Important Information

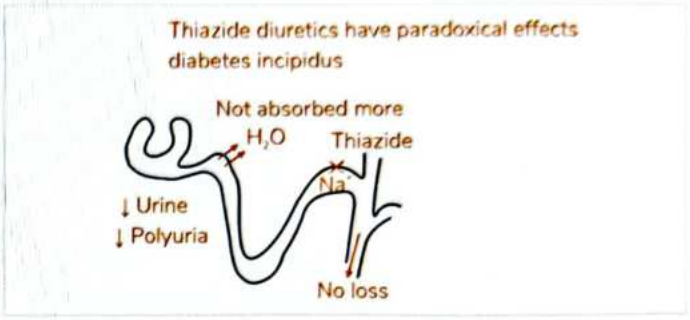
- Vasopressin is separately used as a drug to control Bleeding, Hypovolemic shock, and Cardiac Arrest.
- Felypressin is used with local anesthesia.

Diabetes Insipidus 00:04:10

- Condition in which a patient passes too much urine, causing polyuria and polydipsia.
- Problems of Diabetes Insipidus:

Central (Neurogenic):	Peripheral (Nephrogenic):
No ADH is produced	ADH is produced, but V2 receptors are resistant/mutated
The drug of choice is Desmopressin (DOC)	The drug of choice is Thiazide diuretics

- **Paradoxical effects of Thiazide diuretics in Diabetes insipidus:**
  - The site of action of Thiazide diuretics is the early part of DCT (distal convoluted tubules) that does not allow Na+ to get reabsorbed, and the loss of sodium takes place. As a result, more sodium is absorbed in PCT and water, which causes polyuria (decrease in urine formation).

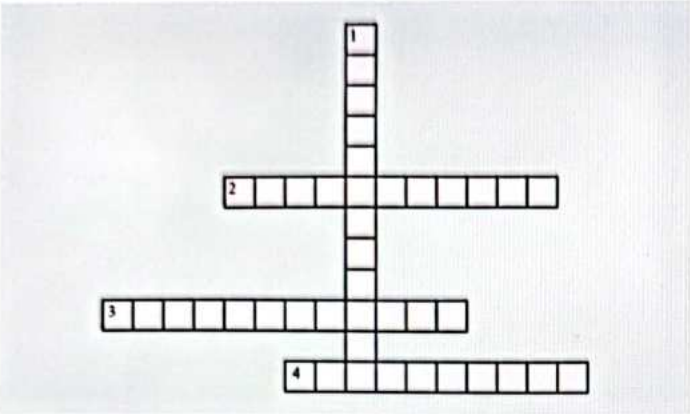


Syndrome of Inappropriate Antidiuretic Hormone (SIADH) 00:08:50

- An excess of ADH in this condition leads to more water and diluted sodium.
- Because ADH acts on V2 receptors, SIADH can be treated by blocking the V2 receptor.
- **Drugs used are:**
  - Demeclocycline (old)
  - **Tolvaptan:** A V2 receptor antagonist used to treat SIADH, correct hyponatremia in CHF patients, and autosomal dominant polycystic kidney disease (PKD).
  - **Conivaptan:** A V1 and V2 receptor antagonist is given intravenously to treat SIADH and manage hyponatremia.

CROSS WORD PUZZLES

Crossword Puzzle



Across

2. used with local anesthesia
3. esophageal varices
4. V1 and V2 receptor antagonist

Down

1. used to treat Central Diabetes Insipidus

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princeku0003@gmail.com
8058527460

40 DRUGS AFFECTING RAAS PATHWAY

Renin-Angiotensin Aldosterone System (RAAS) Pathway

- This system works when the blood pressure falls.
- The RAAS system is hyperactive in a few cases, such as hypotension and chronic CHF.
- This pathway maintains hypotension and CHF.

Pathophysiology 00:00:36

- There is a decrease in renal blood flow when the BP falls. → JG cells detect the decrease in renal blood flow —› JG cells have a receptor known as Beta 1 and release Renin.
- Angiotensinogen gets converted into Angiotensin 1 using Renin.
- Angiotensin 1 gets converted into Angiotensin 2 by the Angiotensin-converting enzyme.
- Angiotensin 2 has two receptors, type 1 and 2.
- **Type 1 receptor functions**
  - Angio- Blood vessel Tension - Contraction Hence, it can cause Vasoconstriction
  - It may increase adrenaline and nor-adrenaline.
  - The activity of Aldosterone can be increased. Aldosterone can cause Sodium and Water retention
- All three functions of the Type 1 receptor lead to an increase in Blood pressure.
- Excess Aldosterone can cause Myocardial Apoptosis, Myocardial fibrosis, and Ventricular Remodelling, it may be chronic and may be problematic in patients with chronic CHF.
- If Aldosterone activity isn't lowered, it increases the mortality rate among patients.
- The heart may stop pumping blood due to these factors. Hence, the patient may either die or require an immediate heart transplant.

Targets to Block RAAS Pathway 00:04:30

- Block Beta receptors which are called Beta Blockers. (These blockers tend to block the effect of adrenaline on the heart, thus lowering the blood pressure.)
- Inhibit Renin which is called Renin Inhibitors. The drug is known as Aliskiren. (It induces vasodilation by blocking the activity of renin.)
- ACE Inhibitor is required to break Bradykinin and Substance P. (Neurotransmitter, which alters the cellular signalling pathways.) ACE inhibitors inhibit the conversion of ACE1 to ACE2.
- Angiotensin Receptor Blockers. (These blockers play a vital role in relaxing the veins and lowering blood pressure.)
- Spironolactone (The most effective drug used to treat blood pressure and heart failure.)

> **Important Information**
>
> - When ACE Inhibitor comes into the act, the breakdown of Bradykinin is inhibited, leading to Dry Cough and Angioedema.

ACE Inhibitors 00:08:37

- Active Drugs
  - Captopril
  - Lisinopril
- Pro Drugs
  - Ramipril
  - Perindopril
  - Enalapril

Uses 00:10:31

- First-line drugs for Hypertension
- Decrease mortality in chronic CHF
- Decreases Microalbuminuria, Preferred in patients with hypertension with CKD/DM
- Sclerodermal Hypotension Crisis.
- Myocardial infarction.
- Hypertension Emergency.

Adverse Effects 00:13:22

- Dry Cough
- Angioedema (Swelling of the layers of skin, which is often characterized by an allergic reaction)
- Hypotension
- Renal Agenesis (Teratogenic in pregnancy)
- High Potassium
- Rash, Dysgeusia (Distortion of taste in patients)

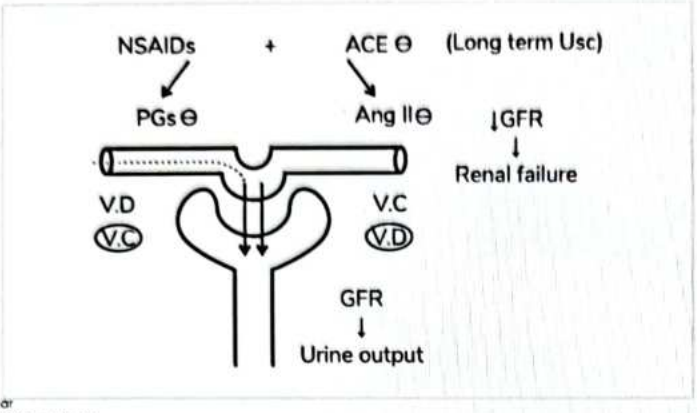
Contraindications 00:16:36

- Hyperkalaemia.
- Bilateral Renal Artery Stenosis (leads to renal failure).
- Pregnancy.
- Angioedema.
- Creatinine > 3 mg/dl.

Drug Interactions 00:17:55

- Angiotensin Converting Enzyme Inhibitor + spironolactone → Increases Potassium which leads to Hyperkalemia

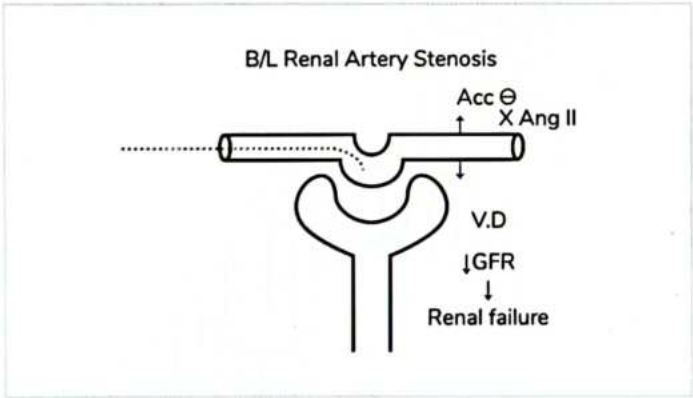
- NSAIDs + Angiotensin Converting Enzyme Inhibitor → Decreased Glomerular Filtration Rate, leads to Renal Failure



- The afferent arteriole has prostaglandins which cause vasodilation.
- The efferent arteriole has ACE2, which causes vasoconstriction.
- Blood filtration occurs when blood flows through these arterioles, known as Glomerular Filtration Rate. (It determines that the kidneys are functioning properly.)
- When ACE inhibitors are used for longer periods, it inhibits ACE2. This causes afferent arteriole to become constricted and efferent arteriole to become dilated.
- This causes a decrease in the glomerular filtration rate.

Bilateral Renal Artery Stenosis

00:20:27



- When Angiotensin Converting Enzyme Inhibitor enters the act, it blocks Angiotensin 2 activity.
- The blood flowing from the afferent arteriole is not filtered and sent to the efferent arteriole.
- This leads to a decrease in Glomerular Filtration Rate, which eventually causes Renal Failure.

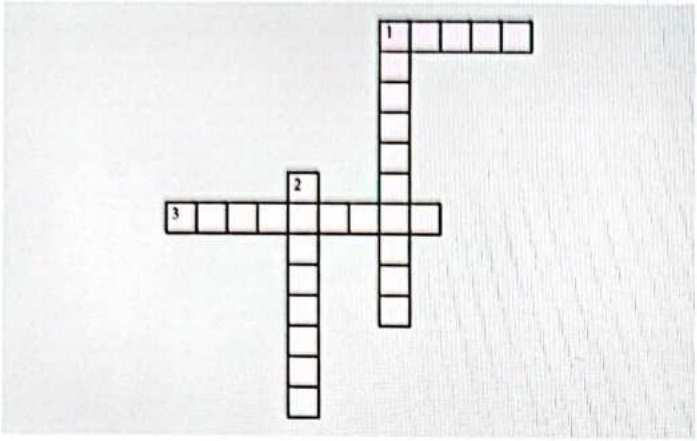
Angiotensin Receptor Blockers

00:22:15

- Candesartan- used as Migraine prophylaxis
- Irbesartan
- Losartan- Decreases uric acid (Uricosuric action), decreases TXA2
- Valsartan
- Olmesartan
- Azilsartan
- Telmisartan- Longest acting, it has PPAR γ agonist.
- Except dry cough and angioedema all the uses, adverse effects, drug interactions and contraindications are same as ACE inhibitors

CROSS WORD PUZZLES

Crossword Puzzle 1



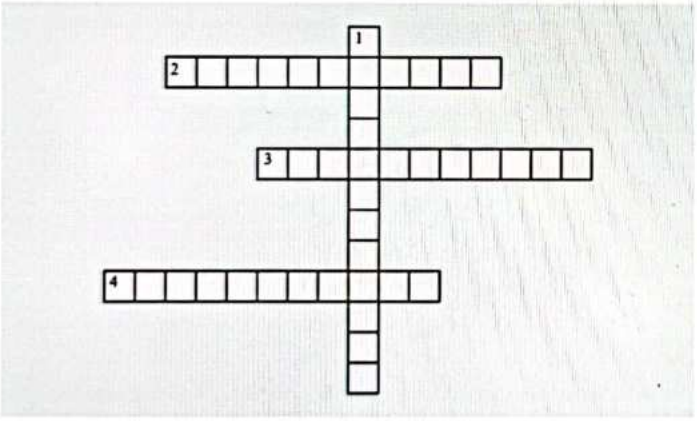
Across

1. _____ the receptor present on the JG cells.
3. _____ is an active drug

Down

1. _____ breakdowns done by ACE inhibitors
2. _____ is an Angiotensin receptor blocker

Crossword Puzzle 2



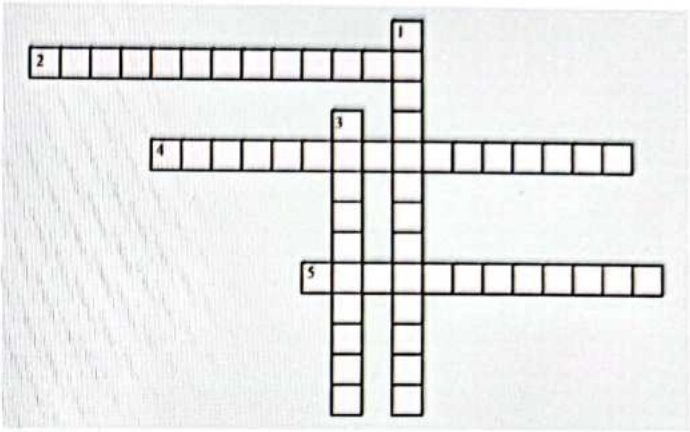
Across

2. _____ causes hyperactive RAAS system
3. _____ causes Water Retention
4. _____ refers to Angio.

Down

1. _____ is converted into Angiotensin 2 by Angiotensin Converting Enzyme

Crossword Puzzle 3



Across

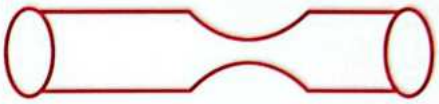
2. _____ increases the activity of Aldosterone
4. _____ occurs in efferent arteriole
5. _____ occurs due to decrease in Glomerular Filtration Rate

Down

1. _____ is present in afferent arteriole
3. _____ is the swelling of the skin layers

41 ANTI ANGINAL DRUGS

Classification

Classical angina	Variant angina
Problem: Since the obstruction or the plaque is stable it is also known as stable angina.  Atheromatous Plaque	**Problem:** The coronary artery is spasmodic which is why it is also called vasospastic angina. Vasospastic / Prinzmetal 
Patient in rest - No Chest pain. Exertion - Chest pain.	The patient has chest pain even during rest.
The two aspects of classical angina are demand and supply. To tackle this the demand can be decreased and the supply can be increased. Demand: • Heart: Beta 1 receptors. • Blood Vessel: If the vein is constricted, it will increase preload. And on an artery called after load. To decrease these two demands, Preload and afterload can be reduced by inducing vasodilators. • Nitrate drugs are called vasodilators. • CCBs • Nicorandil. • Beta Blocker • Newer Drugs } ↓ Demand	There is no exertion and there are no demands. The pain is due to less supply of oxygen. In this case, to increase the supply vasodilators are used: • Nitrates drugs. • CCBs • Nicorandil. Beta-blockers will block the beta receptors and alpha will take over. Which will cause severe Vasoconstriction. That is why beta blocker is contraindicated.

Important Information

- If the treatment for angina pectoris is stopped and the patient has atheromatous plaques which may rupture. The acute coronary syndrome may occur. Acute coronary syndrome consists of three complications- Unstable angina, NSTEMI and STEMI.

Nitrates 00:12:00

- **Nitroglycerine:** It is also called by another name glyceryl trinitrate.
  - It is given as a sublingual tablet or sublingual spray. It is used during an acute attack of angina.
  - Nitroglycerine is also given as oral tablets or as a transdermal patch in cases of prophylaxis of angina.
  - If a patient is having hypertension emergencies or acute CHF the nitroglycerine is given in an IV.
- Isosorbide dinitrate is also given in two forms
  - Sublingual
  - Oral in prophylaxis.

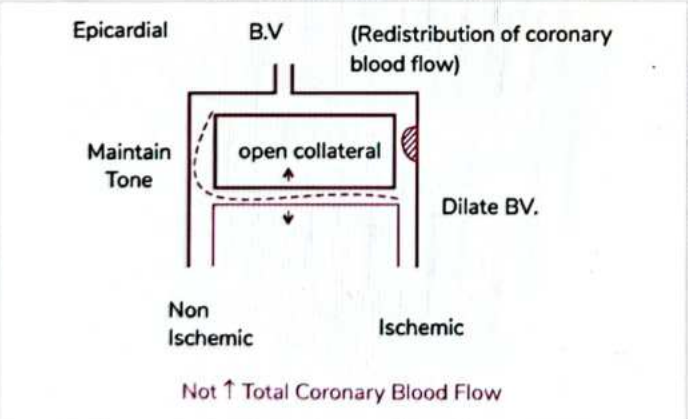
- Isosorbide mononitrate has no or least first-pass metabolism. Oral in prophylaxis.
- Erythrityl Tetranitrate given orally in prophylaxis.
- Pentaerythritol Tetranitrate: Oral in prophylaxis. It is a longer-acting nitrate.
- Amyl nitrate is not used in therapy and it is also a shorter-acting nitrate.

Mechanism of action of Nitrates

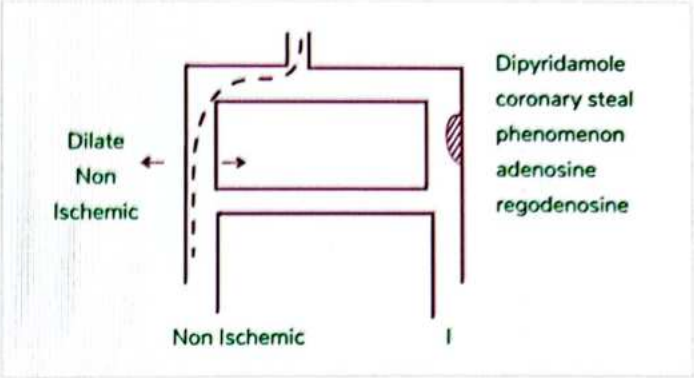
- When nitrate is given, nitrates are metabolized and turned into Nitric oxide.
- **Mitochondrial** Aldehyde dehydrogenases is an enzyme that is used to metabolize nitrate. These enzymes are present more in the vein than in arteries.
- Soluble guanylate cyclase will convert GTP into cGMP. This cGMP inhibits Myosin light-chain kinase. This will result in smooth muscle relaxation.
- Venodilation is more as compared to arteriolar dilation.
- The cGMP action is terminated immediately into 5'GMP; this is done by the enzyme Phosphodiesterase V (PDEV).

Uses of Nitrates

- Stable angina. The major aim of using nitrates in classical angina is that they decrease preload. Which decreases diastolic pressure. Which will result in sub-endocardial perfusion. This will lead to decreased myocardial oxygen demand.
  - They act on epicardial blood vessels. For instance, there is a blockage in the coronary artery. The zone is called an ischemic zone. When nitrate are used, there will be dilation of blood vessels only in the ischemic zone.
  - Nitrates also help in opening the collateral; this is called the redistribution of coronary blood flow.
  - They will not increase total coronary blood flow



  - If they are used in large quantities, reduce the afterload.
  - **Dipyridamole** will dilate the non-ischemic zone. So whatever blood comes in will be diverted towards the non-ischemic zone this is called the coronary steal phenomenon. Other drugs which produce similar phenomena are adenosine and Regadenoson. All these drugs are used for testing. It is called cardiac stress testing. Dobutamine increases the workload of the heart.



- **Prinzmetal Angina:**
  - **Aim:** Increase the supply. And causes endothelium-independent coronary Vasodilation.
- **Acute coronary syndrome:** It can be used in unstable angina, NSTEMI and STEMI.
- **Esophageal spasm.**
- **Biliary colic.**
- **Acute and chronic CHF.**
- **Hypertension emergency.**
- **Cyanide poisoning.** (Drug of choice for cyanide poisoning is Hydroxocobalamin).

Adverse effects of using Nitrates

00:32:15

- They are vasodilators:
  - Dilating the blood vessels of the head will cause headaches.
  - Flushing of the face.
  - Hypotension.
- Reflex tachycardia. (Nitrates with beta-blockers are used/ Verapamil).
- They are smooth muscle relaxers. They can decrease the motility of the small intestine causing constipation.
- Methemoglobinemia. (Suppose the patient has consumed cyanide the patient will be given Sodium nitrite or Amyl nitrite. They will combine with the cyanide and form cyanmethemoglobin). DRUG OF CHOICE FOR CYANIDE POISONING- Hydroxocobalamin.
- Dependence: Coronary dilation depends on the nitrates. When the nitrate is suddenly stopped there is a chance of coronary spasm.

Important Information

- When nitrate is used continuously the patient can develop a condition called tolerance. To avoid it drug-free withdrawal should be given. If the patient is wearing a patch which works 24/7 they should be asked to remove it during the night.

- **Monday's disease:** The disease is seen in workers who work in a nitrate factory. On Monday when they go to work the nitrate will cause their headache and the tolerance build-up and will reduce the headache. Again after Friday when there is a drug free interval they will again have the headache on the next Monday.

Drug interaction of Nitrates

- Nitrate + beta blockers can be used.
- Nitrate + Verapamil can be used.
- Don't use the Nitrate + Sildenafil group of drugs; this combination causes severe hypotension.

Calcium Channel Blockers (CCB) 00:43:22

- Calcium channels are of three types:
  - L - Long Lasting
  - T - Transient. Example: Flunarizine.
  - N - Neuronal. N types of channels are blocked by **Pregabalin and Gabapentin.**

Role of calcium

- Whenever the action potential comes to a smooth muscle the calcium is present inside, this calcium will combine with Calmodulin. And myosin light chain kinase will undergo myosin light chain kinase phosphorylation. This phosphorylation will convert the myosin into Myosin p, which will combine with actin and that will cause the contraction of smooth muscle.
- The nitrate will not allow this phosphorylation. It will increase the cyclic GMP. Which will prevent smooth muscle contraction.

Types of calcium channel blockers

- **Non-DHP (non-dihydropyridine)** - Verapamil and Diltiazem. They work on two tissues:
  - Heart: Decreases the heart rate, decreases the conduction and also decreases the force of contraction.
  - Blood Vessels: They cause vasodilation and decrease blood pressure.
- **DHP (dihydropyridine):** The drug nifedipine mainly acts on the blood vessels. They relax the smooth muscles of the blood vessels. When the vasodilation of the blood vessel occur the BP will fall. And when the BP falls the reflex mechanism is Reflex Tachycardia.

Important Information

- Combination of verapamil and beta-blockers should be avoided. Both of them have similar actions so they might cause bradycardia and AV Block.

Uses calcium channel blockers

- **Non-DHP drugs:**
  - Verapamil: It is used in hypertension, angina and arrhythmia. It is also used in migraine prophylaxis and nocturnal leg cramps.
  - Diltiazem: It is used in hypertension, angina and arrhythmia. It is used in pulmonary hypertension. For pulmonary hypertension inhaled nitrous oxide is used.
- **DHP Drugs:**
  - Nifedipine is used for a sustained release. It is used in two conditions: hypertension in pregnancy and uterine relaxation in pre-term delivery.
  - Amlodipine: It is used in hypertension and the advantage of amlodipine is less chance of tachycardia.
  - Nicardipine: Is given by IV in hypertension emergencies.
  - Clevidipine: Is given by IV in hypertension emergencies.
  - Nitrendipine: Nitrous oxide release.
  - Nimodipine: It can cross the blood-brain barrier. It is used in the condition called subarachnoid haemorrhage.
  - In PVD and Reynaud's disease CCB are the drugs of choice.

The adverse effect of calcium channel blockers

- CCB is predominantly arteriolar dilators.
  - Headache. (That is why it is not recommended to give in attack of migraine. But it can be given as prophylaxis.)
  - DHP's increase heart rate.
  - Non- DHP's decrease heart rate.
  - Flushing.
  - Hypertension.
  - Constipation.
  - Gum hyperplasia.
  - Pedal oedema
- The CCB is contraindicated in the patient with Gastroesophageal reflux disease (GERD). In this case, the acid is coming back to the oesophagus and CCBs are muscle relaxers.

Nicorandil 01:00:35

- **Nicorandil** is a potassium channel opener, which is one of its major mechanisms.
  - Cells are negatively charged and the only positive ion present is potassium. When the potassium channel is opened the potassium will exit and the cell will become more negative this is called hyperpolarization. This will make the cell less excitable leading to smooth muscle relaxation.
- Minor mechanisms include nitrous oxide release.

Beta-Blockers

01:02:21

- Beta blockers include:
  - Bisoprolol
  - Metoprolol
  - Atenolol
- Beta blockers are used in classical angina. As they decrease the heart rate, conduction and force of contract contraction. All these decrease the workload of the heart ultimately resulting in lesser demand for oxygen.
- Beta-blockers are contraindicated in Prinzmetal angina. Beta Blockers are the only drugs that increase life expectancy in angina patients. As the decrease the risk of arrhythmia and infarct size.

Newer Drugs

01:04:58

- **Ivabradine:** It is known to inhibit the funny sodium channel at SA Node. Which decreases the heart rate and oxygen demand.
  - It is used in stable angina and the management of CHF.
  - Adverse effects can cause vision impairment such as Luminous phenomena.
- **Ranolazine:** It inhibits late sodium channels. This late sodium enters the heart and is exchanged with calcium, the increase of calcium will increase angina and arrhythmia.
  - It has no effect on heart rate and blood pressure.
  - It is used in stable angina.
- **Trimetazidine:** They work as partial fatty oxidation inhibitors.
  - It is used in a stable in angina.

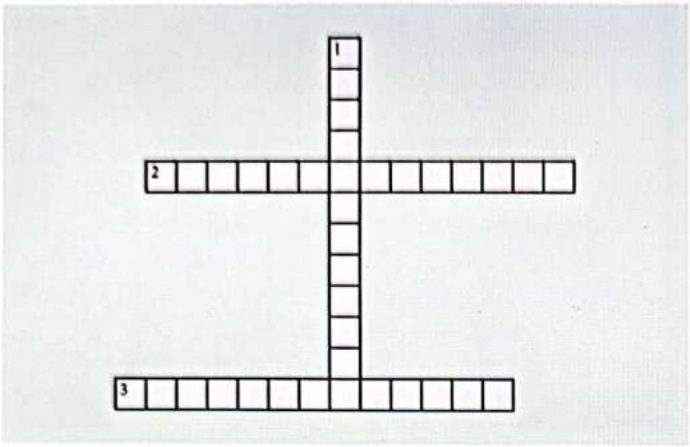
Acute Coronary Syndrome

01:11:20

Diseases	ECG Changes	Cardiac Marker	Management
Unstable Angina	Present	Normal	• Both these cases are managed in a similar way. They are given morphine. As it decreases sympathetic outflow, and anxiety and shifts the blood flow from pulmonary to systemic. • Oxygen needs to be given. • Nitrates (If the patient has hypotension never use nitrates.) • Dual anti-plated therapy. Combination of: o Aspirin 162-325mg o Clopidogrel 300 mg /prasugrel/Ticagrelor • IV metoprolol. • Enoxaparin • Statins • ACE inhibitors /ARBs • Thrombolytics Contraindicated.
NSTEMI	ST depression	Elevated	
STEMI	ST elevated	Elevated	• Drugs are the same that are used in NSTEMI. • Thrombolytics Patient ↓ Medical contact (<2 hrs) Cardiac center (No thrombolytis) Cardiac Center (>2 hrs) ↓ Thrombolytis

CROSS WORD PUZZLES

Crossword Puzzle 1



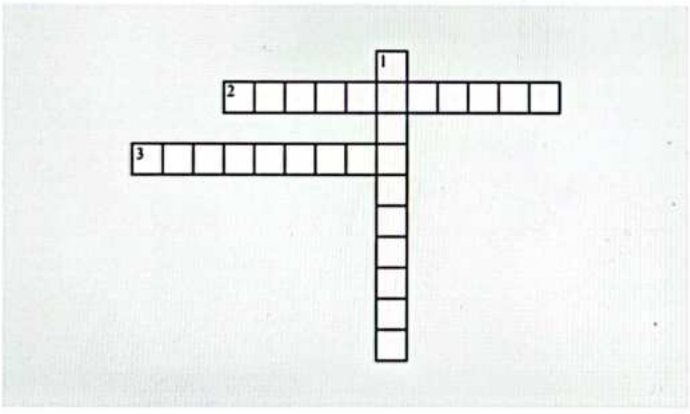
Across

2. _____ is also called by another name glyceryl trinitrate.
3. In _____ the patient has chest pain even during rest.

Down

1. Classical angina is known as _____.

Crossword Puzzle 2



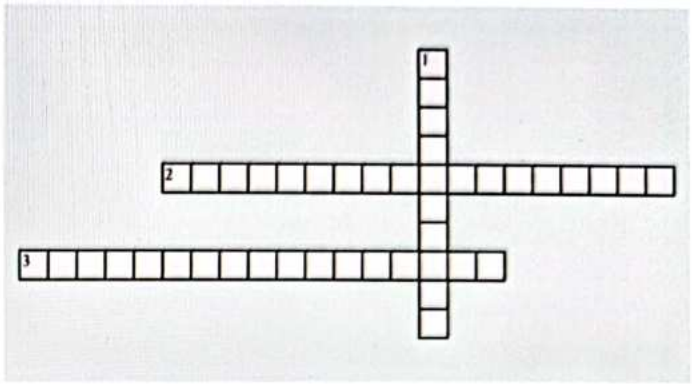
Across

2. _____ is a shorter-acting nitrate.
3. When nitrate is used continuously the patient can develop a condition called _____.

Down

1. The drug _____ mainly acts on the blood vessels.

Crossword Puzzle 3



Across

2. CCB is predominantly _____.
3. When the BP falls the reflex mechanism is _____.

Down

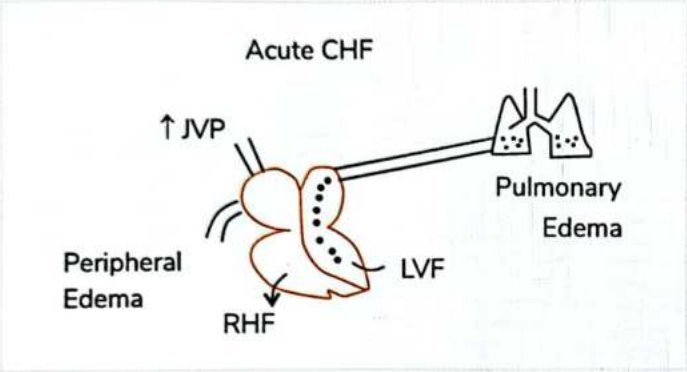
1. _____ is a potassium channel opener, which is one of its major mechanisms.

42 PHARMACOTHERAPY OF CHF

Basic Concept

- Congestive heart failure (CHF) is a condition in which the heart fails to perform its function, commonly due to several reasons, including, myocardial infarction, coronary artery disease, or edema in ventricles. CHF is of two types: acute heart failure and chronic heart failure.
- Acute CHF, also known as decompensated heart failure, which occurs instantaneously and the heart fails to pump blood. It needs immediate medical attention.
- Chronic CHF, also known as compensated heart failure, is a long-term cardiac condition where congestion progresses gradually.

How does it occur? 00:02:30



- When the left ventricle fails to pump blood with sufficient force, oxygenated blood received from the lungs accumulates in the heart creating more pressure on lungs. It leads to fluid accumulation in lungs causing pulmonary edema.
- When the right ventricle fails to pump blood, pressure in the peripheral blood vessel network builds up causing peripheral edema.

Pharmacological intervention of acute CHF

- There are three aspects in the management of acute heart failure:
  - Reduction of edema
  - Decreasing workload on the heart
  - Increasing working capacity of the heart

Reduction of edema

- The principle of treatment is removal of excessive fluid accumulated in lungs or periphery. Most effective and commonly used diuretics are loop diuretics because they produce vasodilatory prostaglandins.
- In turn, the prostaglandins cause veins that bring blood to the heart shifting the bloodstream from pulmonary to systemic circulation. It makes the space required for breathing. The actual diuretic action begins later.
- The most commonly used loop diuretics is furosemide.

Important Information

- Mannitol is a contraindicated IN Left ventricular failure and Pulmonary edema as it increases the extracellular fluid and blood volume increasing workload on the heart muscle. Hence, it worsens the condition.

Decreasing the workload on the heart 00:07:43

- Excessive workload occurs either due to preload or afterload. Preload refers to the work done by heart muscles during ventricular filling before contraction, while afterload is the work done against the force during pumping blood.
- Dilation of blood vessels that makes more space to accommodate excessive fluid reduces the workload. The vasodilators are the drugs that facilitate the process. Commonly used vasodilators are Nitroglycerine, Nesiritide, and Sodium nitroprusside.
- The route of administration of the drugs is intravenous as it is an emergency.

Nesiritide 00:09:22

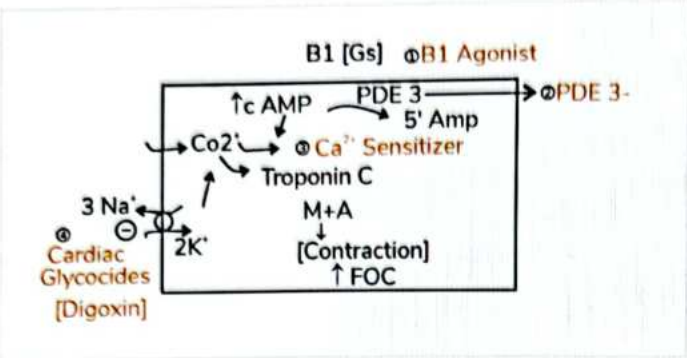
- It is a Brain Natriuretic Peptide (BNP) analogue.
- It is not given orally, only IV.
- It is used in the treatment of Acute CHF
- It works through two mechanisms.
  - **Natriuresis:** it refers to the loss of sodium and water through urine reducing ECF. As a result, the workload on the heart decreases.
  - **Stimulation of mGC:** Nesiritide stimulates membrane-bound guanylyl cyclase, which produces cyclic Guanosine Monophosphate(cGMP) from Guanosine Triphosphate (GTP). cGMP is a vasodilator and decreases preload and afterload.

Increase the working capacity of the heart. 00:12:40

- Due to increase in the blood volume, heart muscle needs more working ability to push excessive blood that enters the ventricles.
- The drugs that increase the working ability of cardiac muscles are adrenergic beta-1 agonists, phosphodiesterase 3 inhibitors and calcium sensitizers. They increase the force of contraction.

Target process for the drugs

- Beta-1 receptors are G-protein coupled receptors that induce the cascade required for cardiomyocyte contraction. Upon stimulation by its agonists, it increases the levels of cAMP which breaks down to 5' AMP by phosphodiesterase 3. cAMP lead to the influx of calcium ions. Troponin C binds with calcium ions mediates the combination of myosin and actin causing the contraction of cardiac muscle.



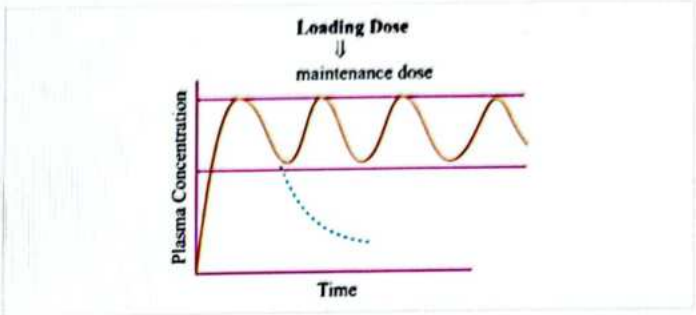
Drugs targeting beta1 receptors and its downstream cascade 00:16:00

- **Beta1 agonists**
  - They enhance the stimulation of the receptors and promote the force of contraction.
  - Dobutamine, Dopamine, Noradrenaline, and Adrenaline are the common beta agonists.
  - Regular use of Beta 1 agonists leads to tolerance.
- **Phosphodiesterase 3 inhibitors**
  - After the stimulation of the beta1 receptor, cAMP undergoes catalysis by phosphodiesterase and becomes 5' AMP. Hence, phosphodiesterase inhibitors in cardiomyocytes prolong the high levels of cAMP and increase the force of contraction (increase in inotropic action). On the other hand, they cause vasodilation and decrease workload.
  - These drugs are also called as Ionodilators
  - The drugs include Amrinone (adverse effect is Thrombocytopenia), Inamrinone, Milrinone, Enoximone and Vesnarinone.
- **Calcium sensitizers**
  - They enhance the interaction between calcium and troponin C increasing the availability of myosin and actin. Thus, increases the force of contraction without increasing the concentration of calcium ions.
  - An additional property of these drugs is Phosphodiesterase 3 inhibition.
  - The drugs include Levosimendan, and Pimobendan.
- **Cardiac glycoside**
  - These inhibit the Na+K+ ATPase pump which leads to influx of calcium ions into the cardiac myocyte which leads to increase in force of contraction of the cardiac muscle.
  - Digoxin is the only cardiac glycoside available.

Digoxin 00:24:35

Pharmacokinetics

- The half-life of digoxin is 40 hours with a narrow therapeutic window of 0.5 to 1.4 ng/ml blood.
- It implies that the intermittent administration based on the half-life takes 8 days (4-5 t½ = 200 hours) to achieve steady concentration.
- Hence, a loading dose followed by a maintenance dose is the best strategy to achieve prolonged therapeutic dosage during acute CHF.



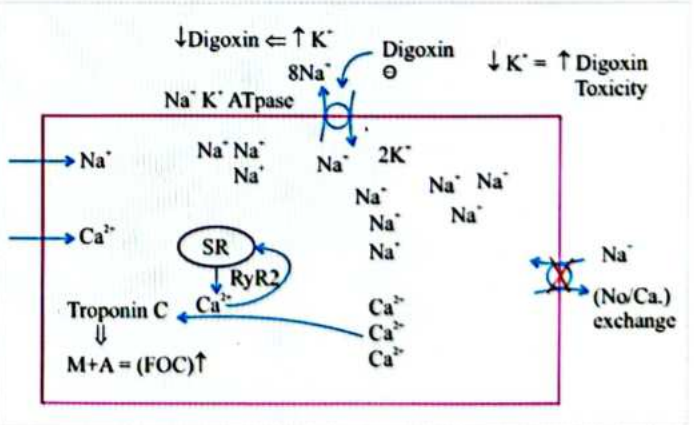
- Digoxin administration must be subjected to caution due to its low toxic dose of 2 ng/ml.
- Therapeutic drug monitoring is crucial because dialysis does not help reduce drug concentration as it has a high volumetric distribution.
- Additionally, digoxin must be administered at lower dosage in patients with renal abnormalities.

Uses of digoxin 00:30:05

- Digoxin is used to treat atrial fibrillation and flutter.
  - It acts as an AV blocking agent through vagomimetic action and decrease heartbeat, decreases conduction.

Mechanism of action of digoxin in CHF 00:33:43

- Digoxin blocks NA+K+ ATPase pump and inhibits efflux of sodium from cardiomyocytes.
- It increases calcium concentration by inhibiting calcium-sodium exchanger as it requires sodium influx, but it is not feasible due to high concentration of sodium. Thus, it enhances the working capacity of cardiac muscles, increase force of contraction.



Adverse effects of digoxin 00:40:10

- GI tract upset causing nausea, vomiting, and diarrhoea.
- Xanthopsia that renders yellow vision.
- Gynaecomastia.
- Digoxin toxicity.

Digoxin toxicity 00:41:25

- Digoxin toxicity can induce all types of arrhythmias except atrial flutter and Mobitz type 2.
- The exception for atrial flutter is due to digoxin's ability to increase atrial excitability.
- It does not cause Mobitz type 2 because it occurs below the AV node while the target of digoxin is above AV node.
- The most common arrhythmia is ventricular bigeminy while the most characteristic one is atrial tachycardia with AV block.

Three influential factors for digoxin toxicity 00:41:25

- **Drug factors:** (Mnemonic- Thank Q VACC)
  - Thiazides or Loop diuretics, Quinidine, Verapamil, Amiodarone, Clarithromycin, and Captopril inhibit p-glycoprotein, which eliminates digoxin.
- **Electrolyte abnormality:**
  - Hypokalemia
  - Hypomagnesemia
  - Hypercalcemia
- **Certain diseases:**
  - Renal failure, hypo- and hyper-thyroidism, myocarditis, and WPW syndrome increases the possibility of digoxin toxicity.

Management of digoxin overdose 00:49:13

- Since dialysis cannot eliminate excessive digoxin, an antidote or a few drugs are the options for the management of the side effects.
- **Antidote:** Digibind, Digifab or digoxin immune antibody are orphan drugs, which are not easily available.
- Other drugs to manage arrhythmias caused by digoxin are in the below table.

Arrhythmia induced by digoxin	Drugs to neutralise the effects
Ventricular tachycardia	Lignocaine
Supraventricular tachycardia	Beta blockers
AV block or bradycardia	Atropine
Chronic toxicity or tachycardia	Potassium supplements or infusion

- DC cardioversion must not be done for digoxin toxicity.
- K+ supplements are not used in acute Digoxin toxicity since K+ is already high which can lead to Hyperkalemia.

ECG changes with digoxin 00:54:22

- The following abnormal changes appear during safe dosing of digoxin and do not necessarily indicate the toxicity.
  - Prolonged PR interval due to blockage of AV
  - Shortened QT
  - ST depression in the form of a reverse check sign called a hockey stick sign.
  - Flattened T-waves.

Management of chronic CHF 00:56:40

- Chronic CHF is also known as compensated heart failure because it allows the heart time to rectify the errors in its functioning. Sympathetic nervous system is activated in response to low cardiac output caused by chronic CHF. It results in the activation of alpha1 and beta1 receptors on the cardiac cells.
- Alpha 1 causes constriction of veins increasing preload and constriction of arterioles increasing the afterload.
- Beta 1 increases heart rate, stroke volume, and cardiac output. Additionally, it activates the RAS pathway that converts renin into aldosterone. Aldosterone enhances the retention of sodium and water to increase cardiac output.
- Though the corrective action increases cardiac output, increased activation of the RAS pathway leads to high levels of aldosterone, which causes ventricular remodelling. It can lead to myocardial fibrosis and apoptosis, causing chronic CHF.
- The main aim of treatment in Chronic CHF is to reduce edema and prolong the life of the patient by decreasing the workload of the heart

Drugs used for chronic CHF

Vasodilators 00:59:31

- Vasodilators are used to relax endothelial tissue of blood vessels to accommodate excessive fluid, reducing the stress on the heart. Two vasodilators are used commonly.
  - Hydralazine is an arterial dilator.
  - Isosorbide dinitrate is a venodilator.

Spironolactone 01:01:42

- It is a mineralocorticoid receptor antagonist that act as potassium-sparing diuretic.
- Eplerenone is another drug similar to spironolactone.

SGLT-2 inhibitors

- They include Empagliflozin, Dapagliflozin, and Canagliflozin.
- They prevent glucose and sodium cotransport to decrease edema.

ACE inhibitors and ARBs

ARNi

- ARNi is a combination of Valsartan and Sacubitril.
- It is ARBs and Neprilysin inhibitors.
- The latter component increases the levels of natriuretic called BNP and ANP by inhibiting the enzyme neprilysin (Inhibited by Sacubitril).
- It also regulates vascular permeability by inactivating bradykinin and Sub P but it poses the risk of angioedema.

Beta blockers 01:05:54

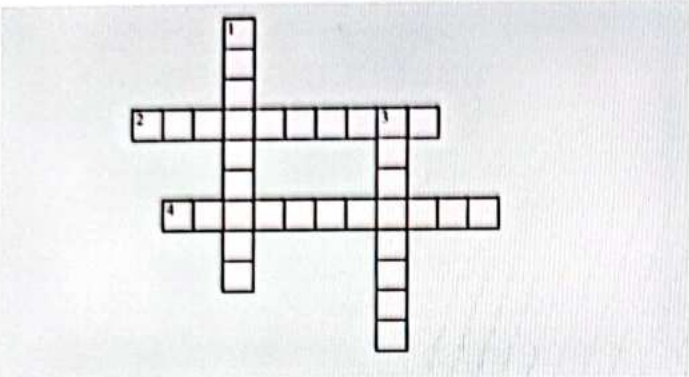
- Beta Blockers decrease the pumping ability of the heart by regulating heart rate, therefore decrease heart rate.
- But studies have shown them to decrease the mortality of patients with chronic CHF by inhibiting Renin.
- They also reduce workload.
- However, they are started with a very low dose of one-eighth of standard dose. Further, the dosage is increased gradually based on the patient's tolerability.
- Beta blockers used in chronic CHF are Bisoprolol, Metoprolol, Carvedilol, and Nebivolol.

Important Information

- In African-American population Hydralazine with Isosorbide dinitrate is used in treatment of chronic CHF.
- Ivabradine decrease mortality in CHF.

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

2. Risk posed by neprilysin
4. Route of administration of vasodilators in the management of acute CHF

Down

1. The Half-life digoxin
3. Contraindicated diuretic in acute CHF

43 HYPERTENSION

- Hypertension means elevated blood pressure.
- When the BP is elevated there are two major complications the initial complication is the patient may have a Hemorrhagic stroke or Hypertensive emergency.

Introduction 00:00:55

- Hypertension is a condition in which the blood pressure of the body is ≥ 140/90 mmHg.
- Some of the immediate complications of hypertension are:
  - Haemorrhagic stroke.
  - Hypertension emergency.
  - Hypertension urgency.
- Some of the long-term complications are:
  - Retinopathy.
  - Nephropathy.

Physiology of Hypertension

- Whenever the BP is decreased there is a stimulation of central sympathetic outflow. It is stimulated to maintain the BP and when that gets stimulated the ganglion is stimulated as well. Which leads to the stimulation of sympathetic fibre they start releasing noradrenaline. This reacts on two receptors:
- **Alpha1 receptor:**
  - It is present in the blood vessels. The action of Alpha 1 causes vasoconstriction. This results in an increase in total peripheral resistance. This will lead to increasing diastolic blood pressure.
- **Beta 1 receptor:**
  - When beta one is stimulated it increases heart rate and also the stroke volume. This means there will be an increase in cardiac output which ultimately results in the rise of systolic blood pressure.
  - Beta one receptors are also present in JG cells in the Kidney sense to decrease blood pressure and start secreting renin. Which produces angiotensin 2 and then it produces aldosterone. And this aldosterone is going to cause Sodium and water retention, lead to increase in SBP and DBP.

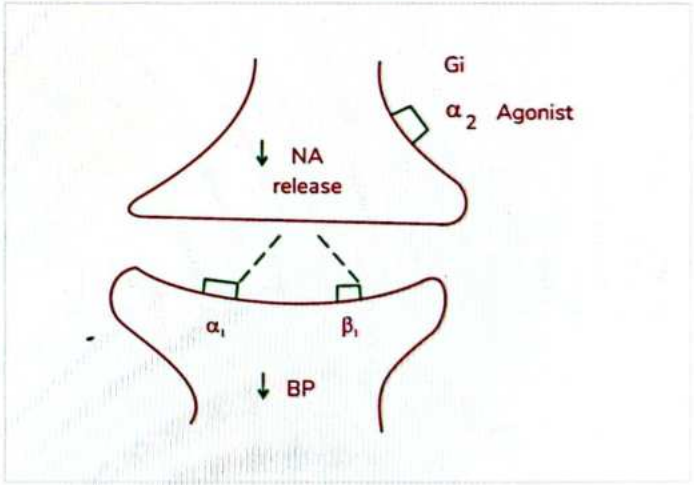
Targeted areas to reduce blood pressure.

- **Block the sympathetic outflow:** Drugs that block the outflow these drugs are called Central sympatholytics.
- **Ganglion should be blocked:** Drugs that block the ganglion are called ganglionic blockers. Nowadays ganglionic blockers such as Hexamethonium and Trimethaphan are not used. (Reserpine inhibit VMAT lead to NA depletion is one of the earlier drugs used to lower the blood pressure in the patient but it was stopped as it increases the risk of suicide among the patient.)
- **Block the Alpha receptors:** The drugs used for blocking the alpha receptors are called alpha-blockers.
- **Block the beta receptor:** The drugs are called beta blockers.
- **Alpha + beta blocker:** They can block both alpha receptors as well as beta receptors.
- **Block the renin:** The drugs are called renin inhibitors.
- ACE inhibitors or ARBs.
- The Sodium and water retention can be removed by using diuretics.
- Hypertension can be managed by not allowing sodium (Potent vasoconstrictor) or calcium to enter the blood vessels.
- Open the potassium channel which will dilate the blood vessel.
- A drug which is responsible for nitric oxide.

Central sympatholytics 00:12:35

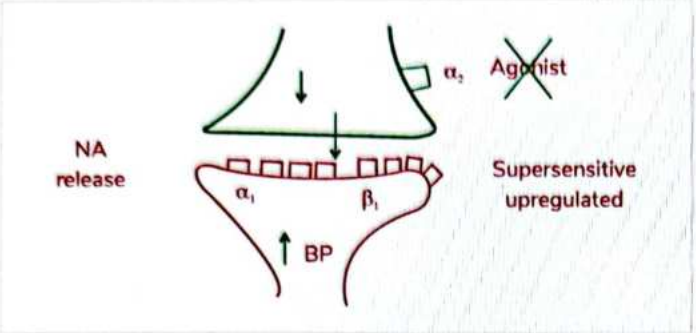
Clonidine

- α2 receptor is the pre synaptic receptors (Gi coupled receptors) and it can decrease Noradrenaline release.
- In the post synaptic terminal α1 and β1 receptors are present.
- If NA is not released BP decreases.
- Clonidine acts as a presynaptic alpha II agonist. It decreases NA release leading to reduction in BP.



- Uses:
  - It is used for resistant hypertension.
  - It is used in opioid withdrawal reactions.
  - Used for diabetic patients having diarrhoea.
  - Postmenopausal hot flush (Transdermal patch).
- Adverse effects:
  - Dry mouth
  - Sedation

- Fatigue
- Erectile dysfunction.
- Clonidine withdrawal reactions. Everyday use of Clonidine causes decreases in Noradrenaline release and α1 and β1 receptors increases and upregulates. Suddenly stopping Clonidine causes a sudden increase in Noradrenaline release causing a Hypertension crisis. Phentolamine is a drug of choice for contradicting clonidine withdrawal reactions.



Methyldopa

- This is a prodrug which after metabolism becomes an Active metabolite called Alpha methyl norepinephrine.
- It acts on presynaptic alpha 2 agonists and decreases NA release and reduction in blood pressure.
- Uses: It is mainly used as a hypertension drug in pregnancy.
- Adverse effects:
  - Dry mouth
  - Sedation
  - Gynecomastia in males.
  - The patient may have Coomb's test positive. Every one in 6 patients have Coomb's test positive. Coomb's test positive indicates risk of Haemolysis. If the patients have symptoms of haemolysis, the drug is stopped. If no symptoms of haemolysis, the drug can be continued

Ganglionic blockers

- Hexamethonium and Trimethaphan are historical blockers that are no longer used in the practices.

Alpha-blockers 00:23:30

Prazosin

- It is called alpha1 selective blocker.
- It is used in hypertension and peripheral vascular disease.
- If a patient has hypertension with benign prostatic hyperplasia alpha-blockers are used.

Phantalomime

- It is a non-selective Alpha-blocker and also a reversible Alpha-blocker, IV given.
- It is used in pheochromocytoma.
- It is used in clonidine withdrawal reactions.
- Cheese reaction.

Phenoxybenzamine

- It is a selective Irreversible alpha-blocker. Which is given orally to the patient.
- It is given to manage conditions such as Pheochromocytoma.

Beta-blockers 00:25:40

- Beta-blockers have two important roles. One is in the heart and another one is in the RAAS pathway.
  - **Heart:** It is known to decrease the heart rate and stroke volume, decreasing cardiac output. Which will decrease systolic blood pressure.
  - **Renin:** The drug inhibits renin which decreases the RAAS pathway. It will contribute to the decrease of systolic and diastolic blood pressure.
- Commonly used beta blockers are cardio selective beta blockers. Such as:
  - Atenolol
  - Metoprolol
  - Nebivolol
  - Bisoprolol
  - Esmolol (I.V): It is given in a hypertension emergency.
- Uses:
  - Hypertension + post-M.I. - reduces the risk of Arrhythmia and decreases the infarct size.
  - Hypertension with anxiety.
  - Migraine.
  - Hyperthyroidism.
  - Chronic CHF.
  - Hypertension with Arrhythmia.

Alpha + beta blockers

- **Labetalol** is used in hypertension. It is a first-choice drug in case of hypertension during pregnancy and hypertension emergency of pregnancy. It is also used in hypertensive emergencies.
- **Carvedilol** is used in hypertension.

Renin inhibitor

- The name of the renin inhibitor is AlisKiren.
- It is used to treat hypertension only.
- It is contraindicated during pregnancy.
- **Drug interaction:** It cannot be combined with ACE inhibitors or ARBs.

Ace inhibitors

- ACE Inhibitors are capable of dilating both the arteries and the Venous.
- They decrease in systolic and diastolic blood pressures.
- There is a chance of increased renin activity.
- **Uses of ACE inhibitors:**
  - First-line drugs in hypertension.
  - Hypertension with chronic CHF.

- Hypertension with diabetes.
- Hypertension with CKD.
- Hypertension with microalbuminuria.

- ACE+ARBs cannot be combined. They are contraindicated in pregnancy
- Aliskiren is contraindicated in pregnancy as well.

Diuretics

- Diuretics are drugs which increase Sodium and water excretion.

Thiazide diuretics

- Drugs include:
  - Chlorothiazide.
  - Chlorthalidone.
  - Hydrochlorothiazide.
- Short-term mechanism:
  - By loss of sodium.
  - By loss of water.
  - By doing that they decrease the blood volume and finally decrease the BP.
- Long-term mechanism:
  - Loss of sodium will lead to decrease in arterial compliance.
  - BP will be decreased.
  - BP will decrease to 5-10mmHg. They are also called mild anti-hypertensive.
- Drawbacks of Thiazide diuretics:
  - Lipid abnormality.
  - Decrease the potassium.
  - The patient may complain of muscle weakness and fatigue.
  - Increase of uric acid.
- In the case of patients having hypertension + gout, this drug needs to be avoided.

Loop diuretics

- Examples of Loop diuretics are Furosemide.
- They are used in hypertension with GFR (< 30 ml/min).
- They are also used in hypertension emergencies.
- Since they develop tolerance, these drugs cannot be used every day in the treatment of HTN.

Spironolactone

- Used in cases where the patient has resistant hypertension. The major reason for resistant hypertension is excess aldosterone and this drug can control it.
- Conn's Syndrome.
- It is also used to manage Hypokalemia due to diuretics.

Sodium blocking

- Since there is no drug to block sodium the patient is asked to reduce their consumption of sodium on a daily basis.
- Recommended intake is less than 5 gm/day.

Calcium channel blocker

00:42:20

- CCB is the first line in antihypertensives.
- Calcium channel blockers are of two types:
  - Non DHP: Examples Verapamil and Diltiazem.
  - DIPINs: Examples are Nifedipine, Amlodipine and Nitrendipine.
- Uses of CCB: Hypertension with peripheral vascular disease.
- The advantages of CCB are:
  - They will not lead to any sexual adverse effects.
  - No metabolic adverse effects.

K+ channel opener

Diazoxide

- Its adverse effect is hypergylcemia. This drug acts on pancreatic Beta cells. And there it opens the potassium channels. When the potassium channels are open there will be a decrease in insulin release. The patient will have hyperglycemia.
- It is used in insulinoma.

Minoxidil

- Earlier it was used in hypertension but the problem is it is a dominant arteriolar dilator.
- Adverse effects: Females started developing Hirsutism.
- Used in androgenic alopecia.

Hydralazine

- It is a potassium channel opener.
- It is a Calcium channel blocker and Nitric oxide Donor.
- It is used in hypertension, Hypertension emergency and Preeclampsia in pregnancy.
- It is used in chronic CHF along with Isosorbide dinitrate.
- Adverse effects: Drug-induced lupus.

Important Information

- Procainamide (Antiarrhythmic) can cause drug induced Lupus.
- Nicorandil (Antianginal) is K+ channel opener.

Nitrous oxide donor

00:50:45

- Examples of NO Donor are:
  - NTG is given by I.V. and used in hypertension emergencies.
  - Sodium nitroprusside: Artery and veins are equally dilated.
- Pharmacokinetics:
  - They are very short-acting drugs. Duration of action: 2-5 mins.

- When infused with IV it can generate cyanide, which in turn forms Thiocyanate in the liver which leads to development of Hypothyroidism
- It has to be freshly prepared and covered with black paper. If the light falls it will inactivate the drugs.

- Uses:
  - Hypertension emergency.
  - Acute CHF.
  - Ergot induced vasospasm.
  - Dissecting aortic aneurysm.
- It should be avoided during pregnancy as it can produce cyanide which is very harmful to the foetus.

Guidelines for hypertension

00:56:19

- There are 12 drugs for Hypertension, and it is unethical to randomly appoint drugs to the patient.
- When a patient is diagnosed with hypertension there is the first line of drugs.
- First line drugs:
  - A: ACE Inhibitors/ARBs
  - C: CCBs
  - D: Thiazide diuretics.
- With the use of all three Drugs if the BP is not coming down this is called resistant hypertension.
  - Spironolactone
  - Clonidine
  - Alpha-blockers
  - Beta Blockers
- When the patient has the comorbidity mentioned above the line of drugs are not used. For instance,
  - A patient has hypertension with BPH- Prazosin.
  - A patient has hypertension with migraine- Beta blockers.
  - A patient has hypertension with gout - Thiazides are contraindicated.

Anti-hypertensive drugs can produce the following problems.

Drugs	Metabolic Adverse Effects	Sexual Dysfunction
ACE Inhibitors/ ARBs	NO	NO
CCBs	NO	NO
Thiazides	Increase Glucose, Uric acid and Lipids	Erectile dysfunction
Beta Blockers	Dyslipidemia	Erectile dysfunction
Alpha Blockers	Good effect on metabolism.	Inhibits ejaculation

Hypertension crisis

01:02:33

Hypertension Emergency	Hypertensive Urgency
BP >180/ 120 mmHg	BP >180/120 mmHg
• Results in end-organ damage. • The BP is reduced in minutes • The patient is admitted to ICU and kept under IV drugs.	• There won't be any end organ damage. • The BP needs to be decreased in hours. • Manage the patient in wards with oral drugs.
Drugs Given: • Phentolamine • Hydralazine • Labetalol (First choice) • Fenoldopam • Enalaprilat • NTG, Nicardipine (First choice) • Sodium Nitroprusside • Clevidipine • Esmolol (Mnemonic- Peak High Looking FENCE)	Drugs Given: • Amlodipine • Labetalol • Captopril • Clonidine.

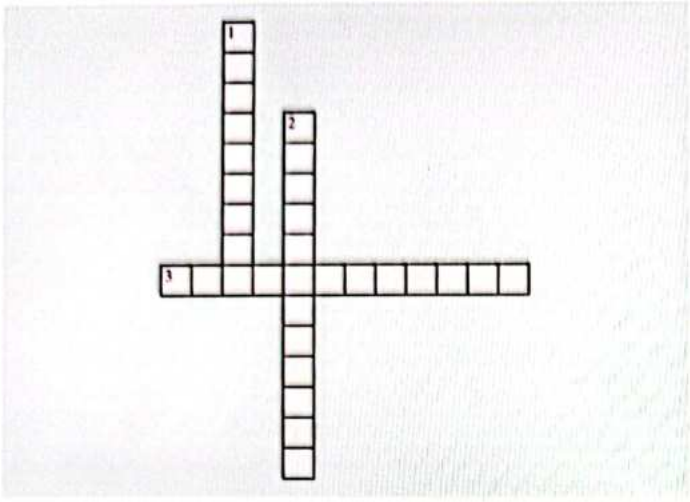
- Safe drugs in Hypertension in pregnancy: (Mnemonic- Let Me Do Care HTN Pregnancy)
  - Labetalol
  - Methyldopa
  - DHPs- Nifedipine (Sustained release)
  - Clonidine
  - Hydralazine
  - Prazosin
- Drugs with high teratogenic risk:
  - ACE inhibitors
  - ARBs
  - Aliskiren

Avoided in pregnancy:

- Thiazide Diuretics: Reduces the Uteroplacental circulation.
- Sodium Nitroprusside: Generates cyanide.
- Spironolactone: It has androgen-blocking properties. If the foetus is male and blocking of androgen can lead to feminine properties.
- Atenolol and non-selective beta-blockers: They increase the risk of small for gestational age babies

CROSS WORD PUZZLES

Crossword Puzzle 1



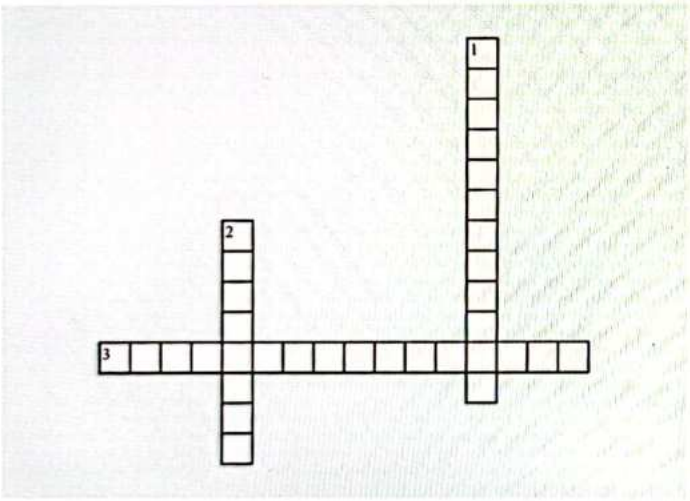
Across

3. _____ is a drug of choice for treating clonidine withdrawal reactions.

Down

1. _____ drug acts as a presynaptic alpha II agonist.
2. _____ means elevated blood pressure.

Crossword Puzzle 2



Across

3. _____ is a selective Irreversible alpha-blocker.

Down

1. _____ is a non-selective reversible Alpha-blocker.
2. _____ is called hyper selective Alpha-blocker.

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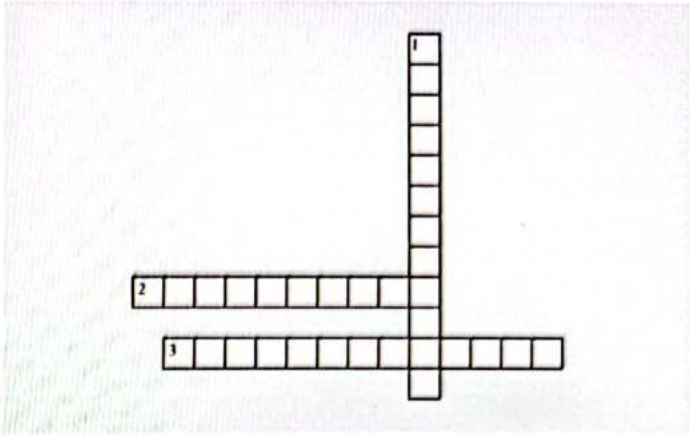
Crossword Puzzle 3



Across

2. Examples of Loop diuretics are_____.
3. _____ are capable of dilating both the arteries and the Vein.

Down

1. Diazoxide's adverse effect is _____.

44 DRUGS FOR PULMONARY HYPERTENSION

Calcium Channel Blockers (CCB)

- Dihydropyridines (DHPs)
  - Amlodipine
  - Nifedipine - Sustained Release formulation (SR)
- Non-Dihydropyridine (Non-DHPs)
  - Diltiazem

Prostaglandin I_2 Analogues

- Epoprostenol
- Treprostenil
- Iloprost

Prostacyclin Receptor Agonist

- SELEXIPAG

Phosphodiesterase (PDE) V Inhibitors

- They increase cyclic GMP and cause vasodilation.
  - Tadalafil
  - Sildenafil

Inhaled NO

- It is preferred in Pulmonary Hypertension in Neonates.

Endothelin Receptor Antagonist

- It can cause vasoconstriction.
- We use endothelin receptor inhibitors to block Endothelin:
  - Bosentan
  - Ambrisentan
  - Macitentan.
- This can be remembered by memorising the 'entan' of all three drugs as ENdoThelin Antagonist (ENTAN).

Oral Soluble Guanyl Cyclase Agonist

- It converts GTP into Cyclic GMP.
- The drug is **RIOCIGUAT.**

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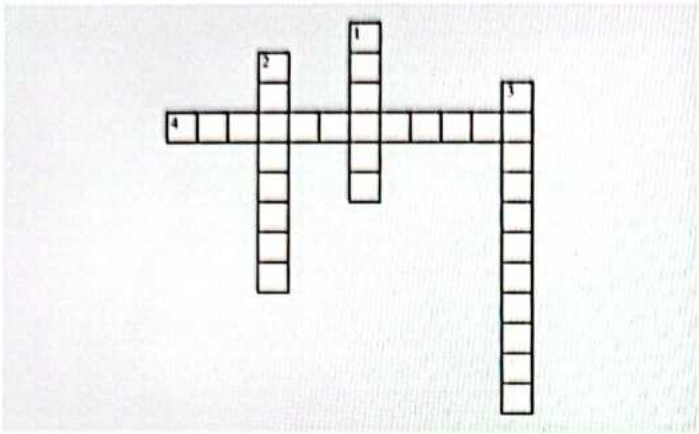
CROSS WORD PUZZLES

Crossword Puzzle 1



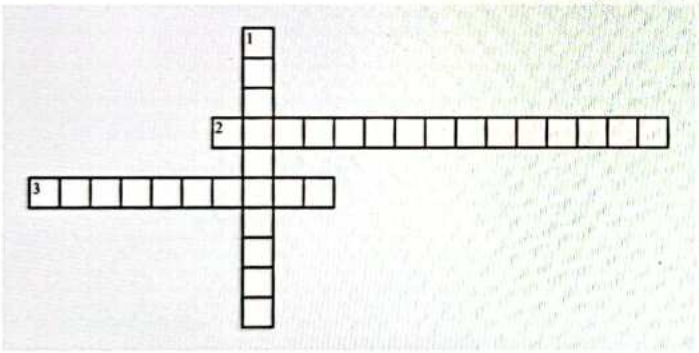
Across

4. Phosphodiesterase (PDE) V inhibitors increase cyclic GMP and cause _____.

Down

1. Oral Soluble Guanylyl Cyclase Agonist converts GTP into ____ GMP.
2. Inhaled NO is preferred in Pulmonary Hypertension in ____.
3. _____ can cause vasoconstriction.

Crossword Puzzle 2



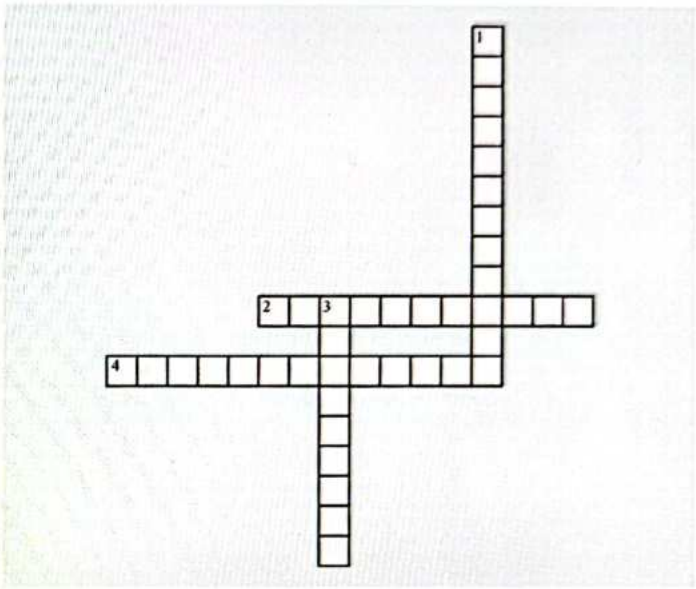
Across

2. Amlodipine is an example of _____.
3. ____ is a dihydropyridine for Sustained Release formulation (SR).

Down

1. Macitentan is an example of endothelin receptor _____.

Crossword Puzzle 3



Across

2. Bosentan is an example of ____ receptor inhibitor.
4. Epoprostenol is an example of _____ I2 Analogues.

Down

1. SELEXIPAG is an example of _____ Receptor Agonist.
3. _____ is a Non-Dihydropyridine (Non-DHPs) drug.

45 ANTI-ARRHYTHMIC DRUGS

Arrhythmia

- Arrhythmias are rhythm disturbances in the Heart. Either the heart is beating too fast or too slow.
- The reasons for arrhythmia include the following:
  - Myocardial infarction
  - High doses of drugs
  - Toxins
  - Electrolyte imbalance
  - Hyperkalemia and Hypokalemia

Management of Arrhythmias

- Certain arrhythmias are severely dangerous. For example, ventricular fibrillation. If the ventricle is fibrillating, it cannot effectively pump blood out and therefore, the patient may die. Thus, it is important to manage arrhythmias.
- The patient's condition must be checked to see if the patient is stable (BP is fine, >90mmHg) or unstable (low BP) to manage the arrhythmia.
- If the patient is unstable, Direct Current Cardioversion (shock) should be done.
- If the patient is stable, then pharmacological cardioversion should be given.

Types of Arrhythmia

00:11:19

Refer Diagram 45.1

- The normal heart rate is between 60-100 beats/min.
- A heartbeat less than 60 results in Bradyarrhythmia, and a heartbeat more than 100 causes Tachyarrhythmia.
- The problem lies in Impulse generation and impulse conduction.
- The SA node is either generating too fast or too slow.
- The heart's conducting system is either too fast or slow because the impulse conduction is blocked (heart block).
- The common types of arrhythmias include the following:

Bradyarrhythmia:

- A heart rate < 60 beats/min causes Bradyarrhythmia.
- This arrhythmia originates from the atria.
- The patient may have a heart block or a problem in the conduction of the AV node (also known as AV block).
- The main drug for Bradycardia and heart block is Atropine which can increase the heart rate and conduction.
- The drug Isoprenaline is used to manage arrhythmias.

Tachyarrhythmia:

- The heart rate is more than 100 beats/min.
- This originates from atria, PSVT, SVT (heart rate is 150-200 beats/min), atrial flutter (200-350 beats/min), and atrial fibrillation (350-500 beats/min).
- The drugs that block conduction and are used in atrial flutter and atrial fibrillation are
  - Beta blockers, which can block conduction. The impulse will not come faster from the atrial ventricle.
  - Non-DHPs: These are calcium channel blockers. E.g., Verapamil, Diltiazem.
  - Digoxin: it is the least preferred drug.
  - These drugs are known as AV-blocking agents.
- The arrhythmias in Ventricle include
  - Ventricular Tachycardia: The impulse may get generated in the ventricle.
  - Ventricular Fibrillation
  - Pulseless Ventricular Tachycardia
- Ventricular Tachycardia and Pulseless VT are the emergency conditions. The patient may die in these situations, so defibrillation has to be done, and then only the drugs are required.

Important Information

- For any Tachyarrhythmia, if the patient is unstable, DC cardioversion should be done.
- If the patient is stable, then the drugs should be given.
- For Ventricular Tachycardia, the drug of choice is Amiodarone. If this drug is not available, then Lignocaine can be given. If Lignocaine is also not available, then beta blockers are given.
- For Ventricular Fibrillation and Pulseless Ventricular Tachycardia, if the patient is unstable, defibrillation should be done. If the patient is not responding, then Amiodarone or Lignocaine can be given.

Action Potential of Atrial, Ventricle and Purkinje Fibres

00:11:55

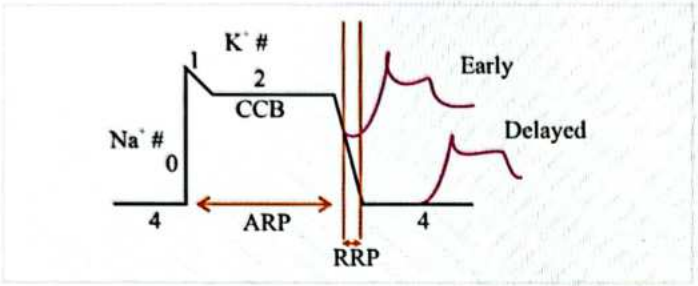
How to bring the rhythm back?

Refer Diagram 45.2

- In arrhythmias, the tissues should be made refractory.
- These are fast-conduction fibres.
- The resting membrane potential in the atria and ventricle is -90mv.

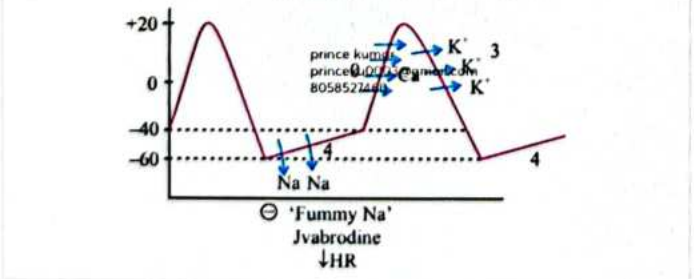
- Even if a stronger impulse is given, the tissues will not react.
- The different phases of the action potential are
  - **Phase 0:** In this phase, the sodium enters the cells, and a positive line is obtained (the graph goes up)
  - **Phase 1:** After the peak, the sodium channel closes, and the potassium keeps on going out, and the graph falls.
  - **Phase 2:** This is the plateau phase because the potassium goes out and the calcium comes in. there is a balance.
  - **Phase 3:** At the end of phase 2, the calcium channel also closes. Only the potassium goes out.
  - **Phase 4:** The cells come back to the normal position. Potassium comes inside, and the sodium goes out.
  - Finally, the same action potential is achieved, and it continues.

Refractory Period



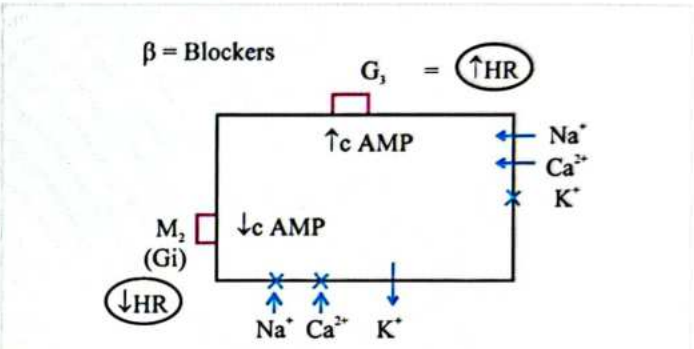
- **Absolute Refractory Period (ARP):** In phase 0,1, 2 tissues are in the Absolute Refractory Period. This means that whatever impulse is given, they do not get excited.
- **Relative Refractory Period:** It is seen in phase 3.
  - If a stronger impulse is given, another impulse can get generated, known as early depolarization.
  - There can be a delayed action potential that can get generated in phase 4, also called delayed after depolarization.
- Sodium, potassium, and calcium entries should be slowed down to make the tissue refractory.
- The refractory period will increase, the duration will increase, and one more impulse will not be able to stimulate the tissues.
- The drugs called Na+ channel blockers, K+ channel blockers, and Ca2+ channel blockers work on these.

Action Potential of Nodal Tissues (SA Node and AV Node) 00:18:38



- The resting membrane potential in the SA node is around -60mv.
- Here, in phase 4, the Na+ is entering inside cell. Since this is not normal, it is funny. Therefore, the Na+ channels are called "Funny Na+ channels"
- To maintain the automaticity, Na+ keeps on coming in phase 4.
- In phase 0, calcium comes inside, and the potassium goes out.
- There are only phases 0, 3, and 4 in the SA and AV nodes. There are no 1 and 2 phases.
- To slow the heart rate, sodium should not be allowed to enter faster into phase 4.
- Ivabradine (not anti-arrhythmic) inhibits the funny sodium channel and decreases the heart rate.
- When the sodium is not allowed to enter, the slope of phase 4 decreases, and the heart rate keeps on decreasing.
- The nodal tissues are controlled by 2 important receptors:

GS Coupled Receptor



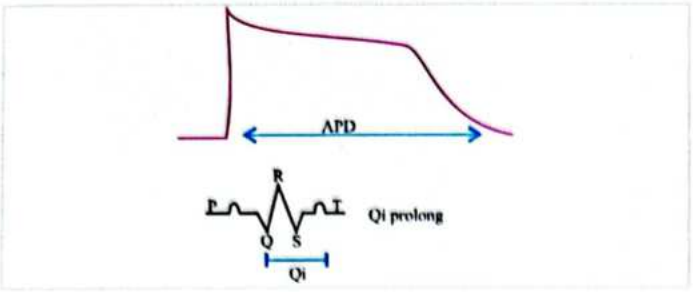
- It is a β1 receptor in the SA node. It increases the cyclic-AMP activity, allowing the entry of Na+ and Ca2+ inside the cell.
- It does not allow the potassium to go out.
- When the Ca2+ and Na+ enter, there is an increase in heart rate because they are going to stimulate.

M2 Receptor (Ga Coupled Receptor)

- This receptor is present in the heart.
- It decreases the cyclic AMP and does not allow the entry of Na and Ca.
- It opens the K+ channel, and the potassium goes out.
- The cell thus becomes hyperpolarized, and the heart rate increases.
- To decrease the heart rate in Tachyarrhythmia, β-blockers (anti-arrhythmic drugs) should be given.
- Calcium channel blockers (CCBs) are also used in arrhythmias. They also act on the nodal tissues and decrease the heart rate. The drugs are
  - Verapamil
  - Diltiazem

Blocking K^+ Channel

00:26:23



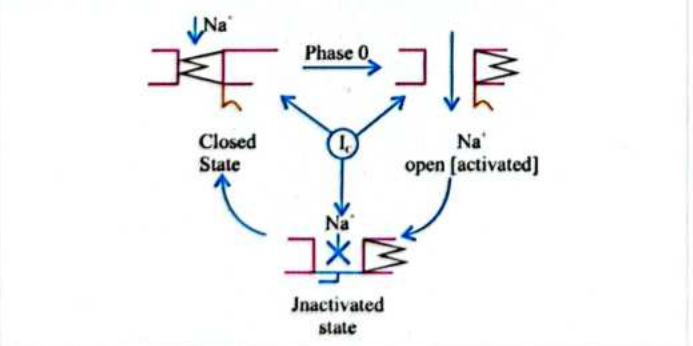
- Any K+ channel blocker will increase the Action Potential Duration (APD).
- APD becomes prolonged.
- ECG has P, Q, R, S, and T waves. The interval between Q and T waves is the QT interval.
- Any drug which blocks the K+ channel will cause QT prolongation (APD is increased).
- The refractory period also increases.
- The advantage is that the tissues will not get excited.
- If excessive blockage occurs, it can cause arrhythmia called Long QT syndrome.

Important Information

- Sodium ions quickly take the impulse from the brain to the periphery.
- Anti-epileptic drugs, the sodium channel blockers.
- Long QT syndrome is a Ventricular Tachycardia with prolonged QT interval. It can be congenital by birth. For this, the drug of choice will be beta blockers.
- Long QT syndrome can be acquired by Class Ia and Class III drugs.
- Antibiotics that can produce them are Bedaquilline, which can cause QT prolongation. The drugs FQs and Macrolides can cause this, so the drugs should be stopped.
- If the patient has an acute attack of Long QT syndrome or Torsades de Pointes, the drug of choice should be Magnesium sulfate.

Classification of Antiarrhythmic Drugs

00:40:35

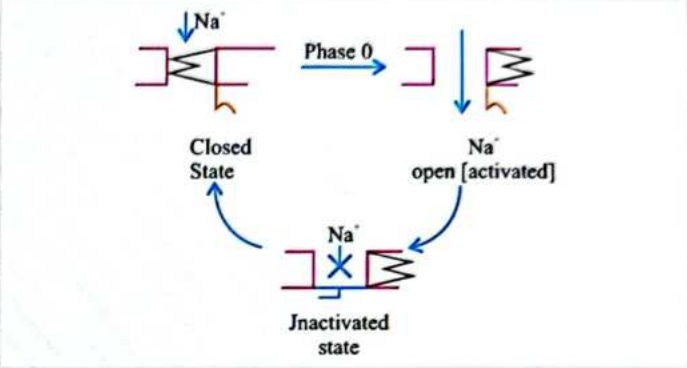


- The classification is given by Vaughan – William Singh (Mnemonic- Saved by Pharma Class)
  - Class I antiarrhythmic drugs – they mainly block Na channels.
  - Class II antiarrhythmic drugs – block beta receptors.
  - Class III antiarrhythmic drugs – block K+ channels.
  - Class IV antiarrhythmic drugs – block Ca+ channels.
  - Miscellaneous.

Class I Anti-Arrhythmic Drugs

00:28:25

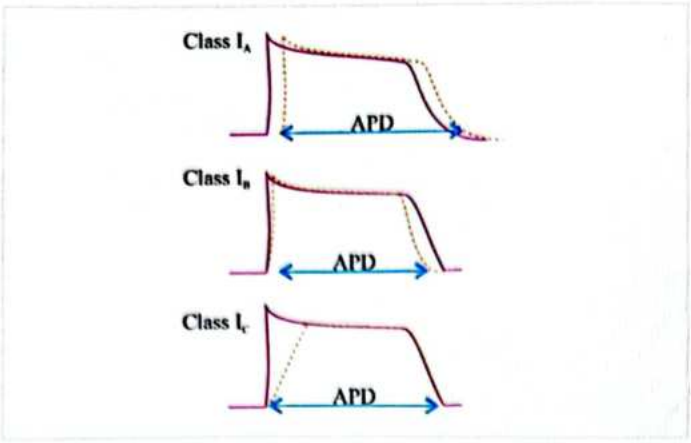
- These are Na+ channel blockers.
- Classified into Ia, Ib, and Ic.
- Sodium channels in the cell membrane exist in three forms:



  - **Closed state of the Na+ channel:** The M gate is closed, so the Na+ channel cannot enter.
  - **Open/activated state of Na+ channel:** In phase 0, once the Na+ starts entering, the M gate opens up. The H gate is still open and the Na+ can enter inside.
  - **Inactivated state of Na+ channel:** In this state, the M gate is still open, but the H gate will close the channel, so the sodium cannot enter.

- Antiarrhythmic drugs can block all the states but they are attracted to some particular states
- Class Ia drugs block the open state of the Na+ channel.
- Class Ib, particularly the Lignocaine group will block the inactivated state more than the open state.
- Class Ic can block all the states. It seems to be dangerous because it can block all the states.

- Antiarrhythmic drugs themselves can cause arrhythmia if they block these channels for a very long period which can be dangerous. So there is a risk.
- Class Ia drugs bind to the Na+ channel for 1-10 seconds.
- Class Ib drugs bind to the Na+ channel for <1 second.
- Class Ic drugs bind to the Na+ channel for a very long time (>10 seconds).



- When the Na+ is blocked, the slope decreases and there is a decrease in dv/dt. This is done moderately by class Ia drugs. They block the K+ channel and the APD will increase.
- In class Ib class, they decrease the dv/dt slope because they do not bind to the N+ channel for a very long time. Thus, the slope has decreased mildly. The Action Potential Duration (APD) will shorten, as they open the K+ channel.
- Class Ic drugs decrease the dv/dt slope because they bind to the Na+ channel for a very long time. There is a marked decrease in the slope. There is no effect on the K+ channel, so the APD remains the same.

Class Ia Drugs 00:40:30

- Class Ia drugs can be used in atrial and ventricular arrhythmias. It is avoided in long QT syndrome
- The drugs are:

Quinidine

- It increases AV conduction.
- It is an alpha-blocker. It decreases blood pressure.
- It increases the release of insulin. The patient may develop hypoglycemia so monitoring should be done.
- It is a direct skeletal muscle relaxant.
- It has been shown to cause diarrhoea.
- It is obtained from a plant product known as Cinchona bark. If given at a high dose, it can cause Cinchonism, leading to
  - Tinnitus (ear problem).
  - Diplopia (eye problem).
  - CNS excitation.

Disopyramide

- It has maximum anticholinergic properties.
- It can cause dry mouth, blurring of vision, Tachycardia, and constipation.

Procainamide

- It is a commonly used drug.
- It is a derivative of local anaesthetic procaine, which is a sodium channel blocker.
- It has the least or no anticholinergic properties.
- This drug undergoes acetylation.
- It is known to produce drug-induced lupus.
- Patients on Procainamide can come back with Malar rash, joint pains, and positive antinuclear antibodies. If the drug is stopped, the disease is reversed.

Class Ib Drugs

Lignocaine

- This drug is used for Ventricular Tachycardia.
- It is ineffective in atrial arrhythmias for a few reasons:
  - It does not depress the SA node automatically.
  - It has no effect on atrial Action Potential Duration (APD) and Effective Refractory Period (ERP) of atrial tissues.
- It is the most effective drug in MI-induced Ventricular Tachycardia.
- It is preferably used in ischemic tissues and ischemic tissue-induced VT because they bind to the inactive state and do not allow the ischemic tissues to trigger any action potential. Thus, the Na channels of only the ischemic tissues are blocked. Normal tissues are not affected.
- **Mexiletine**
  - It is a derivative of Lignocaine.
  - It can be given orally because it has a less first-pass effect.
  - It is used to prevent Ventricular Tachycardia.
  - It is used in a condition called Diabetic Neuropathy.

Important Information

- Lignocaine is also known as Lidocaine.
- Tocainide and Phenytoin (anti-epileptic drug) are the older drugs that were previously used for anti-arrhythmia.

Class Ic Drugs 00:51:00

- These drugs are most arrhythmogenic.
  - Encainide
  - Propafenone – Has beta-blocking properties.
  - Flecainide – Used for prophylaxis in a patient with Wolff-Parkinson-White (WPW) syndrome.
- They are contraindicated in a patient having structural heart or Ischemic heart disease.
- Used for both atrial and ventricular arrhythmias.

Important Information

- For WPW syndrome, the treatment of choice will be removing the accessory pathway (ablation).
- The patient should be put on prophylaxis until the patient undergoes surgery.
- Prophylaxis is done by the drug Flecainide.
- If the patient develops arrhythmias in WPW syndrome, it can be treated with Procainamide.

Class II Antiarrhythmic Drugs 00:54:00

- These are beta blockers. They decrease the heart rate and increase conduction.
- The drugs are:
  - Propranolol
  - Nadolol
  - Esmolol
  - Metoprolol
- Can be used in atrial and ventricular arrhythmias.
- In atrial arrhythmia, it can be used in atrial fibrillation and atrial flutter.
- Act as AV blockers.
- In ventricular arrhythmia, it can be used in ventricular tachycardia and ventricular premature beats.
- Beta-blockers are the drug of choice for Congenital Long QT Syndrome.

Class III Antiarrhythmic Drugs 00:56:30

- They are potassium channel blockers.
- They increase the ARP, thereby increasing the ERP.
- The tissues become refractory.
- They can convert an abnormal rhythm into a normal sinus rhythm.
- Since they increase the Action Potential Duration (APD), they can cause QT prolongation.
- The drugs used are
  - Vernakalant – It is a multi-ion channel blocker.
  - Bretylium (Not in use)
  - Ibutilide
  - Amiodarone
  - Sotalol
  - Dronedarone
  - Dofetilide
- Used in both atrial and ventricular arrhythmias. For e.g. In atrial arrhythmias, convert atrial fibrillation into normal sinus rhythm.

Amiodarone 01:01:00

- It is a very important drug because it has multiple mechanisms of action.
- The major one is a potassium channel blocker, but the minor mechanism of action is that it is a sodium channel blocker, and calcium channel blocker and it also has beta-blocking properties.
- **Uses:** Used in both atrial and ventricular arrhythmias.
- It is contraindicated in Long QT syndrome because it prolongs the QT interval.

- **Pharmacokinetics**
  - It is an enzyme inhibitor.
  - It inhibits a protein called P-glycoprotein and thus causes Digoxin toxicity.
  - Amiodarone is avoided in Digoxin arrhythmias because
    → It has a very long half-life (3-8 weeks).
    → It contains 37% iodine in the structure. Due to the presence of iodine, it can cause allergy phenomena.

- **Adverse effects:**
  - It can produce photosensitivity- the patient may have Blue Man Syndrome and the skin is called Smurf Skin.
  - It can produce Peripheral Neuropathy. The eye should be checked as it can cause corneal microdeposits known as Cornea Verticillata.
  - The eye should also be checked for Optic Neuritis.
  - Monitor the LFT (Liver Function Test) – it can cause liver toxicity.
  - Monitor the TFT (Thyroid Function Test) – it can produce thyroid dysfunction. It can cause both hypo and hyperthyroidism due to iodine.
  - Check for PFT (Pulmonary Function Test) - which can cause pulmonary fibrosis.
  - Allergy is due to iodine content, and it can produce a rash.

Class IV Antiarrhythmic Drugs 01:07:00

- These are calcium channel blockers.
- Non-DHPs – they increase the heart rate and conduction similar to the beta blockers.
  - Verapamil
  - Diltiazem

- **Uses:**
  - Mainly used in atrial arrhythmias.
  - Very rarely used in ventricular arrhythmias because calcium is required for the contraction of the heart. If it is used, then there will be a compromise in the force of contraction.

Miscellaneous Drugs 01:08:20

- Atropine
- Digoxin
- Magnesium sulfate (drug of choice for Torsades de Pointes).
- Potassium chloride infusion - used in Chronic Digoxin Toxicity Induced Tachycardia.

Adenosine

- It is a very short-acting drug.
- The half-life of the drug is <5 seconds.
- When adenosine is given in the vein, the cells of the vein itself will take it up because the enzymes require ATP.
- The RBCs and endothelium will rapidly take it up.
- It should be given more in the central vein.
- Rapid Bolus should be given.
- **Uses** - It is used in 2 important conditions: PSVT and SVT.

- **Mechanism of Action:**
  - Acetylcholine will activate M2 receptors in the heart and decrease the heart rate and conduction. M2 decreases the cyclic-AMP and will increase the potassium exit out of the cell. So, when the potassium exits, the cell becomes hyperpolarized.
  - Stimulates acetylcholine sensitivity. The potassium channel goes out and the tissue will become less excitable.
  - It will decrease the heart rate and conduction.

- **Adverse effect:**
  - It can produce asystole (transient – doesn't last long).
  - It can cause atrial fibrillation.
  - It can cause bronchoconstriction.
  - It can produce chest tightness.
  - It should not be used in asthmatic patients.
  - It is a dilator of blood vessels – that causes flushing.

- **Drug interaction:**
  - Methylxanthines decrease the activity of adenosines.
  - Dipyridamole increases the activity of adenosine.

- **Clinical Applications**
  - If the patient has taken Methylxanthines and has SVT, PSVT. Adenosine should be given since it decreases the activity of adenosine. The adenosine dose should be increased and given to the patient because the patient is already on methylxanthines.
  - If the patient is on Dipyridamole, it increases the activity. In this case, a lower dose of adenosine should be given to the patient.
  - Dipyridamole also causes Coronary Steal Phenomenon (CSP) because Dipyridamole acts by increasing the adenosine.
  - Coronary Steal Phenomenon is due to the increase in adenosine activity.
  - Another adenosine receptor known as Regadenoson used in cardiac stress testing also causes CSP.

Important Information

- For PSVT, the drug of choice is Adenosine.
- If the patient has PSVT and is asthmatic, Adenosine should not be given. The alternative here will be Verapamil.
- For SVT, Adenosine can be given. If not available, then Verapamil can be given.
- For atrial fibrillation flutter, AV-blocking drugs such as beta-blockers, CCBs (non-DHPs) and Digoxin should be used.
- To make the atrial fibrillation normal sinus rhythm, Class III drugs (Amiodarone, Vernakalant, and Sotalol) or Class Ia drug Procainamide should be given.

Long QT Syndrome

- **Congenital-** Drug of choice is Beta blockers

- **Acquired**
  - Caused by Class 1a, 3, Bedaquilline, Macrolides and fluoroquinolones.
  - Stop the drug.
- Acute attack- Drug of choice is $MgSO_4$

WPW Syndrome

- Treatment of choice- Radiofrequency ablation
- Prophylaxis- Flecainide is used until ablation is performed
- If patient develops arrhythmias, procainamide is used

Clinical Questions

Q. Which drugs are known as AV Blocking agents?
Ans: Beta-blockers, Non-DHPs, Digoxin and Adenosine.

Q. What are the receptors that control the nodal tissues?
Ans: GS-coupled receptor and M2 receptor (GA-coupled receptor).

Q. Which is more dangerous, Ia, Ib or Ic?
Ans: Ic is the more dangerous drug as it can block all three states of the Na channel for a very long time which can be risky.

Q. The drug Quinidine is obtained from the Cinchona bark of the plant. What does it cause if the drug is given at a high dose?
Ans: Cinchonism.

Q. What is the other name of Lignocaine?
Ans: Lidocaine

Q. What is the drug of choice for MI-induced VT?
Ans: Lignocaine, because it does not affect the normal tissue and the normal conduction of the heart.

Q. Can Lignocaine be given orally?
Ans: No, because it has high first-pass metabolism.

Q. Which drugs are contraindicated in a patient having structural heart or Ischemic heart disease?
Ans: Class Ic drugs.

Q. Why Amiodarone is a very important drug?
Ans: Because it has multiple mechanisms of action.

Q. If the patient has intestinal lung disease, which antiarrhythmic drug should be avoided?
Ans: Amiodarone because it causes pulmonary fibrosis.

Q. If the patient has atrial fibrillation and WPW syndrome, what drugs should be avoided?

Ans: AV blocking agents – Adenosine, Beta-blockers, CCBs, and Digoxin should be avoided. In this case, Class Ic drugs like Procainamide and Flecainide should be preferred because Class Ic drugs will increase the refractory period of the accessory pathway.

Diagram 45.1

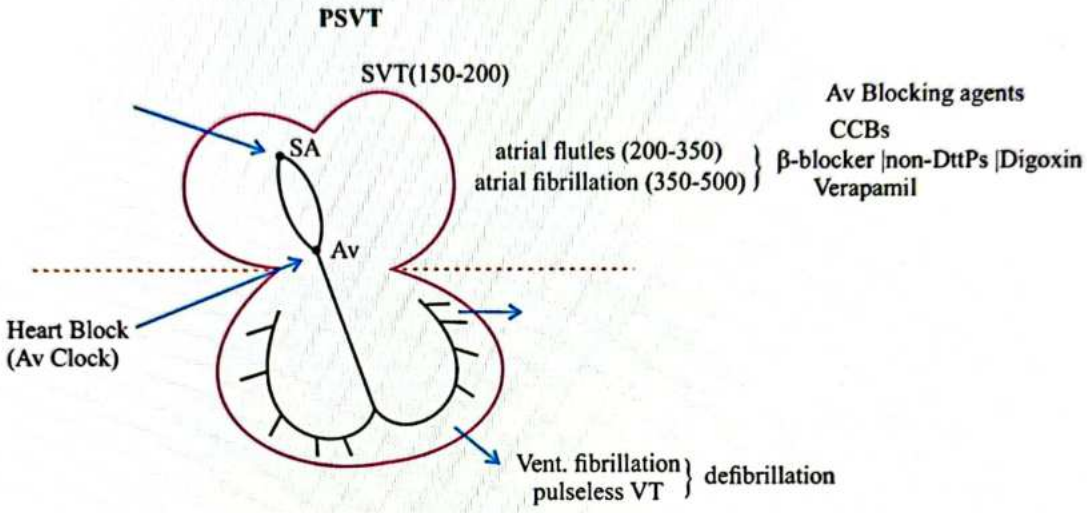
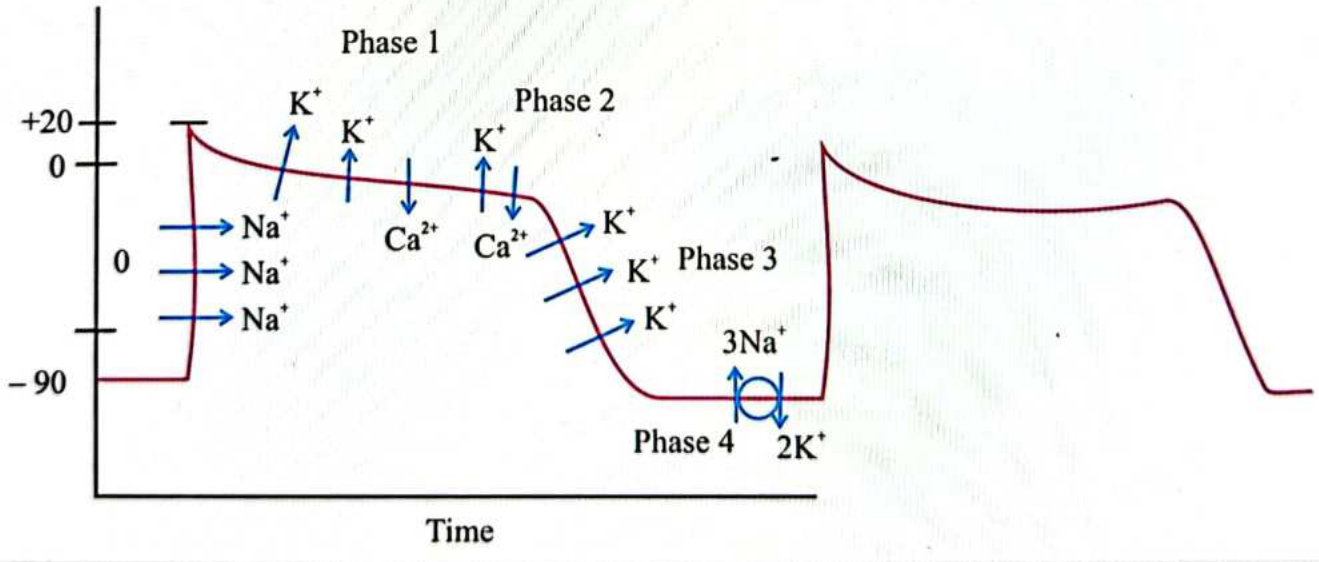
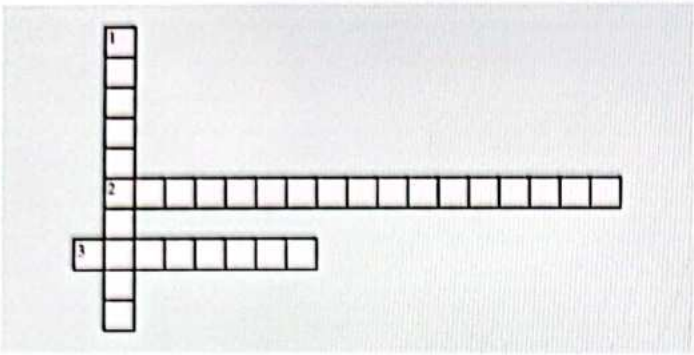


Diagram 45.2



CROSS WORD PUZZLES

Crossword Puzzle 1



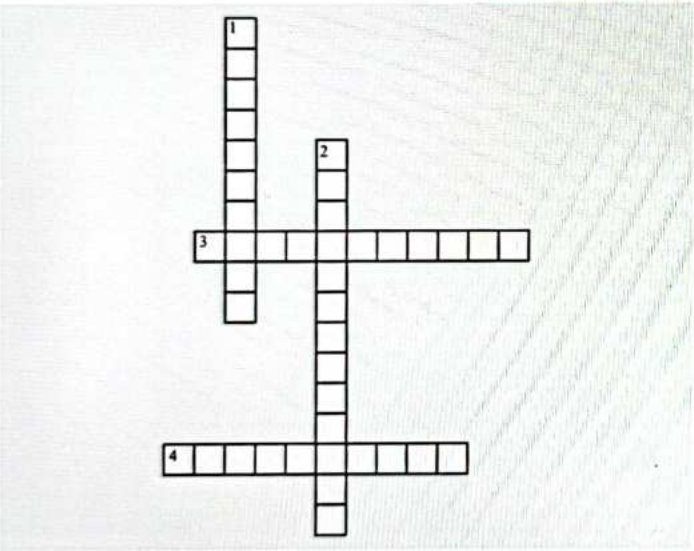
Across

2. _____ Rhythm disturbances in the heart.
3. _____ Digoxin, very least preferred drug for Tachyarrhythmias.

Down

1. _____ Calcium channel blocker.

Crossword Puzzle 2



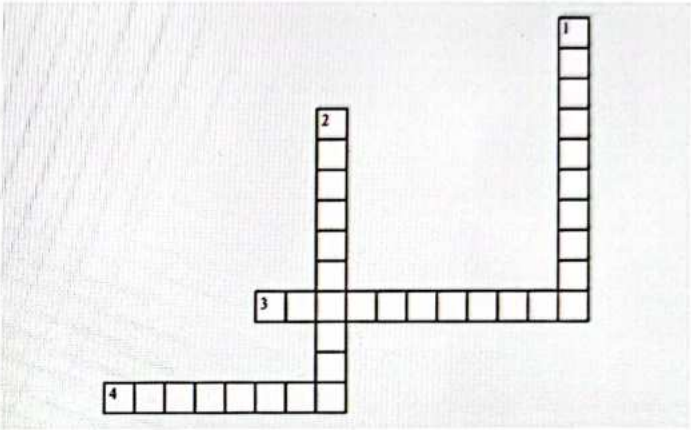
Across

3. _____ Drug of choice for MI induced VT.
4. _____ Not being used commonly due to its adverse effects.

Down

1. _____ An anti-epileptic drug that was earlier used for anti-arrhythmias.
2. _____ Not being commonly used due to its anti-cholinergic property.

Crossword Puzzle 3



Across

3. _____ Famous and an important Class III antiarrhythmic drug.
4. _____ Beta blocker having potassium channel blocking property.

Down

1. _____ Maximizes the QT prolongation.
2. _____ Drug is contraindicated in atrial fibrillation.

46 SEDATIVE HYPNOTICS

Definition and Uses

- **Sedative:** A sedative is a drug that calms down the patient.
- **Hypnotic:** A hypnotic drug is a sleep-inducing drug.
- Sedation is required in medical conditions where a patient is acutely maniac, acutely psychotic, and has acute anxiety, insomnia, and seizures. It's also used in **general anaesthesia**.
- There are certain neurotransmitters in the brain that can be inhibitory or excitatory.

Neurotransmitters

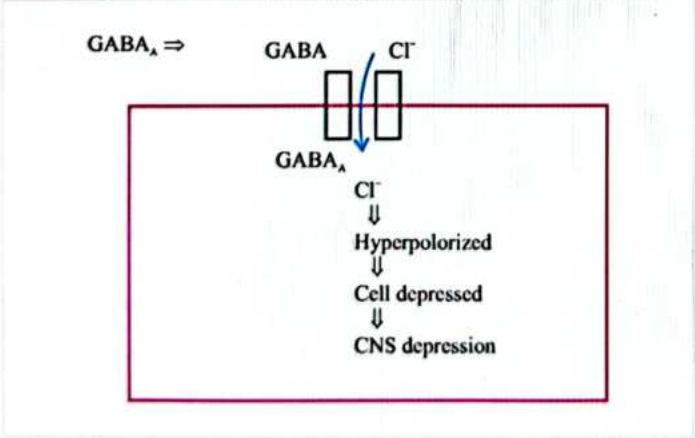
- **Inhibitory Neurotransmitters:**
  - GABA
  - Glycine
- **Excitatory Neurotransmitters:**
  - Glutamate
  - Aspartate
- For sedation to work, either the activity of inhibitory neurotransmitters is increased, or the activity of excitatory neurotransmitters is decreased.
- Neurotransmitters like acetylcholine, serotonin, and norepinephrine are inhibitory as well as excitatory.

Gaba

- The activity of GABA is increased for sedation.
- GABA has three types of receptors:
  - **GABA -A:** It's an ion-channel receptor mainly present in CNS. These are the fastest.
  - **GABA -B:** It's a minor G-protein coupled receptor. An agonist drug Baclofen is available for this. It is used as a central skeletal muscle relaxant and for hiccups. The GABA-B antagonist is Saclofen.
  - **GABA-C**

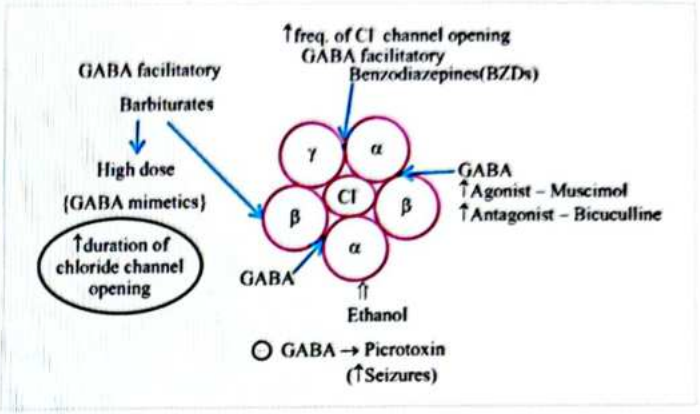
The role of $GABA_A$ in CNS

00:05:41



- A cell with a GABA-A receptor is shown above.
- Whenever GABA-A binds to the receptor, the ion channel gets opened, and there's an influx of chloride (Cl^-).
- The negativity makes the cells hyperpolarized, and the cell gets depressed. If the cells are in CNS, there'll be CNS **depression** leading to a hypnotic sedative effect.

GABA Receptor: Structure



- The receptor has five sub-units surrounding the Cl^- channel at the centre via which the Cl^- ions enter. The top view of the receptor is shown above.
- The five subunits are:
  - Two α
  - Two β
  - One γ

- The interfaces between α and β are where GABA binds.
- The channel opens when GABA binds and Cl^- enters.
- Benzodiazepines (BZDs) bind to α-γ interfaces in a receptor but don't open Cl^- channels. They're GABA facilitatory, telling GABA to bind faster. They increase the frequency of Cl^--channel opening.
- Barbiturates bind to β interfaces and are also GABA facilitatory at normal doses. They act as GABA mimetics at a high dose, opening Cl^- channels on their own. They are very dangerous. They increase the duration of Cl^--channel opening.
- The agonist for the GABA binding site is called Muscimol. An antagonist for the same site is called Bicuculline.
- The antagonist between BZDs and Bicuculline is non-competitive because BZDs bind at the α-γ interface, and Bicuculline binds at the α-β interface.
- Ethanol also stimulates GABA activity.
- The inhibitor of GABA is a toxin called Picrotoxin. By inhibiting GABA, it can stimulate the brain, and a patient can be at an increased risk of seizures.

Barbiturates 00:15:28

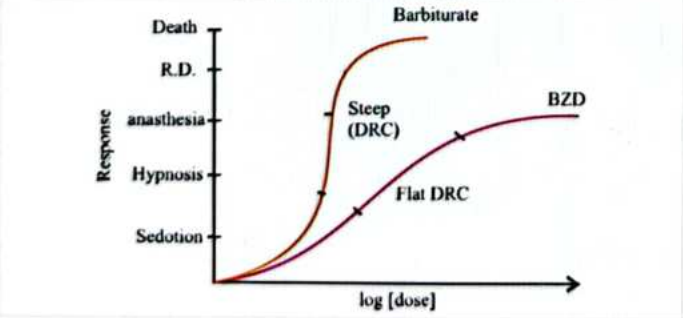
- Barbiturates are called Barbituric acids.
- Pharmacokinetics- Barbiturates are enzyme inducers.
- Contraindication- Acute Intermittent Porphyria.
- Historically, Secobarbital was used to manage Kernicterus. It was used to increase enzyme synthesis and metabolize bilirubin.
- They have high abuse potential and can produce a hangover.
- In case of barbiturate poisoning, two modalities exist. The patient's urine is alkalinized because the acidic drug is ionized and not reabsorbed in the nephron.
- Dialysis is also done to remove the poison.
- There's **no antidote** for barbiturate poisoning.

Drugs of Barbiturates

- **Longer-acting:**
  - Phenobarbitone is used in managing Status Epilepticus and GTCS (Generalized tonic-clonic seizure.).
  - Primidone is used in the management of epilepsies and, afterward, gets converted to Phenobarbitone. It is not an example of a prodrug.
- **Shorter-acting:**
  - Pentobarbitone and Secobarbital.
- **Ultra-short acting:**
  - Thiopentone Sodium is ultra-short acting due to the redistribution phenomenon.
    - → It has high lipid solubility and is used in the induction of anaesthesia. It has a rapid onset of action.
    - → It is also used in narco analysis in truth serum. Scopolamine is another ingredient of truth serum.
    - → It is also used in the management of Status Epilepticus.
  - Methohexitone is another short-acting drug that is used in electroconvulsive therapy.
- Only a small number of barbiturate drugs are used nowadays due to the many shortcomings discussed above.

Benzodiazepines 00:23:35

- Pharmacokinetically, these are not enzyme inducers.
- They produce less abuse and hangovers.
- BZDs have an antidote named Flumazenil.
- They produce high anterograde amnesia. The patient forgets the events that occur after taking the medication. It is particularly important as preanesthetic medication.



- They have a flat DRC (Dose Response Curve). It can be explained via a graph.
- Let's plot a DRC on a graph with X-axis denoting the log of Doses and Y-axis denoting the response.
- As we increase the doses, its response begins with sedation, followed by hypnosis, anaesthesia, respiratory depression, and death, respectively.
- The curves for BZDs (orange curve) and barbiturates (green curve) are shown above in the graph as well. BZDs are safer to use because death is off the limits in this case.
- BZDs have a flat DRC, while barbiturates have a steep DRC.

Drugs of Benzodiazepines

- **Diazepam:**
  - It is used as rectal diazepam for managing a condition called Febrile Seizures.
  - Diazepam is metabolized into Nordiazepam which leads to oxazepam, which is made inactive by glucuronidation.
  - Diazepam is not a prodrug, as all other forms are active. The drug becomes longer acting due to multiple conversions. In a patient with liver disease having slow metabolism, oxazepam is safer to give.
- **Lorazepam:** It is given for acute CNS conditions like anxiety, mania, and psychosis. It is a drug of choice for Status Epilepticus.
- **Chlordiazepoxide:** It's a drug of choice for an alcohol withdrawal condition called Delirium Tremens.
- **Clonazepam and Clobazam:** Used to manage seizures.
- **Alprazolam:** Used to manage anxiety and insomnia.
- **Temazepam, Oxazepam, and Triazolam:** Used to manage insomnia.
- **Midazolam:** Given IV in anaesthesia and in the case of Status Epilepticus. Intranasal midazolam is used in Febrile Seizures.
- **Remimazolam:** Shortest-acting BZD. It is used for procedural sedation; short procedures like in the case of joint dislocation.
- **Clorazepate:** Becomes nordiazepam in the acidic pH of the stomach. It is a prodrug.

Important Information

- Safe drugs for liver disease patients and chronic alcoholics.
- **LOT (Lorazepam, Oxazepam, and Temazepam)** are safer drugs to administer.

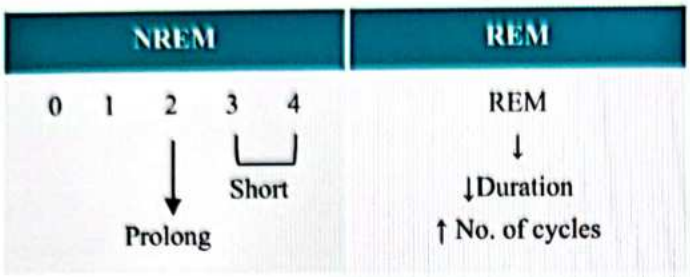
Adverse effects of Benzodiazepines

- Drowsiness
- Tolerance
  - If the drug is used again and again, tolerance gets developed. So, the dose needs to be increased.
- Dependence

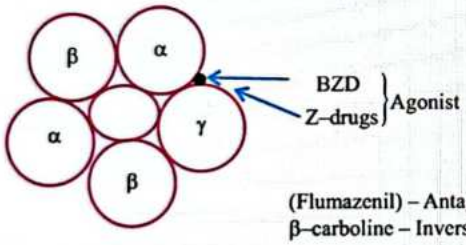
- The drug should not be stopped abruptly. It should be done gradually. Otherwise, the health issue will come back.

- Overdose
  - Overdosed patients will have decreased respiratory rate, low blood pressure, and drowsiness. The antidote for this is Flumazenil.
- There's no use of dialysis in this poisoning.

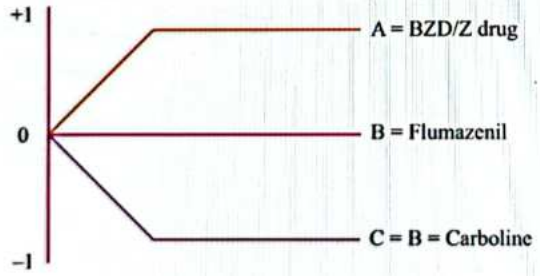
BZD in Insomnia



- **In NREM sleep**, there are 4 stages. BZD prolongs stage 2 and shortens stages 3 and 4.
- **REM sleep** duration is decreased. The number of cycles increases. Due to this interference, the patient will not feel fresh in the morning. There's some drowsiness.
- Certain drugs can bind to the same alpha-gamma interface as BZDs. Such drugs are called Z-drugs.
  - Flumazenil is an antagonist for these drugs and BZDs.
  - Beta-carboline is the inverse-agonist.



(Flumazenil) – Antagonist
β–carboline – Inverse Agonist



- As shown in the response graph above,
  - A is the curve for BZDs and Z-drugs.
  - B is an antagonist Flumazenil.
  - C graph is the inverse-agonist Beta-carboline.
- For BZDs, Z-drugs, and Beta Carboline overdoses, Flumazenil is the antidote.
- The BZD receptor has two sub-types: BZD-1 and BZD-2.
- Z-drugs only bind to BZD-1 receptors. It causes sedation, thus used to treat insomnia.
- BZD-2 receptors have anti-anxiety, muscle relaxation, and anti-seizure properties.

Z-Drugs 00:45:10

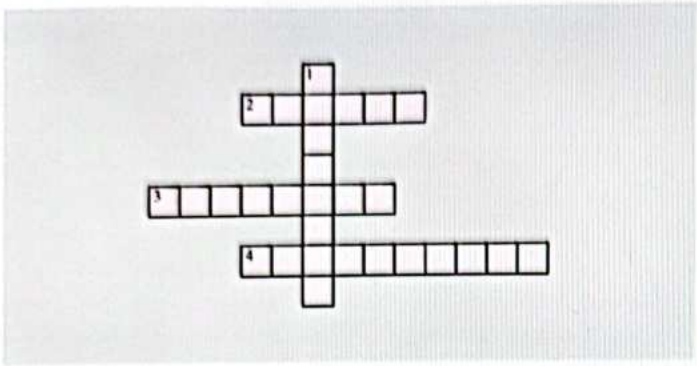
- Z-drugs are approved for insomnia only. They offer refreshing sleep and less interference with sleep cycles.
- **Zolpidem**
- **Zopiclone**
- **Zolepon:** It has a fast onset of action. It can start working within one hour.

Melatonin-receptor agonist drugs

- The pineal gland secretes melatonin, it's important for maintaining circadian rhythm. The pineal gland releases melatonin when it is dark, thus inducing sleep.
- **Ramelton:** It is an MT-1 and MT-2 receptor antagonist. It is used in sleep onset insomnia. A person is unable to start sleeping. Persons with jet lag and shift workers can also use it.
- **Tasimelteon:** It is also an MT-1 and MT-2 receptor antagonist. It is used in non-24-hour sleep-wake cycle disorders. In these patients, sleep starting time changes every day.
- **Agomelatine:** It is also an MT-1 and MT-2 receptor antagonist. It is an atypical antidepressant. It is used for insomnia and patients with depression with insomnia.
- **Orexin:** It is responsible for wakefulness.
- **Suvorexant:** Blocks orexin receptors and is approved for insomnia. It is an orexin antagonist.
- Certain drugs are also used off-label, like 1st generation antihistamines. It means the FDA does not approve them.

CROSS WORD PUZZLES

Crossword Puzzle 1



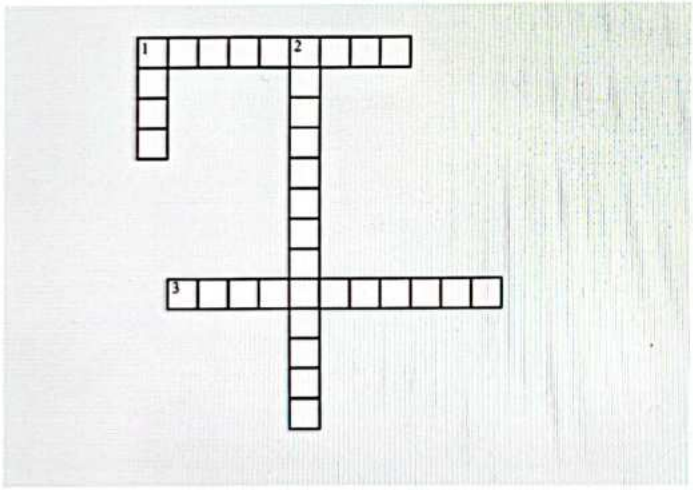
Across

2. _____ is responsible for wakefulness.
3. A _____ drug is a sleep-inducing drug.
4. A drug called _____ blocks orexin receptors are approved for insomnia. It is an orexin antagonist.

Down

A _____ is a drug that calms down the patient.

Crossword Puzzle 2



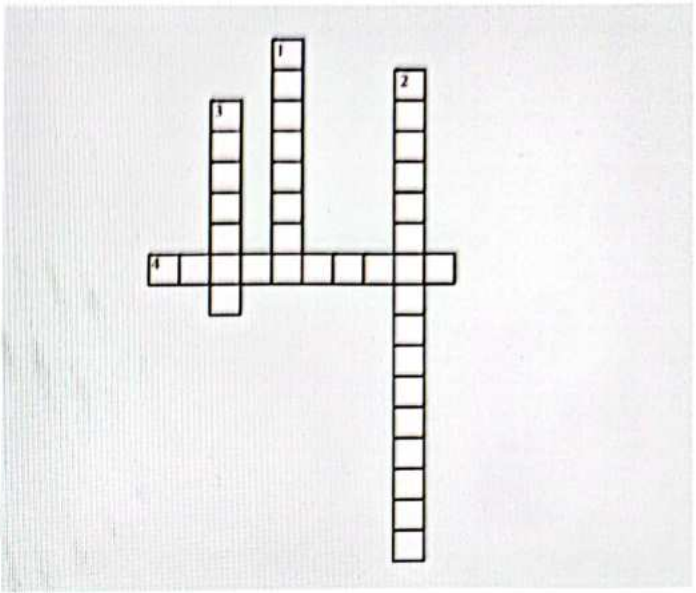
Across

1. _____ and Aspartate are excitatory neurotransmitters.
3. There's no antidote for _____ poisoning.

Down

1. _____ receptor has five sub-units.
2. _____ is a short-acting drug that is used in electroconvulsive therapy.

Crossword Puzzle 3



Across

4. For BZDs, Z-drugs, and Beta Carboline overdoses _____ is the antidote.

Down

1. Z-drugs are approved for _____ only.
2. _____ is a drug of choice for an alcohol withdrawal condition called Delirium Tremens.
3. Diazepam is not a _____.

47 ETHANOL

- Ethanol is also known as ethyl alcohol.
- People who consume it as an alcoholic beverage get addicted.
- It may lead to alcohol dependence, liver failure, and other complications.

Mechanism Behind Alcoholism 00:00:39

- Ethyl alcohol or ethanol increases the activity of GABA, a CNS depressant.
- The theory behind people's inclination towards alcohol is that when people start drinking, initially, one GABA neuron inhibits another GABA.
- In that case, CNS stimulation occurs, and endogenous opioids are released in the brain. These endogenous opioids are responsible for alcohol cravings.
- If someone still drinks alcohol, then GABA inhibits glutamate, leading to CNS depression.
- Therefore, there will be sedation, incoordination, stupor, coma, and death.

Acute Ethanol Poisoning 00:04:45

- Excess drinking may cause acute ethanol poisoning, and it can be managed through
  - Airways, Breathing, Circulation (ABC).
  - Gastric lavage can be done to inhibit further alcohol absorption.
  - Haemodialysis
  - Thiamine with I.V. fluids

Pharmacokinetics 00:05:45

- Follows Saturation kinetics, known as zero-order kinetics.
- In acute alcoholism, there would be enzyme inhibition, and in chronic alcoholism, enzyme induction will occur.
- **Pregnancy** – Alcohol should be avoided during pregnancy. Otherwise, it may lead to teratogenic risk. If its consumption is not stopped, then the baby will have fetal alcohol syndrome which means there will be growth retardation, mental retardation, cardiac defects, and small facial features.

Metabolism of Ethanol 00:08:25

- Ethanol gets metabolized into acetaldehyde in the presence of alcohol dehydrogenase, and acetaldehyde is again metabolized into acetic acid in the presence of aldehyde dehydrogenase.
- If acetaldehyde is more in the body, it can lead to nausea, vomiting, chest tightness, and palpitation. Disulfiram is a drug that inhibits aldehyde dehydrogenase and stops further metabolism, so acetaldehyde increases.

Alcohol Deaddiction 00:12:10

- Disulfiram inhibits aldehyde dehydrogenase by irreversible mechanism, i.e. if the drug binds to the enzyme and the enzyme is gone, again fresh enzyme has to come into action, then only it can metabolize acetaldehyde.
- That is the reason disulfiram is used in aversion therapy, and its other name is ANTABUSE.

Aversion Therapy

- Drinking alcohol, but it feels like not drunk. Instead, nausea, vomiting, and headache are felt. This therapy is always performed with a highly motivated person.
- Disulfiram should be started after 12 hours of consumption of alcohol. Disulfiram will start working after 2 hours, and the peak effect will be there after 12 hours.

Important Information

- If a patient wants to restart alcohol consumption, then stop disulfiram and start alcohol after 7 to 12 days because it's an irreversible enzyme inhibitor.

Decreasing Alcohol Cravings 00:16:15

- Cravings are induced by endogenous opioids, and the following medication can inhibit this:
  - Naltrexone (opioid antagonist)
  - Ondansetron
  - Topiramate
  - Acamprosate

Disulfiram Like Reactions 00:18:05

- Metronidazole- A person having amoebiasis and consuming these drugs must stop consuming alcohol during the treatment. It may cause disulfiram-like reactions such as nausea and vomiting.
- Griseofulvin
- Chlorpropamide- First-generation sulfonylurea antidiabetic drug.
- Cephalosporins- Cefamandole, Cefotetan, Cefoperazone
- Procarbazine
- Metronidazole group

Clinical Applications 00:21:45

Delirium Tremens

- It is a severe form of alcohol withdrawal. Chlordiazepoxide or lorazepam with thiamine should be given.

Wernicke Korsakoff syndrome

- I.V. thiamine is given.

Hypoglycaemia

- Alcoholics should be given thiamine with glucose in case of hypoglycaemia.

Methanol Poisoning 00:24:50

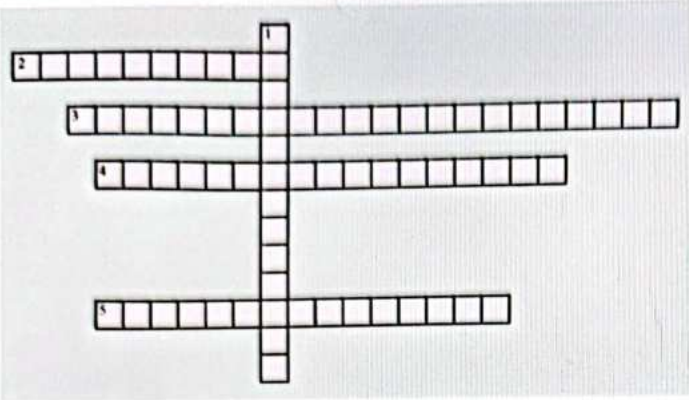
- Methanol is metabolized to formaldehyde in the presence of alcohol dehydrogenase and formaldehyde gets converted into formic acid which leads to retinol damage and metabolic acidosis.
- Fomepizole is used as an antidote for methanol poisoning, but it's an orphan drug, not easily available in that case, ethanol is used.
- Ethanol diverts the metabolism of methanol and competes with the enzyme.
- Flumazenil is used as an antidote in benzodiazepine overdose

Ethylene glycol poisoning 00:28:05

- Ethylene glycol gets metabolized to glycolaldehyde and then into glycolic acid. Both reactions occur in the presence of the enzyme alcohol dehydrogenase. Glycolic acid leads to renal damage and metabolic acidosis.
- To inhibit the enzyme, fomepizole is used as an antidote. If that is not available, ethanol is used, which diverts the mechanism and is used as a drug of choice.
- Fomepizole inhibits alcohol dehydrogenase

CROSS WORD PUZZLES

Crossword Puzzle 1



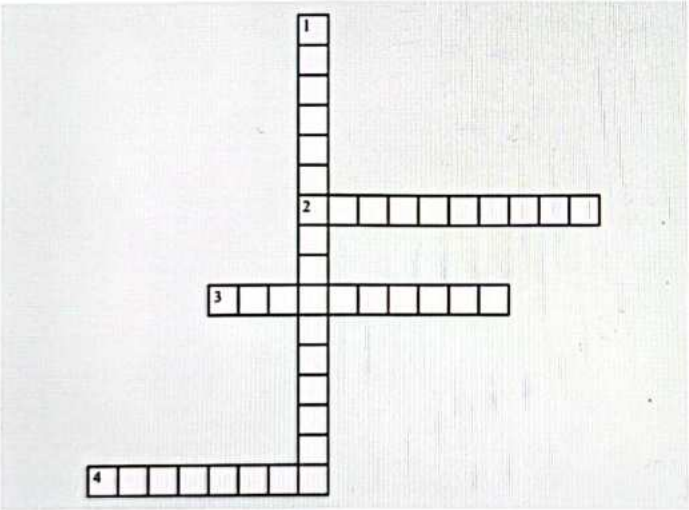
Across

2. _____ is used as an antidote for methanol poisoning
3. Disulfiram inhibits aldehyde dehydrogenase by _____
4. Cravings are induced by _____
5. Drinking alcohol but it feels like not drunk is known as

Down

1. A person having amebiasis uses this drug

Crossword Puzzle 2



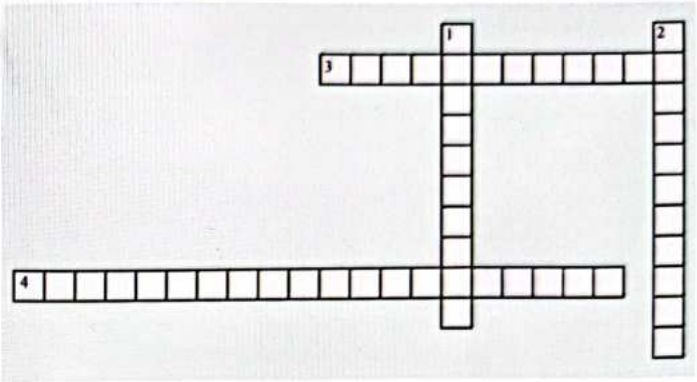
Across

2. _____ used in Wernicke Korsakoff syndrome
3. An antidote for ethyl poisoning_____
4. Alcoholics should be given glucose with _____

Down

1. Given in Delirium Tremens _____

Crossword Puzzle 3



Across

3. _____is more in the body, it can lead to nausea, vomiting, chest tightness, and palpitation.
4. If alcohol consumption is not stopped, then the baby will have_____.

Down

1. Opioid antagonists are used in decreasing alcohol cravings_____.
2. Increase in glycolic acid may cause_____.

48 ANTI EPILEPTIC DRUGS

Seizures

- It is an electrical activity in the brain that stimulates it to burst with electrical impulses continuously, triggering convulsions.
- Epilepsy is a condition where seizures repeatedly occur without stimulus (more than or equal to 2 episodes of unprovoked seizures).
- The CNS becomes hyper-excited, and all the other body parts develop seizures.
- In this situation, CNS should be suppressed, and the conduction from CNS to the periphery should be blocked.

Triggering factors for Seizures

- Tumours
- Head trauma
- CNS infections like meningitis
- Drugs – Imipenem in high doses, INH overdose

Targets in the management of Seizures or Epilepsy

- Decrease the activity of glutamate (exhibitory neurotransmitter).
- Increase the activity of GABA - Gamma-aminobutyric acid (inhibitory neurotransmitter).
- Sodium ions rapidly take the impulse from the brain to the periphery, so these can be blocked.
- Blocking the 'T' type of calcium channel ions is problematic, particularly in the absence of seizures.
- Opening the potassium channel and making the cell depressed.

Important Information

- Sodium ions quickly take the impulse from the brain to the periphery.
- Anti-epileptic drugs are sodium channel blockers.

Anti-Epileptic Drugs 00:05:25

- **Sodium channel blockers:** By blocking the sodium channel, they decrease the impulses from the brain to the periphery.
  - Phenytoin
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Topiramate
- **Other sodium channel blockers:**
  - Zonisamide
  - Rufinamide
  - Felbamate
  - Lacosamide

Phenytoin 00:07:25

Pharmacokinetics of Phenytoin

- It is an enzyme inducer (can increase the enzyme synthesis and drug interaction).
- Saturation kinetics.
- Therapeutic drug monitoring (normal level – 10-20 µg/ml). If the drug is less than this value, it will not work; if more, it will cause toxicity.
- Phenytoin, when given intravenously, should be mixed with normal saline.
- Do not mix with dextrose because it can get precipitated.
- It can lead to a disorder called Purple Glove Syndrome (very rare).
- It belongs to "class-1B" antiarrhythmics. If administered rapidly through IV, it can cause arrhythmia. In case of arrhythmia, ECG monitoring should be done.
- To prevent various irritations, a more water-soluble drug, Fosphenytoin (Pro drug), is given. After metabolism Fosphenytoin is converted to Phenytoin.
- The advantage of Fosphenytoin is that it can be mixed with both normal saline and dextrose during administration.

Uses

- GTCS (Generalized Tonic-Clonic Seizures).
- Status Epilepticus.
- Trigeminal neuralgia (it is a 2nd line drug).

Contraindications:

- Phenytoin should not be used in Myoclonic and Absence seizures because they increase seizures.

Adverse Effects (all starts with H)

- Hypersensitivity (allergic)- Can present as Steven-Johnson Syndrome, or a patient may develop lymph node enlargement known as pseudo lymphoma.
- Hyperplasia of gums.
- Hirsutism (growth of facial hair in female).
- Hyperglycaemia (glucose level may rise).
- High doses of drugs can cause Cerebellar ataxia, Nystagmus, and Arrhythmia.

- Hydantoin Foetal Syndrome- If used in pregnancy, the child will develop cleft lip and palate, small fingers (Microdactyly), and cardiovascular defects.
- Hypovitaminosis- It causes three vitamin deficiencies – Vitamin D, Vitamin K (causes Osteomalacia), and a decrease in folic acid.
  - If Phenytoin is given during pregnancy, it can decrease vitamin K and lead to Hemorrhagic Disease of new-born. The mother, at term, is given vitamin K orally, and the new-born is given a vitamin K injection.
  - Decrease in folic acid can lead to Megaloblastic Anaemia.

Important Information

- Phenytoin belongs to class-1B antiarrhythmics.
- If the patient is given Lignocaine, a Class 1B antiarrhythmic, the patient could develop Lignocaine toxicity and seizures. In this case, Phenytoin should not be used because Phenytoin and Lignocaine have the exact mechanism on the heart, which can lead to arrhythmias.

Carbamazepine

00:19:25

Pharmacokinetics of Carbamazepine

- Enzyme inducer.
- Auto inducer- Induces the enzyme so that the enzyme metabolizes the Carbamazepine itself.
- Requires TDM (therapeutic drug monitoring) – should be 5-10 µg/ml.

Uses

- In epilepsy, it is used in GTCS.
- Drug of choice for focal or partial seizures.
- Used in bipolar disorder and mania.
- Drug of choice for a neurological condition known as Trigeminal Neuralgia.

Contraindications:

- Myoclonic and absence seizures.

Adverse Effects

- It can cause HAT:
  - H - Hepatotoxic, hyponatremia
  - A - Allergy, SJS
  - T - Teratogenicity (neural tube defects, cleft lip and palate) and thrombocytopenia.

Oxcarbazepine and Esilcarbazepine:

- These are Prodrugs
- They become active after metabolism.
- Used for focal seizure.
- Difference between Carbamazepine and Oxcarbazepine and Esilcarbamazepine:
  - Have less enzyme induction.
  - Less hepatotoxic.
  - Less allergic.
  - Less thrombocytopenia.
  - More dilutional hyponatremia.

Important Information

- If Carbamazepine is used for a longer time to control seizures, it will cause enzyme induction that will metabolize Carbamazepine. In this case, the Carbamazepine dose should be increased.

Sodium Valproate (Valproic Acid)

00:26:35

- Pharmacokinetics- It is an enzyme inhibitor.
- Multiple mechanisms:
  - Sodium channel blocker.
  - Increases GABA activity.
  - Decreases glutamate activity.
  - It is a T type of calcium channel blocker.

Uses

Epileptics uses	Non-epileptic uses
Drug of choice: • GTCS. • Myoclonic and absence seizures. • Lennox Gastaut syndrome. • Dravet syndrome. • Juvenile Myoclonic Epilepsy. • Status Epilepticus (but not the choice of drug).	• Mania. • Bipolar disorder. • Rapid cyclers. • Migraine prophylaxis. • Tardive dyskinesia.

Adverse Effects (Mnemonic- VALPROATE)

- Vomiting and nausea (most common).
- Alopecia
- Liver toxicity
- Pancreatitis and increase PCOD.
- Rash
- Obesity
- Increase in Ammonia level (antidote – Carnitine)
- Teratogenicity - Neural tube defects. Folic acid (4000µg/day) is used to prevent NTDs. Also causes Thrombocytopenia.
- Therapeutic drug monitoring is required – level should be between 40 – 100µg/ml).
- Enzyme inhibitor.

Important Information

- Sodium Valproate is a broad-spectrum anti-epileptic drug.
- It is used in Status Epilepticus but is not the drug of choice for SE.

Lamotrigine 00:34:00

- It is a Sodium channel blocker.
- Decreases the activity of glutamate.

Uses

- GTCS.
- Myoclonic and Absence seizures.
- Bipolar disorder

Adverse Effects

- Can cause Steven-Johnson syndrome.

Important Information

- Lamotrigine is not used in Status Epilepticus and acute mania.

Topiramate 00:35:35

- Sodium channel blocker.
- It is a carbonic anhydrase inhibitor- It can cause calcium stones.
- It has AMPA antagonism.

Uses

- Decreases cravings in alcoholics.
- Management of obesity.
- Management of migraine prophylaxis.
- Epilepsy- mainly in GTCS and LGS.

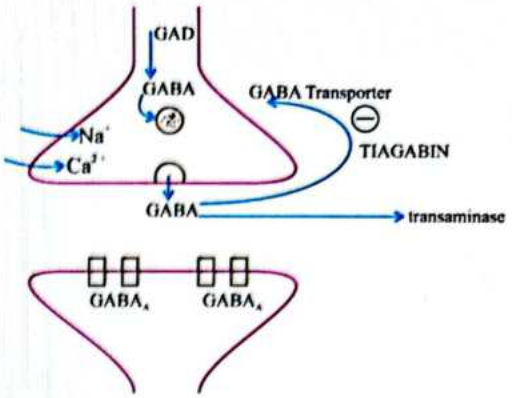
Important Information

- Anti-epileptic drugs causing renal stones are: (MNEMONIC- TOPA-Z)
  - Topiramate
  - Zonisamide

Minor Drugs 00:37:55

- Rufinamide – A new drug used in LGS syndrome.
- Felbamate – Causes weight loss
- Zonisamide – Causes weight loss
- Lacosamide

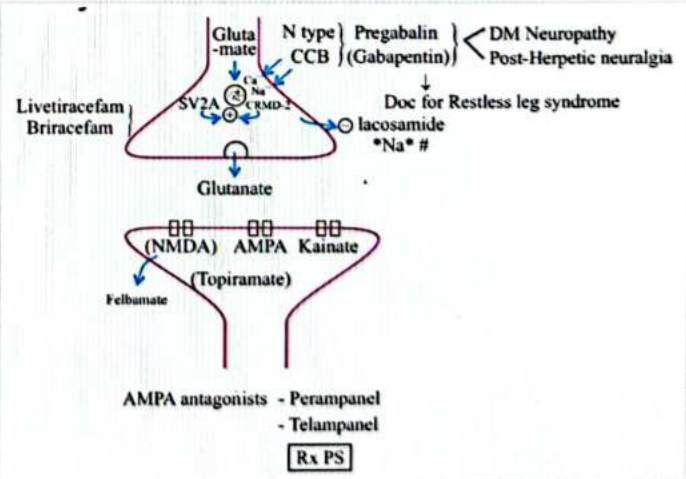
Increase the activity of Gaba 00:39:05



Drug Targets

- Inhibit the GABA transporter by TIAGABINE – Used to manage partial seizures.
- Inhibit GABA transaminase by VIGABATRIN – Used in an infantile spasm patient with Tuberous Sclerosis. This can cause vision impairment.
- Use of Barbiturates:
  - Phenobarbitone – Used in managing GTCS and status epilepticus.
  - Primidone – Also used in managing GTCS and status epilepticus.
- BZDs
  - Lorazepam – Used in the management of status epilepticus
  - Diazepam
  - Midazolam
  - Clonazepam
  - Clobazam
  - Diazepam, Midazolam, Clonazepam, and Clobazam are used in the management of epilepsy by increasing the activity of GABA.

Decrease the activity of Glutamate 00:44:45



- Glutamate has three subtypes: NMDA, AMPA, and Kainate (they allow the entry of either sodium or calcium), which can excite the tissue and lead to seizures.
- The calcium entry (N-type – the neuronal type of calcium) is blocked by N-type channel blockers called Pregabalin and Gabapentin.
- These drugs are used for Diabetic neuropathy and Post-Herpetic neuralgia.
- Only Gabapentin is nowadays the drug of choice for a condition called Restless leg syndrome.
- The adverse effect of glutamate is sedation.
- SV2A protein and CRMP2 protein stimulate the release of Glutamate.
- Lacosamide (sodium channel blocker), inhibiting the CRMP2 and thereby inhibiting the glutamate release.
- SV2A blockers: Levetiracetam and Brivaracetam.
- Other ways to decrease glutamate activity include:
  - Block NMDA with the anti-epileptic drug Felbamate (sodium channel blocker).
  - Block AMPA by Topiramate.
- There are no drug targets for Kainate.
- Other AMPA antagonists include Perampanel and Telampanel – used for partial seizures.

Blocking T type of calcium channel

00:51:00

- Ethosuximide- Used in absence seizures

K^+ channel openers

- Ezogabine/Retigabine – Manages partial seizures.
- It causes retinal toxicity. So, a routine eye examination should be done.
- Causes blue pigmentation of skin, nails, and lips.

Important Information

- A patient undergoing treatment for partial seizures with Retigabine. Phenytoin is added since the seizures are not controlled by Retigabine. The dose of retigabine is increased. Reason ⇒ Phenytoin is enzyme inducer and increase metabolism of Retigabine.

Types of Seizures

- GTCS- Valproate is the drug of choice
- Myoclonic- Valproate is the drug of choice
- Juvenile myoclonic epilepsy- Valproate is the drug of choice
- Absence seizures- These are of 2 types: Atypical and Typical seizures
  - Atypical seizures- Valproate is the drug of choice.
  - Typical seizures- Seen in childhood. Ethosuximide is the drug of choice.
  - Other drugs include: Lamotrigine, Acetazolamide, Zonisamide, and Clonazepam.
- Partial/Focal seizures- Carbamazepine is used.
- Febrile seizures- Occurs during high-grade fevers, especially in children.
  - Should give intranasal Midazolam at home. (Rectal Diazepam was given earlier).
  - IV (access to the hospital- Lorazepam/diazepam should be given.
- Infantile spasm (West syndrome)- ACTH is the drug of choice.
- Infantile spasm + Tuberculosis- Vigabatrin is used.
- Lennox Gastaut syndrome and Dravet syndrome- Valproate is used.
- Eclampsia – Magnesium sulfate is the drug of choice.
- Status Epilepticus- In this case, the seizures continue for more than 30 minutes.
  - Lorazepam or Diazepam (intravenous) should be given in this case.
  - Lorazepam is the first choice.
  - If the patient still has seizures, Phenytoin or Fosphenytoin is added.
  - Phenobarbital is added if the convulsions still occur.
  - The last option is general anaesthesia given with either Midazolam or Propofol.
  - Other options to control status epilepticus are (given IV):
  - Valproate
  - Levetiracetam
  - Thiopentone sodium

Applications of Anti-Epileptic Drugs in Pregnancy

01:01:25

Case 1

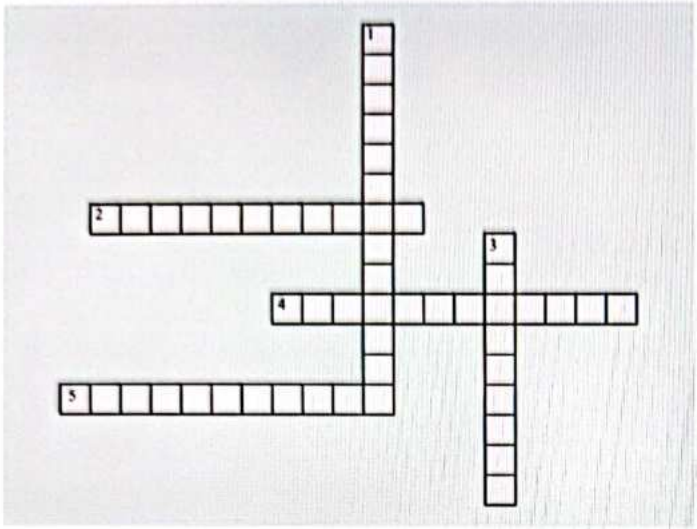
- If a married woman with epilepsy, who is on anti-epileptic therapy Valproate becomes pregnant. What should be done?
  - Valproate should be continued. Folic acid should be added (4000 µg/day) to prevent neural tube defects.
  - Anomalies should be checked. If there are gross anomalies, the fetus should be aborted, or else Valproate should be continued.

Case 2

- A married woman on Valproate is planning for pregnancy.
  - Change from Valproate to Levetiracetam and Lamotrigine. If there are no seizures, a patient can become pregnant (pregnancy can be planned)
  - Check for seizures for 2-3 months. If seizures do not occur, pregnancy can be planned.

CROSS WORD PUZZLES

Crossword Puzzle 1



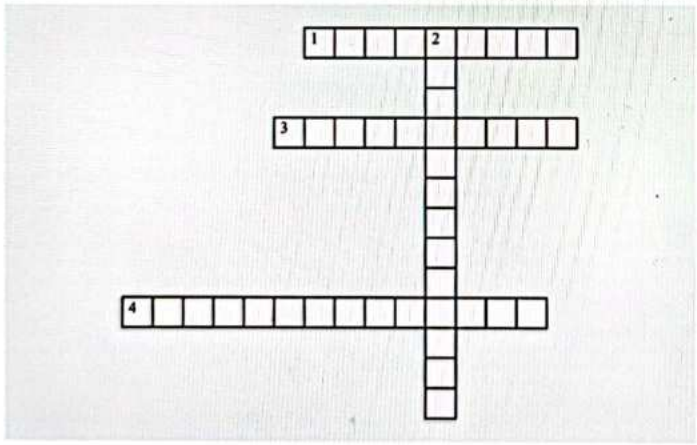
Across

2. _____ is used in children with Tuberous Sclerosis with infantile spasm .
4. _____is used in bipolar disorder.
5. _____ is a new drug used in LGS syndrome.

Down

1. _____after metabolism converted to Phenytoin.
3. _____incduces seizures.

Crossword Puzzle 2



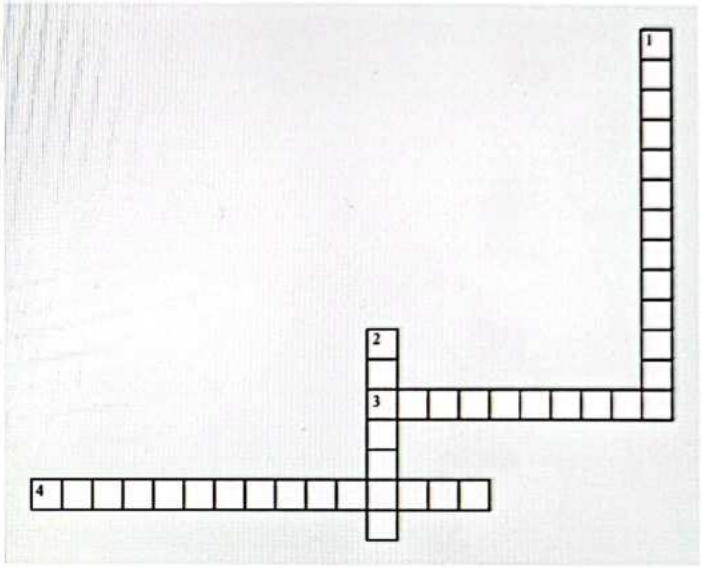
Across

1. _____is the drug of choice for Eclampsia.
3. _____is a drug of choice for Atypical absence seizures.
4. _____is a drug of choice for partial/focal seizures.

Down

2. _____is a drug of choice for Typical absence seizures.

Crossword Puzzle 3



Across

3. _____ is used in the management of status epilepticus.
4. _____is known as lymph node enlargement.

Down

1. _____ is mixed with normal saline and dextrose during administration.
2. _____ is also known as Valproic acid.

49 ANTI PARKINSONIAN DRUGS

Parkinson's Disease 00:00:31

- Seen in the elderly population.
- **Symptoms:**
  - Bradykinesia (slowing of movements)
  - Rigidity
  - Tremors

- The Dopamine decreases, and the activity of Acetylcholine increases in the Substantia Nigra.

Aim of Anti-Parkinsonian Therapy

1. ↑ Dopamine level
2. ↓ Acetylcholine level
3. MAO-B Inhibitor
4. COMT Inhibitors
5. D2 Agonist

Increase the level of Dopamine.

Levodopa (Pro-drug)
↓
Dopamine
↓ ↓ ↓
COMT D2 MOA-B
(Catechol Ortho Methyltransferase) (Mono amino oxidase)

- Dopamine acts on the D2 receptor.
- Dopamine can not be given orally due to Dopamine can not cross BBB (Blood-brain barrier)
- Due to that, Dopamine is given as levodopa (Pro-drug).
- Inhibit Enzyme COMT and MOA-B to increase the level of Dopamine.
- Giving a D2 agonist drug increases the Dopamine level.

Drugs 00:06:15

Levodopa (Pro-drug)

- It has a very short half-life ($t_{1/2}$ = 1-2 hr)
- Levodopa ⇒ crosses BBB ⇒ Dopamine
- In central levodopa is metabolized to dopamine with the help of Central decarboxylase enzyme.
- Levodopa metabolized in the periphery ⇒ Dopamine with the help of peripheral decarboxylase enzyme.

Receptor action of Dopamine in periphery

Refer Table 49.1

- B6 will convert levodopa into Dopamine periphery.

Drug Interaction L-Dopa

- Levodopa should not combine with D2 blockers.
  Ex. Typical Anti-psychotic, Metoclopramide
- Levodopa + Vitamin B6 ⇒ ↓ Levodopa efficacy

Important Information

- Vitamin B 6 is the stimulator of peripheral decarboxylase.
- Levodopa-induced Nausea, vomiting → Rx. Domperidone

Contraindication of L-Dopa

- L-dopa is not used in a patient with acute psychosis.
- Not used in a patient with gastric ulcer.
- Not used in a patient with Angle-closure glaucoma.

Important Information

- **Dopamine → Rx Parkinson's Disease**
  ↓
  Excess in brain
  ↓
  D2 Receptor
  ↓
  Psychosis → Rx → Atypical anti-psychotics (Ex. Quetiapine, clonazepam, Pimavanserin)
- Dopamine causes dyskinesia, that is treated with amantadine.

Q. Why is carbidopa combined given with L-dopa?

- Diminished peripheral metabolism of L-dopa in GIT and other tissues (thus increasing $t_{1/2}$).
- Increase availability of levodopa to CNS.
- Reduce the dose of levodopa and its side effects.
- Important ⇒ Levodopa: carbidopa: 4:1

Advantages of The Combination of Carbidopa With L-Dopa

- Levodopa becomes long acting in brain.
- Peripheral adverse effects not seen.
- Decreases the episode of Parkinson.

Disadvantages of the Combination of Carbidopa With L-Dopa 00:17:15

- No ↓ psychosis
- No ↓ dyskinesis
- No ↓ Postural hypotension

MAO-B Inhibitor (Monoamine Oxidase) 00:22:25

Types of MAO

MAO

↓	↓
A	B
↓	↓
Metabolizes	Specific for
↓	↓
NA, 5HT, Dopamine	Dopamine

Drugs Acting On MAO

Selegiline (Deprenyl)

- Pk ⇒ Metabolized ⇒ Amphetamine ⇒ Seizures
- It increases Dopamine activity ⇒ develops psychosis symptoms.
- Advantage is **neuroprotective effect.**

Rasagiline

- It has 5 times more potent.
- It is not metabolized to amphetamine.

Safinamide

- New MAO Inhibitor approved for Parkinson's disease.

COMT Inhibitors (Catechol Ortho Methyltransferase) 00:26:13

- Levodopa can be metabolized by COMT into 3-O - methyldopa.
- Entacapon Does not cross BBB.
- Tolcapone ⇒ BBB (Inhibit in periphery and central COMT)
- Tolcapone shows Hepatotoxicity.

D2 Agonist 00:29:35

Ergot Derived

- **Drugs:** Bromocriptine, Cabergoline, Pergolide
- **Adverse Effects**
  - Vasoconstriction ⇒ Gangrene
  - Fibrosis

Non- Ergot derived.

- **Drugs:** Ropinorole, Pramipexole, Rotigotine [Available as transdermal patch]
- **Uses**
  - Parkinson's disease
  - Restless Lung syndrome
- **Adverse Effect**
  - Increase Compulsive behaviour like Hypersexuality, Gambling, Kleptomania

Apomorphine

- It is a non-ergot derived drug.
- Given as S.C. Injection
- **Rx:** Acute off Episodes
- **Adverse Effects**
  - Nausea
  - Vomiting

Important Information

- DOC for restless leg syndrome is Gabapentin.

Decreased ACH Level 00:35:13

- Drugs ↓ Ach level is called Central anticholinergics.

Drugs Lowering Ach Level

Central anticholinergics	Antihistamines with anticholinergic properties
• Benzhexol (Trihexyphenidyl)	• Promethazine.
• Benztropine	• Diphenhydramine
• Biperiden	• Dimenhydrinate

Amantadine

- Amantadine produces Anti-dyskinetic properties.
- It Produces NMDA Antagonism.
- It has Anti-cholinergic properties.
- **Adverse effects**
  - Livedo reticularis
  - Ankle oedema

Newer Drugs For Parkinson Disease

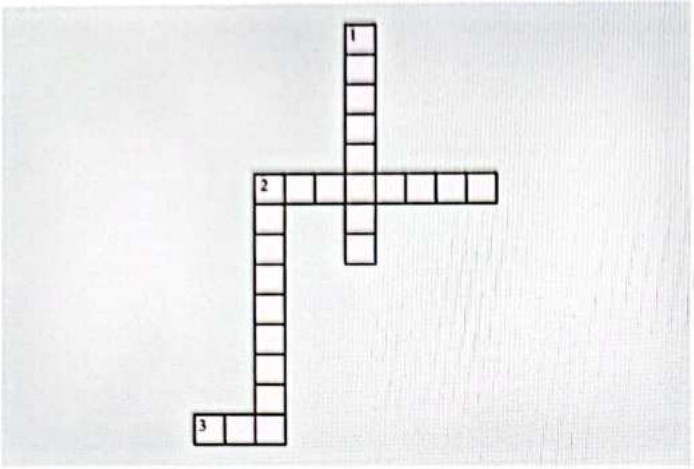
- **Opicapone ⇒ COMT Inhibitor:** To decrease off episodes of Parkinson disease.
- **Istradephylline ⇒ Adenosine antagonist:** To decrease episodes of Parkinson Disease.

Table 49.1

D1	D2	Higher dose	
↓	↓	↓	↓
Vaso-dilation	Acts on CTZ	Stimulate ß1	Stimulate α1
↓	↓	↓	↓
↓ BP	Nausea	HR ↑	Vasoconstriction
	Vomiting	↓	↓
		Risk Of arrhythmia	↑ BP

CROSS WORD PUZZLES

Crossword Puzzle



Across

2. Levodopa cross BBB converts into
3. Combination of L-Dopa and carbidopa increase availability of levodopa into

Down

1. In Parkinson's disease Ach level
2. In Parkinson's disease Dopamine level

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50 MANIA AND BIPOLAR DISORDER

Definitions

- A person's mood is elevated in mania. i.e., a person is hyperactive.
- Patients with depression have a low mood and lack interest in pleasurable activities.
- Bipolar disorder (BPD) is a condition in which a patient remains in mania for a few months and in a depressed mood for a few other months. These cycles of mania and depression alternate.
- The following drugs are used to treat both mania and BPD:
  - Lithium
  - Valproate (antiepileptic).
  - Carbamazepine
  - Antipsychotics.
- Lamotrigine is used to treat BPD only

Lithium 00:02:30

Pharmacokinetics of Lithium

- Lithium is available in its salt form, lithium carbonate.
- It has a narrow therapeutic index (TP), which means it's less safe.
- We can perform therapeutic drug monitoring (TDM) for lithium.
- The half-life (t 1/2) of lithium is 24 hours (1 day).
- In order to achieve a clinical steady state, 4-5 days are required.
- It has 100% absorption.
- It doesn't undergo metabolism.
- It has no plasma protein binding (PPB)

Important Information

- Lithium is not administered directly but is available in its salt form, i.e., lithium carbonate.

Excretion of Lithium 00:04:50

- More than 95% of lithium is excreted via urine.
- Approximately 4% of lithium is eliminated via sweat.
- Less than 1% of lithium is excreted via tears, saliva, and breast milk. Thus, lithium is safe for lactating females.

Therapeutic Drug Monitoring (TDM) 00:06:15

- It is critical to wait 4-5 days before beginning TDM in order to achieve steady state.
- If the drug is administered at 9 a.m., then we should withdraw the blood 10 to 12 hours after the dose and check the lithium levels.

Levels of Lithium 00:07:24

- Normal levels of lithium are between 0.6 and 1.0 mEq/L for the prophylaxis of mania and BPD.
- During acute mania, the lithium levels of 1.0–1.5 mEq/L are maintained.
- If the lithium level is >1.5 mEq/L, then there are chances of lithium toxicity. Hospitalization isn't required if there are no symptoms.
- If the lithium level is > 2 mEq/L, then hospitalization is required.
- If the lithium level is >3 mEq/L, then dialysis is required since there's no antidote for it.
- Lithium is maintained at a level of 0.4–0.8 mEq/L when it's used as an adjuvant therapy for depression.

Mechanism of Action of Lithium 00:09:50

- There are two theories of the mechanism of action of lithium:
  - In the first theory, mania is considered to be caused by the activation of Gq receptors. By interrupting the activation of Gq receptors, lithium helps in the treatment of mania.
  - The second theory is that depression is caused by a decrease in brain-derived neurotrophic factor (BDNF). BDNF has two important uses: It increases neural-adaptation and neuroplasticity (the increased production of synapses in the brain). Lithium helps in the treatment of depression by increasing the levels of BDNF.

Lithium acts by two Mechanisms

- First by increasing BDNF.
  - Lithium decreases Glycogen synthase kinase (GSK)-3 β.
  - This leads to an increase in the activity of β catenin.
  - This in turn leads to the increase of BDNF.
  - In this way, lithium helps in treating depression by increasing BDNF.
- The second mechanism of action involves reduction in Gq activity.
  - Gq splits into Diacylglycerol (DAG) and Inositol trisphosphate (Ip3).
  - IP3 is further split into IP2, which in turn splits into Ip1.
  - IP1 splits into inositol, which in turn converts to phosphatidylinositol phosphate (PIP) and finally to phosphatidylinositol 4,5-bisphosphate (PIP2).
  - PIP2 activates Gq and the cycle continues.
  - Phospholipase C (PLC) splits PIP2 into DAG and Ip3.
  - IP3 and DAG are responsible for causing mania.
  - Lithium inhibits the conversion of IP2 to IP1 and IP1 to inositol.

- With the decrease in the inositol, the Gq activation also decreases, which in turn decreases the mania. Thus, lithium can be used in the treatment of mania.
- Lithium is also called a mood stabilizer. Thus, it can be used in the treatment of mania, depression, and bipolar disorder.

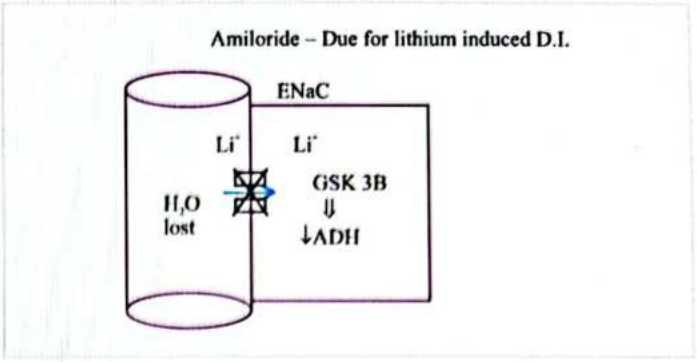
Uses of Lithium 00:16:28

- Lithium is used in the prophylaxis of mania and BPD, and it's the drug of choice in these conditions.
- It can also be used in acute mania, but it's not the drug of choice as it starts working after 2-3 weeks. Thus, benzodiazepines and antipsychotics are used in acute mania, and lithium is added to the therapy as an additional drug.
- It can also be used in unipolar depression.
- Lithium is also used to treat leukopenia and hypnic headaches.
- It has an anti-suicidal effect.

Adverse Effects of Lithium 00:20:20

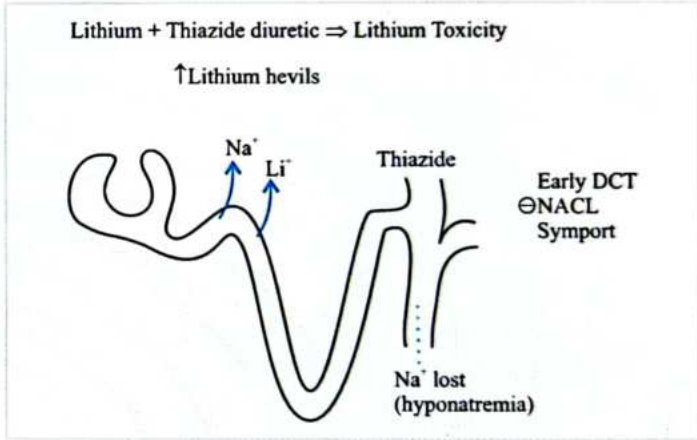
- The adverse effects of lithium can be remembered by the following acronyms:

- **Mnemonic: All Fat Sick H E N F E L L**
  - All: The drug causes alopecia and acne.
  - Fat: The patient can gain weight.
  - Sick: It can cause seizures and sinus node dysfunction. Sinus node dysfunction can produce atrioventricular (AV) block, due to which AV-blockers are contraindicated with lithium.
  - H: It mainly causes hypothyroidism. It can also cause hyperthyroidism in rare cases.
  - H: High doses of lithium can cause coarse tremors, ataxia, tinnitus, diarrhea, and seizures.
  - E: Lithium can cause Ebstein's anomaly, a cardiovascular defect called tricuspid atresia, which has a teratogenic effect when administered to pregnant women.
  - The other teratogenic effects of lithium are "floppy baby" (hypotonic) and fetal goiter (hyperthyroidism).
  - N: Lithium causes nephrogenic diabetes insipidus (DI) via the following mechanism:
    → Lithium enters the cell from the lumen via the ENaC channel and inhibits kinase (GSK)-3 β, which in turn inhibits the antidiuretic hormone (ADH). This leads to water loss, which is polyuria and DI. Amiloride is the drug of choice for lithium induced DI as it inhibits the ENaC channel.



  - F: Lithium causes fine tremor, which is its most common AE.
  - E: It produces ECG changes like "T wave" flattening, which is a normal finding.
  - L: It causes leukocytosis (an increase in WBC count). Thus, it's used in the management of leukopenia.
  - L: Lithium can cause loose stools (diarrhea).
  - In cases of hypothyroidism, the patient is continued on lithium with the addition of levothyroxine. Lithium mainly causes hypothyroidism, but in rare cases, it can also cause hyperthyroidism.

Lithium Drug Interactions 00:28:28



- Can lithium and thiazide diuretics be combined together?
  - Thiazide diuretics act on the earlier part of the distal convoluted tubule (DCT) and inhibit sodium chloride symport. Thus, sodium is lost in the urine, causing hyponatremia. This leads to sodium reabsorption from the proximal convoluted tubule (PCT). Since the body treats sodium and lithium in the same manner, lithium also gets reabsorbed from the PCT due to hyponatremia. Since lithium has a narrow therapeutic index, its reabsorption leads to lithium toxicity.
  - Thus, lithium and thiazide diuretics should not be combined, as this can lead to lithium toxicity.
- Other diuretics, like loop diuretics, do not produce lithium toxicity.

Diseases that cause Lithium Toxicity 00:31:00

- Fasting, dehydration, and diarrhea can cause hyponatremia, which can lead to lithium toxicity in patients receiving lithium.
- In cases of heavy sweating, if the patient is administered water alone without electrolytes, then that can trigger hyponatremia, which can lead to lithium toxicity in patients receiving lithium. Thus, sodium chloride should be added to the water in cases of heavy sweating to avoid lithium toxicity in patients receiving lithium.

Case Examples 00:32:32

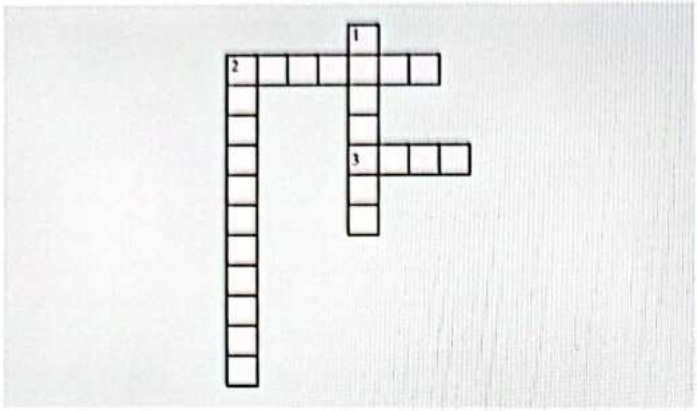
- **Case 1:** A patient who had bipolar disorder, was prescribed only antidepressants by the psychiatrist.
  - His depression was treated, but it manifested into his mania.
- **Case 2:** A patient with bipolar disorder was prescribed lithium.
  - The patient's depression as well as mania were treated, since lithium is a mood stabilizer.

Summary 00:34:26

- Lithium is the drug of choice in the treatment of mania and BPD.
- For BPD rapid cyclers, valproate is the drug of choice. If the cycle of BPD is more than four times a year, the patient is called a "rapid cycler."
- Carbamazepine and Antipsychotics.
- Lamotrigine is approved only for the treatment of BPD and not for mania.
- In cases of acute mania, lithium is not the drug of choice due to its slow action. Therefore, in acute mania, benzodiazepines and antipsychotics are given, and lithium is added as an additional therapy.
- Valproate has the highest teratogenic effect, followed by carbamazepine, which is followed by lithium. As a result, all three drugs are contraindicated in pregnant women with mania or bipolar disorder. In such patients, atypical antipsychotics are preferred.
- Lamotrigine is safe in pregnancy, but atypical psychotics are preferred.

CROSS WORD PUZZLES

Crossword Puzzle 1



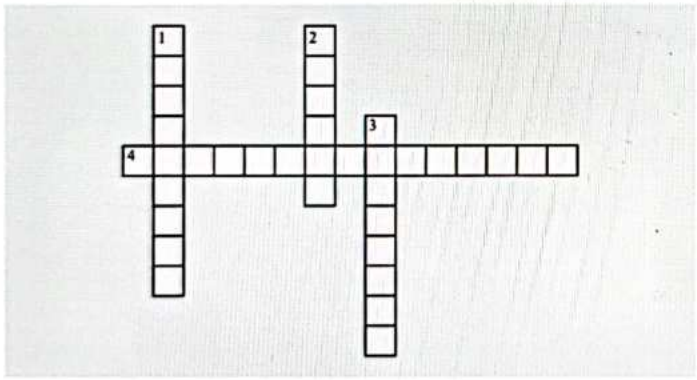
Across

2. _____ is the main drug for the treatment of mania and BPD.
3. _____ than 1% of lithium is excreted via tears, saliva, and breast milk. Thus, lithium is safe for lactating females.

Down

1. _____ disorder is a condition in which a patient remains in mania for a few months and in a depressed mood for a few other months.
2. _____ is used to treat BPD only, and not used for the treatment of mania.

Crossword Puzzle 2



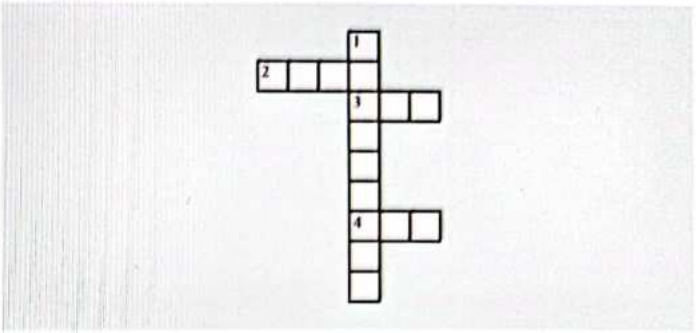
Across

4. _____ is required if the lithium level is > 2 mEq/L.

Down

1. _____ synthase kinase (GSK)-3 β levels are decreased by lithium.
2. _____ levels of lithium are between 0.6 and 1.0 mEq/L for the prophylaxis of mania and BPD.
3. _____ is required if the lithium level is >3 mEq/L.

Crossword Puzzle 3



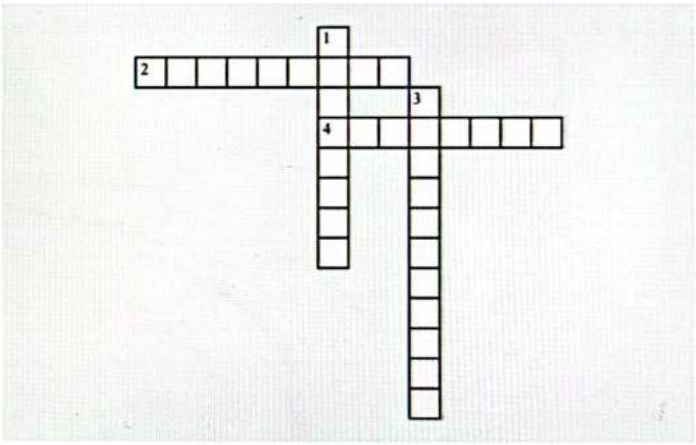
Across

2. _____ tremor is the most common adverse effect of lithium.
3. _____ and IP3 are responsible for causing mania.
4. _____ is further split into IP2, which in turn splits into IP1.

Down

1. _____ in the activity of Gq is the second mechanism of action of lithium.

Crossword Puzzle 4



Across

2. _____ has the highest teratogenic effect.
4. _____ diuretics and lithium should not be combined, as it can lead to lithium toxicity in patients receiving lithium.

Down

1. _____ dehydration, and diarrhea can cause hyponatremia, which can lead to lithium toxicity in patients receiving lithium.
3. _____ is safe in pregnancy.

51 ANTI PSYCHOTIC DRUG

Definitions

- **Psychosis:** A disease where the patient loses insight, has hallucinations, and delusions.
- **Schizophrenia:** Split personality disease.
  - Two theories are proposed to manage Schizophrenia:
    - → One is dopamine excess in the brain and the other is excessive serotonin.
    - → Antipsychotic drugs are used to manage psychosis and mainly schizophrenia.

Dopamine Theory 00:01:30

- Dopamine acts on two important receptors D1 (CVS) and D2 (CNS).
- The role of dopamine in the mesolimbic pathway in the brain is reward function.
- Excess of Dopamine causes psychosis.
- Dopamine also triggers D2 in the chemoreceptor trigger zone (CTZ) outside the blood-brain barrier. This causes nausea and vomiting in the patients.
- Dopamine is also present in the basal ganglia and is responsible for kinesia (movement).
- In Parkinson's disease, less dopamine results in bradykinesia, that is, slowing of movements.
- Dopamine also acts as a thermostat (D2). This is to control the body temperature.
- Another role of dopamine is in the tubulo-infundibular pathway when the D2 receptor is activated, dopamine decreases a hormone called prolactin.
- In order to treat psychosis, D2 receptor blockage can be done. If D2 receptors are blocked in the CTZ zone, nausea and vomiting decrease.
- If D2 receptors are blocked in basal ganglia, these lead to a condition called extrapyramidal symptoms. For example, the blocking of dopamine in the elderly leads to drug-induced Parkinson's disease due to bradykinesia.
- If D2 is blocked in the thermostat, the temperature of the body increases, referred to as Malignant Syndrome. Since the drugs that block dopamine are referred to as neurolept, it is also called Neurolept Malignant Syndrome.
- If the D2 receptors are blocked in the tubulo-infundibular pathway, it will lead to increased prolactin.

Typical Antipsychotics (Neurolepts) 00:08:02

- These are called typical because these mainly block D2 receptors and they can also block 5HT2 receptors (less).
- Typical antipsychotics also block alpha receptors, muscarinic receptors, and histamine receptors.

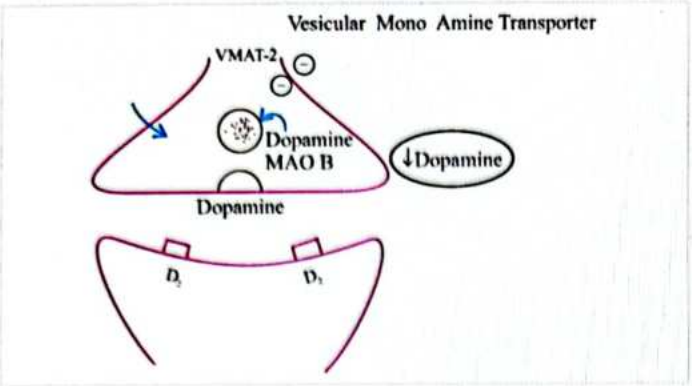
Drugs of Typical Antipsychotics

- **Phenothiazines (end with azine)**- These block alpha, muscarinic, and histamine receptors more than D2 receptors.
  - Chlorpromazine
  - Thioridazine- Not used nowadays as it causes retinal toxicity
  - Trifluoperazine
- **Thioxanthene (end with thixol)**
  - Flupenthixol
  - Zuclopenthixol
- **Butyrophenones (end with peridol)**- These block D2 receptors more than alpha, muscarinic, and histamine receptors. Therefore, more extrapyramidal symptoms are seen.
  - Haloperidol
  - Droperidol

Uses of Typical Antipsychotics

- Schizophrenia: Treats only positive symptoms.
- Acute psychosis: The drug used is Haloperidol.
- Antiemetic: Prochlorperazine drug is used.
- GERD: The drug used is Levosulpiride, it also crosses the blood-brain barrier and can cause extrapyramidal symptoms.
- Hiccups: Chlorpromazine.
- Tics disorder: The syndrome for tics is Tourette's syndrome. Vocal tics are sudden spasmodic contractions of a group of muscles. VMAT 2 inhibitors such as Tetrabenazine (drug of choice) are used. Haloperidol and atypical antipsychotics such as Aripiprazole (FDA-approved) are also used.
- Clonidine and Guanfacine are also used to treat Tourette's syndrome.
- Huntington's chorea: Initially the excess of dopamine causes chorea.
  - Block D2- Haloperidol
  - VMAT2 inhibitors (Dopamine depletors)- Tetrabenazine
- **Droperidol anesthesia is used under two conditions:**
  - Neurolept anesthesia
  - Neurolept analgesia
- When Haloperidol is given as I.M. through the Z track technique, allows the drug to stay in the muscle for a longer period and can be administered once a month.

VMAT2 Inhibitors 00:19:09



- Dopamine is stored inside a vesicle. Action potential leads to the fusion of vesicles and the release of dopamine that acts on the D2 receptors in the CNS.
- Dopamine that is present outside the vesicle is pushed back into the vesicle by a transporter called VMAT2 (Vesicular MonoAmine Transporter 2).
- The Dopamine outside the vesicle is metabolized by the enzyme MAO B. This results in a decrease in dopamine release.
- VMAT 2 inhibitors are also known as dopamine depletors, required in Huntington's chorea.

Adverse Effects of Typical Antipsychotics 00:23:16

- Increase in Prolactin by blocking D2 receptors
- They are alpha blockers and there will be Hypotension
- They block muscarinic receptors leading to:
  - Dry mouth
  - Blurring of vision
  - Tachycardia
  - Constipation
  - Urinary retention
- They block histamine and lead to sedation.

- **Extra Pyramidal Symptoms:**
  - In acute dystonia or oculogyric crises, rolling of eyeballs upwards or turning of the neck towards one side are seen. It can start within hours to days of drug administration.
  - Due to the blockage of acetylcholine, there is an increase in Acetylcholine activity.
  - For treatment, Central anticholinergics like Benzhexol (Trihexyphenidyl) is used. Even common antihistamines such as promethazine can also be used.

- **Drug-Induced Parkinson's disease:**
  - Elderly patients are more to this disease
  - can start from the 5th to 30th days of starting antipsychotics
  - Due to blockage of D2 receptors and increase in acetylcholine.
  - Central anticholinergics are also the DOC here for the management.

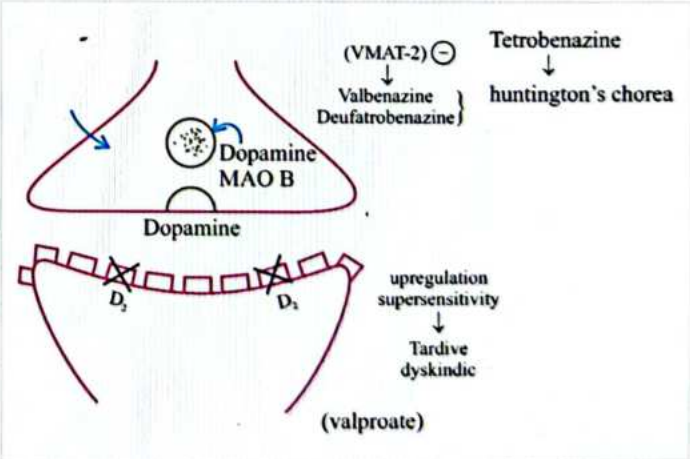
- **Akathisia:**
  - Inability to sit in one place.
  - It can appear 5-60 days after starting antipsychotics.
  - Reason is unknown.
  - The drug of choice is Propranolol. Benzodiazepines (BZDs) can also be used.

- **Neurolept malignant syndrome:**
  - It takes days to months to develop.
  - When the muscles of the body contract, the temperature rises.
  - The skeletal muscles have ryanodine receptors (RYR1) in the sarcoplasmic reticulum.
  - Whenever the muscles have to contract, the sarcoplasmic reticulum with the help of ryanodine receptors will release calcium resulting in muscle contraction.
  - Calcium ion is responsible for Neurolept malignant syndrome.
  - Patients will have hyperthermia and muscle rigidity.
  - This can be managed by ryanodine receptor blockage through the usage of the drug Dantrolene Sodium (DOC).
  - The specific antidote for Neurolept Malignant Syndrome (NMS) is the D2 agonist Bromocriptine.

Important Information

- Dantrolene Sodium is also used in Malignant Hyperthermia (when succinylcholine muscle relaxant or Halothane group of General Anesthetics, the ryanodine receptors are hyperactive, and more and more calcium ions are released leading to malignant hyperthermia).

- **Tardive Dyskinesia** 00:34:55
  - It takes months to years to develop.
  - Dopamine becomes super sensitive.



- VMAT-2 performs the function of keeping dopamine inside the vesicles.
- Whenever the receptors are blocked for a long duration, the number of receptors undergo upregulation and become super sensitive which can cause Tardive dyskinesia.
- This happens due to excess dopamine, so VMAT 2 inhibitors such as Valbenazine and Deutetrabenazine (FDA-approved) are used and are the drug of choice. This results in the depletion of Dopamine.
- Valproate is also used for the treatment of Tardive dyskinesia.

- **Perioral tremors:**
  - Its takes years- months to develop
  - There is no effective therapy for perioral tremors.
  - Anti-parkinson's drugs are tried but not so effective as it is a long-term complication.

Atypical Antipsychotics 00:42:04

- These block serotonin (5HT2) receptors more than the D2 receptors.

Advantages	Disadvantages
• Can treat both positive and negative symptoms of schizophrenia. • Treat resistant cases • Fewer chances of Extra pyramidal symptoms • Less blockage of alpha, M, and H receptors.	• Causes Metabolic syndrome: obesity, dyslipidemia, risk of diabetes. • Olanzapine produces more metabolic syndrome than Clozapine.

Drugs of Atypical Antipsychotic

- **Clozapine**
- **Olanzapine**
- **Quetiapine**
- **Asenapine**
- Risperidone
- Paliperidone
- Lurasidone
- Ziprasidone

- **Other atypical antipsychotics:**
  - Aripiprazole
  - Brexpiprazole
  - Cariprazine
  - Amisulpride

- Don't confuse "piprazole" with "pantoprazole"

Clozapine 00:48:42

- Advantage-
  - It has anti-suicidal effect
  - Used in resistant cases
  - Fewer extrapyramidal symptoms.

- Adverse effects:
  - Can produce Agranulocytosis (dose independent).
  - Seizures (dose dependent).
  - Myocarditis.
  - Wet pillow syndrome- Causes Sialorrhea due to M4 agonism by Clozapine. The treatment is Atropine given locally
  - Anticholinergic properties
    → Risk of mydriasis
    → Contraindicated in angle closure glaucoma

Olanzapine

- Causes Maximum metabolic syndrome (weight gain)

Asenapine

- Used a sublingual tablet

Quetiapine

- It has calming effect
- Adverse effect is cataract.

Risperidone

- Extrapyramidal symptoms (EPS) and an increase in prolactin are observed at high doses.
- Z track technique is used for I.M. drug administration to decrease the leaking of drug back into the subcutaneous tissue as well as skin (seen in 90-degree technique).
- BPD is bipolar disorder.

Important Information

- Drugs administered using Z-track technique
  - Iron injections to prevent staining.
  - Anti-psychotics to prevent the leaking of drug back into the subcutaneous layer and skin.

- Uses:
  - Schizophrenia
  - Bipolar disorder
  - Irritability in autistic disorder in children
  - Mania

Aripiprazole

- It is a partial D2 agonist more than 5HT2 blocker.

- Uses:
  - Schizophrenia
  - Tourette's syndrome
  - Irritability in autistic disorder in children

Brexpiprazole

- It is partial D2 agonist
- It is also a 5HT1A partial agonist
- Uses:
  - Schizophrenia.
  - Depression.

Cariprazine

- It is a D2, D3 partial agonist.
- Uses:
  - Bipolar disorder

Amisulpride

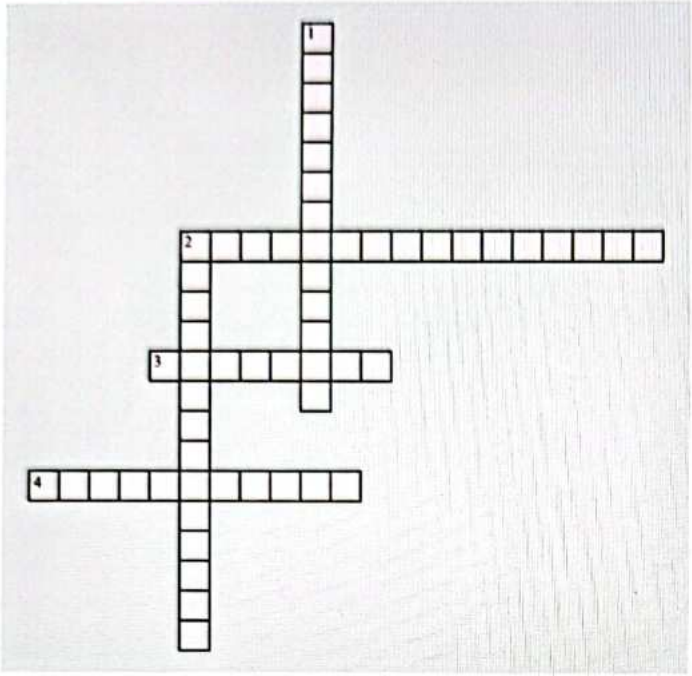
- It is a D2 blocker.
- The advantage is fewer Extra pyramidal symptoms.
- **Uses:**
  - Treatment of postoperative nausea and vomiting.

Management Aspects

- Antipsychotics + Benzodiazepines - Acute psychosis
- Atypical antipsychotics- Psychosis in pregnancy
- Pimavanserin:
  - It is 5HT2 antagonist
  - Used in Parkinson disease psychosis

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

2. _____ drug is used as antiemetic
3. _____ acts on two important receptors 01(CVS) and D2(CNS)
4. _____ is used to treat acute psychosis.

Down

1. _____ is a split personality disorder.
2. _____ is not used nowadays as it causes retinal toxicity.

Crossword Puzzle 2

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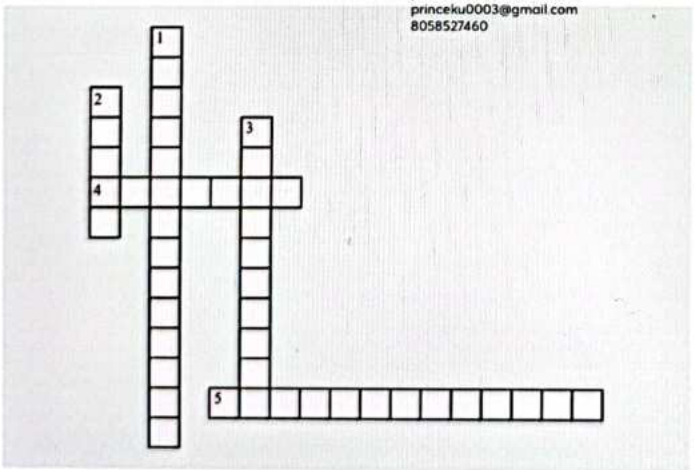


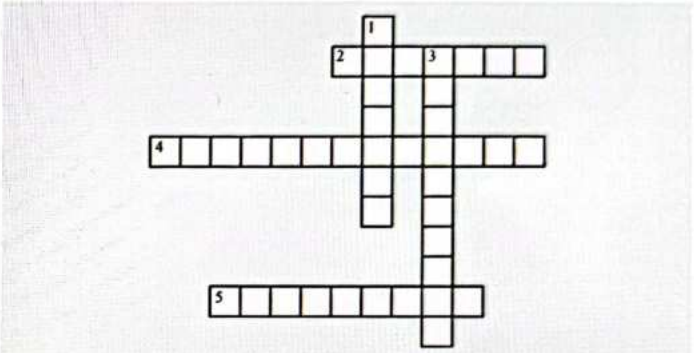
Across

4. _____ antipsychotics also block alpha receptors, muscarinic receptors, and histamine receptors.
5. _____ is used to treat GERD.

Down

1. _____ is used to treat hiccups.
2. _____ inhibitors are also known as dopamine depleters.
3. _____ is also used to treat Tourette's syndrome.

Crossword Puzzle 3



Across

2. _____ dyskinesia takes months to years to develop.
4. _____ is the specific antidote for Neurolept Malignant Syndrome.
5. _____ cases can also be treated with atypical antipsychotics.

Down

1. _____ ion is responsible for Neurolept malignant syndrome.
3. _____ sodium is also used in Malignant Hyperthermia

52 ANTI DEPRESSANT DRUGS

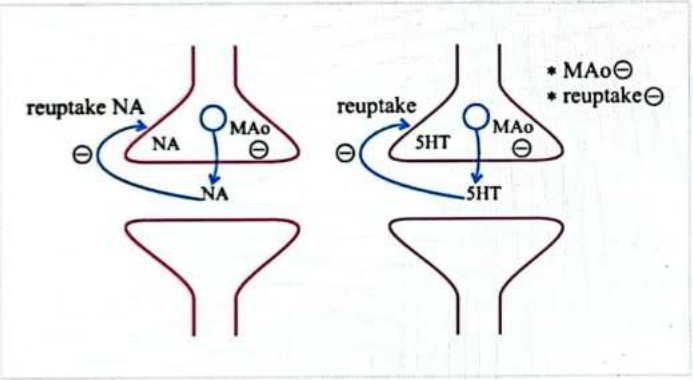
Historical Importance

- The drug Reserpine is a banned drug which was earlier used to treat hypertension.
- Reserpine is a VMAT inhibitor which depletes Noradrenaline (NA), Serotonin (5HT), and Dopamine (D).
- Thus, the intake of Reserpine caused suicidal tendencies and the drug got banned.
- Another drug Iproniazid which was used to treat Tuberculosis is an MAO inhibitor and thus made the patient happier.
- Even though Dopamine gives a happiness boost, we don't increase its levels to treat depression as increased levels of dopamine cause psychosis.

Methods to increase the levels of NA, 5HT, and BDNF

00:03:40

- The aim of antidepressant drugs is to increase the amount of Noradrenaline (NA), Serotonin (5HT), and Brain Derived Neurotrophic Factor (BDNF).



- The diagram shows the Reuptake of Noradrenaline and Serotonin back to cells from their synapses using NA and 5HT transporters.
- After the reuptake, they are metabolized by the enzyme MAO (Monoamine Oxidase).
- So, to increase the levels of NA and 5HT, two types of drugs can be used:
- MAO inhibitors
- Reuptake inhibitors

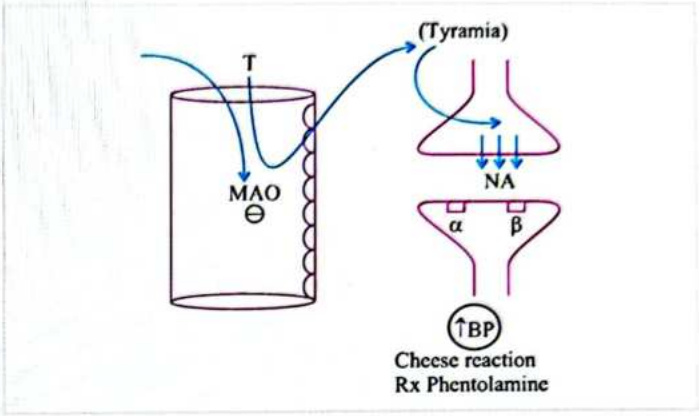
MAO (Monoamine Oxidase) Inhibitors

00:05:40

- There are two types of MAO inhibitors.
- **Irreversible MAO inhibitors:**
  - Tranylcypromine
  - Iproniazid
  - Isocarboxazid

- **Reversible MAO inhibitors:**
  - Moclobemide
  - Clorgyline
- These drugs are not in use anymore.

Cheese Reaction



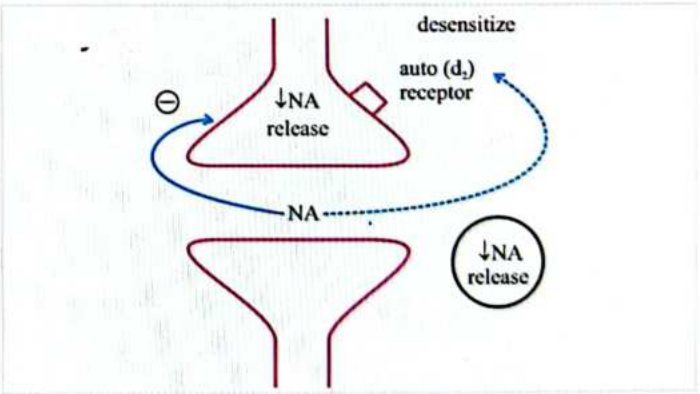
- The intake of cheese, beer, or wine causes an increase in blood pressure in patients on MAO inhibitors.
- In normal cases, the Tyramine released by cheese is metabolized by MAO in the intestine.
- In patients on MAO inhibitors, the Tyramine gets absorbed and causes the release of NA.
- This noradrenaline increases blood pressure.
- This condition can be managed by an anti-hypertensive drug Phentolamine.

Tricyclic Antidepressants (TCAs)

00:10:15

Mechanism of actions:

Inhibit the reuptake of noradrenaline and serotonin:



- In any synapse, there are autoreceptors (α2 receptors for NA) which help in decreasing the release of NA. When TCAs are taken, noradrenaline is not taken back and its concentration increases in the synapses.

- These increased levels of NA desensitize the auto receptors.
- This entire process takes 2-3 weeks to happen and it reaches its peak in 4-8 weeks.
- Thus, antidepressants take a few weeks to work.

Neurotrophic Hypothesis:

- When you increase the levels of NA and 5HT in the brain, it in return increases the levels of BDNF (brain-derived neurotrophic factor) and NGF (Nerve growth factor).
- These growth factors act on RTK (Receptor Tyrosine Kinase) and RTK increases axon/dendritic proliferation.
- All these results in an increase in total synapse connections in the brain and this process of synapse growth is called neuroplasticity.
- More synapses result in a decrease in depression.

Other Receptors Blocked by TCAs

- Alpha receptors: When Alpha receptors are blocked, BP falls and Hypotension kicks in.
- Histamine receptors: When Histamine receptors are blocked, the patient starts feeling sedation.
- Muscarinic receptors: This will cause several anti-cholinergic reactions such as:
  - It causes passive mydriasis which further causes blurring of vision.
  - Other side effects are dry mouth, constipation, and urine retention.
  - It can also cause tachycardia resulting in long QT.

- TCAs have a narrow therapeutic index and with all the above-mentioned complications, TCAs are no longer primarily in use to treat depression.

Important Information

- TCAs are contraindicated in patients with closed-angle glaucoma due to the risk of mydriasis.

Drugs of TCAs

- Imipramine: Its metabolism will give rise to Desimipramine. Both the drug and its metabolite are active in nature.
  - It is used to treat nocturnal enuresis due to its anticholinergic properties.
- Amitriptyline: Its metabolism will give rise to Nortriptylline.
  - It is prescribed for Diabetic neuropathic pain and migraine prophylaxis.
- Cloimipramine: It increases the activity of serotonin. Also
  - It is used to treat OCD (obsessive-compulsive disorder).
- Doxepin: It has histamine-blocking properties.
  - It is used to treat pruritus (Topical use).
- Dothiepin

TCA Overdose/Poisoning

- TCA overdose can be recognized by 3Cs:
  - Convulsions
  - Cardiotoxic: It can increase Heart rate, long QT, and cause arrhythmias.
  - Coma
- TCA poisoning also causes high anion gap acidosis.

Management

- Take care of the A, B, and C. (airway, breathing, circulation)
- Gastric lavage within 6 hours.
- Using an antidote which is I.V Sodium bicarbonate. It activates the sodium channels in the heart which were causing arrhythmias. Also, it makes the blood alkaline and treats acidosis.
- If the patient develops seizures, Lorazepam is given.
- If the patient develops arrhythmias, then lignocaine or beta blockers are given.
- Avoid: Class I and Class III antiarrhythmics are avoided because they increase QT intervals.

SNRIs (Serotonin Noradrenaline Reuptake Inhibitors)

00:25:36

Mechanism of action of SNRIS

- They inhibit NA and 5HT reuptake.
- They increase the BDNF.
- Additionally, there is no blockade of alpha, muscarinic and histamine receptors.

Uses

- General anxiety disorder (GAD)
- Neuropathic pains
- OCD
- Depression

Drugs of SNRIs

- Venlafaxine
- Desvenlafaxine
- Milnacipran: It is also used for fibromyalgia
- Duloxetine: It is also used to treat stress urinary incontinence (due to muscarinic blockade), fibromyalgia, and diabetic neuropathy.

Adverse effects of SNRIS

- It increases blood pressure and heart rate due to an increase in noradrenaline.

SSRIs (Selective Serotonin Reuptake Inhibitors) 00:29:50

- SSRIs are the drug of choice for treating depression.

Mechanism of action of SSRIs

- They inhibit the reuptake of serotonin.
- They increase the BDNF.

Advantage of SSRIs over TCAs

- SSRIs don't block alpha, histamine, and muscarinic receptors.
- They have a good margin of safety.
- Their efficacy is better than TCAs.
- They don't cause any psychomotor or cognitive impairment.

Drugs of SSRIs

- Fluoxetine: It gets metabolized to an active compound called Norfluoxetine which makes it the longest-acting SSRI.
- Fluvoxamine: It is the shortest-acting SSRI.
- Paroxetine: It is contraindicated in pregnancy as it causes CVS defects in the fetus.
- Sertraline
- Citalopram
- Escitalopram: It is the most specific SSRI.
- Dapoxetine

Uses of SSRIs

- Mild to moderate depression.
- OCD (obsessive-compulsive disorder)
- Phobia, Panic disorders
- GAD (General anxiety disorder)
- PTSD (post-traumatic stress disorder)
- Binge eating disorders
- Bulimia nervosa
- Premature ejaculation (Dapoxetine)

Adverse effects of Serotonin

- When SSRIs are given there is increase in serotonin, which leads to following adverse effects:
  - Serotonin acts on 5HT2 receptors which increases anxiety in the patient on the initial days of taking the drug. In such cases, benzodiazepines are prescribed initially.
  - They can cause insomnia (prescribe them in the morning).
  - They cause sexual dysfunction like anorgasmia and delayed ejaculation.
  - Serotonin also causes bruxism.
  - Serotonin also acts on 5HT3 receptors and causes nausea, vomiting, and diarrhea.
  - Serotonin also acts on 5HT4 receptors which causes diarrhea.

Other adverse effects of Serotonin

Discontinuation Syndrome

- This happens when you suddenly stop the intake of shorter-acting drugs like:
  - SNRI - Venlafaxine
  - SSRI - Fluvoxamine and Sertraline
- The patient will develop: (FINISH)
  - Flu-like symptoms
  - Insomnia
  - Nausea and Vomiting
  - Imbalance
  - Sensory disturbance
  - Hyperarousal (anxiety)

Serotonin Syndrome

- This happens due to high levels of serotonin in the body.
- It causes:
  - Hypothermia
  - Myoclonus
  - The rigidity of the muscles
  - Seizures
- The drug of choice to treat serotonin syndrome is Cyproheptadine. It is a 5HT2 antagonist.
- **Risk of serotonin syndrome:** It occurs due to the combination- MAO inhibitors + SSRIs. They are:
  - Pethidine + SSRIs
  - Linezolid + SSRIs
  - Dextromethorphan +SSRIs

Atypical Antidepressants 00:45:30

Trazodone

- It blocks both α1 and α2 receptors along with 5HT2 receptors.
- Adverse effect: It causes Priapism and cardiac arrhythmias.

Nefazodone

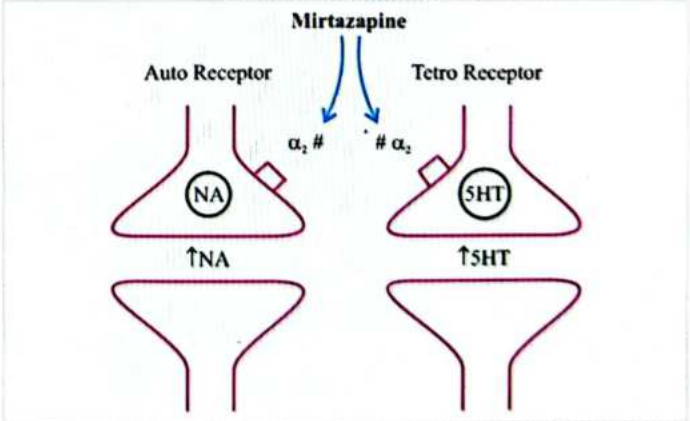
- Same mechanism of action as Trazodone.
- Adverse effect: It causes hepatotoxicity.

Mianserin

- It blocks presynaptic α2 receptors. This increases noradrenaline release.

Mirtazepine

- It is classified as a NaSSA (Nor adrenergic and specific serotonergic antidepressants).
- **Mechanism of action of Mirtazapine:**
  - It blocks the Alpha-2 receptors in adrenergic and serotonergic neurons and thus increases NA and 5HT.



- As it is also a 5HT2 receptor blocker, it shows less/no sexual dysfunction.
- It also blocks 5HT3 receptors.
- It is also known to block Histamine receptors (H1 particularly) which causes sedation.
- Thus, Mirtazapine is useful in patients with depression + insomnia.

Bupropion

- It is an NDRI (Noradrenaline dopamine reuptake inhibitor).
- Uses: It is used in the following cases:
  - Smoking cessation therapy.
  - Management of obesity.
  - Management of depression.
- **Adverse effect:** It increases seizures and anxiety.

Amoxapine

- It is chemically related to Loxapine.
- Loxapine is a D2 blocker and it is used in the treatment of psychosis.
- **Uses:** Amoxapine can be given to patients with depression and psychosis. (Psycho Depression).

Agomelatine

- It is a melatonin receptor agonist and acts on MT1 and MT2.
- **Uses:** It is given to patients with depression and insomnia.

Amineptine and Tianeptine

- They increase serotonin reuptake.

Important Information

- **Buspirone:** It is a 5HT1A partial agonist and is used to treat general anxiety disorder or chronic anxiety.
- Do not confuse it with Bupropion.

Newer/Novel Antidepressants

00:56:55

- **Esketamine nasal spray:** This is used for resistant depression.
- **Brexanolone:** It is used to treat postpartum depression. It is given as a 60 hr continuous infusion.
- **Vortioxetine:** It is a 5HT reuptake inhibitor, 5HT1A partial agonist, and 5HT3 blocker.
- **Vilazodone:** It is also known as SPARI (Serotonin partial agonist reuptake inhibitor). It is a 5HT1A agonist and also has SSRI properties.
- Both Vortioxetine and Vilazodone are used to treat major depression disorder.

Important Information

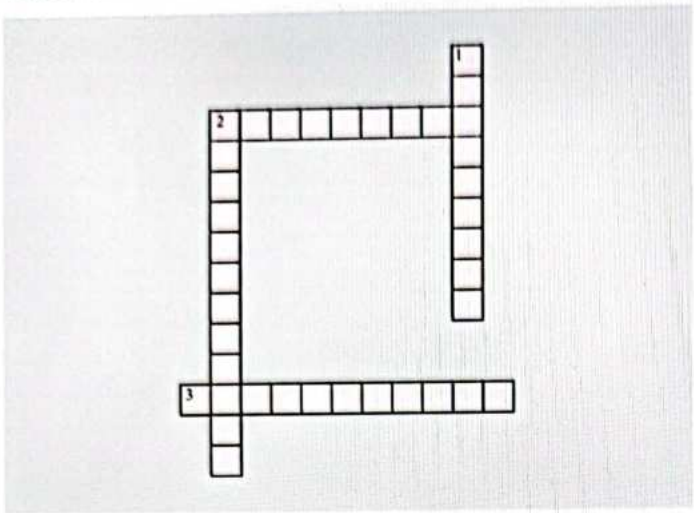
- The drugs used to treat depression that can cause sexual dysfunction are SSRIs, SNRIs, and TCAs.
- The anti-depressants drugs that cause less/no sexual dysfunction are Bupropione, Mirtazapine, Vilazodone, and Vortioxetine.

Principles of drug treatment of depression

- SSRIs are the first choice of drug to treat depression.
- It will take 2-3 weeks to start working.
- The full effect will be seen in 4-8 weeks.
- In cases where SSRIs are contraindicated, alternatively, SNRI or atypical antidepressants are given.
- When depression is controlled, don't stop the medication.
- Next, the patient is kept on maintenance therapy: This decreases the chances of relapse.
- TCAs: These are given in nonresponding cases.
- In case the patient has suicidal tendencies, ECT (electroconvulsive therapy) is given.

CROSS WORD PUZZLES

Crossword Puzzle 1



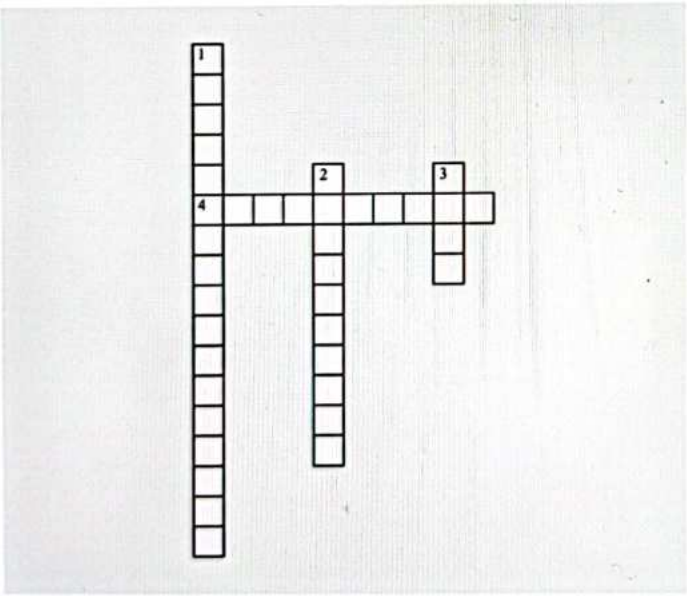
Across

2. Excessive dopamine causes _____.
3. _____ is useful in patients with depression + insomnia.

Down

1. _____ is a banned drug which was earlier used to treat hypertension.
2. Cheese reaction is managed by _____.

Crossword Puzzle 2



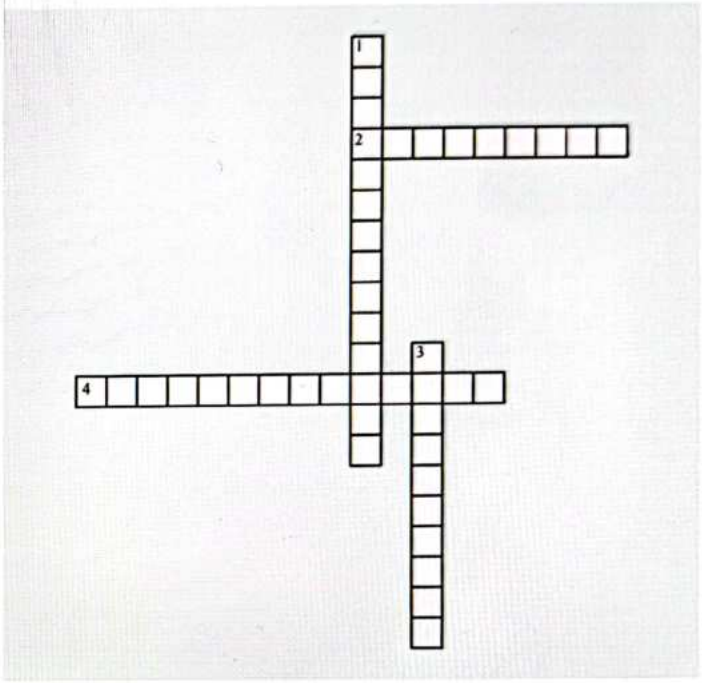
Across

4. TCAs are known to block 3 types of receptors, alpha, histamine and _____.

Down

1. TCA overdose is treated by I.V _____.
2. _____ is an SSRI that is contraindicated in pregnancy.
3. Cheese, beer, or _____ causes an increase in blood pressure in patients on MAO inhibitors.

Crossword Puzzle 3



Across

2. Esketamine nasal spray is used for _____ depression.
4. Adverse effect of Nefazodone is _____.

Down

1. The drug of choice to treat serotonin syndrome is _____.
3. Vortioxetine and _____ are used to treat major depression disorder.

53 OPIOIDS

00:00:55

- Opioids are natural substances obtained from the poppy plant or Papaverum somniferum.
- Opioids may lead to addiction, dependence, used for the treatment of cancer pain, and general anesthesia.
- The poppy plant contains a juice (opium) which mainly contains morphine.
- Morphine is also called opiate, found naturally in opium.
- Alteration in the chemical structure of morphine produces synthetic, semi-synthetic compounds under laboratory conditions.

Classification of Opioids

00:02:10

i. **Natural Occurring Compounds**
   - Codeine, Thebaine, Papaverine.

ii. **Semi-Synthetic Compounds**
   - Heroin, Hydrocodone.

iii. **Synthetic Compounds**
   - Pethidine, Fentanyl, Methadone.

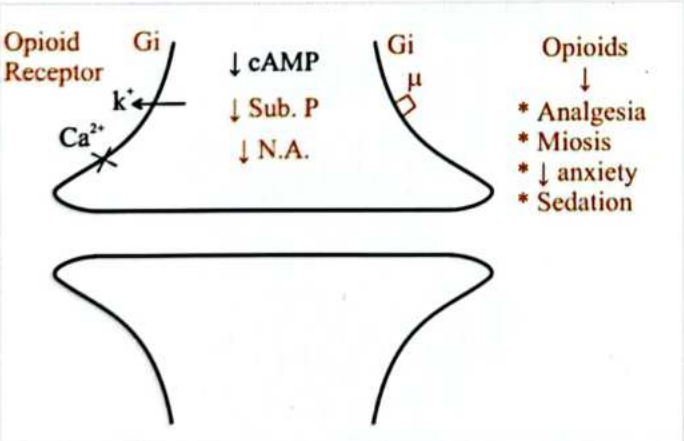
- **Endogenous Opioids**
  - Endogenous opioids are naturally occurring peptides in the brain.
  - Examples: Endorphins, Enkephalins, Dynorphins.

Opioids Action

00:04:08

- Opioids can act on three receptors- mu, kappa, and delta (μ, κ,δ)
- Endorphins act on μ, Enkephalins act on κ , and Dynorphins act on δ.

Opioids Mechanism of Action At The Cellular Level



- Opioid receptors are Gi-coupled (Gi) receptors.
- μ receptor (Gi) is present in the pre-synaptic neuron.
- It decreases cAMP, opens K+, and closes the Ca+ channel.
- K+ goes outside, and Ca+ ion does not allow it to come inside. As a result, it causes hyperpolarization.
- It decreases the release of the substance P (responsible for pain in the brain) and Nor-adrenaline.
- Opioids give an analgesic effect by decreasing the level of substance P in the brain and a miosis, sedative, and anti-anxiety effect by decreasing Nor-adrenaline (sympathetic nervous system).

Function of Opioids

00:07:15

- **μ receptor:**
  - When μ receptor is stimulated, it causes euphoria (causes happiness, excitement), and the person wants this effect.
  - It will cause physical and psychological dependence.
  - It can also produce miosis, constipation, analgesia, and sedation. When taken in higher doses, it causes respiratory depression.

- **κ receptor:**
  - When κ receptor is stimulated, it causes dysphoria (opposite of euphoria). A person experiences hallucinations and displeasure.
  - It also produces miosis, analgesia, respiratory depression, diaphoresis, and sedation.

- **δ receptor:**
  - When δ receptor is stimulated, it causes analgesia.

Important Information

- The majority of the action is shown by μ receptor.

Effect of Morphine (Addiction Drug)

00:10:36

Mnemonics: Please Scream

- **Please** – Physical and psychological dependence
- **S-** Sedation,
  - Smooth muscle: relax longitudinal muscle and contract circular muscles.
    → Therefore in GI – Constipation (decrease GI motility), GU- Urine retention (due to sphincter contraction), Biliary- increase biliary colic
- **C-** Cough suppressants (not mediated by opioid receptor), Constipation.
- **R-** Retention of urine,
  - Release histamine- leads to vasodilation, bronchoconstriction (so opioids C/I in bronchial asthma)

- Respiratory depression at higher dose
  → Carbon dioxide drive in brain and hypoxia drive in periphery gets suppressed. In brain increase PCO2 increase ICP. Therefore, opioids are C/I in head injury.
  → Rx: Naloxone (opioid antagonist)

- **E-** Euphoria, emesis (opioids stimulate CTZ center in brain)
- **A-**Analgesia – used in spinal and supra spinal.
  - Increases the tolerance to pain and decreases the perception of pain.
  - Used in visceral pain and cancer pain.
  - Anti anxiety
- **M-**Miosis

Important Information

- Opioids release histamine that causes vasodilation, a decrease in blood pressure, and bronchoconstriction. Thus, contraindicated in bronchial asthma.
- If a patient comes for the treatment of undiagnosed abdominal pain, opioids should not be used because Opioids constrict the sphincter of the gall bladder and cause biliary colic.
- Overuse of opioids causes respiratory depression. Medulla (brain) and peripheral have a vasomotor center.
- There are two mechanisms by which a person can breathe.
- When the partial pressure of carbon dioxide (CO2) is increased, the vasomotor center gets activated, the person can breathe, and the CO2 is washed out.
- In the periphery, the carotid body and aortic body are present, which decreases the oxygen; hence, it is called hypoxic drive.
- Opioids shut down the center that detects the CO2, so CO2 retention increases. It can also increase intracranial pressure and worsen the situation. Hence, it is contraindicated in patients with head injuries.
- Opioids are also vasodilators. So, it can also worsen the edema in the brain.
- When respiratory depression occurs, it must block the carbon dioxide center because it is a significant stimulation.
- In this condition, Naloxone (antidote for opioid poisoning) is given, an opioid antagonist.
- When opioid poisoning occurs, the patient comes with hypoxia. If the doctor gives oxygen, the hypoxic drive shuts down, and the patient experiences further respiratory depression.
- Opioids can induce emesis by stimulating the chemo-trigger zone (CTZ), leading to nausea and vomiting.
- Opioids increase the tolerance of pain (analgesia) and decrease the perception of pain.
- Opioids are helpful in visceral pain and cancer pain.

Opioid Drugs

I. Pure Opioid Agonist

00:23:05

- These drugs stimulate the opioid receptor (μ,κ,δ).
- Example: Morphine

Morphine

- **Pharmacokinetics:** Opioid pharmacokinetically undergoes a glucuronidation reaction. It is metabolized into morphine-3 glucuronide and morphine-6 glucuronide.
- Morphine-3 glucuronide can cause seizures. Morphine-6 glucuronide is a highly active metabolite.
- Morphine is contraindicated in renal failure or decreases the dose in renal failure.

Important Information

- If morphine is given in renal failure without decreasing the dose, metabolites will accumulate and causes seizure (morphine-3 glucuronide) and respiratory depression (morphine-6 glucuronide).

- **USES**
  - Cancer pain relief
  - Left ventricular failure or Pulmonary edema
    → Morphine is given to treat Myocardial Infarction. Because when a heart attack occurs, a person experiences anxiety, and to overcome this anxiety, morphine is used.
    → It dilates the vein (vasodilator) and shifts the blood from pulmonary to the systemic circulation. As a result, it will relieve pulmonary edema.
    → It also decreases dyspnea, air hunger, and pain.
  - Refractory diarrhea and refractory cough due to lung cancer.
- **Contraindication of morphine:**
  - Head injury
    → Increased CO2 retention increase ICP
    → Respiratory depression
    → Miosis
  - Bronchial asthma
  - Biliary colic

Acute Morphine Poisoning/Opioid Poisoning

- Signs of opioid poisoning are coma, pinpoint pupil (miosis), and respiratory depression.
- Pinpoint pupil (miosis) can also be seen in pontine hemorrhage, opium and carbonate poisoning.
- In Opioid and Carbomate poisoning, the patient develops symptoms like diarrhea, urination, bronchoconstriction, emesis, lacrimation and increased respiratory rate. Here antidote is Atropine.

- Other signs in morphine poisoning are hypotension, hypothermia, and hyporeflexia.
- An antidote for opioid poisoning is Naloxone. It is given intravenously.
- Naloxone is given as 0.2 to 0.3 mg every 2-3 minutes till respiration is fixed.
- If the patient is administered morphine via the intravenous route, gastric lavage is used.
- Morphine is a primary drug that can get secreted in the stomach (acidic pH).
- When the basic drug comes in the acidic medium of the stomach, then it becomes a ionized form and does not absorb in the stomach. But can be absorbed from small intenstine hence, gastric lavage is used to drain the morphine from the stomach.
- It is seen in drug addicts or overdoses of morphine.

Pethidine (Meperidine)

- It is a derivative of atropine (anti-cholinergic property).
- It has anticholinergic side effects like dry mouth, blurred vision, constipation, and urinary retention.
- Pethidine may cause mydriasis and less chance of miosis because of its anticholinergic properties.
- It is not used in myocardial infarction or tachycardia.
- It has less effect on the biliary, gastrointestinal tract (GIT), and genitourinary (GU).

- **Uses**
  - Analgesic
    → 1 mg of morphine (more potent) = 10 mg of pethidine (less potent).
  - Biliary colic
  - Pethidine is used in biliary colic disease because it has anticholinergic properties. Hence, it relieves spasms.
  - Drug of choice in postoperative shivering
    → Due to α2 receptor-mediated action.

- **Pethidine metabolism**
  - Pethidine metabolized into two important compounds, i.e., meperidine acid and nor-pethidine.
  - Nor-pethidine is excitatory in nature so the patient may develop seizures.
  - Pethidine is metabolized to meperidine acid, and the patient will not develop seizures.
  - Pethidine is metabolized into meperidinic acid by the hydroxylation of phase-I reaction and nor-pethidine by demethylation.

- **Drug interactions**
  - When pethidine is used with monoamine oxidase inhibitors (MAO), they inhibit the hydroxylation step. As a result, more pethidine is converted into nor-pethidine, and the patient ultimately develops seizures.
  - Pethidine is not used with serotonin reuptake inhibitors (SSRIs) because pethidine also increases serotonin (5-HT). SSRIs also increase serotonin. As a result, the combination of these drugs causes serotonin syndrome.

Codeine

- Codeine is a cough suppressant mainly used for dry cough.
- Codeine is a prescription drug because it causes drug addiction.
- Codeine is converted into morphine by CYP 2D6, and morphine produces analgesia, sedation, and euphoria.
- Suppose the person does not produce CYP2D6 properly (poor metabolizer). As a result, the person does not develop an analgesic effect, and only the cough suppressant effect is seen.

Pholcodine

- It is also used for dry cough.

Dextromethorphan

- It is a derivative of opiate but acts through NMDA- receptor antagonist.
- Used in dry cough.

Methadone

- It is a μ receptor agonist, NMDA receptor antagonist, 5-HT inhibitor, and NA reuptake inhibitor.
- It cannot be combined with an MAO inhibitor or SSRI inhibitor. Because there is a risk of serotonin syndrome.

- **Pharmacokinetics**
  - It has a slow onset of action but is long-acting.
- **Uses**
  - Cancer pain and opiate deaddiction program.

Loperamide

- It decreases GI motility and secretions and closes the sphincter.
- **Uses**
  - Management of secretory diarrhea and traveler's diarrhea.

- **Contraindications**
  - Contraindicated in patients with infective diarrhea. Because if motility stops, the infection may grow more.
  - It is contraindicated in children less than four years old. It may cause a paralytic ileus because motility is decreased.
- It does not cross the blood-brain barrier. So, it will not cause addiction.

Diphenoxylate

- It is also used for diarrhea.

- It can cross the blood-brain barrier and causes euphoria.
- Diphenoxylate is always given with atropine. Atropine also crosses the blood-brain barrier, and the patient experiences delirium effects (confusion, hallucinations). So, the patient will not get addicted to the delirium effect.

Tramadol and Tapentadol

- These drugs are partial μ agonists (an opioid mechanism) and inhibit 5-HT and NA (a non-opioid mechanism).
- It is used in chronic pain and the management of depression due to the nonopioid mechanism.

Papaverine

- It is a naturally occurring drug used for erectile dysfunction.

Propoxyphene

- It is the least potent drug used as an analgesic with NSAIDs.

Levopropoxyphene

- It is used in the treatment of dry cough.

Synthetic opioids 00:47:37

- It is used in treating cancer pain and for general anesthesia (neurolept anesthesia and neurolept analgesia).
- Drugs : Fentanyl, Sufentanyl, Alfentanyl, Remefentanyl

Fentanyl

- It is 80 times more potent than morphine.
- **Uses:**
  - Cancer pain
  - General anesthesia - neurolept anesthesia and neurolept analgesia

Sufentanyl

- It is 1000 times more potent than morphine and highly plasma protein bound. So, it will act as a long-acting drug.

Alfentanyl

- It is used in total intravenous anesthesia (TIVA).

Remefentanyl

- It is shortest acting drug metabolized by Esterases.
- It is used in the treatment of daycare surgery.

II. Complex-acting opioids 00:55:00

- These drugs are called complex-acting opioids because these are partial μ agonists and partial κ antagonists.
- Example: Buprenorphine.

Buprenorphine

- These drugs are the least effective but more safe.
- These drugs also possess a ceiling effect for respiratory depression.
- These drugs, by increasing the dose, cause respiratory depression reaches a level then it does not produce action. So, these are the safest drugs.

Uses

- Analgesia, opioid de addiction program.

μ antagonist and κ agonist

- κ agonist causes dysphoria.
- Examples: Pentazocine, Nalbuphine, Butorphanol
- Butorphanol is administered as a nasal spray to manage cancer pain.

Pentazocine

- Pentazocine is a μ antagonist, κ agonist, and partial μ agonist.
- It increases the heart rate by stimulating the sympathetic nervous system.
- It has a lower biliary spasm, GI, and GU.
- It is used as an analgesic.

Important Information

- If the patient is a heroin addict and he comes with pain. Can pentazocine be given in this condition?
- No, because pentazocine is a μ antagonist, it blocks the opioid receptor, and the patient may experience withdrawal symptoms.

III. Pure opioid antagonist 01:00:00

- These drugs are called pure opioid antagonist because it blocks all the receptors (μ,κ,δ).
- These drugs are classified into subtypes.
- Central acting and Peripheral acting drugs.

Central-acting drugs

- These drugs enter the brain and cross the blood-brain barrier.
- Example: Naloxone, Nalmefene
- Naloxone is administered via the IV route, and it is a drug of choice for opioid poisoning.
- Naloxone is also used in obstetrics when an opioid is used during labor.
  - Opioids can enter the fetus. The level of opioids is more for the fetus.
  - when the baby is born. Then the baby may have overdosed and can undergo respiratory depression. Naloxone reverses it.

Naltrexone

- Naltrexone is an oral drug.
- **Uses:**
  - To decrease the craving for alcohol
  - opioid overdose
  - obesity
  - Decrease relapse in opioid addicts.

Peripheral-acting drugs

- These drugs are used in the treatment of opioid induced constipation.
- In the case of morphine, it enters the brain and produces the action by decreasing the pain, but when morphine is used in the long-term, it causes constipation.
- To manage constipation, it needs to block the action of morphine in the small intestine. So, it needs a drug that will not cross the blood-brain barrier but block the morphine action only in the periphery.
- These types of drugs are used in opioid-induced constipation.

Peripheral-acting opioid antagonist

- Methylnaltrexone, Naloxegol, Naldemedine, Alvimopan.
- These drugs cannot cross the blood-brain barrier and are used in managing opioid-induced constipation.
- Alvimopan
  - It is used in treating paralytic ileus due to gut resection.
  - It increases the risk of myocardial infarction (black box warning). It should not be used in more than 15 doses.

Important Information

- The opioid drug causes tolerance. If the opioid drugs use repetitively, it causes the receptor to become desensitized.
- Example: If a 10 mg drug is given for analgesia and by repetitive drug use, then the analgesic effect will not be seen in this dose. It needs to increase the dose to get the same effect.
- No tolerance is seen in the following 3 effects: convulsions, constriction of pupil and constipation.
- Because these drugs cause euphoria, patients will have physical and psychological dependence.
- When these are used for the long term- it decreases substance P and nor-adrenaline. When it is used for a long time, it is stimulated by μ.
- When suddenly stops these drugs, receptors increase (NA), the patient may develop anxiety, insomnia, and an increase in substance P, and the patient may develop hyperalgesia and pain.
- If the consumption of these drugs stops, it may cause physical dependence resulting in withdrawal symptoms. The patient may develop an increase in salivation, yawning, and lacrimation. In psychological dependence, patients may feel more craving for drugs.
- For managing withdrawal symptoms, clonidine and lofexidine are used, which is a α-receptor agonist.
- μ agonist is also used in the treatment of opioid withdrawal symptoms. Buprenorphine and methadone are used to replace opioids.

Opioid Deaddiction 01:14:07

- When the patient comes with opioid deaddiction and wants to quit it. If he quits by himself, he will get withdrawal symptoms. So, the opioid de addiction program will do.
- For the management of opioid deaddiction, long-acting opioid agonists are used (methadone, buprenorphine). It gradually tapers the dose and then stops.
- If methadone is used for the long term, it may become addictive. So, monitoring is important while using methadone.
- Once the patient is de-addicted, he may also have a relapse (addicted again).
- Naltrexone is used to treat relapses. It blocks the opioid receptor.

Opioid in Pregnancy 01:17:48

Case 1. When an opioid is used in delivery (labor)

- When the baby is born, he may have respiratory depression.
- For management- The drug of choice is Naloxone.

Case 2. When the mother is opioid-addicted

- When a baby is born, the baby will also be addicted (irritable). He may have withdrawal symptoms.
- For management- Methadone/ morphine is given, and the dose is gradually reduced.

Important Questions

Q1. Opioids can act on which three receptors?
Mu, kappa, and delta (μ,κ,δ).

Q2. Naloxone and Nalmefene are examples of?
Central-acting drugs.

Q3. What happens when κ receptor is stimulated?
It causes dysphoria.

Q4. What is the drug of choice when an opioid is used in delivery (labor)?
Naloxone.

Q6. Levopropoxyphene is used to treat which disease?
It is used to treat dry cough.

C/I ⇒ Head injury
- * ↑CO_2 retention = ↑ICP
- * Respiratory depression
- * Miosis

⇒ Bronchial asthma
⇒ Biliary colic

Q. What are the signs of (coma, pinpoint pupil (miosis), and respiratory depression)?
Acute morphine poisoning.

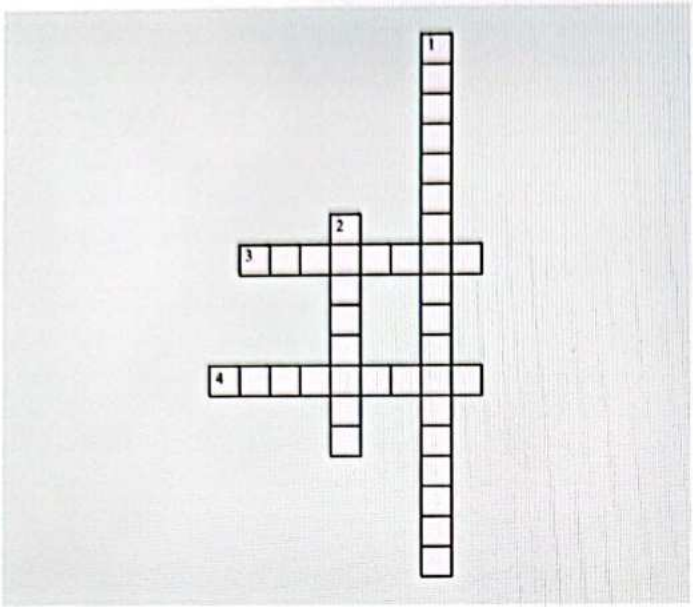
Q. ____is used for diarrhea and can cross the blood-brain barrier and causes euphoria.
Diphenoxylate

Q. How do we obtain opioids?
We obtain opioids from the poppy plant or Papaverum somniferum.

C. Cough suppressant, constipation
* Not mediated by opioid ®
R. Retention of urine
= Release histamine, V.D, ↓BP
↓
Broncho constriction
C/I = Branchial asthma

CROSS WORD PUZZLES

Crossword Puzzle 1



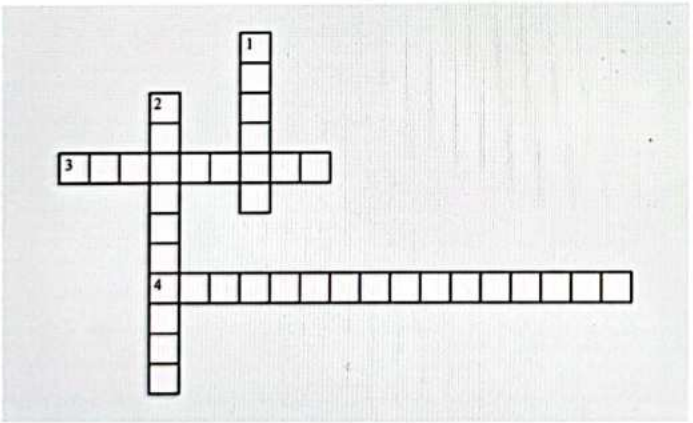
Across

3. ____ is the antidote given to opioid poisoning.
4. _____ is a derivative of atropine with (anti-cholinergic properties).

Down

1. ____are the signs of opioid poisoning.
2. ____ is contraindicated in renal failure or decreases the dose in renal failure.

Crossword Puzzle 2



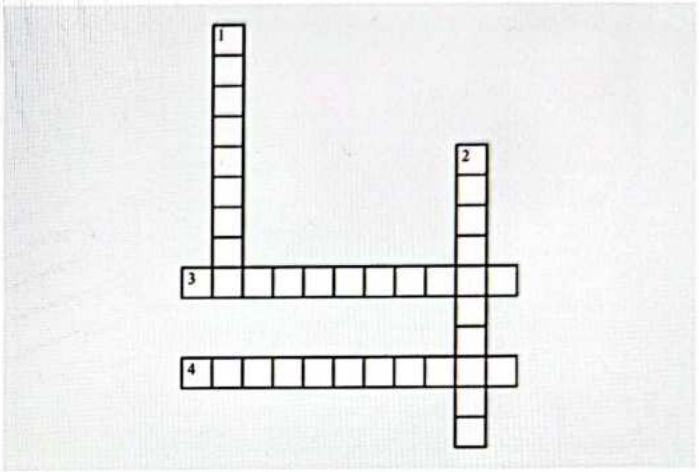
Across

3. ___ is used in treating paralytic ileus due to gut resection.
4. ___is a derivative of opiate but acts through NMDA-receptor antagonist.

Down

1. ____ is the enzyme that converts codeine into morphine.
2. _____ tolerance if the opioid drugs use repetitively, it causes the receptor to desensitize.

Crossword Puzzle 3



Across

3. ___ is a μ antagonist, agonist, and partial μ agonist.
4. ___ increases the heart rate by stimulating the sympathetic nervous system.

Down

1. ____ is 1000 times more potent than morphine and highly plasma protein bound
2. ____ has a slow onset of action but is a long-acting drug.

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54 DRUGS FOR ANXIETY

Definition

- Anxiety is a mental state wherein a person develops unease or nervousness in anticipation of a future event.
- For example, an unpleasant feeling experienced by students before exams is anxiety.

Pharmacological Management of Anxiety

Benzodiazepines 00:01:00

- They include Clonazepam, Chlordiazepoxide, and Alprazolam.
- The drug of choice for acute anxiety→ are benzodiazepines fast onset of action.
- They cause CNS depression to reduce anxiety.
- Can benzodiazepines be used to treat chronic anxiety?
  - No, they induce dependence, tolerance, and sedation. Consequently, patients depend highly on them to feel better, and the dose for the desired effect increases with use.

5HT1A Partial Agonists 00:02:50

- They include Buspirone, Gepirone, and Ipsapirone.
- They are used to treat general anxiety disorder.

Advantages	Disadvantages
• No dependence • No sedation • No tolerance	Do not act fast ↓ Ineffective in managing acute anxiety.

Mechanism of action

The drugs partially increase the activity of the 5HT1A receptor.
↓
Reducing the release of 5HT
↓
Reduce anxiety.

H1 Blockers 00:04:40

- Also called Antihistamines.
- Example: Hydroxyzine.
- Not popular → they cause sedation.

Selective Serotonin Receptor Inhibitors (SSRIS) 00:05:15

- It is not preferable for acute anxiety as they enhance the disorder initially.
- **Mechanism of the action:**

SSRIs inhibit the reuptake of serotonin.
↓
Serotonin level in synaptic cleft increases.

↓
It acts on 5HT2 and causes anxiety.
↓
Prolonged exposure to serotonin causes desensitization of 5HT2.
↓
Decreases anxiety

- **Drug regimen for general anxiety disorder with SSRIs:**

Prescription starts with SSRI and benzodiazepine.
↓
After 3 or 4 months, SSRI is continued without benzodiazepine.

Beta-Blocker 00:07:15

- Propranolol is the most common beta blocker.
- It crosses BBB and decreases performance anxiety by regulating sympathetic overactivity.

Management of Panic Attacks

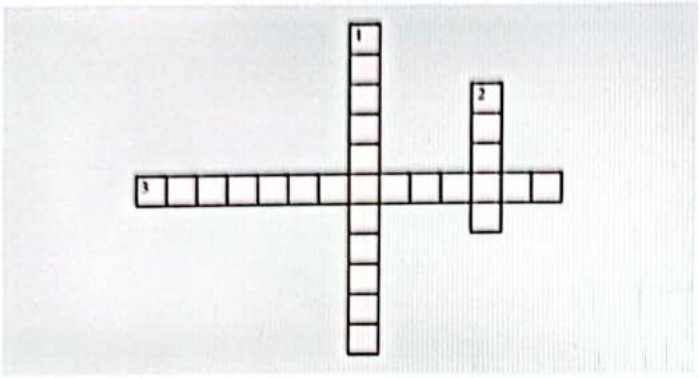
- Benzodiazepine is the first-line drug when a person experiences a panic attack for the first time.
- If it persists, the patient should start maintenance therapy with SSRI combined with benzodiazepine for 3 to 4 months. Benzodiazepine should be gradually discontinued.

Drugs For the Management of Phobia

- SSRIs
- Gabapentin
- Propranolol

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Drugs of choice for acute anxiety.

Down

1. Most used beta blockers for anxiety.
2. Drug of choice for chronic anxiety.

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55 HYPOTHALAMUS PITUITARY HORMONES PHARMACOLOGY

- Endocrine pharmacology revolves around correcting hormonal imbalances, which cause various disorders.
- The primary approach in the field is to compensate for the deficiency of hormones.

Overview of Hormones 00:00:25

Hormones released by the hypothalamus

Releasing or stimulatory hormones
- Growth hormone-releasing hormone.
- Gonadotropin-releasing hormone.
- Cortisol-releasing hormone.
- Thyroid releasing hormone.
- Growth hormone inhibitory hormone.
- Prolactin inhibitory hormone.

- Oxytocin
- Antidiuretic hormone or vasopressin.

Hypothalamic hormones stimulate pituitary glands.

Hormones released by the Pituitary gland
- Thyroid-stimulating hormone.
- Luteinizing hormone
- Follicular stimulating hormone
- Growth hormone
- Prolactin
- Adreno-corticotropic hormone

Growth Hormone-Related Drugs 00:02:50

Refer Table 55.1

Drugs For Acromegaly 00:09:15

- The excessive activity of growth hormones causes Acromegaly.
- Three pharmacological approaches to treat acromegaly are:

Growth hormone receptor antagonists,	Somatostatin analogues	D2 agonists
Pegvisomant (Produces vision impairment)	Octreotide, lanreotide, and pasireotide.	Bromocriptine and cabergoline

Growth Hormone Inhibitory Hormone 00:11:38

- Also called somatostatin.
- Endogenous somatostatin is short-acting.
- An Analogue called octreotide is 40 times more potent.

Uses of Octreotide
- Treatment for excessive growth hormone activity: Acromegaly
- To treat esophageal varices due to their vasoconstrictor activity.
- Decreases the activity of insulin and glucagon: Insulinoma and Glucagonoma.
- It decreases intestinal secretion treating secretory diarrhoea, VIPoma, and carcinoid syndrome.
- Antidote for sulfonylurea-induced hypoglycemia.
- To treat inoperable thyrotrope adenoma.
- Octreoscan to detect the neuroendocrine tumour.
- Thyrotroph adenoma (inoperable cases).

Adverse Effects of Octreotide 00:17:10
- Gallstones
- Increased risk of DM
- Vitamin B12 deficiency

Other Somatostatin Analogues

Lanreotide	Pasireotide
Acromegaly and neuroendocrine tumour	Acromegaly and Cushing's disease.

D2 AGONIST 00:18:48
- It is an alternative to the prolactin-inhibitory hormone dopamine.
- Decrease the activity of prolactin. Hence, it reduces galactorrhoea and infertility.
- Dopamine cannot cross BBB; therefore, we use D2 agonists.

D2 agonists	
Ergot-derivatives	**Non-ergot**
• Bromocriptine • Cabergoline	• Quinagolide

- Cabergoline is longer-acting than Bromocriptine.

Uses of D2 Agonists 00:20:30

- Acromegaly
- Prolactinoma
- Hyperprolactinemia
- Infertility induced by hyperactivity of prolactin.
- Galactorrhoea
- Parkinsonism

Important Information

How does prolactin cause infertility?
High prolactin levels inhibit the release of luteinizing hormone, which impairs ovulation. It results in infertility.

How does a D2 agonist treat acromegaly?
Dopamine does not affect growth hormones in healthy individuals. But in acromegaly it decreases growth hormone in Acromegaly. Hence, D2 agonists are effective against acromegaly.

Important Information

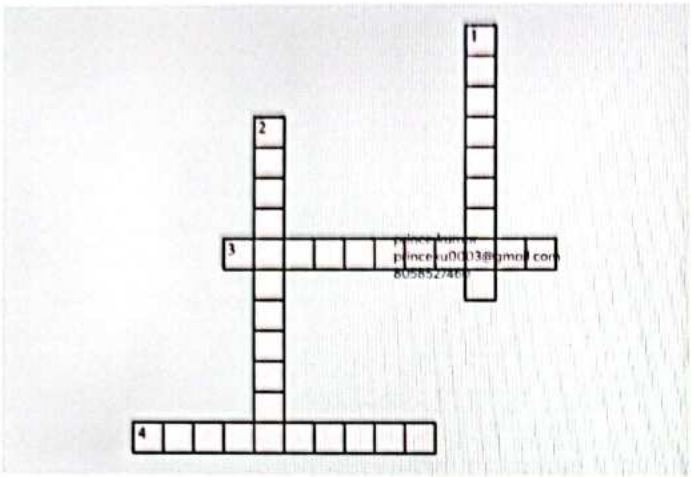
- Doctors commonly prescribe D2 agonists to inhibit milk production when a mother wants to stop breastfeeding.

Table 55.1

Hormone	Drugs and preparations	Disorders
Growth hormone-releasing hormone	Sermorelin and Hexamorelin	Growth hormone deficiency
	Tesamorelin	HIV associated lipodystrophy
Growth hormone	• Somatrem • Somatotropin	• Growth hormone deficiency • Turner's and Noonan syndrome • Short stature
Insulin-like Growth Factors 1(IGF-1)	Recombinant IGF1 called Mecasermin	• Growth hormone receptors have mutations. • The body develops auto-antibodies against growth hormones.
IGF 1 + binding protein	Mecasermin Rinfabate	• HIV-associated adipose redistribution syndrome. • Severe insulin resistance. • Severe muscular dystrophy.

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. _____Somatostatin used to treat Cushing's syndrome.
4. An analogue that is 40 times more effective than growth hormone inhibitory hormone is _____

Down

1. _____ Hormone that can cause infertility.
2. Commonly used Non-ergot D2 agonist is _____

56 PHARMACOTHERAPY OF DIABETES MELLITUS

Diabetes Mellitus

- Diabetes mellitus is one of the most common diseases across the world and India.
- India is considered as the diabetic capital of the world and the reason is Insulin resistance. The genetic makeup of the Indians is more prone to diabetes.
- Due to the presence of high levels of glucose in diabetics, immediate complications like Diabetic ketoacidosis can occur or long-term complications like micro or macro vascular complications can occur.

Clinical Cases

Case 1

- A 42-year-old male patient presents with C/O of increased urination, increased thirst and appetite. His investigations are Fasting plasma glucose of 180 mg/dl and Post prandial plasma glucose of 250 mg/dl. Urine analysis shows glucose 2+.
  - Classical features of polyuria, polydipsia and polyphagia along with high glucose in the circulation points towards Diabetes mellitus Type 2.

Case 2

- A 2-year child is brought by her mother after routine investigations and Random blood glucose is 300 mg/dl.
  - In children it is Diabetes mellitus Type 1.

Case 3

- A pregnant lady has come with PPBS of 250 mg/dl.
  - Here the patient is diagnosed with Gestational diabetes mellitus.

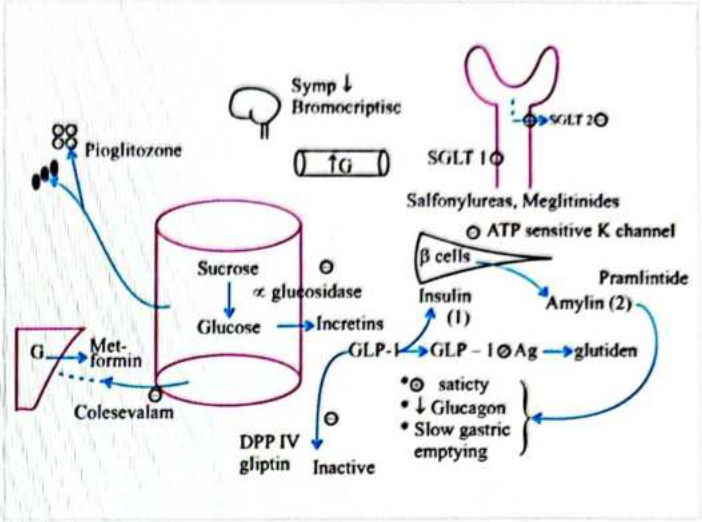
Diagnostic criteria for DM

00:02:50

- According to the American Diabetic Association, the following are the criteria to diagnose Diabetes:
  - Glycated haemoglobin (HbA1C)- ≥ 6.5%
  - Fasting plasma glucose- ≥ 126 mg/dl
  - Postprandial plasma glucose- ≥ 200 mg/dl
  - Random blood sugar- ≥200 mg/dl along with the symptoms of Hyperglycemia.

Pathophysiology of DM

00:04:24



- Presence of Insulin in intestine sucrose → glucose by enzyme α glucosidase, glucose gets absorbed and reaches the liver and stored as glycogen.
- Skeletal muscle and adipose tissue also will take up glucose.
- Pancreas has beta cells; beta cells release Insulin by inhibiting the ATP-sensitive K+ channel.
- Pancreas also secrete Amylin.
- If glucose is high in the blood, then the chance is to get glucose in urine.
- Glucose is more than 180 mg/dl; then they will come in urine.
- Nephron has two transporters, i.e.SGLT 2 and SGLT 1.
- Whenever the glucose comes by filtration, it will take up SGLT 2 and SGLT 1.
- If glucose is taken orally, then release Incretines (Glucagon-like peptides)
- Incretins are GLP-1 causes an increase in Insulin.
  - GLP-1 stimulates satiety.
  - ↓Glucagon
  - Slow gastric emptying
- GLP-1 is inactivated by DPP-4.
- Beta cells of pancreases also release Amylin which have the same functions as GLP-1.
- Glucose release is also controlled by the brain (by the sympathetic system).

Complications of DM

- Short Term ⇒ Immediate Diabetic Ketosis
- Long Term ⇒ Retinopathy, Nephropathy, Neuropathy

Targets to control DM

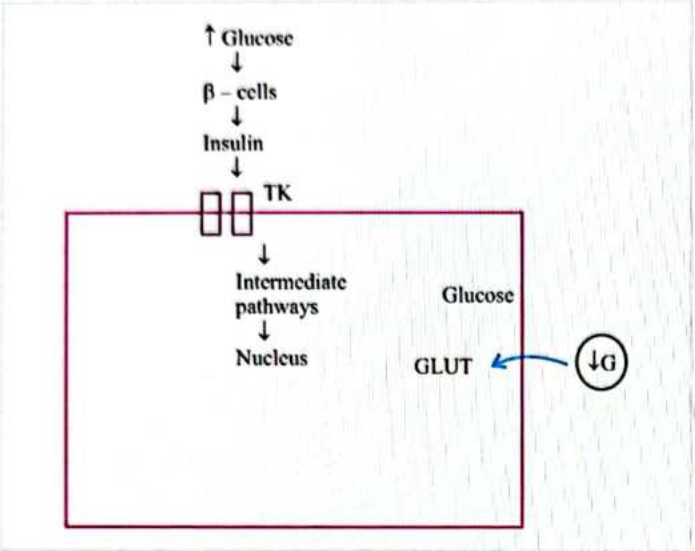
- Give Insulin itself

- Give drugs which stimulate amylin receptors (Pramlintide)
- Give GLP-1 receptor agonist
- Inhibit α Glucosidase
- Inhibit glucose absorption

Insulin

00:13:41

Mechanism of action



- Along with this there is also entry of k+ from blood in to the cells leading to hypokalaemia
- **In Liver**
  - ↓Gluconeogenesis
  - ↑Glycogen synthesis
  - ↓Glycogenolysis
- **In Skeletal Muscle**
  - ↑Glucose uptake
  - Protein breakdown is inhibited
- **In Adipose tissue**
  - ↑Glucose uptake
  - Leading to weight gain
  - Inhibition of fat breakdown

Pharmacokinetics

- **Question: Can Insulin be given orally?**
  - No, orally if you give it. It is broken down because it's a protein.
  - If renal Failure occurs, then decrease the dose of Insulin.

Source

00:18:53

- Animal Origin
  - Pork Insulin⇒ adverse effect allergy
  - Beef ⇒ adverse effect allergy
- Monocomponent Insulin / purified Insulin ⇒ Less allergic
- Human Insulin (Prepared by Recombinant DNA technology)
- Insulin analogue (E.g. Lispro, Aspart, Glulisine, Glargine)

Insulin Preparation

00:21:25

Refer Table 56.1

- **Question: How much is % and nature of semilente and ultralente?**
  - 30 % amorphous in semilente, and ultrafine is 70 % Crystalline.

Uses of insulin

- T1DM
- T2DM
- Gestational D.M.
- Shift from oral drug to insulin if patient has surgery, stress and infections

Emergency use of insulin

- **Diabetic ketoacidosis**
  - Due to high glucose in blood patient will undergo osmotic diuresis leading to dehydration and ketone bodies leading to acidosis
  - Treatment:
    → IV regular insulin
    → IV fluids
    → KCl- in case of hypokalaemia
    → $NaHCO_3$- manage acidosis
    → Antibiotics- SOS
- **Non- ketotic Hyperosmolar Diabetic Coma**
  - Seen particularly in T2DM
  - Treatment:
    → IV Fluids
    → Less Need Insulin, KCL
    → No need $NaHCO_3$
- **Hyperkalaemia**
  - Treatment:
    → Salbutamol in form of nebulisation
    → INSULIN + Dextrose
    → Patient with ECG changes add calcium gluconate
- **Question:** Why do we add dextrose along with insulin in the treatment of Hyperkalaemia?
  - Since the patient is a non-diabetic with Hyperkalemia, if insulin alone is given, he will develop hypoglycemia.

Adverse Effect

00:34:38

- **Hypoglycaemia**
  - Symptoms: Tremors, palpitation, Sweating
  - Diabetic patients don't give Non-selective β blockers because they cause hypoglycemia unawareness.
  - Treatment: Conscious (Oral- Sugar, Honey) and Unconscious (I.M. Glucagon, I.V dextrose)

- Weight Gain
- Allergy
- Hypokalaemia
- Edema- Mild due to Na+ retention.
- Lipodystrophy- Insulin given repeatedly at the same site.

Sites for injecting insulin 00:38:30

- Buttocks
- Upper outer arms
- 2 inches away from umbilicus
- Antero-lateral aspect of thigh

Insulin given by

- Insulin Syringe
- Insulin pen-device
- Continuous insulin pump device

Amylin Receptor Agonist 00:41:55

Pramlintide

- Subcutaneous route
- No Hypoglycaemic effect
- Approved for DMT 1 and DMT 2
- Stimulate satiety
- ↓ Glucagon
- Slow gastric emptying
- Contraindicated in Diabetic Gastroparesis

GLP 1 Receptor Agonist 00:44:27

- Derived from:
  - Human GLP1 Backbone- E.g. Liraglutide, Albiglutide, Dulaglutide, Semaglutide (Given orally and SC).
  - Exendin - 4 Backbone- E.g. Exenatide, Lixisenatide.
- Given by Subcutaneous route
- Stimulate satiety
- ↓ Glucagon
- Slow gastric emptying
- Increase insulin release
- Adverse effects:
  - Increase risk of pancreatitis
  - Increase of medullary carcinoma of thyroid.
- Contraindications:
  - Diabetic gastroparesis
  - MEN syndrome
- No Hypoglycaemia
- Causes weight loss.

Important Information

- Liraglutide and Semaglutide are approved for management of obesity.
- Teduglutide (GLP-2 receptor agonist) is approved for short bowel disease to slow gastric emptying.

Oral anti-diabetic drugs

Biguanides 00:51:27

- Phenformin (Not Used ↑ lactic acidosis)
- **METFORMIN**
  - **MOA of Metformin:**

Stimulate AMP Kinase ↓ Inhibit Gluconeogenesis ↓ Hepatic Glucose output	Inhibit Glucose Absorption	↑ Glucose uptake ↓ Insulin sensitizer (Used in Management of PCOD)

  - **Adverse Effects of Metformin:**
    → GIT upset (Gastritis, bloating)
    → B12 Deficiency
    → Risk of Lactic acidosis (increase lactate production caused by hypoxia, CHF and sepsis, Lactate metabolism is interfered with and increase in Metformin in Renal failure). Smokers have no risk of Lactic acidosis.

- **Question:** Whether Metformin should be used in Renal Failure or not?
  - If GFR = 30-45 ml/min, then ↓ dose by 50%.
  - If GFR < 30 ml/min, you must stop metformin.
  - Serum creatinine level is stopped if:
    → > 1.5 mg/dl (In Male)
    → > 1.4 mg/dl (In Female)

Thiazolidinediones 00:58:49

- Rosiglitazone (Banned, ↑ CV deaths)
- **PIOGLITAZONE**
  - **MOA of Pioglitazone:**

Pioglitazone
↓
PPAR γ
↓
↑ Insulin Responsive genes (Adipose tissue)
↓
↑ Insulin Sensitivity
↓
↓ Insulin Resistance

- **Uses:** DMT 2
- **Adverse Effect:**
  - → Na+ and Water Retention [Contraindicated in CHF].
  - → Weight gain.
  - → No hypoglycaemia.
  - → ↑ Risk of bladder cancer (Black box warning).
  - → Osteoporosis (more in females).
  - → Rarely it produces macular edema.

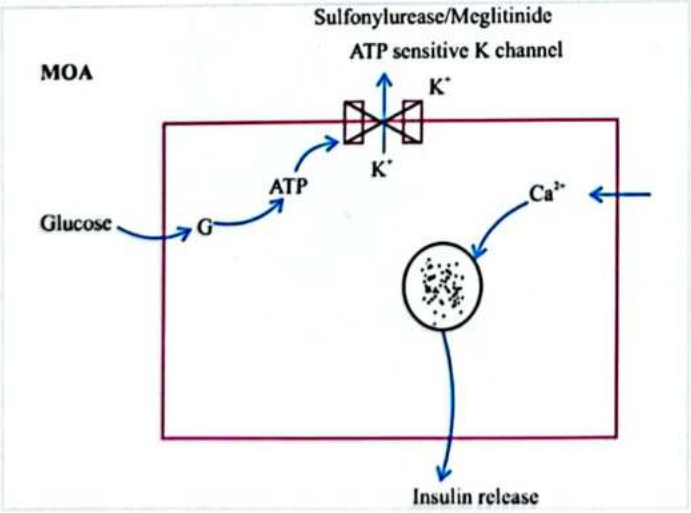
Sulfonylurea

01:05:13

- **Classification:**

I Generation	II Generation
1. Chlorpropamide (Adverse effects: Disulfiram resistant, Cholestatic jaundice and Dilutional hyponatremia) **2. Tolbutamide** (Highly plasma protein drug, it follows saturation kinetics)	1. Glibenclamide (also called Glyburide) 2. Glipizide 3. Gliclazide 4. Glimepiride (Most potent)

- **MOA of Sulfonylureas:**



→ Glucose enter into β Cell of pancreas (at least 30% β cell mass should be present).
→ Glucose ⇒ ATP ⇒ ATP sensitive K+ channel (put K+ outside)
→ ATP blocks ATP-sensitive K+ channel due to that K+ staying inside and Ca + + entering into the cell ⇒ Storing Insulin inside ⇒ Release of Insulin outside the cell.

- **Adverse effects of Sulfonylureas:**
  - Allergy.
  - Hypoglycaemia.
  - Weight gain.
  - Sulfonylurea induced Hypoglycemia.

Important Information

- Diazoxide acts as a K+ channel opener leading to reduced insulin release and causing Hyperglycemia. Diazoxide is used in the treatment of insulinoma.

- **Question:** Sulfonylurea-induced Hypoglycemia do we have an antidote for these?
  - Yes. Antidotes are Octreotide.

Meglitinides

- These drugs have the same MOA as Sulfonylureas.
- The two important drugs are:
  - Repaglinide
  - Nateglinide
- The short half-life of 1-2 hours.
- They are mainly used three times a day to reduce PPBS.
- **Adverse effects:**
  - Decrease glucose
  - Weight gain

α Glucosidase Inhibitors

01:14:35

- In the intestine sucrose is converted into glucose by α glucosidase.
- α glucosidase inhibitors are used to inhibit the conversion of sucrose to glucose.
- The drugs are:
  - Acarbose
  - Miglitol
  - Voglibose
- Adverse effects:
  - Bloating
- Uses:
  - T2 DM
  - Reduce PPBS (taken along with food)

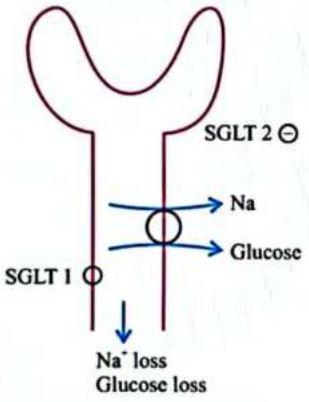
Important Information

- A patient on insulin taking Acarbose and presents with hypoglycemia. In such cases table sugar should not be given as first line management because table sugar is sucrose which is inhibited by Acarbose to convert into glucose

DPP4 (Dipeptidyl-Peptidase 4) inhibitors 01:17:25

- DPP4 will metabolize GLP-1 into inactive form.
- By this GLP-1 activity increases leading to increased insulin release, slowing gastric emptying, producing satiety and decreasing glucagon.
- The drugs are:
  - Sitagliptin
  - Saxagliptin
  - Alogliptin
  - Linagliptin (Undergoes bile elimination and Entero hepatic recycling)
  - Vildagliptin
- Adverse effects:
  - Nasopharyngitis.
  - Rarely pancreatitis

SGLT2 (Sodium Glucose Transporter 2) inhibitors



- These drugs lead to Na+ and glucose loss in urine.
- Advantages:
  - Diuretic effect (beneficial in heart failure)
  - Weight loss
  - No hypoglycaemia
- Disadvantages:
  - UTI
  - Genital mycotic infections.
- The drugs are:
  - Empagliflozin
  - Dapagliflozin
  - Canagliflozin
  - Ertugliflozin
- Adverse effect:
  - Genetical mycotic infection
  - UTI
  - Rarely produce Fournier's gangrene
  - Euglycemic ketoacidosis
  - Risk of lower limb amputations is seen in Canagliflozin
  - Can cause Osteoporosis leading to fractures.

Colesevelam 01:25:50

- It is also known as Bile acid sequestrant
- It inhibits glucose absorption from the intestines.

Bromocriptine

- The proposed mechanism is that in the early morning there is a sympathetic drive increasing the glucose activity, Bromocriptine suppresses the sympathetic drive and in turn reduces the glucose activity.
- It is a D2 agonist and an ergot.
- It is used in low dose and fast release.

Newer Drugs

- PPAR α and γ agonists
  - The drug is called Saroglitazaar.
  - This drug is approved in patients with diabetes and dyslipidemia
- SGLT 1 and 2 inhibitors
  - The drug is called Sotagliflozin
- GLP-1 and GIP (Glucose dependent insulinotropic polypeptide) receptor agonist
  - The drug is called Tirazepatide
- GLP-2 Agonist
  - The drug is Teduglutide
  - Used in short bowel disease

Speciality of anti-diabetic drug 01:31:16

Weight

- Weight Neutral- Metformin, DPP4 inhibitors.
- Weight Gain- Insulin, Sulfonylureas, Meglitinides and Pioglitazone
- Weight Loss- GLP-1 , SGLT 2.

Glucose-

- Hypoglycemia- Insulin, Sulfonylurea and Meglitinides.
- Rest of the drugs are Anti-hyperglycaemic agents.

DMT 1 and DMT 2

- Insulin
- Pramlintide
- Rest of the drugs are approved only for DMT 2

Injections

- Insulin except Afrezza
- GLP 1 Agonist except Semaglutide (given as oral and SC)
- Pramlintide

↓ Micro and macrovascular events

- Metformin

↓ Max HBA1C

- Insulin
- Metformin/ Sulfonylureas/ Meglitinides (↓ 1-2%)
- Rest all (↓ < 1%)

Case Study

Case 1

- **A 42-year-old male patient complains of increased urination, thirst and appetite. His investigations are Fasting plasma glucose of 180 mg/dl and Postprandial plasma glucose of 250 mg/dl. Urine analysis shows glucose 2+.**
  - The patient is DMT 2
  - Diet Modification
  - Regular Exercise
  - Single drug Metformin
  - If not controlled Metformin along with DPP4/ SGLT2 inhibitors/Sulfonylureas
  - Triple drug therapy is used if it's still not controlled. Last resort is Injections.

Case 2

- **A 2-year-old child is brought by her mother after routine investigations, and Random blood glucose is 300 mg/dl.**
  - The patient is DMT 1
  - Drug Treatment Insulin

Case 3

- **A pregnant lady has come with PPBS of 250 mg/dl.**
  - Gestational D.M.
  - Drug Treatment Insulin

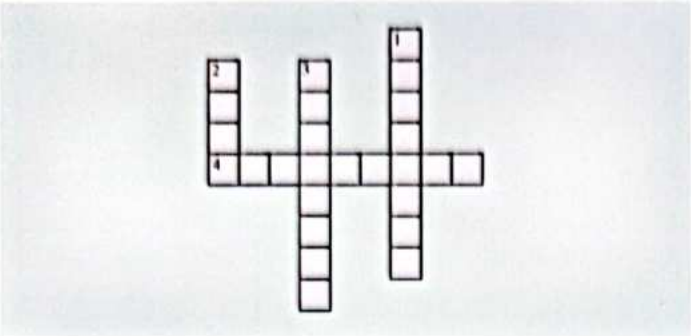
Pharmacotherapy of diabetes mellitus

Table 56.1

Preparation	Onset	DOA
Rapid acting (given S.C): • Lispro • Aspart • Glulisine	15-20 min	2-3 hr
Inhaled: • Afrezza(Contraindicated in Bronchial asthma/ COPD, smokers and lung cancer)	15-20 min	2-3 hr
Short acting: • Regular Insulin (S.C/ IV)	30 min -1 hr	4-6 hr
Intermediate acting insulin: • NPH Insulin (Neutral protamine hagedorn) • Lente Insulin (Semilente and ultralente)	1-2 hr	12-16 hr
Long acting: (Not mixed with other insulins) • Glargine (present in acidic pH) • Detemir	2-4 hr	24 hr
Longest acting insulin: • Degludec	2-4 hr	42 hr

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

4. Nature of Semi-Lente is _____

Down

1. Glucose stored in the liver is called _____
2. _____ cell Secrets from Pancreas
3. Renal failure insulin dose is _____.

57 PHARMACOTHERAPY OF OSTEOPOROSIS

- Osteoporosis means osteo plus porous. Osteo means bone and porous means the bone becomes weak and fragile. So, it's a condition where the bones become weak and fragile.
- The bones become so weak that even a simple fall may result in a fracture.

Major Causes of Developing Osteoporosis 00:00:24

- **Menopause:** In postmenopausal women, the oestrogen level drops down causing osteoporosis.
- **Ageing:** This type of osteoporosis is called senile osteoporosis.
- **Drugs:** This type of osteoporosis is called drug-induced osteoporosis, e.g., long-term use of steroids can cause osteoporosis.

Bone Cells 00:00:50

Types of bone cells

- Bone consists of two types of cells namely osteoblast and osteoclasts.
  - **Osteoblasts:** These are the cells which are responsible for bone formation.
  - **Osteoclasts:** These are the cells which are responsible for bone resorption.

Roles of bone cells

- Both osteoblasts and osteoclasts are essential. Usually, these cells are present in balance and have their roles to play. The osteoblasts lay down the bone where the osteoclasts trim it, leading to normal bone formation.
- Osteoclasts become hyperactive leading to increased bone resorption.

Fundament of Treating Osteoporosis

- Osteoporosis treatment aims at stimulating or increasing the activity of osteoblasts and suppressing or decreasing the activity of osteoclast.

Pathophysiology of Osteoporosis 00:03:16

Bone formation requires vitamin D and calcium.

↓

Decreased calcium causes secretion of parathormone (PTH). PTH is made from 1 to 84 amino acids.

↓

PTH acts on osteoblasts. Continuous stimulation of osteoblasts causes osteoblasts to secrete a ligand named rank ligand.

↓

RANK ligand binds to the receptor on osteoclasts leading to the activation of these cells.

↓

Activated osteoclasts start bone resorption leading to calcium release.

↓

We should not activate the osteoclasts as it causes bone resorption.

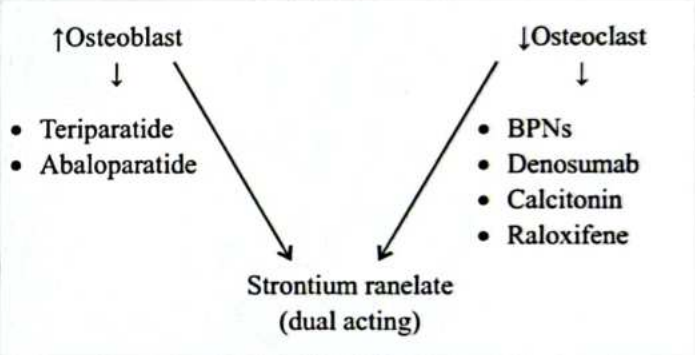
Different Strategies Used in Osteoporosis Management 00:05:26

- Eight strategies are used in treating osteoporosis.

Refer Table 57.1

Purpose of Osteoporosis Management 00:09:55

- Purpose of osteoporosis management is to increase the activity of osteoblasts and to decrease the activity of osteoclasts.



Drugs used in the management of osteoporosis and their functions

Drug name	Drugs used to increase the activity of osteoblasts	Drugs used to decrease the activity of osteoclasts
Teriparatide	✓	X
Abaloparatide	✓	X
Strontium ranelate (it is called as dual acting drug)	✓	✓
Bisphosphonates (BPNs)	X	✓

Denosumab	X	✓
Calcitonin	X	✓
Raloxifene	X	✓

Q. Which drug increases bone formation or anabolic effect?
a. Teriparatide
b. BPNs
c. Denosumab
d. Calcitonin

Drugs Used in the Management of Osteoporosis 00:11:59

Teriparatide

- It's a recombinant parathormone (rPTH).
- It's made up of 1 to 34 subunits.
- It's not a complete parathormone unit.
- It's an anabolic agent meaning it forms a bone.
- It is also called a bone forming agent.
- **Route of administration:**
  - It is administered subcutaneously.
  - It is administered intermittently.
- **Patient population:**
  - It is prescribed only in severe cases of osteoporosis.
- **Adverse effects:**
  - As it's a parathormone derivative it can cause hypercalcemia.
  - If used for more than two years, it can increase the risk of osteosarcoma as the drug is inducing the activity of osteoblasts.

- **Black box warning:**
  - As it increases the risk of osteosarcoma if used for more than two years, it is recommended to prescribe this drug only in severe cases of osteoporosis and not in patients suffering from mild to moderate osteoporosis.
- Another example of a recombinant parathormone (rPTH) drug is Abaloparatide:

Denosumab 00:14:50

- Drugs ending with mab are monoclonal antibodies, so it's a monoclonal antibody.
- It's a MAB against the RANK ligand, so it will not allow the RANK ligand to bind and activate the osteoclasts.
- **Route of administration:**
  - As it's a MAB, it's not given orally.
- **Patient population:**
  - It is prescribed for patients suffering from severe osteoporosis.
- **Adverse effects:**
  - It can cause Hypocalcemia because if you don't activate the osteoclasts they will not go and erode the bone because when you erode the bone the calcium level increases.

Bisphosphonates (BPNs) 00:15:46

- Examples of BPNs are Alendronate, Residronate, Pamidronate and Zoledronate which is also known as Zoledronic acid.
- **Route of administration:**
  - These drugs are administered intravenously.
- **Mechanism of action of BPNs**
  - They inhibit osteoclast activation.
  - They cause osteoclast apoptosis.
  - They inhibit a vital enzyme called farnesyl pyrophosphate, which plays an important role in the Mevalonate pathway which is required for cholesterol. This pathway is important for the survival of osteoclasts.

Q. Which additional property does the drugs of the class bisphosphonate withhold?
Ans. Bisphosphonates have additional properties to inhibit farnesyl pyrophosphate, a vital enzyme in the Mevalonate pathway.

- **Uses:**
  - This is the drug of choice for any kind of osteoporosis (Senile, postmenopausal or steroid-induced).
  - It is also used in treating hypercalcemia of malignancy, where the calcium level goes up in the course of cancer. Three important therapies are used to treat hypercalcemia.
    → Calcitonin, which has a fast onset of action, reduces the calcium faster.
    → Loop diuretics can be used to treat hypercalcemia. As we all are aware, the loop loses calcium. Furosemide is one of the loop diuretics used to treat hypercalcemia.
    → BNPs are used to treat hypercalcemia but have a slow onset of action.
  - It is used in treating Paget's disease of bone–
    → Osteolysis occurs during Paget's disease.
    → Osteoclasts are responsible for the process of osteolysis.
    → So, if the osteoclasts are suppressed, osteolysis won't occur. Thus, BNPs are used to treat Paget's disease of bone to suppress the activation of osteoclasts.
  - It is used in treating osteolytic bone metastasis-
    → As you know, cancers can spread to other organs (metastasizes). For example, breast cancer may spread to the bone.

→ When cancer metastasized to the bone, the osteoclasts get activated, leading to bone erosion, making the bone porous and prone to fracture.

- **Adverse effects when orally administered:**
  - Many times, these drugs are administered orally, which can cause gastritis and esophagitis in patients under treatment.

- **Precautions to take to avoid gastritis or esophagitis associated with BPNs**
  - To avoid adverse events, the drug should be taken on an empty stomach.
  - Take the drug with a full glass of water.
  - Don't lie down for at least 30 min after taking the drug. Immediate lying down can cause the drug to come back and irritate the oesophagus.
  - Try to avoid consuming any food or beverages for 30 min after taking the drug.

- **Adverse effects when Zoledronate is administered intravenously:**
  - Infusion reaction, where the patient can get chills and fever on administering the drug.
  - Nephrotoxicity.

- **Other adverse effects associated with BNPs are**
  - Osteonecrosis of the jaw bone.
  - If BNPs are used for more than five years, they increase the risk of fractures, in particular, intertrochanteric fractures.
  - They can cause hypocalcemia.

Q. When we use this drug to prevent fractures, then why is this drug causing fractures?

Ans. Both osteoblasts and osteoclasts are essential for us, and under normal conditions, they are balanced. When we suppress the osteoclasts for almost five years, the bone grows abnormally without osteoclasts. Hence, using the drug for less than five years is recommended.

Calcitonin 00:26:03

- There are two derivatives of calcitonin, namely human calcitonin and salmon calcitonin.
- Salmon calcitonin is more potent than human calcitonin.
- Calcitonin can be used to manage various conditions like,
  - Hypercalcemia
  - Osteoporosis
- It is mainly used to treat postmenopausal osteoporosis.
- **Route of administration:**
  - It is mainly administered intranasally (using nasal spray).

SERM (Selective Estrogen Receptor Modulators), Raloxifene 00:27:06

- It is mainly used to treat postmenopausal osteoporosis.

Newer Drug in Osteoporosis - Romosozumab

- It acts by targeting sclerostin, which is produced by osteocytes.
- Sclerostin inhibits the activity of osteoblasts and stimulates the activity of osteoclasts, hence it's a responsible agent for bone resorption.
- When it is targeted by the drug, it doesn't inhibit the activity of osteoblasts and at the same time, it doesn't stimulate the activity of osteoclasts. So, it's a dual-acting drug, increase osteoblast, decrease osteoclast.
- It's a bone-forming agent i.e. anabolic agent.

Key Takeaway

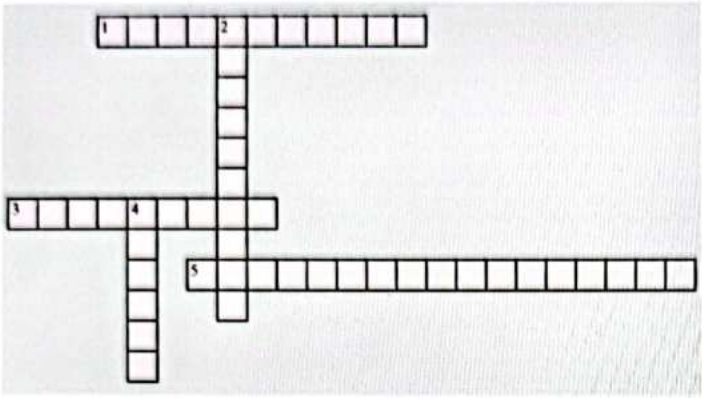
- For treating osteoporosis, we need to increase bone formation and decrease bone resorption.
- Teriparatide and Abaloparatide are drugs which increase bone formation by increasing the activity of osteoblasts, but they shouldn't be used for more than two years as it increases the risk of osteosarcoma. These drugs are used only in patients suffering from severe osteoporosis.
- Strontium ranelate is a dual-acting drug.
- Bisphosphonates are the drugs which suppress the activity of osteoclasts, and they are the drug of choice for osteoporosis. They mainly act by inhibiting the activation of osteoclasts, and they are also used in the management of hypercalcemia of malignancy. They shouldn't be used for more than five years as they increase the risk of causing fractures.
- Denosumab are drugs which target the RANK ligands.
- Intranasal Calcitonin and Raloxifene are used to treat postmenopausal osteoporosis.

Table 57.1

Strategy	Information
Strategy A – Vitamin D supplementation	Vitamin D is essential for increasing calcium levels and bone formation. Hence, we can prescribe vitamin D supplements as primary therapy for osteoporosis.
Strategy B – calcium supplementation	We can also prescribe calcium supplements to patients suffering from osteoporosis. Vitamin D and calcium can be prescribed as a combination therapy.
Strategy C – Diuretics	Drugs can be used in managing osteoporosis. Certain diuretics like thiazide diuretics increase the calcium level and hence can be used in managing osteoporosis. Usually, we prescribe Hydrochlorothiazide to manage osteoporosis.
Strategy D – Recombinant Parathormone	PTH works differently when given continuously than when given intermittently. As we already saw, when PTH is given continuously, it activates osteoclasts leading to bone resorption. On the other hand, when PTH is given intermittently, it increases osteoblasts' activity, leading to increased bone formation. It's important to note that when PTH is given continuously, bone resorption occurs, whereas when it is given intermittently, it stimulates the fibroblasts leading to bone formation. Recombinant paratharmone (rPTH) is available in the market under the name Teriparatide, which is made up of 1-34 subunits, and it is used in the management of osteoporosis as it increases the fibroblastic activity, ultimately leading to increased bone formation.
Strategy E – Denosumab	This group of drugs help in controlling osteoporosis by inactivating osteoclasts. It blocks the RANK ligand.
Strategy F – Bisphosphonates	This group of drugs help in controlling osteoporosis by inactivating osteoclasts.
Strategy G – Calcitonin	The drugs of this group inhibit the process of bone resorption.
Strategy H – SERM	Raloxifene of this group inhibits the process of bone resorption.

CROSS WORD PUZZLES

Crossword Puzzle 1



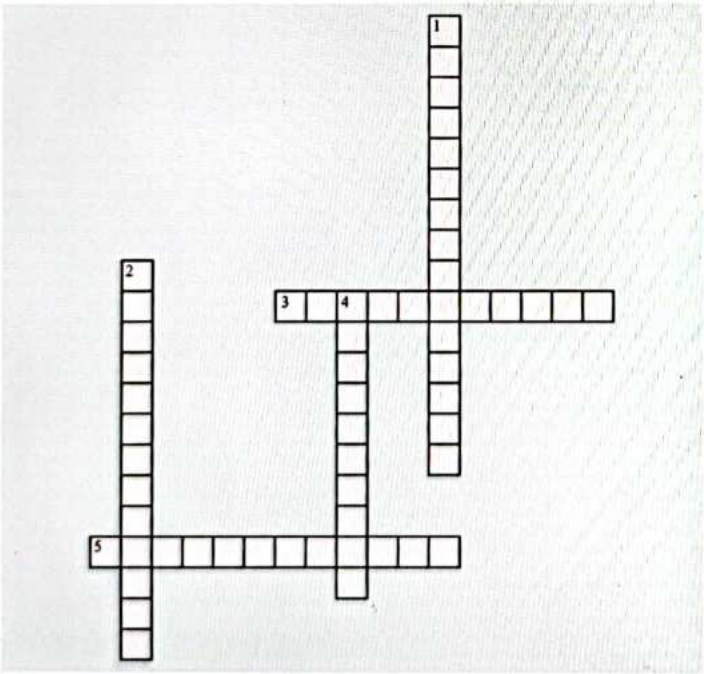
Across

1. Responsible for bone formation
3. Monoclonal antibody to treat osteoporosis
5. Dual therapy to treat osteoporosis

Down

2. Responsible for bone resorption
4. Osteoporosis is related to an older age

Crossword Puzzle 2



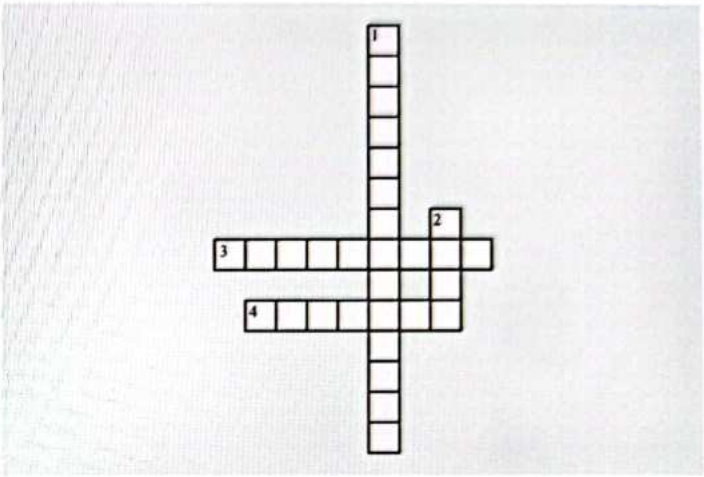
Across

3. Drug used to treat osteoporosis which targets sclerostin
5. It is a recombinant parathormone

Down

1. Class of drugs that cause jaw necrosis
2. Condition where the level of calcium increases in body
4. Which pathways is disturbed by Bisphosphonates

Crossword Puzzle 3



Across

3. Hormone level is dropped in postmenopausal women
4. Supplements given to treat osteoporosis

Down

1. Adverse event caused by Zoledronate
2. Abbreviation for Selective Estrogen Receptor Modulator

58 CORTICOSTEROIDS

- **Glucocorticosteroids**: The main corticosteroid here is cortisol, required to maintain stress, also known as the stress hormone.
- **Mineralocorticoids**: Aldosterone is the main mineralocorticoid, which causes sodium and water retention, which is required to maintain blood pressure.
- Adrenaline and angiotensin II require steroids to work efficiently (permissive action).
- The cortex of the Adrenal gland releases Mineralocorticoids, Glucocorticoids and Sex steroids.
- The medulla of the Adrenal gland releases Adrenaline and Noradrenaline.

Mineralocorticoids 00:02:20

- **Aldosterone:**
  - Causes Na+ and water retention
  - Increases BP
  - Causes edema
  - Decreases K+
  - Produces ventricular remodeling and increases mortality in chronic CHF patients.
- Hence, the activity of aldosterone is suppressed in chronic CHF patients.
- Most of the endogenous substances are short-acting and cannot be used; hence, preparations are used.

Preparations of Mineralocorticoid 00:04:00

Preparations	Mineralocorticoids properties	Glucocorticoids properties
DOCA (Desoxy corticosterone acetate)	100	0
Fludrocortisone	150	10
Aldosterone	3000	0.3

- Aldosterone cannot be used in therapy because it is very short-acting.
- **Fludrocortisone uses:**
  - Used in the treatment of Addison's disease (Hydrocortisone + Fludrocortisone).
  - To manage Hypotension.

Glucocorticoids 00:07:05

Actions in CNS

- Increases mood changes and behavioral changes (Contraindicated in Psychosis)
- Decreases seizure threshold (Contraindicated in Epilepsy).
- Reduces cerebral edema (Dexamethasone is the drug of choice)

Actions in CVS

- It causes Na+ and water retention leading to a rise in BP and edema.
- These are contraindicated in Hypertension and CHF patients
- They have permissive action on Adrenaline and Angiotensin 2.
- The reason steroids are added is to increase the permissive action on Adrenaline and Angiotensin 2 and in turn increasing the effect.

Actions in Respiratory System 00:11:00

- They are known to decrease inflammation and Production of Prostaglandins, Histamines and Leukotriene
- It is used in the management of Bronchial asthma.
- They are known to increase beta 2 responsiveness causing bronchodilation and are used in Status asthmaticus (I.V. Hydrocortisone is preferred here).
- It is known to increase pulmonary surfactant and used in preterm delivery cases.

Actions on Immunity (Bone Marrow)

- Steroids suppress T cells more than B cells.
- Cell-mediated immunity is suppressed more than Humoral immunity.
- Steroids are Immunosuppressant drugs.
- Immunosuppressants are used in organ transplant patients and in autoimmune diseases such as rheumatoid arthritis, where a person's immune system attacks their body's own cells.
- The adverse effects of immunosuppressants include opportunistic infections.
- Used in the treatment of leukemia and lymphoma because the increased T cells and B cells can be suppressed.
- These are contraindicated in Kaposi's sarcoma.
- Kaposi's sarcoma is a cancer of HIV patients as the steroids can worsen the immunosuppression.
- They increase neutrophils.
- Steroids increase RBC and hence are used in the treatment of Autoimmune Hemolytic Anemia.
- They also increase thrombocytes
- Steroids decrease monocytes, Eosinophils, and Basophils and hence are used in the treatment of allergic conditions like Loeffler's syndrome and Bronchial Asthma as in asthma patients the eosinophilic activity is high.

Anti-Inflammatory Action of Steroids 00:18:20

- They decrease IL- Interleukin 1,2,6
- They also decrease ICAM: Intracellular Adhesion Molecule
- They decrease ELAM: Endothelial leukocyte adhesion molecule
- Annexin 1 is produced by steroids, which inhibits the enzyme phospholipase A2 (PLA2).
- Membrane phospholipids (MP) are converted into arachidonic acid (AA) with the help of phospholipase 2.
- Arachidonic acid is acted upon by two enzymes, COX (cyclo-oxygenase) and LOX (lipoxygenase).
- Prostaglandins (PGs) and leukotrienes (LTs) are inflammatory mediators.
- Steroids also inhibit the chemotaxis of neutrophils.
- Uses:
  - Rheumatoid arthritis
  - Gout
  - Steroids suppressed the inflammatory process in Covid-19 (Cytokinin storm). Steroids are the only drugs that reduced mortality in Covid-19.
- Adverse effect is poor wound healing is seen as healing is an inflammatory process.

Actions on Skeletal Muscles

- Steroids increase the protein breakdown in the muscles causing myopathy

Actions on Bone

- They decrease calcium absorption and increase calcium elimination leading to Osteoporosis
- Drug of choice for steroid induced Osteoporosis is Bisphosphonates

Effects of Steroids on Metabolism 00:23:10

Glucose	Increases glucose levels	Contraindicated in diabetes mellitus
Protein	Breakdown of protein	Causes Myopathy and skin atrophy
Fats	Cause lipolysis in periphery and deposit in the center	Causes Cushing's habitus
Calcium	Decrease calcium absorption and increase calcium elimination	Causes Osteoporosis
Hormones	T4 to T3 conversion is inhibited by Hydrocortisone	Used in Thyroid storm

Preparations of Glucocorticoids

Refer Table 58.1

- Prednisone is a prodrug that gets converted to prednisolone.
- If 20 mg of hydrocortisone is used, the equivalent dose of prednisolone will be 5 mg.
- The lower the dose, the more potent the drug.
- So, here, the most potent is dexamethasone (0.8 mg).
- In cases of cerebral edema, dexamethasone is used. In case of hydrocortisone, which has a mineralocorticoid activity of 1, causes sodium and water retention, worsening the edema.
- In Addison's disease or crises, hydrocortisone is used as it has both glucocorticoid and mineralocorticoid activity of 1:1.

Adverse Effects 00:31:40

Adverse effect of Glucocorticoids:

"Have GOOD CLIPS"

Have - Hyperglycemia, hypertension
G - Glaucoma (on topical use), growth retardation (if used in pregnancy)
O - Osteoporosis, oedema
O - Osteonecrosis (avascular necrosis)
D - Diabetes mellitus precipitation
C - Cushing syndrome, Cataract (on systemic use)
L - Limb muscle atrophy, Lipolysis in periphery and redistribution

- Glaucoma is caused by topical use (eye drops), while cataract is a side effect of systemic use. (Mnemonic- GTCS)
- In pregnant women, prednisolone is used because it cannot cross the placenta.
- Peptic ulcers can occur in the GIT due to decreased PGs production.

Hypothalamus-Pituitary-Adrenal Axis 00:36:35

- Hypothalamus-Pituitary-Adrenal (HPA) Axis.
- The hypothalamus releases the cortisol-releasing hormone, which acts on the pituitary, and the pituitary releases ACTH. ACTH acts on the adrenal gland, and the adrenal gland releases corticosteroids.
- The excess of steroids (long term) can control and inhibit the HPA axis. So, when the steroids are stopped, the axis is not activated and corticosteroids are not released, and the patient can experience stress, low BP, and cardiovascular abnormalities, and may go into a coma.
- Therefore, to avoid such incidents, the HPA axis must be activated.
- HPA axis suppression occurs when 20-25 mg of hydrocortisone or its equivalent is given for 2-3 weeks.

How to avoid HPA Axis Suppression 00:39:30

- Give alternative day
- Wherever possible, local steroids are preferred over systemic steroids.
- Start with a low dose.
- Short acting steroids are preferred over long acting steroids.
- The dose is not divided and it is given early morning.
- When steroids are stopped, they should be gradually tapered.

Contraindications of Steroids 00:43:43

- Epilepsy: Decreases seizure threshold.
- Psychosis: Causes behavior changes.
- CHF, Hypertension and edema: increased sodium and water retention.
- Viral and fungal infections: decreased immunity can flare up viral and fungal infections. In Covid-19, in the first week, antiviral drugs were used and steroids were started in the second week.
- Ileocecal TB: steroids increase the risk of perforation.
- Peptic ulcer: Steroids decrease the gastroprotective prostaglandins.
- Renal Failure: Increased sodium and water retention and steroids are eliminated by kidneys also, increasing the levels of the steroid.
- Osteoporosis
- Kaposi sarcoma
- Glaucoma

Uses of Steroids

Diagnostic Use

- **Dexamethasone suppression test:**
  - To check the integrity of the HPA axis.
  - Diagnose Cushing syndrome.

Replacement Use

- **Addisonian crisis (emergency)**- I.V Hydrocortisone is used
- **Addison's disease (Chronic)**- Hydrocortisone + Fludrocortisone is used.

- **Pregnancy-**
  - **Preterm delivery**
    - → In the case of preterm delivery, steroids increase lung surfactant production, decrease respiratory stress, and also decrease the risk of patent ductus arteriosus which can develop after the birth.
    - → Betamethasone 12 mg given I.M, 12 mg repeated after 24 hours.
    - → Dexamethasone 6 mg I.M, four doses given 12 hours apart
  - Congenital adrenal hyperplasia (CAH)
  - Steroids have also been shown to decrease necrotizing endocarditis in the newborn.

Congenital adrenal hyperplasia 00:52:53

- In this condition there is 21 hydroxylase deficiency (most common), the enzyme required for steroid synthesis.
- Corticosteroid synthesis is inhibited due to an enzyme deficiency, and the hypothalamus and pituitary keep increasing pressure on the adrenal gland for steroid synthesis, resulting in adrenal hyperplasia.
- Babies born will have low BP, low Na+ and high K+.
- Due to 21 hydroxylase deficiency, cholesterol biosynthesis will move towards more and more testosterone synthesis.
- CAH also has virilization features, resulting in ambiguous features, particularly in female fetuses.
- The treatment is done with hydrocortisone, as it has both glucocorticoids as well as mineralocorticoid activity.
- If a woman gives birth to a child with CAH and is pregnant for the second time (risk of CAH).
- Dexamethasone should be given in the sixth week of pregnancy, or as soon as the pregnancy is diagnosed.
- If the fetus is male the drug can be stopped, but if the fetus is female the drug should be continued till delivery.

Other Therapeutic Uses 00:57:40

- Rheumatoid arthritis
- Gout
- Psoriasis
- Allergy
- BA: Bronchial Asthma
- Organ transplant
- Leukemia
- Lymphoma
- GVHD: Graft versus host disease (Dexamethasone is preferred)
- CINV: Chemotherapy-induced nausea vomiting (Dexamethasone is preferred)
- Duchenne muscular dystrophy: The drug used is Deflazocort.
- T.B. meningitis: Steroids are used because if inflammation is not suppressed, the patient may end up with seizures.
- For neurocysticercosis, antihelminthic drugs like albendazole are used. These drugs lead to the release of larvae, increasing inflammation and causing seizures; hence, steroids are used.
- COVID-19 (decreases mortality).
- Lepra Reaction: In both types 1 and 2 the drug of choice is steroids.

Management of Cushing's Disease 01:01:03

- In this disease, there is an excess of steroid synthesis in the body. The strategies to manage are:
- Inhibit steroid synthesis
  - Aminoglutethimide
  - Ketoconazole

- Etomidate
- Metyrapone
- Mitotane (adrenolytic property), used in medical adrenalectomy
- Trilostane
- Osilodrostat inhibits the 11 beta-hydroxylase enzyme, required in steroid synthesis.

- Somatostatin analog (SST analog)
  - Pasireotide, which inhibits ACTH activity.
- Glucocorticoid receptor antagonist.
  - Mifepristone

PRACTICE QUESTIONS

Q. What drug is given along with adrenaline in anaphylaxis?

Q. A pregnant lady is in preterm delivery, what drugs are used for fetal lung maturity?

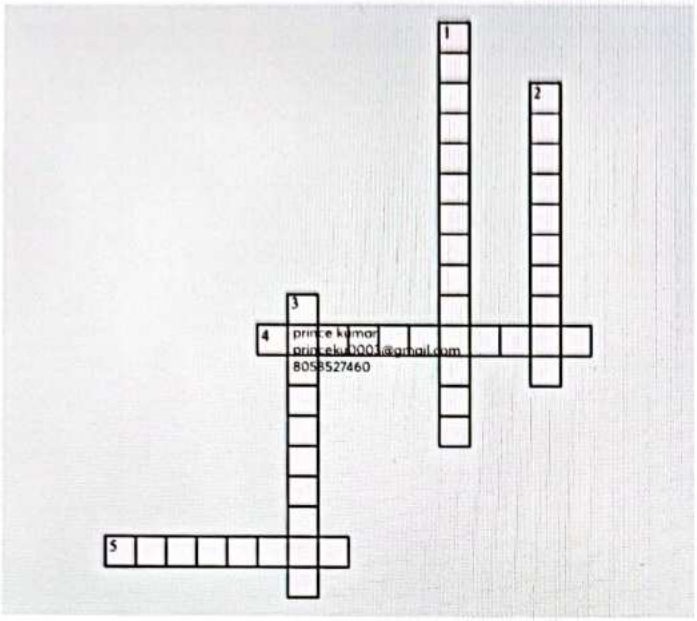
Q. A 32-year person on a drug for arthritis develops moon like face, Buffalo hump, high BP and increased glucose. Which drug may be responsible?

Table 58.1

Duration of action	Steroid	Glucocorticoid activity	Mineralocorticoids activity
Short acting (t ½ < 12hr)	Hydrocortisone (cortisol)	1	1
	Cortisone	0.8	0.8
Intermediate acting (t ½ 12-36 hr)	Prednisolone	4	0.8
	Prednisone	4	0.8
	Methyl Prednisolone	5	0.5
	Triamcilone	5	0
	Deflazocort	3-4	0
Long acting	Betamethasone	25	0
	Dexamethasone	25	0

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

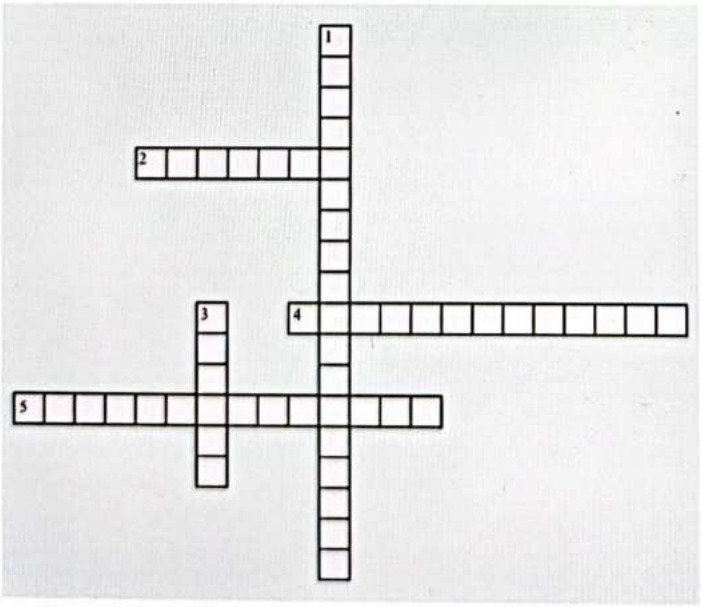
4. _____ acid is acted upon by two enzymes. COX (cyclo-oxygenase) and LOX (lipoxygenase).

5. _____ is used in medical adrenalectomy.

Down

1. _____ and leukotrienes are inflammatory mediators.
2. _____ of neutrophils is inhibited by steroids.
3. _____ is a prodrug that gets converted to prednisolone,

Crossword Puzzle 2



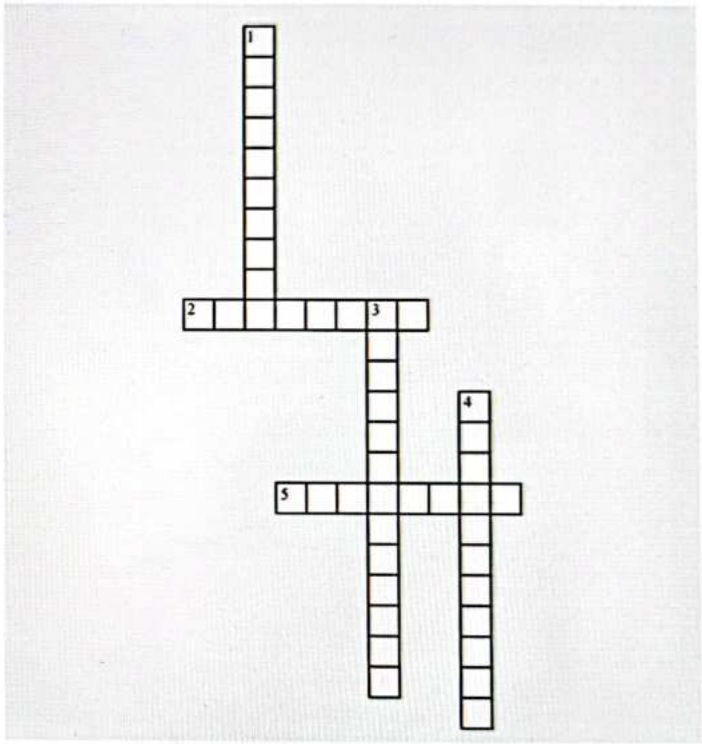
Across

2. _____ inhibits the enzyme phospholipase A2.
4. _____ infections are the adverse effects of immunosuppressants.
5. _____ is used in the treatment of status asthmaticus.

Down

1. _____ are used in organ transplant patients.
3. _____ sarcoma is a cancer of HIV patients.

Crossword Puzzle 3



Across

2. _____ increases the permissive action of adrenaline,
5. _____ is the main corticosteroid.

Down

1. _____ and angiotensin II require steroids to work efficiently.
3. _____ is the glucocorticoid used in cerebral edema.
4. _____ is the main mineralocorticoid

59 TESTOSTERONE

- Testosterone, a male hormone, gives rise to more efficacious dihydrotestosterone.
- There are weak androgens as well such as epiandrosterone and dehydroepiandrosterone.

Male Sex Hormones 00:00:58

- Testosterone will give rise to dihydrotestosterone which is more efficacious and the enzyme responsible for the conversion is 5 α reductase.
- There are certain weak androgens as well such as androstenedione and dehydroepiandrosterone. They are secreted from the adrenal gland.

Physiology 00:02:35

- Hypothalamus releases the GnRH hormone. GnRH will act on the pituitary to activate FSH and LH.
- The role of FSH is spermatogenesis.
- The role of LH is testosterone synthesis.

Important Information

- Testosterone hormones are also known as androgens.
- The excess testosterone can cause negative feedback on the pituitary as well as the hypothalamus.

Pharmacokinetics 00:03:37

- The naturally occurring testosterone if given orally has high first-pass metabolism. Due to this reason, it is not given orally.
- It has a short half-life of about 10-20 minutes.
- Natural testosterone is short-acting.

Preparations 00:04:05

- As we cannot give testosterone orally and because it is short-acting so we should give them by other routes. The preparations are Testosterone enanthate and Testosterone cypionate.
- These are oily preparation and cannot be given intravenously as they can cause fat embolism.
- So, these preparations must be given through the Intramuscular route.
- When the drug is given intramuscularly it will stay there as a depot and will be absorbed slowly. This makes the drug longer acting.
- Another preparation of testosterone is Testosterone undecanoate. This testosterone preparation can be given orally as well as intramuscularly. It has an advantage when given orally it is absorbed through lymphatics.

Changing the Structure 00:06:17

- Later the structure of testosterone was changed to make them more anabolic which means bodybuilding. These are known as 17 α alkylated testosterone.
- Some examples of 17 α alkylated testosterone are methyl testosterone, stanozolol, danazol, oxandrolone, and fluoxymesterone.

Specialities of 17 α Alkylated Testosterones 00:08:11

- They are more anabolic which means they will increase muscle mass.
- They can be given orally as they have less first pass metabolism.
- They are less androgenic which means they are not going to increase the prostate size.
- It causes lipid abnormality, increases LDL and decreases HDL, leading to atherosclerosis.

Important Information

- Do not confuse stanozolol as a β blocker. It is a testosterone preparation.

Anabolic Steroids 00:10:15

- The anabolic activity is more than the androgenic activity.
- An experiment was performed on the rat. The rat was castrated which means the testosterone will not be synthesized.
- Then these preparations are given, and the levator ani muscle and ventral prostate of the rat are checked. If they have equal activity on the muscle as well as the prostate it means they don't have much activity.
- But if the ratio keeps on increasing it means it is going to build muscle mass. If the levator ani muscle is more, then the experiment tells it is more anabolic.

Examples of Anabolic Androgen

- Nandrolone
- Oxymetholone
- Stanozolol

Uses of Testosterone 00:13:00

- **Testicular Failure-** When the testis does not produce testosterone, it is called testicular failure. They are of two types:
  - **Primary-** Testosterone is not secreted from childhood only, so the male child will have delayed puberty.

- **Secondary**- Puberty is achieved, but later the testosterone is not produced by the testes, which will lead to loss of libido in males, and they may lose muscle mass. In this case, testosterone preparation can be given.

- **Hypopituitarism**- The pituitary is not working properly.
- **Primary Hypogonadism**
- These are the replacement uses when testosterone is not there, we can replace it.
- **Other uses:**
  - Since testosterone increases spermatogenesis, we can use it in the management of infertility if the person has less androgen levels, we can give testosterone.
  - Anabolic steroid is used when there is severe muscle wasting due to chronic illness, HIV, or cancer. We can also give in osteoporosis, to increase physical activity in sports, and use it to correct malignancy anaemia, haemolysis anaemia, and anaemia due to chronic illness.

  - 17 α alkylated testosterone increases C1 esterase levels and is used to treat conditions like hereditary angioneurotic oedema. Drugs commonly used are Stanozolol and Danazol.

Adverse Effects of Testosterone 00:19:32

- If given to a female she will have virilization side effects which mean she will develop a male voice, moustache, beard, male appearance and this will also increase masculinity in females. So, it should not be used in females.
- If given to children, it may lead to premature closure of epiphysis which means stunted growth and precocious puberty.
- If given at high doses in adults, as we know testosterone causes a negative feedback mechanism, it will decrease FSH, so spermatogenesis will not happen that will lead to oligospermia which will lead to infertility.
- Gynaecomastia.
- Increased risk of acne.
- Two problems that we can face with 17 α alkylated testosterone are cholestatic jaundice and dyslipidemia.

Clinical Questions

Q. Why should we give testosterone?

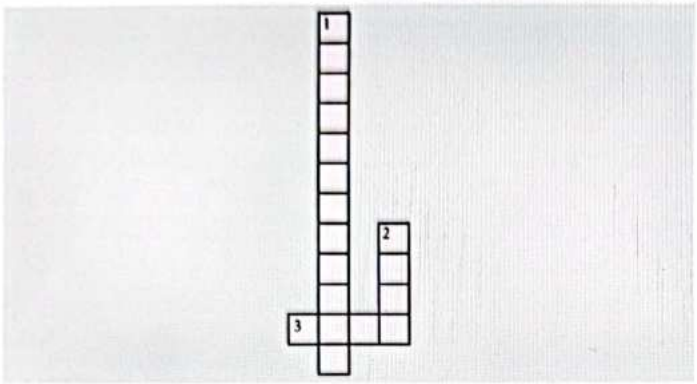
Ans. Because there may be conditions where testosterone is not synthesized which may result in delayed puberty.

Q. What are the advantages of making the drug long-lasting?

Ans. If somebody has testosterone deficiency, and they are being told to take the injections daily. They will follow it. So, in that case, if an injection is given and its effect is for weeks then the patient will surely follow it. This is the advantage of longer-acting drugs.

CROSS WORD PUZZLES

Crossword Puzzle 1



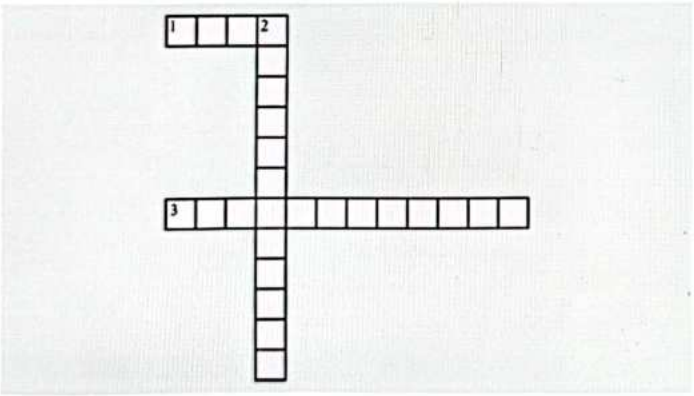
Across

3. Hypothalamus releases _____ hormone.

Down

1. _____ will give rise to efficacious dihydrotestosterone.
2. At _____ dose of testosterone adults experience adverse effects.

Crossword Puzzle 2



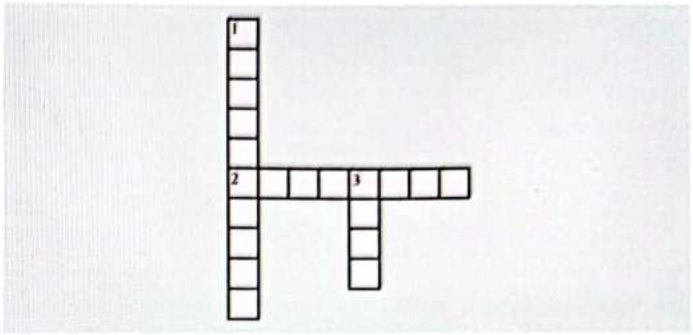
Across

1. Natural Testosterone is _____ acting.
3. _____ is an adverse effect of testosterone in children.

Down

2 _____ causes a negative feedback mechanism.

Crossword Puzzle 3



Across

2. Testosterone hormones are also known as _____

Down

1. Testosterone undecanoate is absorbed through _____
3. Testosterone enanthate and Testosterone cypionate are _____ preparations.

60 BENIGN PROSTATIC HYPERPLASIA

Definition 00:00:18

- In BPH, the prostate gland gets enlarged and presses against the urethra.
- Thus, the patient isn't able to pass the urine properly.
- The residual urine remaining in the bladder leads to an increased frequency and urgency of urination. It is commonly seen in elderly patients. Drugs are given to patients who do not wish to undergo surgery.

Drugs used in Benign Prostatic Hyperplasia (BPH)

- **Fast acting component:** α-Blockers. These further include the α1 selective blockers and α1A selective blocker (for bladder).
  - The α1 selective blockers are useful for both BPH and hypertension (HTN) e.g., Prazosin, Terazosin, and Doxazosin. Terazosin and Doxazosin have a quinazoline moiety, which is effective in prostate smooth muscle apoptosis. Alfuzosin is useful only in the management of BPH alone. The disadvantage of α1 blockers is that the patient may develop hypotension repeatedly.
  - α1A selective blockers are only useful for BPH and have no effect on HTN or BP, e.g., Tamsulosin and Silodosin. An important complication (adverse effect) of Tamsulosin is floppy iris syndrome, which is an intraoperative complication. Tamsulosin and silodosin are the drugs of choice for BPH. They don't affect the BP.
- **Slow-acting component:** These take months to show their effect. They are called 5α-reductase inhibitors.

5α Reductase Inhibitors 00:06:25

- Testosterone is converted into dihydrotestosterone (DTH).
- This conversion is done by an enzyme called 5α reductase inhibitor.
- Increased DTH can lead to BHP, androgenic alopecia, and hirsutism. These can be treated with 5α reductase inhibitors, e.g., Finasteride.
- Thus, the mechanism of action of finasteride is type 2 5α reductase inhibition.
- Dutasteride inhibits both type 1 and type 2 5α reductases. It is approved only for BPH treatment.
- These drugs have shown to decrease the size of the prostate in prolonged use.

Drugs used in the Management of Erectile Dysfunction 00:09:45

Oral Drugs

- Oral drugs are phosphodiesterase (PDE) V inhibitors, e.g., Avanafil, Sildenafil, Vardenafil, and Tadalafil (ASVT). Avanafil is a short-acting drug, while tadalafil is a longer-acting drug.
- Mechanism of action of sildenafil:
  - Stimulation in nerves in penis can release nitrous oxide (NO). This stimulates an enzyme called soluble guanylyl cyclase (SGC), which in turn converts the guanosine triphosphate (GTP) to guanosine 3',5'-cyclic monophosphate (cGMP).
  - The cGMP activates protein kinase G (PKG), which causes vasodilation (VD). This is responsible for penile erection.
  - In erectile dysfunction, the cGMP is broken down into 5'-GMP. The enzyme responsible for this breakdown is PDE V.
  - Thus, to increase the penile erection duration, the cGMP level should be increased. This is done by inhibiting the PDE V enzyme. This increases the vasodilation period and the duration of the erection. This is the mechanism of action of sildenafil.

Q. Can sildenafil and nitrates be combined?

Ans: Both drugs increase cGMP. This leads to a severe fall in BP, resulting in severe hypotension. Thus, any PDE V inhibitor given with nitrate has a risk of severe hypotension.

- **Pharmacokinetics of PDE V inhibitors:**
  - These are not aphrodisiacs. They only prolong the duration of the erection.
  - These should be given 1-2 hours before sexual intercourse.
  - Any PDE V inhibitor given with nitrate has a risk of severe hypotension.

- **Adverse effects of PDE V inhibitors:**
  - Decrease in BP
  - Increased heart rate (HR)
  - Blue or green tinted vision (due to PDE 6 inhibition in the retina).
  - Sometimes there is a prolonged erection.

Other Drugs in the Treatment of Erectile Dysfunction 00:15:30

- **Androgen replacement:** In cases of libido loss due to low testosterone, these can be used.
- **Injectables:** These are given into the penis before the intercourse. The issue with injectables is that they cause pain. Examples of injectables are Phentolamine, Papaverine, and Alprostadil.

Drugs Used in the Management of Premature Ejaculation 00:16:48

- Premature ejaculation is a condition where the person ejaculates early.
- **Selective serotonin reuptake inhibitors (SSRIs):** which delay the ejaculation process, e.g., Dapoxetine (FDA-approved drug) and Paroxetine (off-label use).
- **Tricyclic antidepressants (TCAs):** These are another class of drugs to treat premature ejaculation, e.g., Clomipramine (serotonergic property).

Hormonal Therapy of Prostate Cancer 00:18:00

- Prostate cancer is usually treated by surgery, but it might not always be feasible.
- Prostate cancer is a testosterone dependent cancer.
- The drugs used in its treatment include the following:
  - **Androgen receptor blockers-** Flutamide, Bicalutamide, Enzalutamide, and Nilutamide. All of these are approved for prostate cancer. Flutamide is also approved for acne and hirsutism.
  - **Gonadotropin-releasing hormone (GnRH) agonists-** Leuprolide and Goserelin. These are given as a continuous treatment.
  - **GnRH antagonist-** Abarelix and Degarelix.
  - **Abiraterone:** It acts by inhibiting the 17 α hydroxylase enzyme.
- The continuous use of GnRH agonists will increase the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH). This in turn will increase the testosterone levels. This can lead to a cancer flare-up. Later, the receptors are desensitized, which decreases FSH, LH, and testosterone. To prevent the cancer flare-up, flutamide is given three days before GnRH agonists. This is called combined androgen blockade.

Q. Can flutamide be given alone? 00:24:00

Ans:

- Whenever testosterone levels increase, it causes a negative feedback mechanism in the hypothalamus.
- Flutamide blocks the testosterone receptors in the hypothalamus and the pituitary gland.
- In the absence of negative feedback, there's an increase in testosterone production. This will replace the flutamide from the prostate, causing prostate cancer flare-up.
- Thus, flutamide cannot be given alone. GnRH agonists are continuously given along with flutamide. This desensitizes the testosterone receptors in the pituitary gland. Thus, testosterone won't be released.

Drugs Causing Gynecomastia 00:26:45

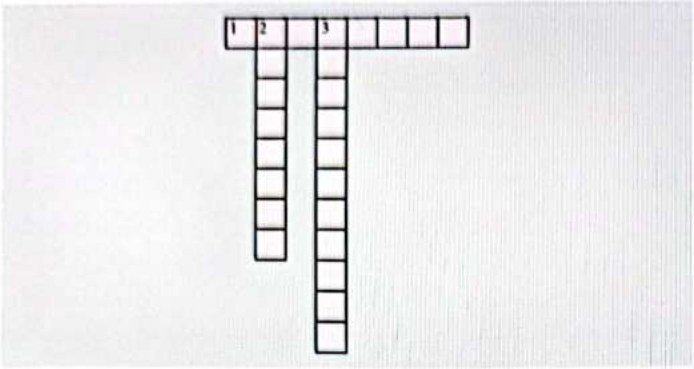
- The drugs causing gynecomastia are: (Mnemonic- "In moving a dashing car SKODA")
  - **In-** Isoniazid (INH).
  - **Moving-** Methyldopa and Metoclopramide.
  - **Dashing-** Domperidone.
  - **Car-** Cimetidine.
  - **S-** Spironolactone.
  - **K-** Ketoconazole.
  - **O-** Oestrogen.
  - **D-** Digoxin.
  - **A-** Anti-androgens.

Summary 00:28:27

- Two important drugs used in the treatment of BPH: α blockers (faster acting). Tamsulosin and Silodosin are the drugs of choice in the treatment of BPH, as they don't produce hypotension. The slower-acting drugs are α reductase inhibitors. They inhibit the conversion of testosterone to DTH. They decrease the size of the prostate.
- Drugs to treat erectile dysfunction are PDE V inhibitors. They increase the cGMP and cause vasodilation and increase of penile erection. They are to be avoided with nitrates as they can cause a severe drop in blood pressure. The injections include Phentolamine, Papaverine, and Alprostadil. Androgen replacement therapy can also be done.
- The SSRI of choice for premature ejaculation is Dapoxetine.
- Prostate cancer is treated with androgen receptor blockers like flutamide. It is also used to treat acne and hirsutism. The GnRH agonists are used continuously, but flutamide is added to avoid flare-ups. Flutamide isn't given alone to avoid blocking the negative feedback of testosterone. Other drugs used in the treatment of prostate cancer include GnRH antagonists (Abarelix and Degarelix) and Abiraterone (17 α hydroxylase enzyme inhibitor).

CROSS WORD PUZZLES

Crossword Puzzle 1



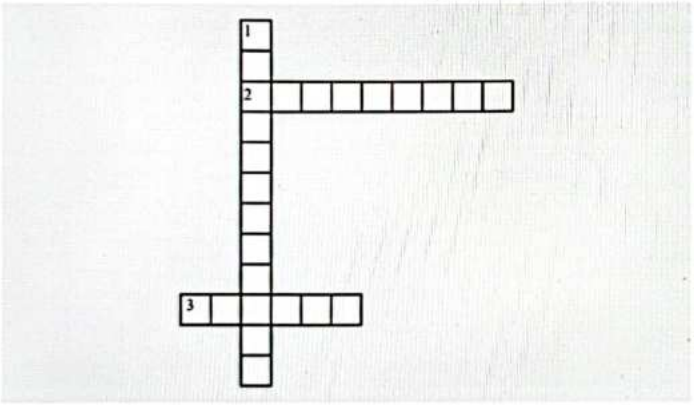
Across

1. _____ gland gets enlarged and presses against the urethra in benign prostatic hyperplasia.

Down

2. _____ urine remaining in the bladder leads to an increased frequency and urgency of urination.
3. _____ components take months to show their effect.

Crossword Puzzle 2



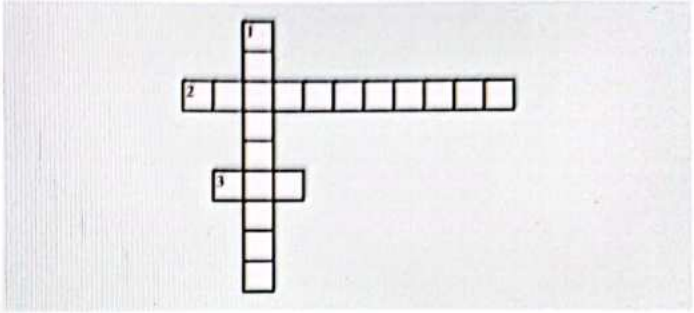
Across

2. _____ and Tamsulosin and are the drugs of choice for BPH.
3. _____ iris syndrome is an intraoperative complication of Tamsulosin.

Down

1. _____ is converted into dihydrotestosterone (DTH).

Crossword Puzzle 3



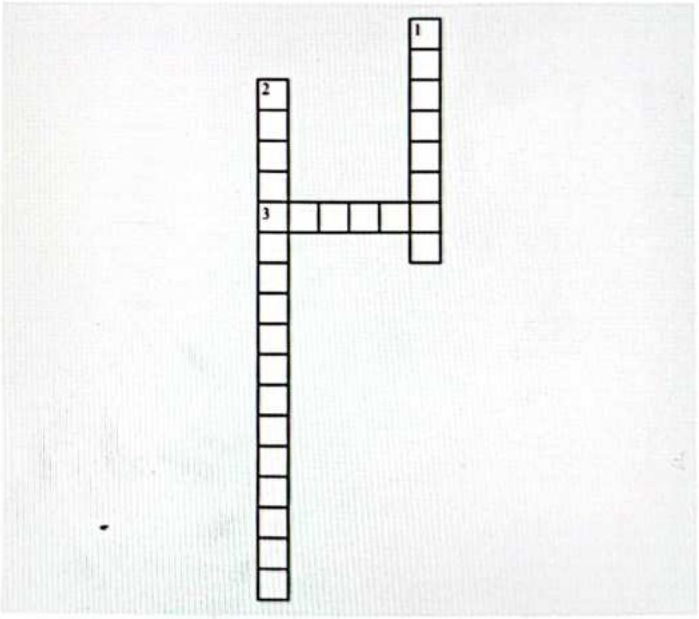
Across

2. _____ acts by type 2 5α reductase inhibition.
3. _____ increase can lead to BHP, androgenic alopecia, and hirsutism.

Down

1. _____ use of Finasteride and Dutasteride is known to decrease prostate size.

Crossword Puzzle 4



Across

3. _____ nerve stimulation can release nitrous oxide (NO).

Down

1. _____ replacement can be used in case of libido loss due to low testosterone.
2. _____ inhibitors are not aphrodisiacs.

61 ESTROGEN AND PROGESTERONE

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- Estrogen and progesterone are important in the female reproductive system and the menstrual cycle.
- The first is the follicular phase, which is the estrogen.
- The luteal phase is progesterone.
- Estrogen is responsible for the secondary sexual characteristics of a female. And progesterone (pro-gestation) is the main hormone for maintaining pregnancy.

Estrogen 00:00:45

- The naturally occurring estrogens are as follows:
  - Estradiol: It is predominantly present in the reproductive phase.
  - Estratriol: It is predominantly present during pregnancy.
  - Estrone: It is predominantly present in menopause.
- The least efficacious one is Estratriol because estrogen isn't much needed during pregnancy.
- Most natural estrogens are short-lived, and this results in the need for artificial estrogens.
- A synthetic preparation is of two types steroidal and non-steroidal preparation.
- The steroidal derivative is called Ethinyl Estradiol. It is commonly used in oral contraceptive pills (OCP), and others include Mestranol and Tibolone.
- Non-steroidal estrogens include DiethylStilbestrol. If this estrogen preparation is given to a pregnant woman, her female child is prone to developing cancer, namely vaginal adenocarcinoma.
- Dienestrol is another non-steroid estrogen.
- Fosfestrol is a prodrug. It is used in the treatment of prostate cancer. Acid phosphatase present in the prostate converts Fosfestrol to Stilbestrol, which works in the prostate.

Uses of Estrogen 00:06:50

- If puberty is not achieved at the right time, estrogen is administered. This condition is called delayed puberty.
- It is also used to treat dysfunctional uterine bleeding.
- Another use is its use as a contraceptive in combination with progesterone.
- It's also used in managing Menorrhagia.

Hormone Replacement Therapy (HRT)

- In menopause, ovaries shrink. Consequently, vaginal dryness occurs, and there's osteoporosis. The patient will have hot flushes and night sweats. Vaginal dryness can lead to painful sexual intercourse (dyspareunia). The patient may end up with fractures if osteoporosis is not treated.
- Hormone Replacement Therapy (HRT) is used in menopausal women.
- Estrogen can stimulate receptors in the breast tissue, and a patient may risk getting cancer. The addition of progesterone in the HRT decreases the risk of breast cancer.
- Estrogen has a cardioprotective effect as it is shown to decrease LDL.
- Progesterone increases LDL levels, and the cardioprotective effect of estrogen is nullified.
- Using HRT for a long time increases the risk of strokes and MI.
- HRT is to be used for a very short period to manage complications like osteoporosis.

Estrogen Antagonists 00:13:00

- SERM (Selective Estrogen Receptor Modulator): It's called a modulator because estrogen acts as an antagonist at certain places and a partial agonist at certain places. For example, Tamoxifene.
- Tamoxifen acts as an estrogen antagonist as well as a partial agonist.

Tamoxifen

Tamoxifen: Estrogen Antagonist	Tamoxifen: Estrogen Partial Agonist
Breast: It is used to treat breast cancer.	Bone: It decreases the resorption of the bone.
Peripheral tissues: The patient can suffer from hot flushes (adverse effect).	**Liver:** It can increase clotting factors. It can increase the risk of venous thromboembolism (adverse effect).
It is used in pre and post-menopausal breast cancer.	It acts as an agonist for endometrium. It can lead to uterine cancer (adverse effect).
It's also used in male breast cancer.	It decreases LDL in patients.
It is used as a prophylactic for breast cancer.	

- If a patient was undergoing treatment for breast cancer and reported vaginal bleeding after two years, Tamoxifen was used to treat the breast cancer.
- CYP2D6 activates Tamoxifene. Another drug, Fluoxetine, is an inhibitor of CYP2D6. These two drugs should not be combined together.

- The adverse effects of Tamoxifen on the eye are corneal deposits and retinal toxicity.
- Tamoxifen is not an approved drug to treat osteoporosis. The drug used in this case is Raloxifene.

Raloxifene 00:20:50

Raloxifene: Estrogen Antagonist	Estrogen Partial Agonist
Breast tissues: It is given as a prophylactic drug in breast cancer.	**Bone:** It decreases the resorption of the bone. Thus, used in post-menopausal osteoporosis.
Peripheral tissues: Hot flushes	**Liver:** It can increase clotting factors. It can increase the risk of venous thromboembolism.
Endometrium: The uterine cancer risk is not increased.	
It is used as a prophylactic for breast cancer.	

- Bazedoxifene is another SERM available in the market.
  - It is used to treat hot flushes and osteoporosis.
- Ospemifene is used to treat vaginal dryness. Therefore, decreasing dyspareunia.
- Ormiloxifene is also called by the name Centchroman. Saheli is its name in Hindi. It's used as a contraceptive and dysfunctional uterine bleeding.

STEAR (Selective Tissue Estrogen Activating Regulator) 00:26:35

- Tibolone is a STEAR drug. Agnostic in brain, vagina, bone, and blood vessels. It's used to decrease the vasomotor symptoms of menopause. It has mild androgenic, progesterone, and estrogenic properties.

Clomiphene Citrate

- It is an estrogen receptor antagonist. It particularly blocks estrogen receptors in the pituitary. Negative feedback is not seen, and FSH and LH concentrations increase. It induces ovulation.
- It is used in Anovulatory Infertility, Assisted Reproductive Techniques, and Male Oligospermia.
- Adverse effects include the following:
  - Multiple ova get released and fertilized, multiple pregnancies at a time.
  - Ovarian Hyperstimulation Syndrome
  - Risk of ovarian cancer

Aromatase Inhibitors 00:32:00

- In postmenopausal women, ovaries cannot produce estrogen. Testosterone is converted into estrogen, which can increase breast cancer risk. Aromatase is the enzyme responsible for causing breast cancer because it converts testosterone to estrogen.
- For the treatment of postmenopausal breast cancer, aromatase inhibitors are used.

Gen I (Outdated)	Gen II
Aminoglutethimide	Irreversible blockers of the enzyme are steroidal derivatives. Examples are Exemestane and Formestane.
	Reversible blockers of the enzyme are no-steroidal. Examples are Letrozole, Anastrozole, Fadrozole, and Vorozole. Another use of Letrozole is to increase ovulation in PCOD patients.

- These inhibitors are used in Tamoxifen-resistant cases.
- It delays the recurrence of breast cancer.
- They have a prophylactic effect beyond five years.
- These delay the disease progression.
- In postmenopausal women, these drugs decrease estrogen in all sites of the body. There's no risk of endometrial cancer or venous thromboembolism.
- The disadvantages are osteoporosis, hot flushes, and vaginal dryness. There's no effect on lipid profile.

SERD (Selective Estrogen Receptor Down-Regulator) 00:39:45

- It's an estrogen antagonist.
- The drug is named Fulvestrant. It stands for full estrogen antagonist.
- This drug has a fast onset of action and is longer-acting. It's given once monthly as an IM Injection.
- It can be used in both Tamoxifen and Aromatase resistant breast cancer.
- It's for postmenopausal breast cancer.

Progesterone 00:42:42

Uses

- In the reproductive age;
  - It's used as a contraceptive.
  - It is used to manage endometriosis.
  - It is used in DUB.
  - It's also used in the postponement of periods.
  - It is used in luteal phase defects.
- Progesterone is used in HRT to reduce the risk of cancer.

Progesterone Reparations 00:45:10

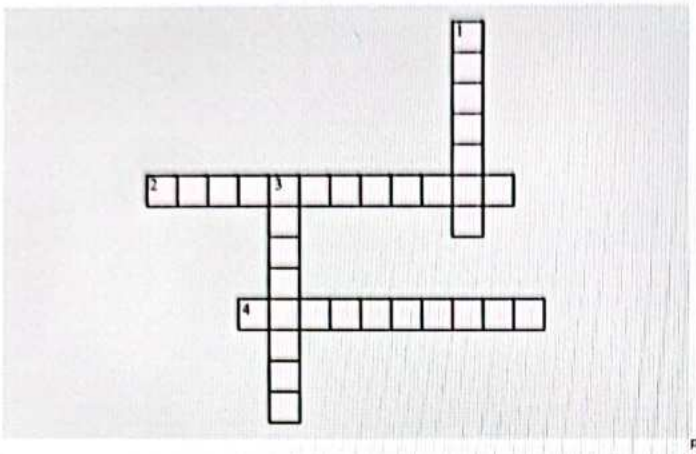
- These are classified as per generations.
- Gen I progesterone's are called Estranes - Norethindrone and Lynestrenol.
- Gen II progesterone's are called Gonanes. Norgestrel and Levonorgestrel.
- Gen III progesterone's are Desogestrel, Norgestimate, and Gestodene.
- Gen IV progesterone's are Nomegestrel and Drospirenone.
- The potency of these drugs increases with each new generation, and Gen IV is the most potent one.
- These drugs have androgenic properties, so the patient develops acne.
- Androgenic property decreases with each new generation, and the IV th generation has anti androgenic properties.
- Drospirenone has anti-mineralocorticoid properties, so it can block aldosterone receptors.

SPRM (Selective Progesterone Receptor Modulator) 00:49:55

- Mifepristone is a progesterone receptor antagonist and glucocorticoid antagonist. In certain tissues, it's a partial agonist.
- It is used in the medical termination of pregnancy. Mifepristone is given first, followed by Misoprostol.
- Mifepristone stops the pregnancy, and Misoprostol causes uterine contraction.
- It's used in emergency contraception and is usable for up to 72 hours.
- It is also used to counteract excess estrogen conditions like endometriosis and fibroids.
- If the progesterone receptor is positive, it can be used in breast cancer and meningiomas.
- It is also used in Cushing's disease.
- Another SPRM drug is Ulipristal. It is mainly used as an emergency contraceptive.
- Around 30 mg is given and is usable for up to 120 hours (5 hours)

CROSS WORD PUZZLES

Crossword Puzzle 1



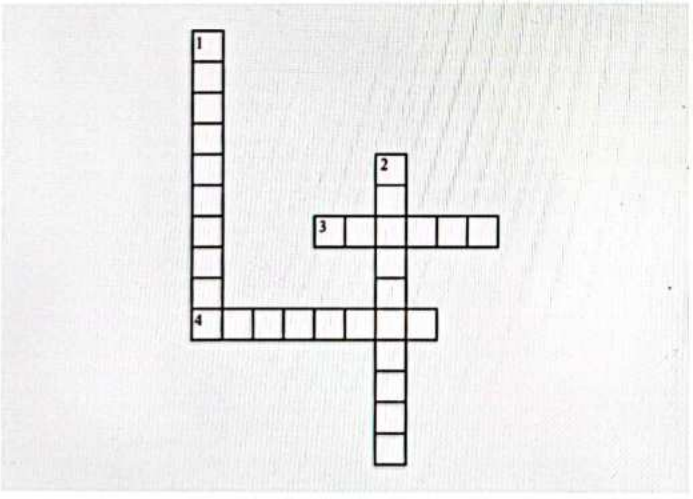
Across

2. _____increases LDL levels, and the cardioprotective effect of estrogen is nullified.
4. _____is a prodrug. It is used in the treatment of prostate cancer.

Down

1. _____Replacement Therapy (HRT) is used in menopausal women.
3. _____is responsible for the secondary sexual characteristics of a female.

Crossword Puzzle 2



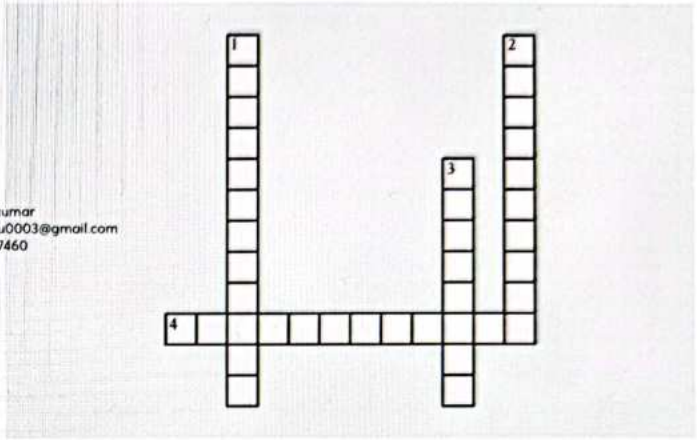
Across

3. _____activates Tamoxifene.
4. _____has a cardioprotective effect as it is shown to decrease LDL.

Down

1. _____acts as an estrogen antagonist as well as a partial agonist.
2. _____is used to treat vaginal dryness. Therefore, decreasing dyspareunia.

Crossword Puzzle 3



Across

4. _____is used in HRT to reduce the risk of cancer.

Down

1. _____is a progesterone receptor antagonist and glucocorticoid antagonist. In certain tissues, it's a partial agonist.
2. _____citrate is an estrogen receptor antagonist. It particularly blocks estrogen receptors in the pituitary.
3. _____is a STEAR drug. Agnostic in brain, vagina, bone, and blood vessels. It's used to decrease the vasomotor symptoms of menopause.

62 HORMONAL CONTRACEPTIVES

- Hormonal contraceptives are used to avoid pregnancy.
- Modes of Contraception:
  - Oral
  - Injectable
  - Implants
  - IUD
  - Patches

MOA of Contraceptives 00:00:55

- FSH and LH are important for maturation of Ova. LH is responsible for ovulation.
- When drugs like estrogen and progesterone are combined, they decrease LH with their negative feedback mechanism leading to decrease in ovulation. This is the specialty of combined oral contraceptive pills.
- They reduce the tubal motility. The ova cannot move a get fertilized with the sperm.
- They interfere with implantation.
- They make the cervical mucous thick, leading to inhibition of sperm penetration. This is seen with progesterone only pills called as mini pills.

Oral Contraceptives 00:04:15

- Types of oral contraceptives are:
  - Combined OCPs
  - Progesterone only pills (Mini pills)
  - Emergency contraceptives

Combined OCPS

- Contains both estrogen and progesterone.
- The mostly commonly used estrogen preparation is Ethinyl estradiol and the standard dose is around 50 µg, lower dose is 35 µg and very low dose is 20 µg.
- Monophasic pills are available in this combination. This means that they contain the same amount of estrogen and progesterone throughout the cycle.
- The problem with monophasic pills is that there is breakthrough bleeding (Bleeding in between the menstrual cycle).
- In biphasic pills estrogen content is same throughput the cycle whereas the progesterone content varies in the first 10 days and the next 10 days.
- In triphasic pills the estrogen dose remains the same whereas the progesterone dose is low in first 6 days, the next 7-11 days it is moderate and the high from 12-21 days.
- Biphasic and triphasic pills reduce the risk of breakthrough bleeding.
- Combined OCPs are better in newly married couples and after evacuation of molar pregnancy.

Progesterone only Pill 00:09:05

- They are also called mini pills.
- They have less efficacy.
- They make the cervical mucous thick, inhibiting the penetration of sperm.
- Taken daily without a break.
- They are used in lactating women, seizures and sickle cell anemia.
- Preferred in estrogen contraindicated patients (>35-year-old, smokers and increased risk of venous thromboembolism).

Emergency Contraceptives 00:11:45

- They are also called as post coital pill or morning pill.
- They should be used within 72 hours.
- Levonorgestrel, 1.5 mg single dose or 0.75 mg and after 12 hours 0.75 mg.
- Combined OCPs, 2 tablets are taken first followed by another 2 tablets after 12 hours. This is called Yuzpe method. Shows less efficacy.
- Mifepristone, 600 mg within 72 hours.
- Ulipristal (Selective progesterone receptor modulator),30 mg can be used up to 120 hours.

Adverse effects of OCPs

- MILD:
  - Nausea
  - Edema
  - Headache
  - Breast tenderness
  - Abnormal bleeding (Breakthrough bleeding)
- Moderate:
  - Acne
  - Weight gain
  - Chloasma
- Severe:
  - CVS- Altered the lipid profile, venous thromboembolism (Increased risk of MI and stroke)
  - CNS- Mood swings, depression.
  - Cholestasis- Gall stones
  - Cancer- Increased risk of breast, cervical and vaginal cancer
  - Increased risk of benign hepatomas.

Benefits of OCPs 00:18:40

- **Ovary:**
  - Reduced risk of ovarian cyst and ovarian cancer.
- **Breast:**
  - Decrease the risk of benign breast disease

- **Endometrium:**
  - Decrease the risk of endometrial cancer, endometriosis and endometrial fibrosis.
- **Bone:**
  - Decrease resorption
- Reduce the risk of anemia.
- Decrease Pre-menstrual tension.

Drug Interactions

- OCPs combined with Rifampicin or other enzyme inducers leads to contraceptive failure.
- OCPs undergo enterohepatic recycling. When they are combined with broad spectrum antibiotics like tetracyclines, there is contraception failure due to interference with enterohepatic recycling.

Parentral Contraceptives

00:22:10

- **I.M DEPOT PREPARATIONS**
  - DMPA- **Depot-medroxyprogesterone acetate**
  - Norethindrone enanthate.
- **IMPLANTS**
  - Norplant (Levonorgestrel)- Can work up to 5 years.
  - Implanon.
- **IUD**
  - Progestasert
- **TRANSDERMAL PATCH**
  - Applied once weekly for 3 weeks with 1-week gap.

63 THYROID HORMONES AND ANTI THYROID DRUGS

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Thyroid hormones and anti-thyroid drugs

Hypothroidism	Hyperthyroidism, Grave's disease Toxic Nodular Goitre
$\downarrow T_3, \downarrow T_4$	$\uparrow T_3, \uparrow T_4$
$\uparrow$TSH	$\downarrow$TSH
$\Downarrow$	$\Downarrow$
R_x Levothyroxine (T_4)	R_x Anti-thyroid drugs

- Antithyroid drugs are the drugs used to treat an overactive thyroid or hyperthyroidism.

Hypothyroidism

- It occurs due to the deficiency of T3, T4, and a increase in the TSH hormone.
- Hypothyroidism is treated with Levothyroxine.

Hyperthyroidism

- It occurs when the thyroid gland makes too much T3, T4, and a decrease in the TSH hormone.
- Deficiency of TSH and too much T3, and T4 are also seen in conditions like Graves disease and toxic nodular goiter.
- Management of these conditions can be treated with antithyroid drugs.

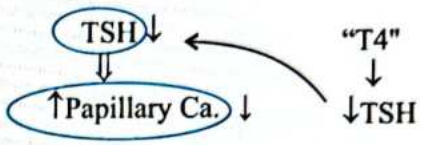
Thyroid Hormones

- Levothyroxine and Liothyronine are the two major thyroid hormones.

Levothyroxine	Liothyronine
T4 hormone	T3 hormone
Less potent and less efficacious hormone	Most potent and most efficacious hormone
Less active	More active
T1/2: 5-7 days	T1/2: 1-2 days
Mainly used in the treatment of myxedema, Myxedema coma, cretinism, papillary sarcoma of thyroid and hypothyroidism	Mainly used in the treatment of Myxedema coma (condition when there is an excessive deficiency of thyroxine level)

- TSH hormone is the stimulating agent to increase the chance of papillary carcinoma.
- T4 decreases the activity of TSH, and papillary cancer also decreases.

Hypothyroidism cretinism papillary Ca. of thyroid



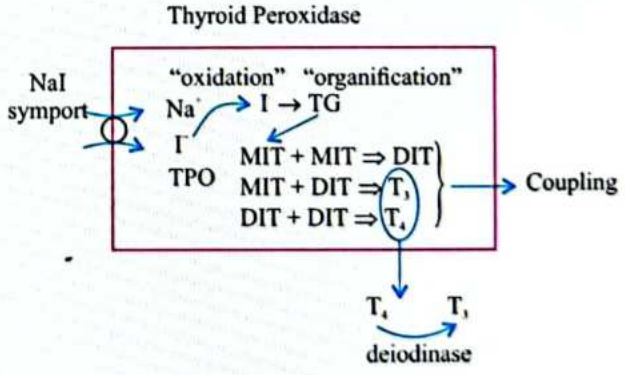
- Papillary carcinoma depends on the level of TSH.
- Surgery is the main line of treatment for papillary carcinoma, but when the surgery is not possible then levothyroxine can be used.
- T4 is given in the treatment of Papillary carcinoma that suppresses TSH.

Golden point

Levothyroxine

- Pharmacokinetics- when given orally, its bioavailability is 75%.
- Food interferes with absorption. So, it should be taken with an empty stomach.
- It should be taken in the early morning so that it can mimic the physiology.

Anti-thyroid drugs



- The approach to treat hyperthyroidism is to decrease the release of T3 and T4 hormones.
- Initially, there is an entry of Na and I (sodium and iodide) called NaI symport.
- When iodine enters the cell, it converts into iodonium called oxidation.
- This iodonium combines with thyroglobulin (tyrosine residual) which converts into mono iodothyronine (MIT).
- This step is called organification.

- MIT combines with one more MIT to form diiodothyronine (DIT).
- MIT+DIT forms T3.
- DIT+DIT forms T4.
- T3 and T4 are stored in the thyroid follicle. Whenever the impulse arises, T3 and T4 release.
- T4 presence is abundant in circulation, and T3 is present in a lesser amount.
- T3 is more active, and secrete in low amounts.
- T4 is converted into T3 by the enzyme deiodinase.
- Combination of MIT, DIT, T3, and T4 are called coupling.
- Oxidation, organification, and coupling reaction are done by the enzyme called thyroid peroxidase (TPO).

Targets of anti-thyroid drugs

- Block NaI symport
- Inhibits the enzyme TPO
- Stop the release of T3 and T4
- Inhibits the enzyme deiodinase (most active form, T3 will not form)
- Destroy the gland

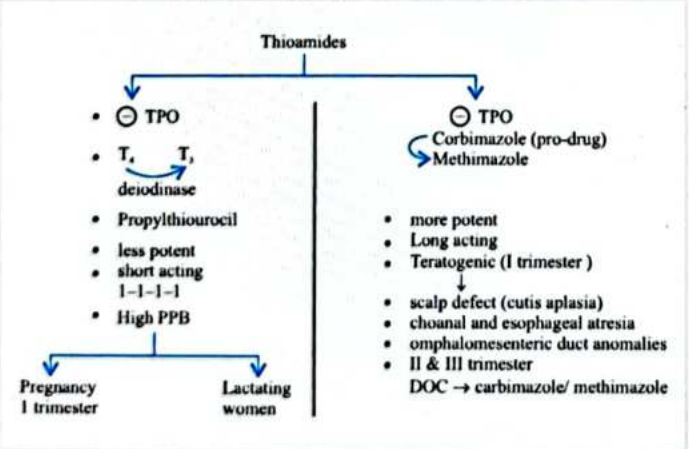
I. Na I Symport Inhibitors

- Drugs (outdated, not used nowadays) -
- Thiocynates
- Perchlorates
- Perchlorates can produce aplastic anemia as an adverse effect
- Fluroborates

II. Thioamides

- Thioamides are divided into two categories-

Golden point



Propylthiouracil

- It can inhibit the TPO enzyme and inhibit the conversion of T4 to T3.
- Advantage- High plasma protein binding, cannot enter the placenta easily.
- Prefered in pregnancy in the first trimester.
- Short-acting, given 4 times a day and less potent.
- Teratogenic in I trimester of pregnancy.
- Hepatotoxic, it cannot be used in 2nd trimester of pregnancy.
- It increases cANCA levels in more than 50% of patients.
- It can be used in the management of thyroid storm because it inhibits the conversion of T4 to T3.

Carbimazole

- It can only inhibit the TPO enzyme.
- Carbimazole is a prodrug, and after metabolism converts into methimazole.
- It can produce scalp defects.
- In the II and III trimester of pregnancy, carbimazole and methimazole is the drug of choice.
- More potent
- DOC for Grave's disease, hyperthyroidism, and toxic nodular goiter.
- Reason to use this drug very often is the very long-acting drug.
- Not hepatotoxic.
- Not used in thyroid storm.

III. Drugs that decrease T3 and T4 release

Drugs

- Sodium iodide (NaI), potassium iodide (KI), or Lugol's iodine.
- Lugol's iodine is made of 5% Iodine and 10% KI.
- It decreases the release of thyroxine and the fastest-acting anti-thyroid drugs.

Uses

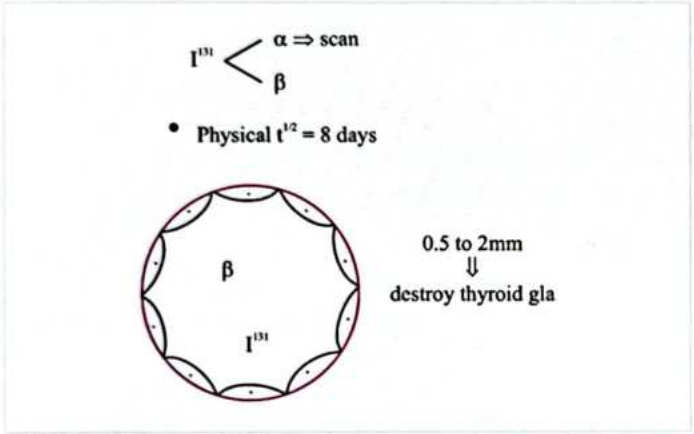
- It is used before surgery of the thyroid for toxic nodular goiter.
- Patients start on either carbimazole or methimazole 2-3 months before surgery which decreases the synthesis of T3 and T4.
- Preoperatively, iodides are given, because-
- It makes the glands firm and less vascular.
- Advantage-
- it decreases bleeding during surgery.
- Clear surgical field.
- Decreases the chance of thyroid storm by decreasing the release of T3 and T4.
- It is used in the management of thyroid storm
- Thyroid storm is a life-threatening condition of the thyroid gland. It develops in cases of untreated hyperthyroidism, grave disease, or toxic nodular goiter.
- When the surgeon cuts the thyroid gland, there's a chance of release of thyroxine in the circulation which can cause tachycardia and arrhythmia.

IV. Deiodinase enzyme inhibitors

- T4 is converted into T4 by the enzyme deiodinase.
- Deiodinase enzyme is inhibited by propylthiouracil, propranolol, and hydrocortisone.
- These drugs are used in the treatment of thyroid storm.

V. Destroy the thyroid gland

- It destroys by the radioactive iodine (I^{131}).
- I131 emits γ and β.
- γ is used for scans to check cancer or toxic nodular goiter.



- β is used to destroy the thyroid gland.
- 8 days half-life or physical half-life
- When radioactive iodine is given to the patient, it enters the thyroid follicle and emits the β particle.
- β particle penetrates around 0.5 to 2 mm.
- By penetrating, it destroys the thyroid gland.

Advantages of I^{131}

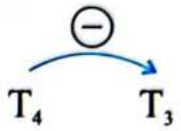
- When a patient is not fit for surgery with some cardiac complications, radioactive I^{131} is used.
- When the patient is not willing for surgery.
- No scar
- Less expensive
- When surgery is already done but some remnant exists because surgery can not be done again, then radioactive I^{131} is used to destroy the remnant after surgery.

Disadvantages

- Permanent hypothyroidism because it is destroying the thyroid gland.
- These patients will get levothyroxine for a lifetime because of permanent hypothyroidism.
- Contraindicated in pregnancy, children, and lactating mother because of permanent hypothyroidism and these people requires very much thyroxine in a phase of life.

Drugs causing hypothyroidism

- Anti-thyroid drugs
- Na. Nitroprusside
- Lithium
- Ethionamide, PAS
- Amiodarone



Adverse effects of Thioamides

- In agranulocytosis, the patient will complain of fever and sore throat.
- In this condition, complete blood count (CBC) is checked, if the WBC count is less, agranulocytosis can be suspected.
- If you stop the usage of thioamides, this condition can be reversed.
- If it is not reversible, then it can be treated by G-CSF (filgrastim).
- Most common adverse effect is rashes.

Drugs Used In Thyroid Strom

- Propranolol
  - Decrease CVS manifestation.
  - Inhibit coversion of T4 to T3.
- IF patient is asthamtic use CCBs Verapamil.
- Propylthiouracil - inhibit conversion of T4 to T3.
- Iodides- decrease T3 and T4 release.
- Hyrdrocortisone - to overcome shock.

Questions

Q. Hypothyroidism occurs due to the deficiency of
Ans: T3, T4, and an increase in the TSH hormone

Q. Hypothyroidism can be treated with
Ans: levothyroxine

Q. Which is the most potent and most efficacious hormone
Ans: Liothyronine (T3 hormone)

Q. Liothyronine is used in the treatment of
Ans: Myxedema coma

Q. Which hormone is the stimulating agent for increase the chance of papillary carcinoma
Ans: TSH hormone

Q. What is the percentage of Levothyroxine when it is given orally
Ans: Pharmacokinetics- When given orally, its bioavailability is 75%.

Q. Levothyroxine is taken with
Ans: Food interferes with absorption. So, it should be taken on an empty stomach

Q. Which drug inhibits the TPO enzyme and inhibits the conversion of T4 to T3?
Ans: Propylthiouracil

Q. Which hormone is more active
Ans: T3 is more active and secretes in low amounts.

Q. T4 is converted into T3 by the enzyme
Ans: deiodinase.

Q. Combination of MIT, DIT, T3, and T4 is called
Ans: coupling

Q. Oxidation, organification, and coupling reaction are done by the enzyme called
Ans: thyroid peroxidase (TPO)

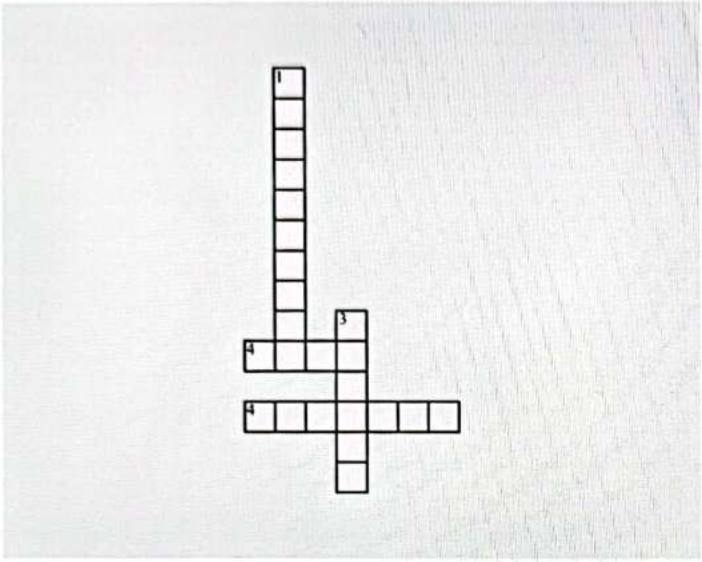
Q. Carbimazole is a prodrug, and after metabolism converts into
Ans: Methimazole

Q. What is an adverse effect of carbimazole
Ans: It can produce scalp defects

Q. DOC for Grave's disease, hyperthyroidism, and toxic nodular goiter
Ans: Carbimazole

CROSS WORD PUZZLES

Crossword Puzzles1



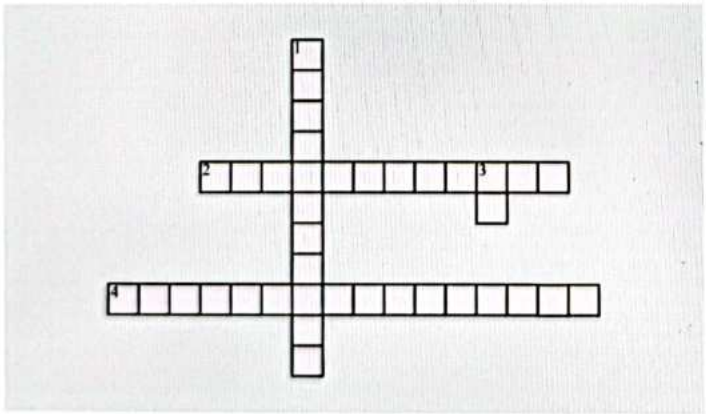
Across

3. _____ Ionizing radiation is used to destroy the thyroid gland.
4. _____ can cause hypothyroidism.

Down

1. _____ is the stimulating agent that increases the chance of papillary carcinoma.
2. _____ are the most common adverse effects of thioamides.

Crossword Puzzles2



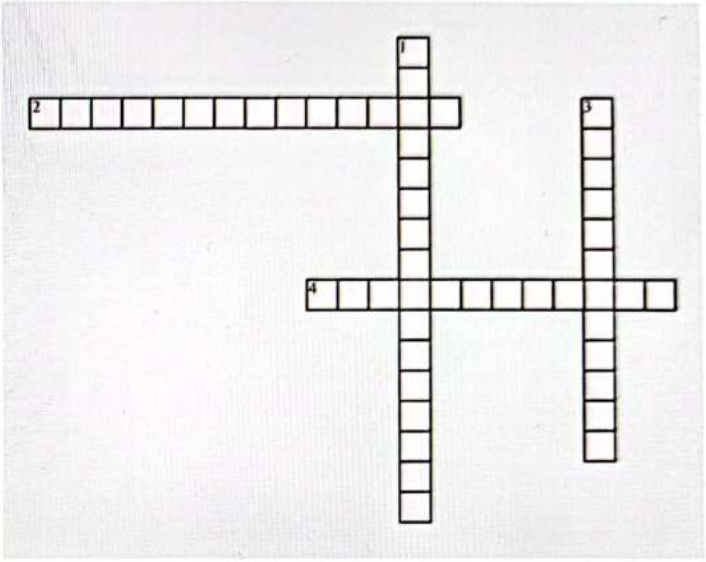
Across

2. _____ can produce aplastic anemia as an adverse effect
4. _____ is a less potent drug.

Down

1. _____ belongs to NaI symport inhibitors.
3. _____ is given in the treatment of papillary carcinoma that suppresses TSH.

Crossword Puzzles3



Across

2. _____ is used in the treatment of thyroid storm.
4. _____ is the fastest-acting anti-thyroid drug.

Down

1. _____ is a hepatotoxic drug.
3. _____ makes the gland firm and less vascular.

64 ANTI MICROBIALS INTRODUCTION AND PENICILLINS

00:00:03

- The branch dealing with anti-microbial drugs is called Chemotherapy, which means killing the cells.
- Chemotherapy used to kill microbes is called anti-microbial drugs.
- Chemotherapy can be also used to kill cancer cells which are called cancer chemotherapy.
- Microbes that commonly cause infections in humans are
  - Bacteria.
  - Virus
  - Fungus
  - Protozoa
  - Helminths

Antibacterial Drugs

- Antibiotics: There are certain chemicals produced by some organisms that kill other organisms, for example, the fungus (penicillium notatum) producing Penicillin and it kills the bacteria.
- Antimicrobials: It is a broad term which includes antibiotics + synthetic drugs
- Bacteriocidal drugs: These drugs kill the bacteria.
- Bacteriostatic drugs: These drugs stop the multiplication of bacteria.
- Cidal drugs: It is given to the patient who is immunosuppressed.

Bacteria

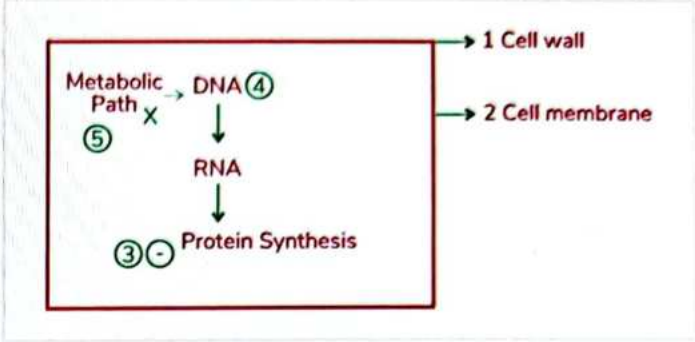
There are divided into

- Gram +ve: Cocci and Bacilli.
- Gram -ve: Cocci and Bacilli.
- Other major bacteria which is dealt with separately and multiply very slowly are Tuberculosis and Leprosy.

Bacterial infections

- Meningitis
- Respiratory infections
  - Upper respiratory tract infection.
  - Lower respiratory tract infection: Community-Acquired pneumonia, Hospital-acquired pneumonia, Ventilator-associated pneumonia.
- GIT Infections: Diarrhoea, dysentery, food poisoning and intra-abdominal infections.
- Urinary Tract Infection
- Sexually Transmitted Disease
- Skin and skin structure infection.

How to kill the bacteria?



- In every bacteria, there is DNA will give rise to RNA and RNA helps in Protein synthesis.
- There is a certain metabolic pathway that is important for DNA synthesis.
- In order to kill the bacteria the drugs will alter the metabolic course of the bacteria in order to stop them from multiplying. Some of the target areas are.
  - Drugs act on Cell Wall.
  - Drugs act on Cell membrane.
  - DNA synthesis inhibitors.
  - Protein synthesis inhibitors.
  - Metabolic pathway inhibitors.

Cell Wall Synthesis Inhibitors

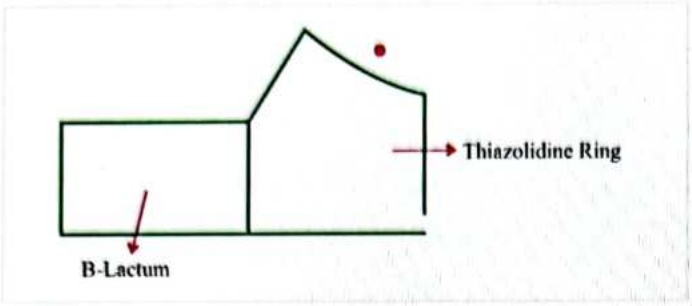
00:15:09

- If bacteria want to multiply it has to produce two daughter bacteria.
- When the drug affects the bacteria's cell wall synthesis the daughter bacteria will have defective cell walls.
- From the external environment, the water will gush inside causing the bacterial cell to swell up and rupture, leading to the bactericidal effects of the drug.

Drugs for cell wall inhibition

- **Beta Lactams:** Inhibits the enzyme called transpeptidase.
- **Bacitracin:** Inhibits Dephosphorylation of bactoprenol. Bacitracin is used topically for treating skin infections, also used in MRSA carriers.
- **Cycloserine:** Inhibits Alanine and inhibits D-ala, d-ala ligase (it is the only static drug). Used in Tuberculosis (tuberculostatic drug), its adverse effect is Psychosis, seizures.
- **Fosfomycin:** Inhibits Enolpyruvate transferase. Used in uncomplicated UTI. Its adverse effect is diarrhoea.
- **Glycopeptides:** (One of the important drugs Vancomycin) inhibits Transglycosylase.

Beta Lactams

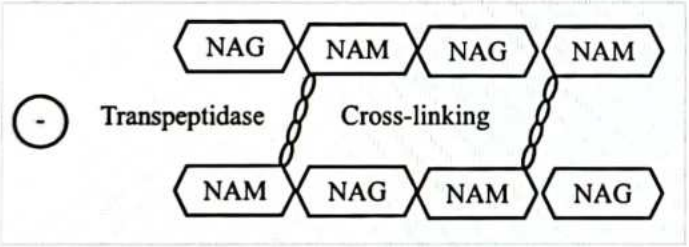


- **Beta lactams drugs:**
  - Penicillin
  - Cephalosporins
  - Carbapenems and
  - Monobactams (it has only beta lactam ring no thiazolidine ring)
  - All the drugs produce allergy, only drugs in the group that don't have a cross allergy is monobactams.

Mechanism of Action:

- Inhibits cell wall synthesis.
- Inhibits transpeptidase.
- All these drugs are Bactericidal.

N – Acetyl Muramic Acid (NAM)
N – Acetyl Glucosamine (NAG)



- **In-depth MOA:** Inside there is a penicillin-binding protein, mainly present in the cytoplasmic membrane of the bacteria. Penicillin-binding protein is the place where the beta-lactams sit. The drug binds itself with the penicillin-binding protein which inhibits an enzyme called transpeptidase, which affects the strength of the cell wall. These NAG (N-acetyl Muramic acid) and NAM (N- acetyl glucosamine) are the building blocks of the cell wall and they are combined using amino acids as shown in the above diagram. Cross-linking is done by the enzyme transpeptidase. Cross-linking makes the cell wall stronger and protects the nucleus.

Penicillin - G

- Penicillin G was discovered by Alexander Fleming.
- The source of drug is Penicillium Notatum (which is a fungus).
- Once it was discovered it was also called Penicillin G/Benzyl/Crystalline/Aqueous Penicillin.
- **Drawbacks of Penicillin G:**
  - Short-acting drugs.
  - It can only be given in I.V./I.M.
  - Cannot be given orally because it is Acid labile, which means when taken orally the acid deactivates the drugs.
  - Narrow Spectrum: They cover only a few problems – Gram +ive more than Gram -ive, Spirochetes, N. Meningococci, Clostridium. And they don't cover Enterobacteriaceae.
  - Resistance.

Solutions to the drawbacks of penicillin:

- Increased the duration of action in two ways:
  - Penicillin is excreted in the Kidney. Penicillin is secreated with the help of OATP in nephron. Probenecid was used as an inhibitor to stop penicillin excretion.
  - Repository penicillins – longer acting
    → Procaine penicillin in I.M. duration of action is 12 to 24hours and adverse effect is seizures.
    → Benzathine penicillin (I.M) which lasts for 21-28 days. It is given in RHD prophylaxis, and it is also a drug of choice for all stages of syphilis except neurosyphilis (the drug of choice for neurosyphilis is Aqueous penicillin.
- Acid Stable Penicillins: They are given orally. Oral penicillins are Amoxicillin, Ampicillin, oxacillin, Penicillin V, Cloxacillin and Dicloxacillin.
- Extended spectrum Penicillins: They cover both G+I've and in Gram negative and they started covering Enterobacteriaceae.
  - Amino penicillins: they can cover gram positive and gram negative bacterias. E.g., Amoxicillin, Ampicillin. They are contraindicated in EBV Infection. These drugs can cause pseudomembranous colitis.

Amoxicillin	Ampicillin
It is longer acting so it is given three times a day.	It is short acting, so it is given four times a day.
It is completely absorbed which reduces the risk of superinfection (like diarrhea).	It is incompletely absorbed which increases the chance of superinfection.
Amoxicillin does not undergo enterohepatic recycling.	Ampicillin undergoes enterohepatic recycling.
Amoxicillin + Clavulanic acid	Ampicillin + Sulbactam
Used in the treatment of H. pylori	Used in the treatment of H influenza, Shigella and drug of choice for E. Fecalis and listeriosis.

- **Anti-pseudomonal penicillins:** They cover pseudomonas and also covers like amino penicillins
  - Carboxy penicillin: Carbenicillin, Ticarcillin
  - Ureido penicillin: Mezlocillin, Azlocillin, Piperacillin
- **Resistance:**
  - 4 Mechanisms of drug resistance is by
    → Inactivating enzyme
    → Inhibit entry.
    → Efflux pump
    → Altering the target
- To prevent resistance: Beta-Lactamase inhibitors + Beta lactams are given. The following combination is given.
  - Clavulanic acid + Amoxicillin
  - Sulbactam + Ampicillin
  - Tazobactam + Piperacillin
  - Vaborbactam + ceftazidime
  - Avibactam + Meropenem
  - Relebactam + Imipenem + Cilastatin
- Sulbactam is shown to kill the bacteria called Acinetobacter.

Beta-lactamase is a broad term:

- If they cut Penicillium it is called Penicillinase.
- If they cut the cephalosporin, it is called Cephalosporinase.
- If they cut the carbapenem it is called Carbapenemase.
- If they cut the monobactam it is called Monobactamase.
- Ecoli and klebsiella are responsible for causing UTI infections. They started producing ESBL (extended-spectrum Beta-lactamase) which cuts penicillin, cephalosporin and monobactam. The drug of choice is Carbapenems. Also, a combination of beta-lactam + beta-lactamase inhibitors can be given such as Piperacillin + tazobactam or Cephalosporins + Beta-Lactamase inhibitors.

Staphlococcus Aureus

- This bacteria in order to survive they started producing the enzyme penicillinase.
- This gives rise to two options either introducing penicillinase inhibitors or introducing a drug which is not cut by this enzyme.
- The drugs which are not cut by the enzyme penicillinase are called penicillinase-resistant penicillins also called anti-staphylococcal penicillins. These drugs include.
  - **Oral:**
    → Oxacillin: It is hepatotoxic.
    → Cloxacillin
    → Dicloxacillin: Commonly available in India.
  - **Injection:**
    → Nafcillin: Adverse effects - Neutropenia and Nephritis (interstitial).
    → Methicillin: Adverse effects Nephritis (interstitial).
- Second approach for staphylococcal aureus is to inhibit the enzyme penicillin. Combination of beta-lactam + beta-lactamase
  - For example, clavulanic acid + amoxicillin.

MRSA Methicillin-resistant Staphylococcus aureus.

- The reason beta-lactams have to bind with PBP is that MRSA alters this protein making beta-lactams ineffective. Chromosomal Mec A gene is responsible for the alteration of PBP. Beta Lactams are ineffective in MRSA expect 5th generation cephalosporins.
- **Management of MRSA:**
  - For nasal Carriers, it is eradicated by using ointments such as Mupirocin ointment or Bacitracin.
  - Drugs of choice Vancomycin and in the case of VRSA the drug of choice is Daptomycin. VRSA pneumonia the DOC is linezolid. All these drugs work on gram-positive bacteria only.

Uses of Penicillin

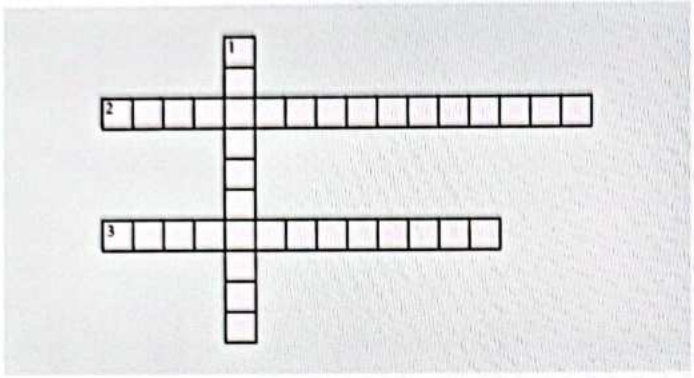
- Leptospirosis, Listeriosis.
- Actinomyces
- Syphilis, Streptococcus pyogenes
- Tetanus
- Meningococcal meningitis
- Anthrax
- Gas gangrene
- Yaws
- Rat bite fever

Adverse Effects of Penicillin

- Hypersensitivity - Type 1 (Anaphylaxis) to avoid this test dose intradermally is done.
- Cross allergy with cephalosporins, carbapenems. And no cross allergy with Monobactams like Aztreonam
- Jarisch Herxeimer reaction - Inflammatory response to dead T.Pallidum. (during syphilis treatment)
  - Treatment of Jarisch Herxeimer reaction is by Aspirin.

CROSS WORD PUZZLES

Crossword Puzzle 1



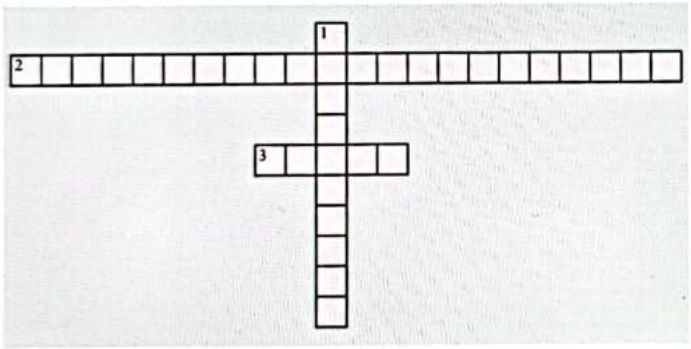
Across

2. _____ are contraindicated in EBV Infection.
3. Sulbactan is shown to kill the bacteria called _____.

Down

1. _____ was used as an inhibitor to stop penicillin excretion.

Crossword Puzzle 2



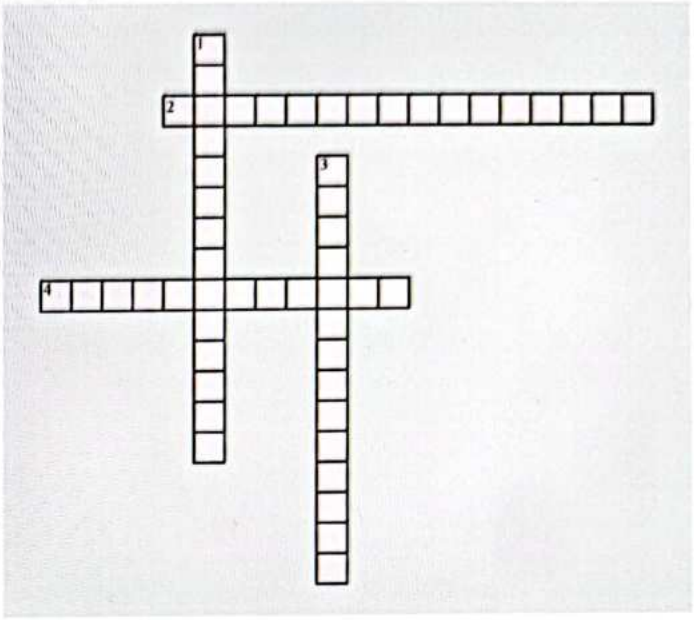
Across

2. The drugs which are not cut by the enzyme penicillinase are called _____ penicillins.
3. _____ and klebsiella are responsible for causing UTI infections.

Down

1. In the case of VRSA, the drug of choice is _____.

Crossword Puzzle 3



Across

2. _____ reaction - Inflammatory response to dead T.pallidum.
4. The branch dealing with anti-microbial drugs is called _____

Down

1. Beta Lactams Inhibit the enzyme called _____.
3. Beta Lactams are ineffective in MRSA except for V gen _____.

65 CEPHALOSPORINS

- Cephalosporins are derived from fungus.
- There is a risk of allergy, type 1 hypersenstivity reaction. as they are derived from fungus.
- It is an antibiotic, there are five generations of cephalosporins.
- It is similar to β lactam, they bind to penicillin-binding protein.
- They inhibit the enzyme transpeptidase, cross-linking, and cell wall synthesis.
- These are bactericidal drugs.

Mechanism of action of cephalosporins 00:58:00

- They inhibit the enzyme transpeptidase.
- They inhibit cell wall synthesis.
- They are bactericidal drugs.

Spectrum of action of cephalosporins 00:01:40

There are five generations of cephalosporins:

1st Generation

- Cover more gram-positive and less gram-negative bacteria.

2nd Generation

- They little cover gram +ve and gram -ve bacteria.
- Majorly they cover anaerobes.

3rd Generation

- They cover gram +ve and anaerobes.
- But their major activity is on gram -ve.

4th Generation

- They also cover gram-positive, major activity is on gram-negative.
- These are used for resistant cases.

5th Generation

- It has anti-MRSA properties.
- It is the only β lactam having MRS activity.
- It also covers gram-positive and gram-negative infections.
- It is also used to treat CAP (community acquired bacterial pneumonia)

Cephalosporins are ineffective 00:04:50

- **M-** MRSA (methicillin-resistant staphylococcus aureus) except 5th generation cephalosporins.
- **A-** Atypical bacteria (Chlamydia pneumonia, Mycoplasma pneumonia, and Legionella pneumonia).
- **L-** Listeria monocytogenes
- **E-** Enterococci.
- **A-**Acinetobacter
- **C-** C. jejuni, Clostridium difficile.

Important Information

- β lactams are combined with macrolides to work against atypical bacteria.
- Cephalosporins do not kill mycoplasma because cephalosporins act on the cell wall and mycoplasma lacks a cell wall.

1st Generation 00:08:15

- **Oral Drug:**
  - Cefadroxil
    → **Uses-** Upper respiratory tract infection, Lower respiratory tract infection.
- **IV Drug:**
  - Cefazolin
    → **Uses-** Used in surgical prophylaxis (during surgery if there is a chance of infection, it can be reduced by cefazolin)
  - Cephaloridine (it is a nephrotoxic drug, so it is not in use).

2nd Generation 00:09:35

- **Oral Drug:**
  - Cefuroxime oxetil, Cefaclor
- **Parenteral:**
  - Cefuroxime,
  - Cefamycins (cefoxitin, cefotetan, cefmetazole)
    → **Uses-** Cefamycins are active on anaerobe B.fragilis.
  - Cefomandole.

3rd Generation 00:13:05

- **Oral drugs:**
  - Cefixime
  - Cefpodoxime proxetil
  - Cefdinir.
- **Parenteral:**
  - Ceftriaxone
  - Cefoperazone
  - Cefotaxime
  - Ceftazidine
  - Ceftizoxime
  - Moxalactam
  - Ceftizoxime.

Ceftriaxone:

- It is long-acting
- Drug of choice for gram-negative infections (serious).
- Drug of choice for STDs (gonorrhoea, chancroid)
- Drug of choice for typhoid.
- Empirical drug of choice for meningitis
- Drug of choice for HACEK organisms.

Important Information

Typhoid:

- **DOC:** Ceftriaxone (I.V) and alternative is Cefotaxime
- **Oral:** we can use Cefixime, Ciprofloxacin, Azithromycin
- **For carriers:** Ciprofloxacin (DOC)

Meningococcal Meningitis

- If penicillin susceptible give penicillin
- **DOC:** Ceftriaxone
- **For prophylaxis:** ceftriaxone, ciprofloxacin, rifampicin
- Empirical drug of choice for meningitis is ceftriaxone.
- But for listeria meningitis the drug is ampicillin.

Pharmacokinetics of Ceftriaxone

- It undergoes bile elimination and renal elimination.
- Safe in renal failure. (No need for dose reduction in renal failure)
  Drug displaces bilirubin from plasma protein, so the problem can occur in neonates (less than 28 days child) kernicterus may occur.
- For neonates preferred drug is cefotaxime.
- It can form biliary sludge in the gall bladder (Pseudolithiasis) if it is undergoing bile elimination.
- They don't have any effect on pseudomonas.

Cefoperazone

- Anti-pseudomonas properties like Ceftazidime, Moxalactam, and Ceftolozane.
- It also undergoes bile elimination.
- Safe in renal failure.
- **Adverse effects:**
  - It can cause severe diarrhoea.
  - It can produce a disulfiram-like reaction because they have a metabolite called N- methyl thiotetrazole, it may also be responsible for decreasing prothrombin (patient may lead to bleeding because prothrombin is required for clotting)
- Cefomandole, Cefotetan, and Moxalactam all have N-methyl thiotetrazole in their structure and responsible for the disulfiram-like reaction.
- If cefoperazone is used with Warfarin, it can increase prothrombin time.

Ceftazidime

- Drug of choice for melioidosis.
- Drug of choice for Pseudomonas, combination of Ceftazidime and Gentamicin is used to avoid resistance.

4th Generation Drugs 00:31:22

- All are parenteral drugs.
- Examples are Cefepime and Cefpirome.
- Used for Resistant gram-negative infections.
- Can be used for Pseudomonas.

5th Generation Drugs 00:31:59

- They are also parenteral drugs only.
- Examples are Ceftobiprole and Ceftaroline.
- Ceftaroline has the same activity as ceftriaxone for gram-negative bacteria but not for psuedomonas.
- Ceftobiprole has the same activity as Ceftazidime for gram-negative.
- Ceftobiprole can be used for Pseudomonas, but Ceftaroline can't be used.
- These drugs are pro-drugs, they metabolize and become active in the body.
- They have anti-MRSA properties.
- Given in resistant gram-negative infections.
- Adverse effects are hypersensitivity can be there, cross allergy, and they can produce Pseudomembranous colitis leading to diarrhea.
- Pseudomembranous colitis most commonly seen with 3rd generation cephalosporins.

New Drug 00:36:11

Cefiderocol

- It enters periplasmic space through a siderophore transporter.
- It has increase stability for β lactamase.
- It does not have any generation, but its chemical structure is similar to 3rd generation Ceftazidime and 4th generation Cefepime.
- **Uses:** complicated UTI, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.

Other β Lactum Drugs

Carbapenems

- **Spectrum of activity:** they cover Gram-positive, Gram-negative Anaerobes.
- They are reserve drugs.
- **MOA:** inhibit transpeptidase enzyme and inhibit cell wall synthesis.

Imipenem

- In nephron they have the dehydropeptidase enzyme
- When imipenam is metabolized by dehydropeptidase it cannot be reabsorbed back, therefore it is short acting and the toxic metabolite lead to nephrotoxicity
- Cilastatin inhibits dehydropeptidase enzyme.
- **Advantage of combining imipenem + cilastatin**
  - Long acting – increase in duration of action
  - Less nephrotoxicity
- Among carbapenems: imipenem causes maximum seizures.

Other Carbapenems

- Doripenem
- Meropenem
- Ertapenem is less effective on psuedomonas
- Oral carbapenem - Faropenem

Carbapenems are DOC in

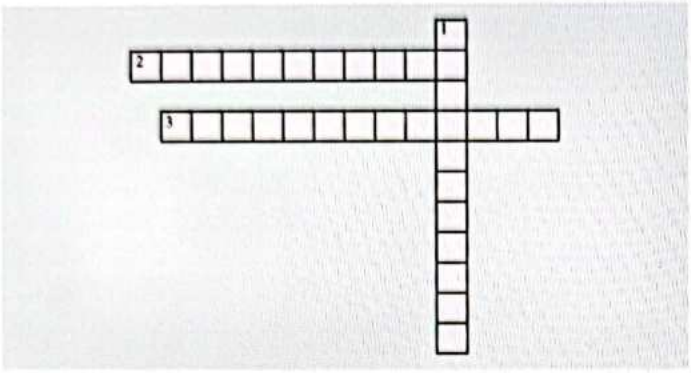
- Serratia
- Enterobacter
- ESBL producing bacteria
- Acinetobacter

Monobactam

- It has only one ring i.e β lactum ring.
- Drug is Aztreonam.
- Acts on gram -ve bacteria only.
- No cross allergy with other beta lactam except ceftazidime.

CROSS WORD PUZZLES

Crossword Puzzle 1



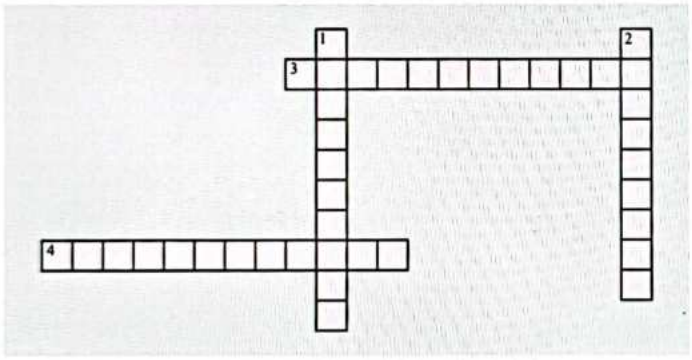
Across

2. Cefiderocol enters periplasmic space through a_____.
3. _____ drugs examples are Cefepime and Cefpirome.

Down

1. _____ is the drug of choice for melioidosis.

Crossword Puzzle 2



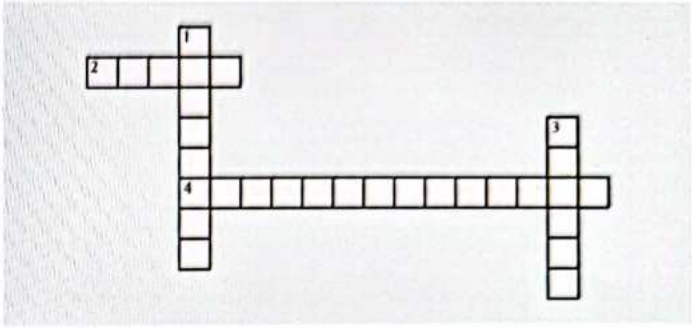
Across

3. _____undergoes bile elimination.
4. _____can cause severe diarrhea.

Down

1. _____ is used in complicated UTIs, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
2. _____is used in surgical prophylaxis.

Crossword Puzzle 3



Across

2. _____generation cephalosporins have anti-MRSA properties.
4. _____are ineffective against Listeria monocytogenes.

Down

1. β lactams are combined with macrolides to work against_____.
3. Cephalosporins are derived from_____.

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66 GLYCOPEPTIDES

Mechanism of Action

- Glycopeptides act on the bacterial cell wall.
- They inhibit the enzyme transglycosylase.
- This inhibits cell wall synthesis.
- They are bactericidal drugs.
- **Spectrum:** They only work on gram-positive bacteria. That's why it will not work on pseudomonas (G -ve bacteria).

Types of Glycopeptides 00:01:10

Vancomycin

- These are very big in size, so if given orally they are not absorbed.
- **When given I.V:** It releases histamine and the patient will develop red-man syndrome.
- **How to avoid:** Prior to giving vancomycin, antihistamines should be given.
- Also, give slow I.V.
- **Uses:** The uses of vancomycin are
  - It is the drug of choice for MRSA (Methicillin-resistant Staphylococcus aureus) infection.
  - It is also the DOC for E.faecium.
  - PMC (Pseudomembranous colitis): Oral vancomycin is given in this condition as it acts locally in the intestine.
- **Adverse Effects:** They are
  - Red-man syndrome
  - Ototoxic
  - Nephrotoxic

Other GPs

- Teicoplanin: It is less ototoxic and nephrotoxic.
- Telavancin
- Dalbavancin: It is longer acting.
- Oritavancin: It has additional inhibition of transpeptidase like penicillin. It is also longer acting.
- **Uses**
  - They are used to treat skin and skin structure infections. They are also given parenterally.

Lipopeptides and Polymyxins 00:08:25

- These drugs act on the cell membrane of the bacteria.

Lipopeptides

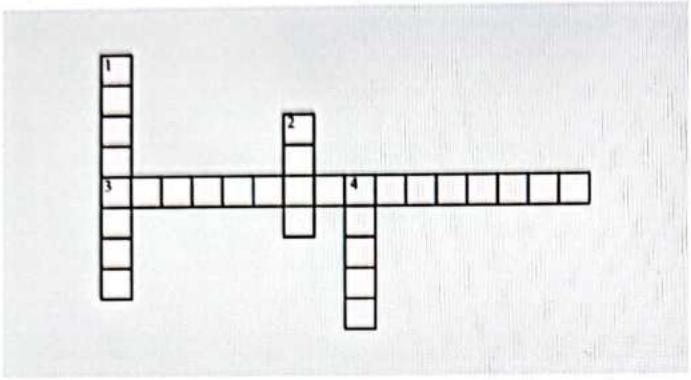
- The drug is Daptomycin.
- It is poorly absorbed orally. So, it is given in as I.V.
- **Spectrum:** They act on gram-positive bacteria only.
- **MOA:** Daptomycin binds to calcium. This creates pores in the cell membrane and also increases the potassium efflux.
- Due to the efflux, DNA, protein, and RNA synthesis is inhibited.
- So, the drug is bactericidal in nature.
- **Uses:** It is used in the treatment of MRSA.
- It is the drug of choice for VRSA (vancomycin-resistant Staphylococcus aureus) infection.
- **Avoid:** The drug is ineffective in lung infections as it is inactivated by the surfactants of the lung.
- **Adverse effect:** It causes myopathy.

Polymyxins

- They are bactericidal in nature.
- **Spectrum:** They work on gram-negative bacteria only.
- The drugs are polymyxin B and polymyxin E (colistin).
- **Adverse effect:** They are highly nephrotoxic, and neurotoxic, and can cause neuromuscular blockade.
- **Uses:** Due to the adverse effects of polymyxin B, it is only used topically.
- Colistin is a reserve drug used against
  - Resistant gram-negative infections
  - Resistant pseudomonas
  - MDR-Acinetobacter
  - NDM-1 producing bacteria

CROSS WORD PUZZLES

Crossword Puzzle 1



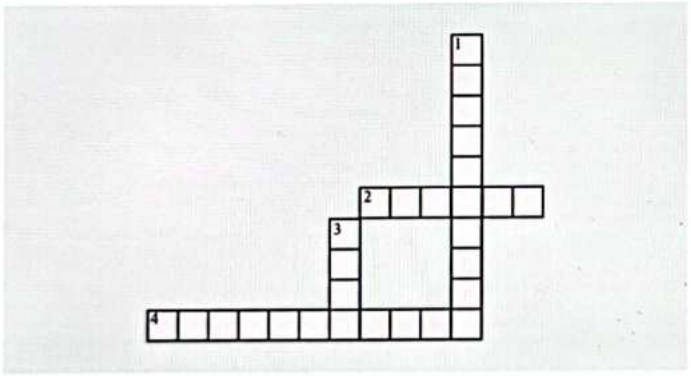
Across

3. Glycopeptides inhibit the enzyme _____.

Down

1. The spectrum of glycopeptides is gram _____ bacteria.
2. Glycopeptides act on the bacterial cell _____.
4. Glycopeptides are bacteria _____ in nature.

Crossword Puzzle 2



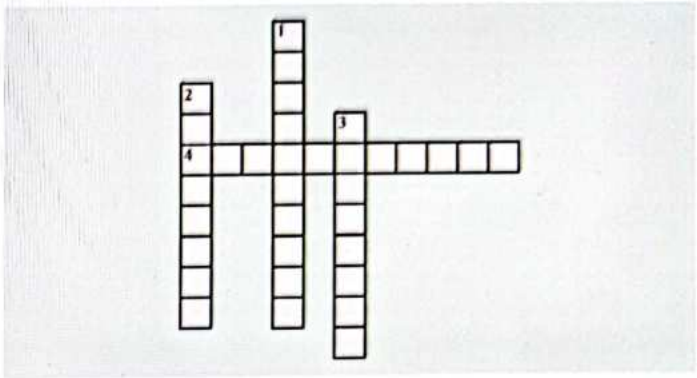
Across

2. Vancomycin causes _____ syndrome.
4. _____ and Oritavancin are longer-acting glycopeptides.

Down

1. _____ is the most commonly used glycopeptide.
3. Vancomycin is the DOC to treat _____.

Crossword Puzzle 3



Across

4. Daptomycin is a _____.

Down

1. _____ is the drug of choice for VRSA.
2. Polymyxin E is also called _____.
3. Lipopeptides and polymyxins act on the cell _____.

67 TETRACYCLINE

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Protein Synthesis Inhibitors 00:00:01

- Broad-spectrum antimicrobial drugs in adults
- Protein synthesis Inhibitors by inhibiting tRNA attachment in the bacterial cells.

Various drugs and their action as protein synthesis inhibitors are

1. By inhibiting tRNA attachment- Tetracycline
2. By inhibiting peptide bond formation- Chloramphenicol
3. By inhibiting translocation: Macrolides, Clindamycin, Quinupristin + Dalfopristin (Streptogramins)
4. Initiation- Aminoglycoside, Linezolid
5. By inhibiting DNA dependent RNA polymerase - Rifampicin
6. By inhibiting Isoleucyl tRNA synthase-Mupirocin (topically used), DOC- MRSA carrier state.

Other drugs that inhibit protein synthesis

- Puromycin
- Pleuromutilin's: Retapamulin (topically used)

Drugs binding to 30S	Drugs binding to 50S
Tetracycline	Rest all drugs
Aminoglycoside	Linezolid (23s fraction of 50S)

Bactericidal	Bacteriostatic
Aminoglycoside	Rest all drugs
Streptogramins (Q + D)	

Mechanism of Resistance 00:10:55

a. Inactivating enzymes- AGs, chloramphenicol
b. Efflux Pump acting- Tetracyclines
c. Methylation of 50S- Macrolides, Clindamycin, Streptogramins

Tetracyclines

Mechanism of Action 00:12:42

Bind reversibly to the 30S ribosomal subunit
↓
Blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex.
↓
BACTERIOSTATIC

Broad Spectrum anti-microbials

Tetracyclines

- MOA- Bind 30s subunit
- Bacteriostatic drug
- Inhibit tRNA attachment

Active against	Ineffective towards
Gram +VE	TB
Atypical Bacteria	E. Coli, Klebsiella and other GRAM-VE
Leprosy	Pseudomonas
Protozoa	
Some Gram-VE	
Protozoa	
Some Gram-VE	

Drugs 00:14:55

Older	Newer
Tetracycline, Oxytetracycline, Chlortetracycline, Demeclocycline	Doxycycline, Minocycline, tigecycline
Incomplete absorption	Good oral absorption
More chance of diarrhoea	Less chance of diarrhoea
Food interactions (milk, antacids)	Less Food interactions

Elimination 00:18:03

- Doxycycline, Tigecycline are eliminated in bile → can be used in renal failure → No dose reduction is required
- Minocycline undergoes renal elimination → Dose reduction is required

Uses 00:19:31

- **Mnemonic: [Large Player Mc Grath Bowls Correctly at Stumps]**
  - L - Lymphogranuloma venereum, leprosy, leptospirosis
  - A - Atypical pneumonia
  - R - Rickettsial infections
  - G - Granuloma inguinal
  - E - Entamoeba histolytica (luminal amoebicide)

- PLAYER - Pylori, plague
- Mc Grath - Malaria, mycoplasma
- BOWLS - Borreliosis, Bartonella, Brucella, balantidiasis
- CORRECTLY - Cholera, Chlamydia
- AT - Acne
- STUMPS - Syphilis, SIADH

- **Doxycycline as drug of choice [BCG RML HOSPITAL]**
  - B - Borreliosis, Bartonella, Brucella
  - C - Cholera, Chlamydia
  - G - Granuloma Inguinale
  - R - Rickettsial infections
  - M - Mycoplasma
  - L - Lymphogranuloma venereum, leptospirosis
- DOC for Balantidiasis - Tetracycline

Adverse Reactions 00:25:34

1. Hypersensitive reaction
2. Superinfection- diarrhoea (due to killing of intestinal bacterial flora)
3. Teeth discoloration and Bone damage [contraindicated in pregnancy, lactation, children]
4. Decrease the activity of ADH →Diabetes Insipidus [demeclocycline]
5. Toxicity- liver, kidney, photosensitivity [doxycycline, demeclocycline], vestibulo toxicity [minocycline]
6. Anti-anabolic effect
7. Pseudotumor cerebri (pressure inside the skull increases)
8. Outdated drug cause Fanconi Syndrome

Newer Drug in Detail

1. Eravacycline
   - Used in complicated intra-abdominal infections
2. Sarecycline: For treatment of acne
3. Omadacycline: For CABP and ABSSSI

Glycylcycline [Tigecycline] 00:33:20

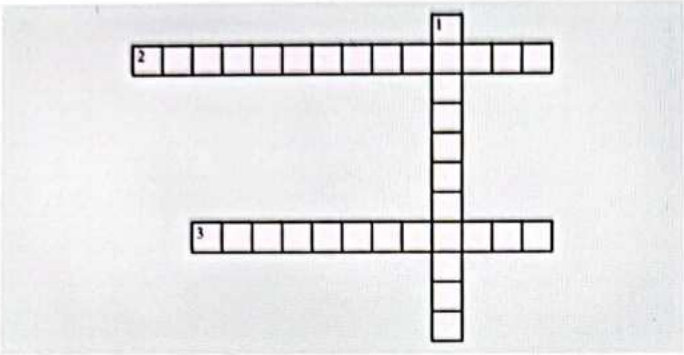
- Safe in renal failure
- Bile elimination
- Not useful in UTI
- Used to treat MRSA, VRSA infection
- Used to treat NDM-1 producing bacteria

Chloramphenicol 00:35:00

- Binds To 50s
- Bacteriostatic
- Inhibits Peptide Bond Formation
- Inhibits Protein Synthesis
- Spectrum: Broad Spectrum
- Pharmacokinetic: Glucuronide conjugation
- Adverse reaction
  - Gray baby syndrome
  - Aplastic anaemia (idiosyncratic reaction)
  - Diarrhoea
  - Bone marrow suppression
- Uses
  1. Topical-eye ointment
  2. Anaerobes
  3. Meningococcal meningitis

CROSS WORD PUZZLES

Crossword Puzzle 1



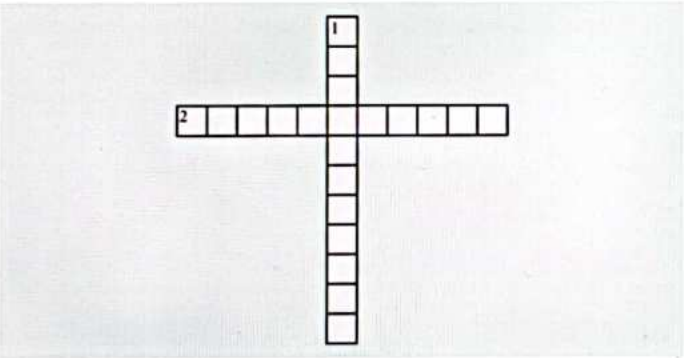
Down

1. Tetracycline which undergo renal elimination

Across

2. Causes grey baby syndrome
3. Causes teeth discoloration

Crossword Puzzle 2



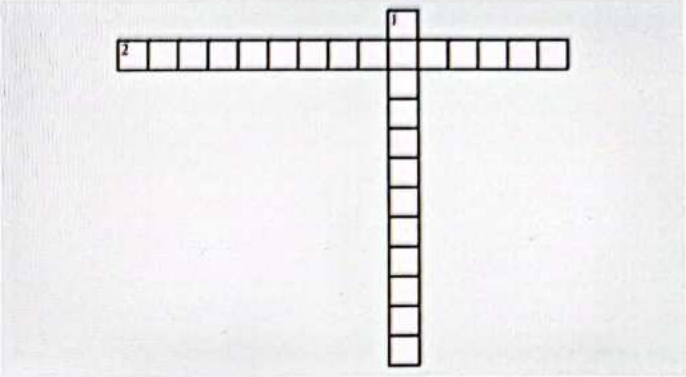
Down

1. DOC in rickettsial infection

Across

2. Not useful in UTI

Crossword Puzzle 3



Down

1. DOC in Balatinidiasis

Across

2. Inhibiting peptide bond formation

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68 MACROLIDES

- Macrolides, Lincosamides, and Streptogramins bind to the 50's unit of the ribosome causing the cessation or inhibition of the translocation step in protein synthesis.
- Macrolides, Lincosamides, and Streptogramins work by preventing the growth of bacteria (bacteriostatic).

Macrolides

00:01:20

- **Mnemonics** for drugs (**CARE**), usually end with "Thromycin"
  - C - Clarithromycin
  - A - Azithromycin
  - R - Roxithromycin
  - E - Erythromycin

Important Information

Ketolides

- It is another category that does not belong to macrolides with a drug name "Telithromycin".
- Telithromycin is banned now, because it had the adverse effect of hepatotoxicity.

Erythromycin

Pharmacokinetics

- It's a microsomal enzyme inhibitor, it has drug interaction.
- When erythromycin combines with other drugs, the metabolism of other drug is hampered.
- Erythromycin undergoes entero-hepatic recycling and it is available as erythromycin estolate.
- Another preparation is E.stearate.
- Erythromycin is a short-acting drug and should be given 4 times a day.

Uses

- Drug of choice for Pertussis and Diphtheria (mainly for eradicating carrier state and treatment of diphtheria).
- But the first drug of choice for diphtheria is Diphtheria antitoxin.

Adverse effects

- Erythromycin can cause stimulation of the motilin receptor in GIT which increases intestinal motility. As a result, the patient may have diarrhoea.
- Erythromycin estolate salt is known to cause cholestatic jaundice.
- Erythromycin stearate is used instead of Erythromycin estolate, it does not cause cholestatic jaundice.

Important Information

- Because of the increase in intestinal motility, erythromycin is used as an off-label drug for the management of diabetes mellitus gastroparesis.
- Diabetes mellitus gastroparesis is a condition where intestinal motility decreases because of diabetes.
- If erythromycin is used in neonates, it increases the risk of hypertrophic pyloric stenosis.

Azithromycin

00:08:10

- Azithromycin has no or least enzyme inhibition, so it causes no drug interaction.
- Azithromycin is a long-acting drug because it has $t_{\frac{1}{2}}$ more than 50 hours.
- Azithromycin causes less diarrhoea than erythromycin.
- When Azithromycin is used for more than 5-7 days, it may cause QT-prolongation.

Uses

- Drug of choice for Atypical pneumonia caused by bacteria (Legionella, Mycoplasma, Chlamydia)
- Drug of choice for the management of disease caused by Campylobacter jejuni.
- Drug of choice for the management of gonococcal or non-gonococcal urethritis.
- Azithromycin is used in STDs (lymphogranuloma, granuloma inguinale, chancroid).
- Azithromycin is also used in typhoid and lung infections.

Clarithromycin

00:12:40

- Clarithromycin is a microsomal enzyme inhibitor and inhibitor of efflux pump (p-glycoprotein).
- Clarithromycin is not used in combination with Digoxin. Because clarithromycin inhibits p-glycoprotein and digoxin is not eliminated. As a result, it causes digoxin toxicity.

Uses

- Clarithromycin is used in the management of Helicobacter pylori eradication regimen.
- Clarithromycin is used in Mycobacterium avium complex, leprosy (drug-resistant leprosy).

Other Macrolides

00:14:40

Fidaxomicin

- Fidaxomicin is a non-absorbable macrolide.
- Fidaxomicin is used in the treatment of pseudomembranous colitis caused by Clostridium difficile that causes infection in the intestine.

Spiramycin

- Spiramycin is the drug of choice for toxoplasmosis in the first trimester of pregnancy.

Tacrolimus

- Tacrolimus is a derivative of macrolides but it inhibits calcineurin.
- Tacrolimus is used as an immunosuppressant.

Lincosamides 00:17:25

- Lincosamides has two important drugs: Lincomycin, Clindamycin.

Clindamycin

- Clindamycin pharmacokinetically undergoes bile elimination. So, Clindamycin is safe in renal failure patients.
- It undergoes bone accumulation. So, the infection of bone can be treated appropriately with the use of clindamycin.

Uses

- Clindamycin is used for anaerobic infections and supra-diaphragmatic infections.
- Clindamycin is used for acne as a gel or ointment.
- Clindamycin is used for Pneumocystis jirovecii, malaria, toxoplasmosis, and toxic shock syndrome.
- Clindamycin is used in combination with Vancomycin to treat Toxic shock syndrome.

Adverse effects

- When Clindamycin is used orally, it causes diarrhoea due to Pseudomembranous colitis by Clostridium difficile.
- Clindamycin kills the normal flora in the gut, other bacteria will grow (Clostridium difficile) that will cause diarrhoea.

Streptogramins 00:23:00

- Streptogramin binds to the 50s subunit.
- Streptogramins are of two types: Streptogramin A and Streptogramin B.
- Streptogramin A is Dalfopristin and Streptogramin B is Quinupristin.
- Streptogramin is used in the ratio of 70:30.
- Both Streptogramin A and B are bacteriostatic but when used in combined form, it shows bactericidal action.
- Quinpristine binds to the 50s subunit and Dalfopristin binds to a separate site and then inhibits protein synthesis.

Uses

- Streptogramins are used in the management of Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant staphylococcus aureus (VRSA), and Vancomycin-resistant enterococci (VRE).

Important Information

- Macrolides, Lincosamides, and Streptogramins can cause resistance due to the methylation of the 50s.

Important Questions

Q. What are the important drugs of the lincosamide class?
Ans. Lincomycin, Clindamycin

Q. What is the adverse effect of Erythromycin estolate salt?
Ans. Cholestatic jaundice

Q. Erythromycin is the drug of choice for
Ans. Pertussis and Diphtheria

Q. Erythromycin is used as an off-label drug for the management of
Ans. Diabetes mellitus gastroparesis.

Q. If erythromycin is used in neonates, it increases the risk of
Ans. Hypertrophic pyloric stenosis

Q. Clindamycin is used in combination with Vancomycin to treat
Ans. Toxic shock syndrome

Q. Drug-resistant leprosy can be treated by
Ans. Clarithromycin

Q. Tacrolimus is a derivative of
Ans. Macrolides

Q. Tacrolimus is used as
Ans. Tacrolimus is used as an immunosuppressant

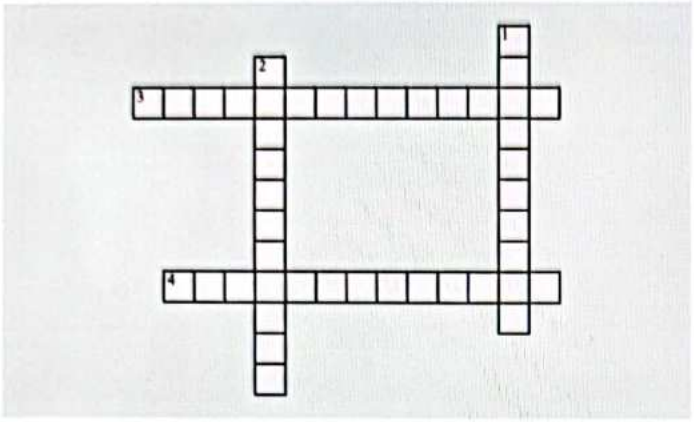
Q. Clarithromycin belongs to which class of antibiotics
Ans. Macrolide antibiotics

Q. When Azithromycin is used for more than 5-7 days, it may cause
Ans. QT-prolongation

Q. Macrolides, Lincosamides, and Streptogramins work by cessation or inhibition of the
Ans. translocation step in protein synthesis

CROSS WORD PUZZLES

Crossword Puzzle 1



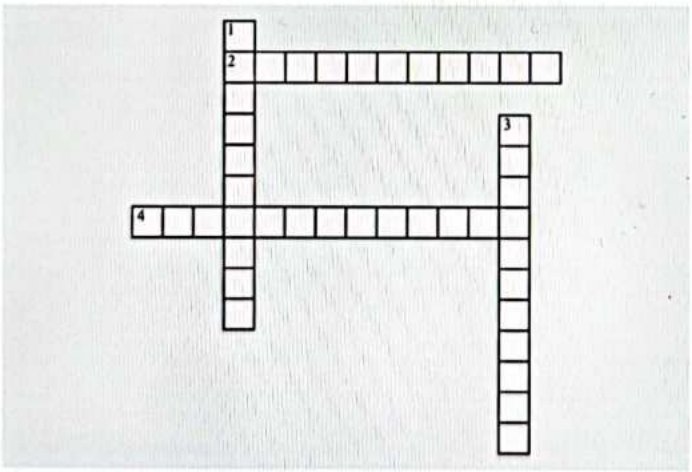
Across

3. ___ is a microsomal enzyme inhibitor and inhibitor of efflux pump (p-glycoprotein).
4. ___ is the drug of class ketolides.

Down

1. ___ is the drug of choice for toxoplasmosis in the first trimester of pregnancy.
2. ____ is non-absorbable macrolide.

Crossword Puzzle 2



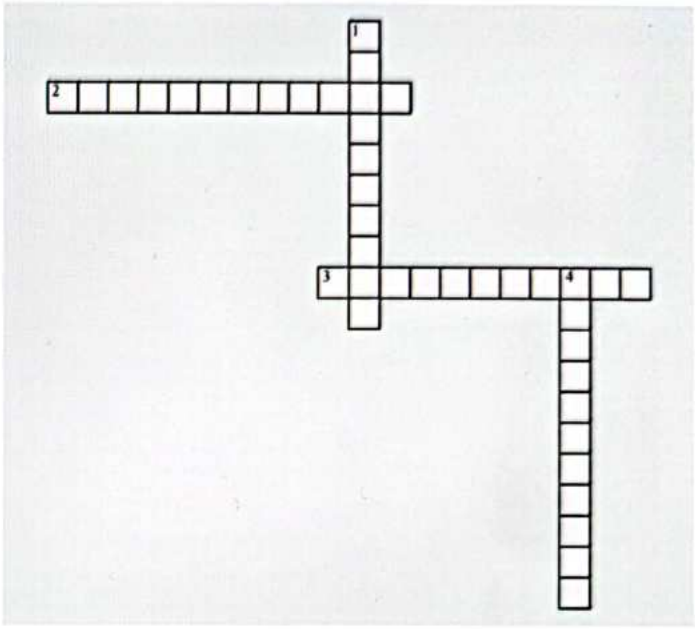
Across

2. ___ has no or least enzyme inhibition, so no drug interaction.
4. ___ is banned now, because it had the adverse effect of hepatotoxicity.

Down

1. ___ is a derivative of macrolides but it inhibits calcineurin.
3. ___ is safe in renal failure patients.

Crossword Puzzle 3



Across

2. ___ is also used in typhoid and lung infections.
3. ___ is used in the treatment of pseudomembranous colitis caused by Clostridium dIfficile.

Down

1. ____ is the drug of choice for toxoplasmosis in the first trimester of pregnancy.
4. ___ is used for anaerobic infections.

69 AMINOGLYCOSIDES AND OXAZOLIDINONES

Aminoglycosides 00:00:34

Mechanism of Action

- They are inhibitors of protein synthesis.
- They bind to 30s ribosomes.
- It is a bactericidal drug.
- Aminoglycosides enter the bacteria with the help of an oxygen-dependent transport mechanism. Once the drug enters the bacteria it will do three things:
  - They inhibit an initiation step.
  - They inhibit polysome formation.
  - Produce misreading of mRNA. (This will lead to the formation of abnormal proteins in the bacteria.)

Specialities of Aminoglycosides 00:04:20

- They are more effective to treat gram-negative bacteria than gram-positive. They are not effective for:
  - Typhoid
  - B. Cepacia
  - Anaerobes
- These drugs are not absorbed orally. They are not metabolized and excreted in the kidney. Clinical Implications
  - In patients with renal failure, the dose needs to be reduced.
  - Since these drugs are very toxic they require Therapeutic drug monitoring (TDM).
- They are effective on
  - Extracellular bacteria.
  - They are effective on alkaline PH.
- They follow concentration-dependent killing and have long post-antibiotic effects.

Drugs 00:10:20

- Below drugs are used in the management of pseudomonas.
  - Tobramycin: Inhaled tobramycin is used in patients with cystic fibrosis, as in this patient is prone for lung infections.
  - Amikacin
  - Gentamicin: Also used in the management of Plague.
- Streptomycin: It is a first-line Reserved drug that is used in TB, Tularemia and Plague.
- Second line injectables for TB
  - Amikacin
  - Capreomycin
  - Kanamycin

Neomycin 00:14:25

- **Topical:** Neomycin is used topically on skin infections.
- **Oral**
  - It is used for gut sterilisation.
  - Hepatic Encephalopathy.
    - → The liver is not working and unable to remove the toxins. Ammonia level increases and enters the brain and leads to abnormal brain function.
    - → Bacteria in the gut generates ammonia and leads to worsening of the brain functions.
    - → Neomycin enters the gut and kills the bacteria. So, ammonia generation is inhibited.

> **Important Information**
>
> - Rifaximin is also used to kill the bacteria in the gut
> - Framycetin is also another drug used topically for skin infection

Paromomycin

- Oral: drug of choice for intestinal carriers of E.histolytica (it will act as luminicidal agent).
- I.V: It is used for Kala Azar.

Aminocylitol: Spectinomycin

- Used in Gonorrhoea only if the patients are:
  - Allergic to Penicillin
  - Intolerant to beta-lactams.
- They are not bactericidal, they are bacteriostatic drugs.

Adverse Effects

- They can cause Allergies.
- Ototoxic (toxic to the ears)
  - Auditory: The patient will have decreased hearing. Maximum with amikacin.
  - Vestibular toxicity: Caused maximum by streptomycin.
- Nephrotoxic: Maximum by Neomycin.
- The neuromuscular blockade maximum by Neomycin.
- Aminoglycosides cannot be given to the patient with Myasthenia gravis. The muscle is already weak when Aminoglycosides are given, there will be the entry of calcium into the synapse resulting in a muscle contraction but in the case of Aminoglycosides will block the calcium channels.

Drug Interactions

- Avoid Vancomycin + AGs = They are Ototoxic and Nephrotoxic.

- Ceftazidime + AGs = Drug of choice for treating Pseudomonas. The combination becomes Synergistic.

Oxazolidinones 00:29:23

Linezolid

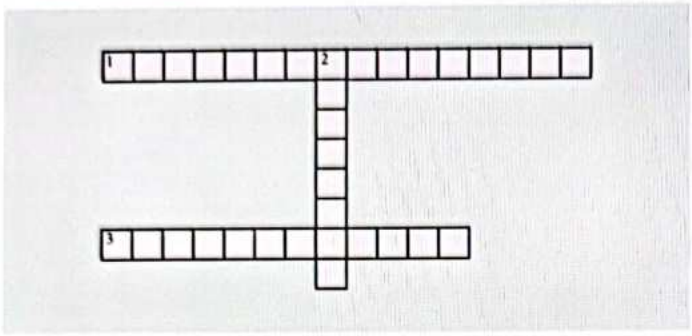
- **Mechanism of action**
  - Inhibits Protein synthesis.
  - It binds to the 50s (23s fraction of the 50s).
  - It inhibits initiation steps.
- It is a bacteriostatic drug.
- It will work only on gram-positive bacteria.
- **Pharmacokinetics**
  - It is given orally to the patient.
  - The drug is MAO inhibitors.
- **Drug interactions**
  - Linezolid + SSRI = can lead to serotonin syndrome.
  - Linezolid + TCAs = can lead to serotonin syndrome.
- **Uses**
  - MRSA
  - VRSA
  - VRSA pneumonia is the drug of choice.
  - Skin and skin structure infection.
  - MDR TB
  - Pre XDR TB
  - XDR TB
- **Adverse effects**
  - More than 2 weeks of usage can cause bone marrow suppression (Thrombocytopenia).
  - For a longer duration of 4-6 weeks of usage, it can produce lactic acidosis, Optic neuritis and Peripheral Neuropathy.
- The drug is eliminated in the bile, it is safe for renal failure.

Tedizolid

- Used in skin and skin structure infection. It will work on gram-positive bacteria only.
- Safe in renal dysfunction and liver dysfunction.

CROSS WORD PUZZLES

Crossword Puzzle 1



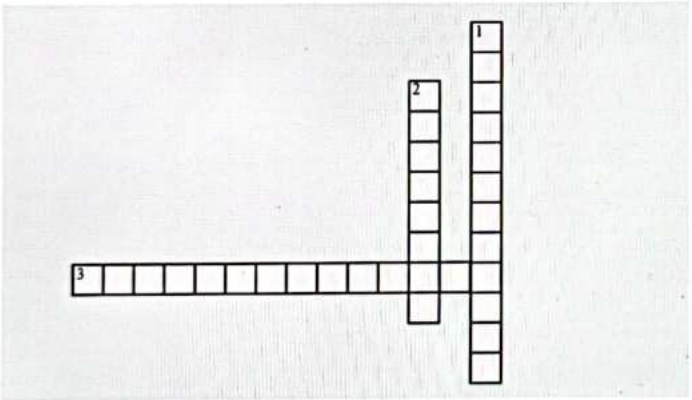
Across

1. Aminoglycosides cannot be given to the patient with _____.
3. The drug is eliminated in the bile, it is safe for _____.

Down

2. The neuromuscular blockade is also caused by _____.

Crossword Puzzle 2



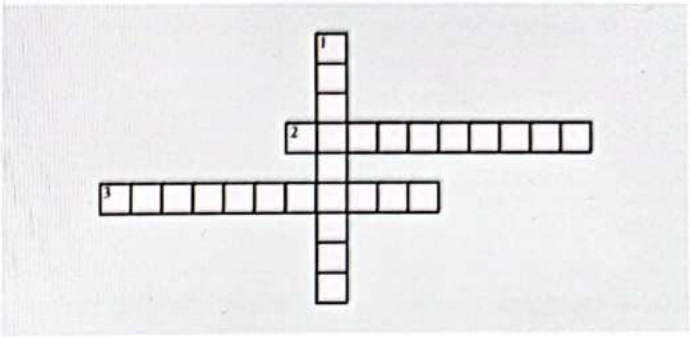
Across

3. _____maximum saw in Neomycin.

Down

1. Vestibular toxicity is caused mostly by _____.
2. _____ is used tropically in skin infections.

Crossword Puzzle 3



Across

2. _____ + SSRI = can lead to serotonin syndrome.
3. Ceftazidime + AGs = Drug of choice for treating _____.

Down

1. _____safe in renal dysfunction and liver dysfunction.

70 SULFONAMIDES

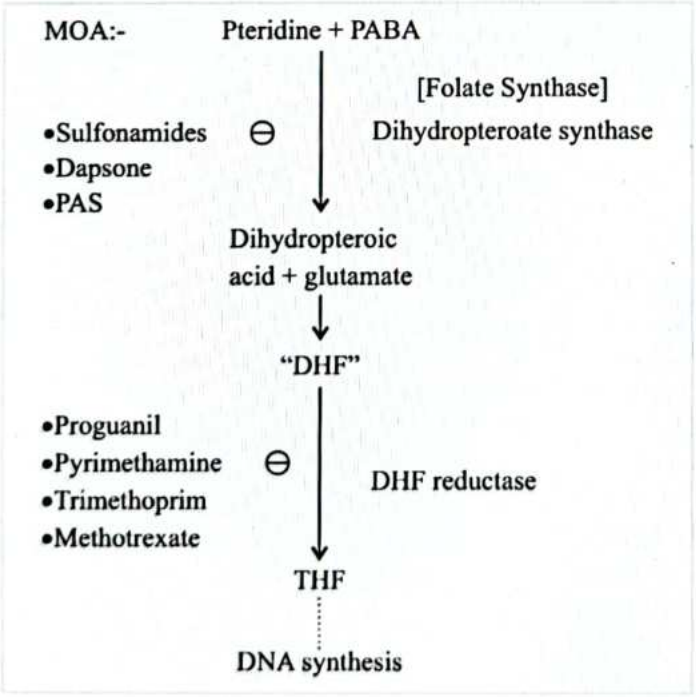
- The chemical substances of natural or synthetic origin that suppress the growth of, or destroy, micro-organisms including bacteria are called antimicrobial drugs.
- The main targets for antimicrobial drugs in a bacteria include the cell wall, cell membrane, the protein synthesis, DNA, and bacterial metabolism.
- Folate turns into tetrahydrofolate which is required for DNA synthesis. It was found that certain bacteria synthesis their own folic acid.
- Drugs such as Sulfonamide interfere with the synthesis of folic acid in bacteria.

Sulfonamides

- These drugs are derived from sulfur and the main adverse effect is allergy.
- These are bacteriostatic in nature covering both gram +ve and gram -ve bacteria.

Mechanism of Action

- Pteridine and PABA combine to form dihydropteroate acid in the presence of dihydropteroate synthase/folate synthetase enzyme.
- Dihydropteroic acid combines with glutamate to form dihydrofolate (DHF) which is converted into tetrahydrofolate (THF) in the presence of dihydrofolate reductase. THF is essential for DNA synthesis.
- Inhibiting folate synthesis in the bacteria that synthesis their own folate result in no synthesis of DNA.



Important Information

- Sulfonamides do not affect folic acid synthesis in humans.
- Proguanil, Pyrimethamine, and Trimethoprim block the DHF reductase of microbes, but methotrexate inhibits DHF reductase in humans. Therefore, it is used as an anticancer drug by inhibiting DNA synthesis in cancerous cells.

Drug Targets

Targets	Drugs
Folate synthase	Sulfonamide Dapsone Para aminosalicylate (PAS)
Dihydrofolate reductase	Proguanil Pyrimethamine Trimethoprim

Sulfonamide Resistance

Microbes acquire resistance to sulfonamides by following mechanism:

- **Altering the target-** Sulfonamides bind to folate synthase. Hence, enzyme affinity decreases when this target is altered and sulfonamides do not bind there.
- **Increasing PABA (Para-aminobenzoic acid)-** PABA is a competitive inhibitor of sulfonamides. Hence, microbes start increasing the PABA level to compete with sulfonamides.
- **Alternate Pathway to synthesis folic acid.**

Q. Why sulfonamides are ineffective in the presence of Pus?

Ans: Pus is rich in PABA. as a result, more PABA binds to folate synthase and Sulfonamide do not stop bacteria from synthesizing folic acid.

Sulfonamide Drugs

Drugs	Use
Sulfadoxine + Pyrimethamine (Sequential blockade)	Pneumocystis jiroveci (pneumonia in HIV patients) Malaria Toxoplasmosis
Sulfadiazine+ Pyrimethamine	Toxoplasmosis (DOC)

Sulfisoxazole (more water soluble)	
Silver sulfadiazine	Used topically for burns patients
Mafenide (non-sulfa drug)	Used topically for burns patients
Sulfacetamide	eye infection (eye drops)
Sulfasalazine (split into two drugs when taken orally i.e., Sulfapyridine and 5 aminosalicylic acid)	
Sulfapyridine →	Rheumatoid Arthritis (RA)
5 aminosalicylic acid →	Ulcerative colitis (UC)
sulfamethoxazole + Trimethoprim (static drugs) [sequential blockade] • When these both static drugs combined, they become cidal • Also known as Cotrimoxazole	Used in Respiratory tract infections, Diarrhea, Urinary tract infection, and prostatitis. Drug of choice (DOC) in isosporiasis, cyclosporiasis, Pneumocystis jirovecii, nocardiosis, and Burkholderia cepacia.

Important Information

- Sulfamethoxazole and Trimethoprim both are static drugs causing sequential blockade but the combination of these drugs results in cidal property. This combination is also known as **Cotrimoxazole.**
- **Pharmacokinetic Advantage:**
  - Both have similar half-life-10 hours.
  - The ratio for in vitro (Tab)dose is 5:1 with respect to Sulfamethoxazole: Trimethoprim. For example, 80 mg of Trimethoprim is used with 400mg of Sulfamethoxazole.
  - The in vivo ratio is 20:1 (circulation).
- Clotrimazole is an anti-fungal drug (Avoid confusion).

Adverse Effects of Sulfonamide

- **MNEMONIC- ABCD, A= Allergy, B=Bilirubin Displacement, C= Crystalluria and D= Deficient**
- **Allergy-** Rash, Steven Johnson syndrome, aplastic anemia, acetylation
- **Bilirubin Displacement-** Sulfonamide displaces bilirubin from plasma protein and bilirubin level increases in blood entering the brain resulting in Kernicterus.
- **Crystalluria-** Patient is advised to have adequate hydration and alkalinization of urine. This condition is less with more water-soluble drugs like sulfisoxazole.
- **Deficient-** G6PD (glucose-6-phosphate dehydrogenase) deficient patient and sulfonamides are contraindicated in this condition causing hemolysis. It can also cause Discoid lupus erythematosus (DLE).

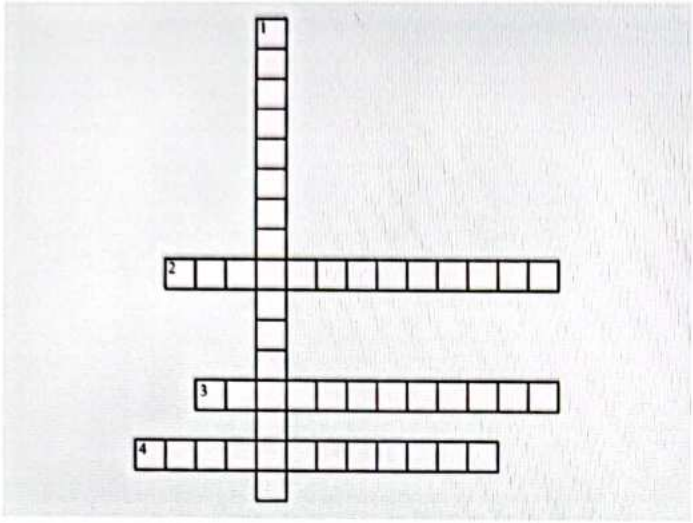
Corner Question

Q. A pregnant lady took an antibiotic during the last trimester for UTI, and the baby born had jaundice. What is your diagnosis?

Ans: The lady was given sulfonamide drugs like **Cotrimoxazole** as the antimicrobial that caused bilirubin displacement and jaundice in the baby.

CROSS WORD PUZZLES

Crossword Puzzle



Across

2. Drug of choice (DOC) in isosporiasis, cyclosporiasis, pneumocystis jirovecii, nocardiosis
3. Are bacteriostatic
4. Adverse effect of sulfonamide

Down

1. is required for DNA synthesis

71 FLUOROQUINOLONES

Mechanism of Action 00:00:26

- Fluoroquinolones inhibit an enzyme called DNA gyrase and they will do that job in Gram-negative bacteria. These inhibit another enzyme, DNA topoisomerase IV, in Gram-positive Bacteria.

Role of DNA gyrase

- When the DNA must replicate, DNA strands (that are twisted) on being opened up, and both the strands try to coil back together, even supercoils.
- The role of DNA gyrase is to nick the DNA, introduce a negative super coil, and will reseal it. DNA gyrase ensures that replication occurs normally.

Role of DNA topoisomerase IV

- The DNA replicating will give rise to the daughter DNA. DNA topoisomerase IV is required to separate the daughter DNA.

What happens when these enzymes are inhibited?

- When the DNA gyrase is inhibited, the supercoil is not corrected, and this will cause DNA damage. This will cause the cell to not survive.
- When DNA topoisomerase IV is inhibited, the daughter DNA will not get separated and again the DNA will be damaged. Both will lead to DNA damage.
- The CIDAL effect will be produced. Fluoroquinolones are bactericidal drugs. They affect both Gram-positive and gram-negative bacteria. Humans have DNA topoisomerases I and II and are not affected. Only the bacteria will get affected because they have a separate DNA topoisomerase IV.

Quinolones

- The first quinolone was Nalidixic acid.
- This had a narrow spectrum and was used to treat UTI and prostatitis.
- The structure of the drug was then changed, and fluoroquinolones were introduced.

Generations of Fluoroquinolones

- Fluoroquinolones have different generations that have different activities.
- They are as follows.
  - The first generation,
  - The second generation,
  - The third generation, and
  - The fourth generation.

The first generation

- **Drugs:** norfloxacin, ciprofloxacin, and ofloxacin.
- The first generation mainly covers the gram-negative more than the gram-positive bacteria.
- Gram-negative bacteria have more chances of causing urinary tract infections.
- Therefore, these drugs are used in the management of UTI and GIT infections.

Second-generation fluoroquinolone

- **Drugs:** levofloxacin
- It has an equal effect on gram-positive and gram-negative bacteria.
- It will also cover atypical bacteria causing pneumonia.
- These drugs are used in respiratory infections (most commonly in the case of tuberculosis and sometimes in UTI).

Third-generation fluoroquinolone

- **Drugs:** gemifloxacin, gatifloxacin, and sparfloxacin.
- These are not used as much nowadays.
- These cover Gram-positive and gram-negative bacteria.

Fourth-generation fluoroquinolone

- **Drugs:** Trovafloxacin, Moxifloxacin
- Trovafloxacin are not used because it is hepatotoxic.
- Moxifloxacin is used which is mainly active on gram-positive bacteria, than in gram-negative ones.
- It is used to treat respiratory infections and is one of the major drugs for managing tuberculosis.
- Moxifloxacin is not effective for UTI and is not used for treating it.

Specialities of These Drugs 00:10:30

- The spectrum of activity of these drugs is Gram-positive and Gram-negative bacteria. These also cover leprosy and tuberculosis.
- For the treatment of tuberculosis, the two major drugs used are levofloxacin and moxifloxacin.
- Respiratory fluoroquinolones: levofloxacin, moxifloxacin, and gemifloxacin.
- Pseudomonas are covered by ciprofloxacin and levofloxacin.
- Moxifloxacin is not useful for the treatment of UTI.

Drugs

Ciprofloxacin

- It is an enzyme inhibitor and therefore more drug interactions.

- **Uses:**
  - It is the drug of choice for typhoid carriers.
  - It is used for mass chemoprophylaxis for meningococcal meningitis.
  - It is also used for the treatment of Traveller's diarrhea.

Ofloxacin
- It is used for the treatment of Leprosy, TB, and diarrhoea.
- **Pharmacokinetics:** This drug has ~100% Bioavailability when used orally.
- This drug and normally fluoroquinolones have the increase risk of seizures.

Levofloxacin
- It is used for the treatment of respiratory infections, and TB.
- **Pharmacokinetics:** this drug has approximately ~100% BA when used orally.

Moxifloxacin
- It is used to treat respiratory infections, tuberculosis, leprosy, and intraabdominal infections. It also covers anaerobes.
- Moxifloxacin is not effective in the case of UTI.
- It can be used in respiratory infections, with the advantage of less chances of seizures.
- But more chances of QT prolongation.
- This drug is very long acting.

Gatifloxacin
- It is more used as eye drops for eye infections.

Norfloxacin
- The major use of this drug is in the case of UTI.

Adverse effect of fluroquinolones 00:19:15

- **Common adverse effect of fluoroquinolones:**
  - Allergies, Steven Johnson Syndrome.
  - They can cause GIT upset like nausea, vomiting, diarrhoea.
  - Diarrhoea: pseudomembranous colitis.
  - They can cause tendinitis and tendon rupture in elderly patients.
  - Cartilage damage.
    → Hence are contraindicated in case of pregnancy lactation and in children.
  - There have been recent reports that these drugs have produced seizures.
  - Peripheral neuropathy may occur on long-term use of the drug.

- **Specific adverse effect of fluoroquinolones:** 00:22:32
  - Gatifloxacin is one of the drugs used to treat respiratory disorders, but it produces dysglycemia (it is a condition where the patient suffers from both hypoglycaemia and hyperglycaemia). This is the reason it is no longer given systemically but is given topically as eye drops.
  - Trovafloxacin has been shown to be hepatotoxic.
  - Sparfloxacin and produce photosensitivity and QT prolongation.
  - Anti-bacterial drugs causing QT prolongation are:
    → Macrolides,
    → Fqs
    → Bedaquilline
    → Delamanid
    → Pretomanid

Pharmacokinetic Importance 00:24:23

- **FQs undergoing bile elimination are:**
  - Pefloxacin
  - Moxifloxacin
  - Trovafloxacin.
    → These are safe in renal failure.
    → These are contraindicated in hepatic failure as they are eliminated by bile. (Trova > Moxi > Peflox).

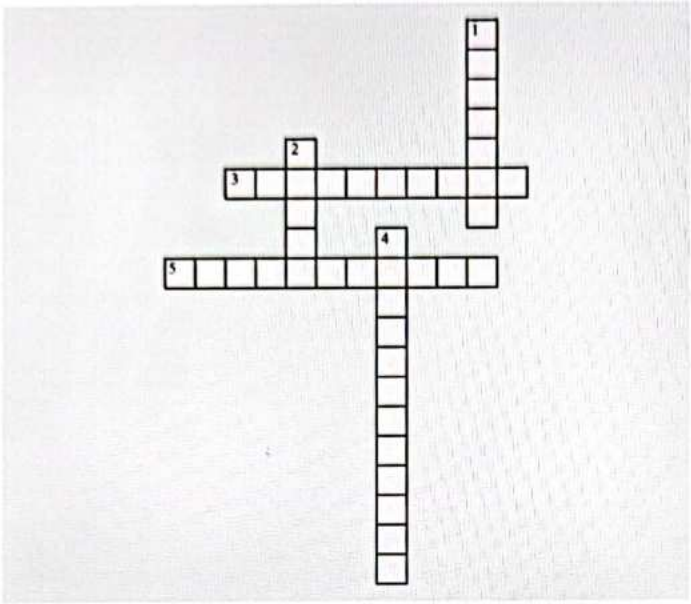
Newer Drugs

Delafloxacin
- It is used to treat ABSSSI (acute bacterial skin and skin structure infection).

Ozenoxacin
- This is used to treat impetigo.
- It is used topically.

CROSS WORD PUZZLES

Crosswords Puzzle 1



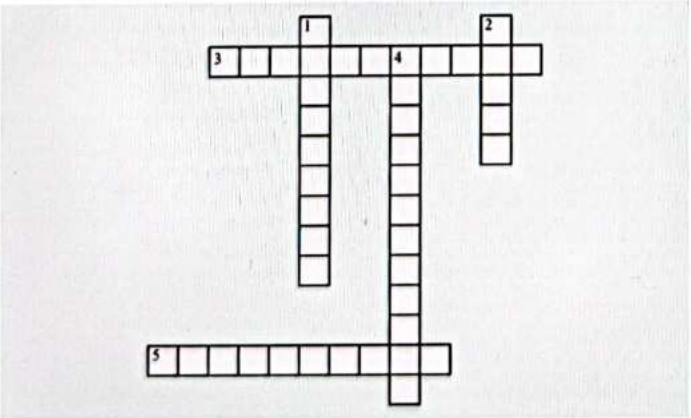
Across

3. _____ is used to treat impetigo.
5. _____ is a condition where the patient suffers from both hypoglycaemia and hyperglycaemia.

Down

1. Pefloxacin, moxifloxacin, and trovafloxacin are contraindicated in _____ failure as they are eliminated by bile.
2. Pefloxacin, moxifloxacin, and trovafloxacin are safe for _____ failure.
4. _____ is used to treat ABSSSI (acute bacterial skin and skin structure infection).

Crosswords Puzzle 2



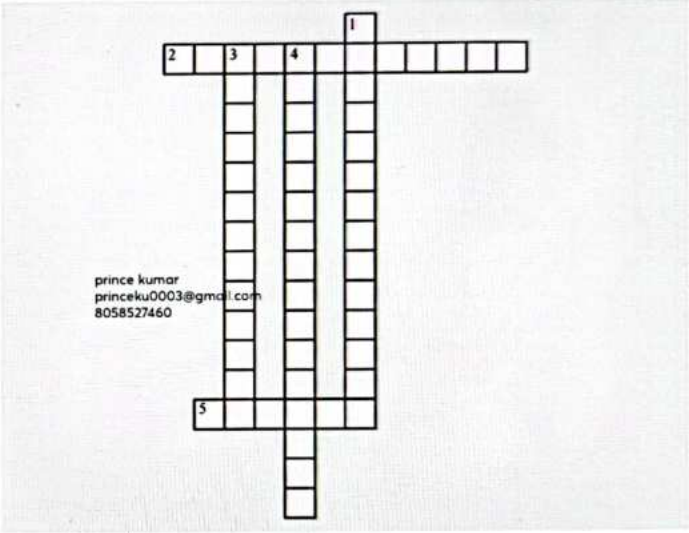
Across

3. The fourth-generation fluoroquinolone drugs are very important and constitute Trovafloxacin but these are not used because they are _____.
5. Fluoroquinolones can cause _____ and tendon rupture in elderly patients.

Down

1. Before Fluoroquinolones, there were Quinolones.; the first quinolone was _____ acid.
2. The _____ generation fluoroquinolones mainly cover the gram-negative more than the gram-positive bacteria.
4. For the treatment of _____, the two major drugs used are levofloxacin and moxifloxacin.

Crosswords Puzzle 3



Across

2. _____ is one of the drugs used to treat respiratory disorders but produces dysglycemia.
5. _____ generation fluoroquinolone drugs constitute levofloxacin and have an equal effect on gram-positive and gram-negative bacteria.

Down

1. _____ is not effective in the case of UTI.
3. Fluoroquinolones inhibit another enzyme, DNA _____ IV, in Gram-positive bacteria.
4. _____ inhibit an enzyme called DNA gyrase and they will do that job in gram-negative bacteria.

72 ANTIMICROBIAL RESISTANCE

- Nowadays the major problem and the future threat for humanity, is antimicrobial resistance.
- The reason for this is using antimicrobials in an inappropriate manner.
  - → Antibiotics are taken for lesser duration (or)
  - → Course of antibiotics is discontinued in between.
  - → Nowadays tuberculosis (TB) is showing multidrug resistant TB or Extensively drug resistant TB.
- So the future is to fight with these resistant organisms.

Resistance 00:00:37

- The meaning of resistance is the drugs will not kill the microbes.
- **Resistance can be of two types:**

Natural Resistance

- Natural resistance means from the beginning they are resistant.
  - Because the target may not be blocked by the drugs (or)
  - The metabolic pathway may not be blocked by the drugs.

Examples

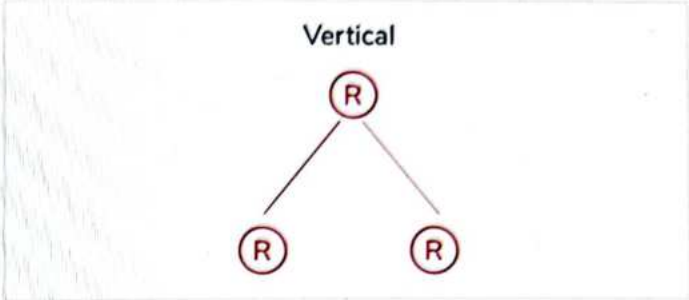
- Aminoglycosides are naturally resistant to anaerobes
  - Because aminoglycosides require oxygen to enter into the cell, but anaerobes do not have oxygen.
- Metronidazole is naturally resistant to aerobes.
  - Because metronidazole has to become reduced, which is seen only in anaerobic environment.
- Tetracyclines do not work in tuberculosis that is called natural resistance.

Acquired Resistance

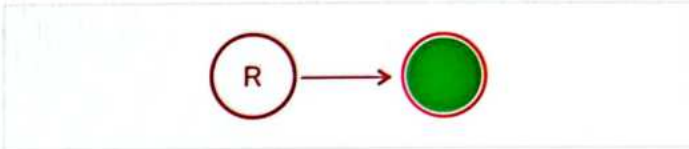
- Acquired resistance means initially the drugs used to kill the microbes but later the drug is unable to kill the microbe.
- The reason for this is
  - → The gene becomes mutated, so in the bacteria or in the microbes.
  - → So this gene mutation leads to resistance.
  - → There are two types of transferring the gene, the mutated gene can be transferred either vertically or horizontally.

Vertical Transmission 00:02:27

- When the bacteria divide it should give rise to two daughter bacteria.
- So, the resistance gene is transferred from the mother bacteria to the daughter bacteria that is from above to below this is called vertical transformation.



Horizontal Transmission



- Conjugation
- Transduction
- Transformation
- If one bacterium has resistance genes and another bacteria which does not have resistance, when they come closer, there is a chance that this resistance gene goes to the sensitive bacteria.
- Then they are processed for
  - Conjugation means by forming sex Pili.
    - → So, there is a tube-like thing between the bacterias and from there the gene gets transferred.
  - Transduction and
  - Transformation

- So, these are a different variety of mechanisms how the gene gets transformed and the nearby bacteria also becomes resistance that is called horizontal resistance.

Cross-Resistance

- If somebody is resistant to sulfamethoxazole and the bacteria is resistant to this sulfamethoxazole, then other drugs in the group are also resistant, that is called cross resistance.
  - In the case of sulphonamides, if sulfamethoxazole is resistant to all other drugs like sulfadiazine, silver sulfadiazine, all drugs are resistant to that.
- Sometimes there is a exception for cross resistance

Exception For Gentamicin

- Gentamicin if it is resistant to the bacteria, then this bacterium can be killed by amikacin.
- So, gentamicin and amikacin are the same group of aminoglycosides; there is no cross resistance.

Partial Cross Resistance

- Suppose somebody is resistant to tetracyclines, there is a high chance the bacteria is also resistant to chloramphenicol.
- Tetracyclines and chloramphenicol are of different groups even though there is a chance of partial cross resistance between these drugs. Such cross resistance is partial cross resistance.

Mechanism of Drug Resistance 00:06:26

- The bacteria must protect itself, then the bacteria will produce by the following mechanisms.

1. **Inactivating enzymes**: Whenever the drug is given to the patient then the drug is inactivated.

- β-lactams are cut by the enzyme β-lactamase.
  - If the bacteria is producing the enzyme β-lactamase,the β-lactams will not work.
- Aminoglycosides, bacteria will produce enzymes that can metabolize.
- Chloramphenicol also has an enzyme which can cut it which is chloramphenicol acetyltransferase.
- These are the methods through which the drug is inactivated which can be easily remembered as **ABC**
  - A-Aminoglycosides
  - B-β-lactamase
  - C-chloramphenicol

2. **By inhibiting the entry of drug**

- The drugs may not enter inside the bacteria.
  - Classical example is that penicillin is not allowed inside gonococci.
  - Gonococci becomes resistant to penicillin by stopping its entry.

3. **Throwing the drug back**

- Suppose the drug enters inside the bacteria.
  - The bacteria will develop a pump called efflux pump.
  - The efflux pump will throw the drug out.
  - E.g., Tetracyclines are thrown out with the help of an efflux pump.

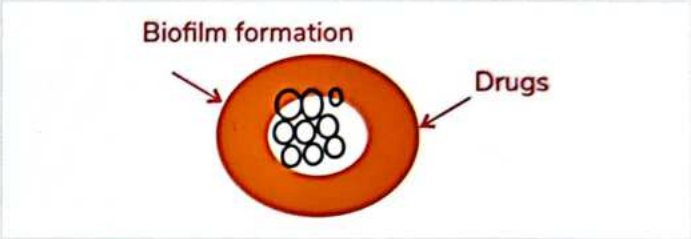
4. **Alteration of drug target** 00:09:25

- If the target is altered
  - E.g., enzyme is altered then the drugs cannot sit, they cannot work
  - **Example**
  - MRSA (methicillin-resistant staphylococcus aureus)
    - → The problem here is the target i.e. Penicillin binding protein is altered.
  - MCQ drugs – macrolides, clindamycin
    - → The target is 50S. 50s is methylated. If it is a methylated target, then they cannot bind.
  - If Alteration of target or alteration of enzyme
    - → E..g Sulphonamides
    - → Dihydropteroate enzymes can get altered and the sulphonamides cannot bind.

5. ***Quorum sensing***

- Quorum means group.
  - The bacterias have started forming a group.
  - So, when the bacteria are with each other and they pass a signal.
  - So, then they will express a gene and that will lead to resistance.
  - So, that phenomenon is called Quorum sensing.
- So, quorum sensing is another level of resistance.

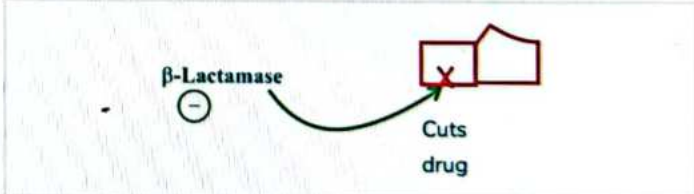
6. **Biofilm formation**



- Group of bacteria form biofilm.
- If a catheter is placed, around the catheter they form a film by forming a coating.
- When antibiotics are given, they can't penetrate the film and they can't enter the bacteria.
- So, when there is a biofilm formed by bacteria, if antimicrobial drugs are given, they don't enter the bacteria easily.

β-Lactamase

- In antimicrobial resistance the most important thing which caused a problem known as production of β-lactamase.



- β-lactamase is an enzyme which will cut the β-lactam ring, then the drug becomes inactive.

β-Lactamase Inhibitors

- There are certain drugs which can inhibit β-lactamase are called as β-lactamase inhibitors.
- The β-lactamase inhibitor is Clavulanic acid, along with that of the β-lactam, amoxicillin needs to be given.
  - E.g.,
    - → Tazobactam should be given with piperacillin.

→ Ampicillin should be given with sulbactam.

β-Lactamase Classification 00:13:15

Ambler Classification Of β-Lactamase Enzymes

Enzymes which contain serine

- This is again classified into four subtypes
- Where they include A, C and D in enzymes with serine and B includes in enzymes with metal(zinc)
  - **Ambler classification A**
    - → Narrow spectrum β-lactamase means they will cut only few β-lactams, not everyone.
    - → Extended spectrum β-lactamase (ESBL)
      - These enzymes can cut penicillin's, they can cut cephalosporins and cut the monobactams.
      - If the bacteria produce ESBL. It cannot be treated with penicillin. Because it is cut, then by cephalosporins and monobactam it is not possible as they are cut by the enzyme.
      - Then the drug of choice for this is carbapenem because it is not cut by ESBL.
      - If carbapenem is not there, then alternate is using β-lactam withβ-lactamase inhibitor combination can be used.
    - → Klebsiella also produces an enzyme called carbapenemase, that cuts the carbapenem.
  - **Ambler classification C**
    - → C stands for cephalosporinase
      - The β-lactamase which cut cephalosporins, so they are called as cephalosporinase.
      - The cephalosporinase is a type of β-lactamase.
      - This enzyme cannot be inhibited by clavulanic acid, tazobactam and sulbactam.
  - **Ambler classification D**
    - → D stands for oxacillinase.
    - → It cuts the oxacillin that is penicillin, even that it is not inhibited by β-lactamase inhibitor.
- So β-lactamase inhibitors are only effective in Ambler classification A.

Enzymes which contain Metal (zinc)

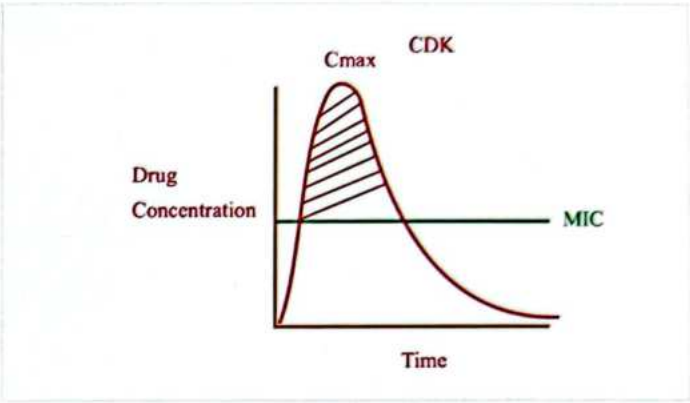
- This group belongs to the" B" that is called metallo β-lactamase, because they contain the metal zinc.
  - This metallo β-lactamase they can cut penicillin, cephalosporins, and carbapenem.
  - They are not going to cut Aztreonam.
  - Hence, the drug of choice is Aztreonam.
- An enzyme like metallo β-lactamase is New Delhi metalloproteinase-1. It was discovered in New Delhi.
  - For this common drug will not work, even aztreonam also. Some reserved drugs such as colistin, polymyxin, and tigecycline are used.

CDK (Concentration Dependent Killing) and TDK (Time Dependent Killing)

00:19:10

Terminology

- MBC stands for minimum bactericidal concentration.
  - It means the minimum amount of the drug i.e Antimicrobial required to kill the bacteria over 24 hours.
- MIC stands for minimum inhibitory concentration.
  - Name itself indicates the minimum amount of antimicrobial drug required to inhibit the growth of bacteria when inoculating them for 24 hours.



- In the above graph, the y-axis represents the drug concentration, and the x-axis represents time.
- There is a level depicted in the graph called MIC (Minimum inhibitory concentration).
  - When the drug reaches above this line the bacteria are killed or inhibited. So, the drug will produce antibacterial effects after this.
- Certain drugs have to give them in high concentration, when they achieve the peak, this peak is called Cmax.
- After reaching the peak, they will come down the line.
- These drugs' antibacterial activity or killing activity depends on Cmax as well as area under the curve (AUC).
- If the drugs are above the MIC line, and if they are achieving the maximum concentration at one time, then their killing capacity is more.
  - If the drug follows this type of killing that is concentration dependent killing (CDK) there is no need to give drugs repeatedly.
  - One dose will be given and stops, the effect will be longer.
  - So, the drug effect depends on C max and AUC.

Important Information

Advantage of CDK 00:19:10

- Single dose or another dose is given.
- No need of repeating the doses.

- Antibacterial effects of certain drugs depend on the time when the drug is above MIC.

- So, if the drug is given repeatedly, then only the drug will produce the maximum effect.
- Repeated dosing must be done to get full effect.
- This type of killing is called TDK (time dependent killing).

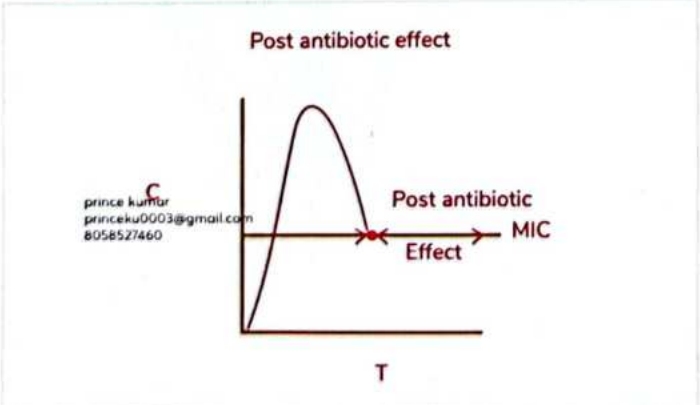
- TDK is followed by drugs like
  - Penicillins and Vancomycin
    → Because penicillin and vancomycin will affect the cell wall and to repair the cell wall it doesn't take so much of time, and these have to be given repeatedly.
- Drug which follows CDK
  - Fluoroquinolone and aminoglycosides
    → If once these drugs are given at high doses, they paralyze the protein synthesis process and they paralyze the DNA synthesis process, to recover that it takes so much of time, so one high concentration will produce the effect for a longer period.
    → That is the reason there is no need for repeated dosing.

Important Information

- **List of drugs follow TDK.**
  - β-lactams
  - Vancomycin
  - Macrolides
  - Linezolid
- **List of drugs follow CDK.**
  - Fluoroquinolones
  - Aminoglycosides
  - Even though they are vancomycin derivatives they are called oritavancin and dalbavancin.
  - Then the anti-tubercular drug Rifampicin
  - Antiprotozoal drug metronidazole
  - Daptomycin
  - Streptogramins

Post antibiotic effect 00:26:30

- Post antibiotic effect is a condition where after drug usage was stopped, still the effect of antibiotics will remain, and the bacteria will not multiply.



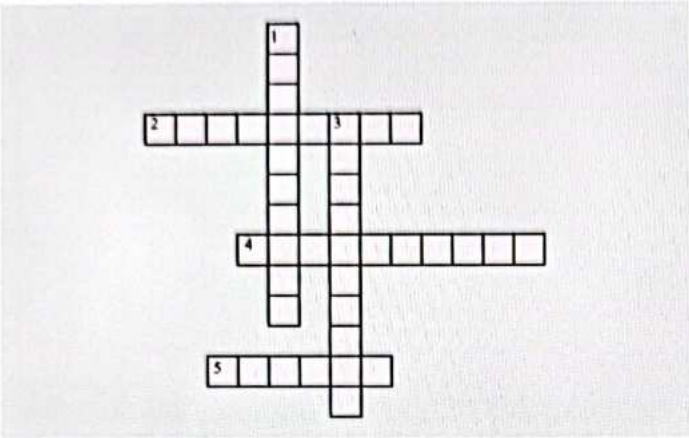
- In the above graph, the Y-axis indicates drug concentration and x-axis indicates time and there is MIC level. If the drug is given,
  - It will go up and then comes down.
  - So, when the drug comes below the MIC whether they follow CDK or TDK, they will have lesser antibacterial properties and they do not have antibacterial properties after that.
  - Certain drugs also have an effect after they come below MIC, still they have an antibacterial effect, that is called post antibacterial effect.
- There are some drugs having short post antibiotic effect and long post antibiotic effect.
  - If it is less than one and half an hour it is short post antibiotic effect.
  - If it is more than one and half an hour it is called a long post antibiotic effect.

Advantage of post antibiotic effect 00:28:22

- No need to give drugs repeatedly because the effect will remain for a longer period, after stopping the usage of antibiotics.
- **Drugs having long post antibiotic effect.**
  - The mnemonic to remember is **SMARTFDC**
  - **S** - Streptogramins
  - **M** - Metronidazole
  - **A** - Aminoglycosides and Azithromycin
    → It is given in a single dose because of the post antibiotic effect.
  - **R** - Rifampicin
  - **T** - Tetracyclines
  - **F** - Fluoroquinolones
  - **D** - Daptomycin
  - **C** - Carbapenems (β lactams)
    → β-lactams follows TDK, but even though they following TDK, carbapenems have longer post antibiotic effect. So such drugs require a dose of once/twice a day.
- **The drugs which have short post antibiotic effect**
  - β-lactams (except carbapenems)
  - Vancomycin

CROSS WORD PUZZLES

Crossword Puzzle 1



Down

1 ..... follows Time dependent killing effect.

3 ..... is the drug of choice in extended spectrum β-lactamase.

Across

2 ..... becomes resistance to penicillin by stopping its entry.

4 ..... is an anti-tubercular drug.

5 .....classification of lactamase consists of four subtypes.

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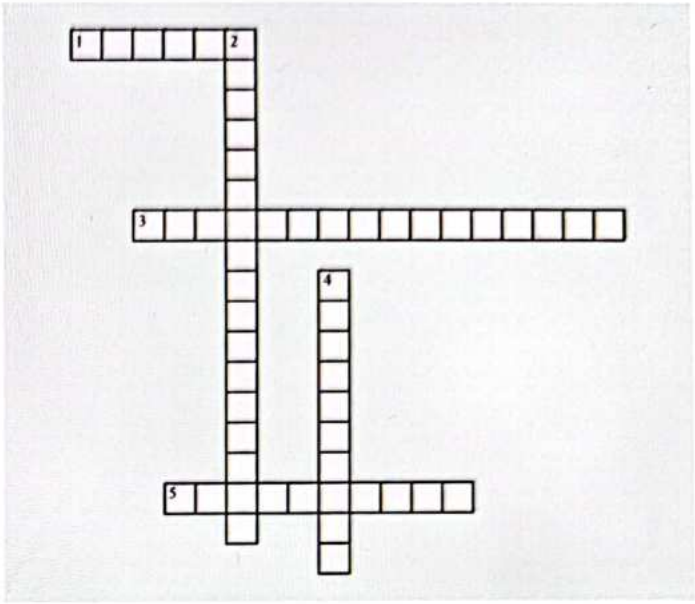
Crossword Puzzle 2



Across

1 ..... sensing means the bacteria have started forming a group.

3 ..... are the drugs that follow concentration dependent killing effects.

5 ..... means the drugs will not kill the microbes.

Down

2 ..... I was discovered in New Delhi.

4 .....is given along with piperacillin.

73 IMPORTANT POINTS IN ANTIBACTERIAL DRUGS

- Antibacterial drugs are a type of antimicrobial substance that are active against bacteria.
- The drugs either kill (bactericidal drugs) or inhibit the growth of bacteria (bactericidal).

Important Antibacterial Drugs

The following table contains information related to various antibacterial drugs:

Action of drug	Drugs	Description
Inhibit cell wall synthesis	Beta-lactam (Penicillin)	Inhibits transpeptidase.
	Bacitracin	Topical antibiotic ointment
	Cycloserine	Anti-tuberculosis drug
	Fosfomycin	Drug used for UTI.
	Glycopeptide (Vancomycin)	Inhibits trans glycosylase.
Inhibits cell membrane synthesis	Daptomycin	Lipopeptide
	Polymyxin (Polymyxin B) colistin	Connect on the cell membrane
Inhibits protein synthesis	Drugs bind to 30S. Tetracyclines Aminoglycosides	Blocks the formation of larger 70S initiation complex
	Drugs bind to 50S. Macrolides Clindamycin Combination of Quinupristin and Dalfopristin Chloramphenicol Linezolid	Interferes with aminoacyl translocation reactions
Inhibits conversion of DNA To RNA (DNA dependant RNA polymerase)	Rifampicin	Anti tuberculosis drug
Inhibits metabolic pathway: Inhibit dihydropteroate synthase:	Sulfonamides PAs Dapsone	Also known as folic acid synthase
Inhibits dihydrofolate reductase	Methotrexate	Anti-cancer drug
	Proguanil	Antimalarial drug
	Pyrimethamine	Antimalarial drug
	Trimethoprim	Antibacterial/ antiprotozoal drug
Undergo bile elimination or are safe in renal failure	Penicillin (Naficillin, oxacillin, cloxacillin and dicloxacillin)	Prevents growth of bacteria
	Tetracycline (Doxycycline)	Treats bacterial infections
	Tetracycline (Tigecycline)	Treats bacterial infections
	Macrolides (Azithromycin, Erythromycin)	Used in uncomplicated skin infections
	Clindamycin	Used in patients with allergic reaction to penicillin

	Combination of Quinupristin and Dalfopristin (streptogramins)	Effective in the treatment of Vancomycin resistant Staphylococcus aureus- VRSA
	Chloramphenicol	Treats eye and ear infections
	Linezolid, Tedizolid	Treats pneumonia and skin infections
	Rifampicin INH	Anti tuberculosis drug
	Fluoroquinolone (Pefloxacin, moxifloxacin, Trovafloxacin)	Acts against gram negative organisms
Drugs effective on gram positive only	Glycopeptides (Vancomycin)	Inhibits bacterial cell wall formation by inhibiting peptidoglycan synthesis
	Telavancin	Acts against gram positive bacteria
	Dalbavancin	
	Oritavancin	Treats skin infections
	Teicoplanin	Acts against gram positive bacteria
	Linezolid, Tedizolid	Treats pneumonia and skin infections
	Daptomycin	lipopeptide
Drugs effective On Gram Negative Only	Polymyxin (Colistin)	Cell membrane
	Aztreonam	Treats infections caused by gram negative bacteria

Important Information

- Tetracycline- Inhibits tRNA attachment.
- Aminoglycosides- inhibits initiation step (name starts with A)
- MCQ drugs- M- Macrolides, C- Clindamycin, Q- Quinpristin + dalfopristin Inhibits translocation.
- Chloramphenicol- Inhibits peptide bonds.
- Linezolid- Inhibits initiation step.
- DNA has two enzymes - DNA gyrase and DNA Topoisomerase IV, these enzymes are inhibited by a group of antibacterial- Fluoroquinolone.
- All cell wall inhibitors are cidal drugs except cycloseine which is a static drug.
- All cell membrane inhibitors are cidal drugs.
- Aminoglycosides are cidal drugs.
- Combination of Quinupristin and Dalfopristin is streptogramins, which is a cidal drugs.
- Fluroquinolones are cidal drugs.
- Cotrimoxazole is a bactericidal drug that is a combination of two bacteriostatic drugs trimethoprim and sulfamethoxazole.

"MNEMONICS"

30S- TEAM: TE- Tetracycline, AM- Aminoglycosides

50S- MCQ: M- Macrolides, C- Clindamycin, Q- Quinpristin-dalfopristin

DRUGS INHIBITING CELL WALL

BBC Found a Ghost: B-Beta Lactams, B-Bacitracin, C-Cycloserine, F-Fosfomycin, G- Glycopeptide

Ineffective Antimicrobials

00:15:40

The following table shows the ineffective antimicrobials:

Microbe	Drug	Reason
Pseudomonas	Vancomycin	Vancomycin only acts on gram positive bacteria, no action on gram negative bacteria.
Burkholderia cepacia	Aminoglycosides, Polymyxins	Intrinsic resistance
Anaerobes	Aminoglycosides	Aminoglycosides require oxygen for transport
Mycoplasma	Drugs acting on cell wall	This bacterium lacks cell wall

MRSA	Beta lactams except for Vth generation cephalosporins	Altered penicillin-binding protein.
Neurosyphilis	Benzathine, Penicillin	The drug cannot cross Blood Brain Barrier
CMV	Acyclovir	Intrinsic resistance
Candida Krusei	Fluconazole	Intrinsic resistance

Most Nephrotoxic Drugs 00:21:01

The following is the list of nephrotoxic drugs:

- Vancomycin
- Aminoglycosides
- Cephaloridine
- Polymyxins
- Amphotericin B (an antifungal drug)

Ototoxic Drugs 00:22:00

The following is the list of ototoxic drugs:

- Vancomycin
- Aminoglycosides
- Antimalarial drugs- Quinine, Chloroquine
- Erythromycin

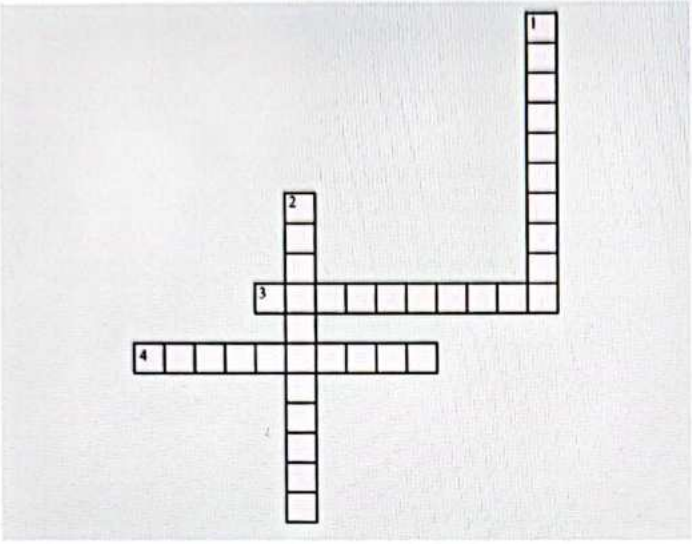
Drugs Causing Seizures 00:22:45

The following drugs can induce seizures:

- Fluoroquinolone- ofloxacin
- Procaine penicillin
- Carbapenems- Imipenem
- Anti tuberculosis drugs- Cycloserine, INH

CROSS WORD PUZZLES

Crossword Puzzle 1
Identify The Drug



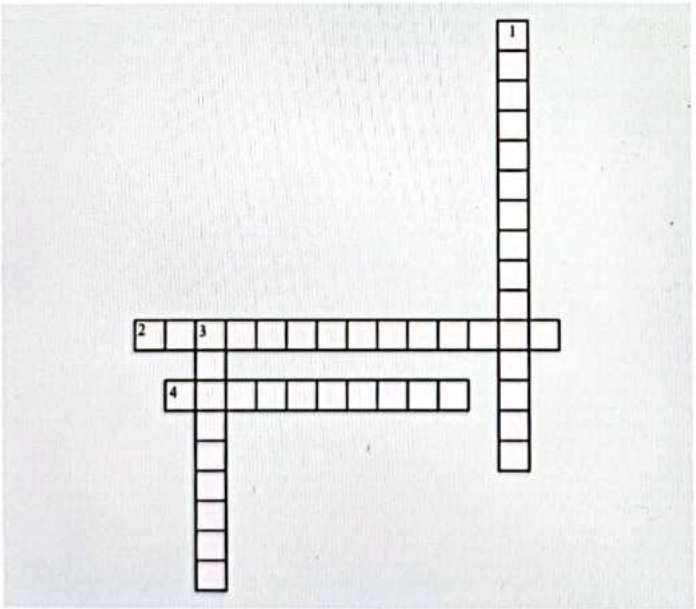
Across

1. ..... Is a lipopeptide
2. Interferes with aminoacyl translocation reactions .....

Down

3. ..... Inhibits transpeptidase
4. Anti tuberculosis drug.....

Crossword Puzzle 2
Identify The Drug



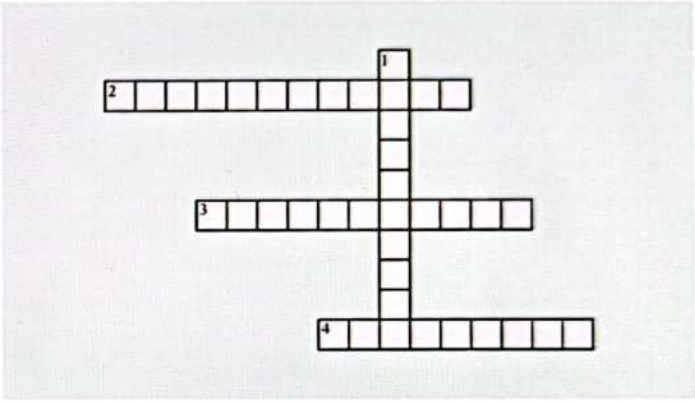
Across

1. Largest group of beta lactam antibiotics .....
2. .....Connects on the cell wall

Down

3. An antimalarial drug.....
4. Treats eye and ear infections.....

Crossword Puzzle 3
Identify The Drug



Across

1. Anti-cancer drug.....
2. .....Used in patients with allergic reaction to penicillin
3. Treats pneumonia and skin infections.....

Down

4. Treats colitis.....

74 IMPORTANT INFECTIONS AND DRUG OF CHOICE

- Infections are the invasion of germs in the body. The germs may be bacteria, viruses, fungi, or other microorganisms.
- Infections can begin anywhere in the body and may spread through it. It can lead to fever and other health problems.
- Certain drugs which are pregnancy safe are -Penicillin, Cephalosporins and Macrolide.
- Drugs avoided during pregnancy:
  - Fluoroquinolone- Can cause cartilage damage.
  - Aminoglycosides- Can cause ototoxicity.
  - Tetracycline- Can cause bone damage and teeth discoloration.

Important infection along with the causative agent and drug of choice

00:01:42

The following table contains important disease condition along with their causative agent and drug of choice:

Condition	Causative agent	Drug of choice
Typhoid	Salmonella typhi	Ceftriaxone For carriers DOC is Ciprofloxacin.
Atypical Pneumonia • Chlamydia pneumonia. • Mycoplasma pneumonia. • Legionella pneumonia.	Chlamydia psittaci	Azithromycin
Pseudomembranous Colitis	Clostridium Difficile	Oral Fidaxomicin or Oral Vancomycin
Skin Infection Caused By MSSA (Methicillin Sensitive Staphylococcus Aureus)	Staphylococcus aureus	Combination of Amoxicillin and Clavulanic acid OR Dicloxacillin
MRSA (Methicillin Resistant Staphylococcus Aureus)	MRSA superbug	Vancomycin For MRSA (nasal) carriers- DOC is Mupirocin.
VRSA (Vancomycin Resistant Staphylococcus Aureus)	Staphylococcus aureus	Daptomycin
VRSA (Vancomycin Resistant Staphylococcus Aureus) Pneumonia	Staphylococcus aureus	Linezolid
Pseudomonas	Pseudomonas aeruginosa	Combination of Ceftazidime and Aminoglycosides called Gentamicin
ESBL Producing E. Coli/ Klebsiella Causing UTI	E. Coli and Klebsiella	Carbapenems Alternative: combination of beta-lactams and beta-lactamase inhibitors
Meningitis		Empirical DOC: Ceftriaxone
Listeria Meningitis		Ampicillin
Pertussis, Diphtheria	Corynebacterium diphtheriae	Erythromycin or Azithromycin
Rickettsia		Doxycycline
Leptospirosis	Leptospira	Doxycycline
Enterococcus Faecalis and Listeriosis		Ampicillin

Enterococcus Faecium		Vancomycin
Campylobacter Jejuni		Azithromycin
Haemophilus Influenzae		Ampicillin (Ampicillin resistance is because of beta lactamase or altered PBP i.e., beta lactam negative ampicillin resistance) DOC in ampicillin resistance is ceftriaxone
Anaerobic Infections		Metronidazole, Clindamycin

Q. When treating combined acquired pneumonia, why do you combine beta-lactams with macrolides?

Ans. Beta lactams act on the cell wall, but mycoplasma does not have a cell wall, so it cannot kill them.

- Oral Fidaxomicin is preferred over Oral Vancomycin.

Causative agents of pseudomembranous colitis

- Third generation Cephalosporins (most common).
- Clindamycin (most potent)
- Fluoroquinolone
- Aminopenicillins

Treatment

- Oral Fidaxomicin
- Oral Vancomycin
- Oral metronidazole
- Oral Rifaximin

To prevent recurrence

- Bezlotoxumab- Works against toxin B (FDA-approved drug).
- Actoxumab- Works against Toxin A (not FDA approved).
- We cannot use Amoxicillin alone while treating skin infections caused by MSSA because it can be cut by penicillin produced by Staphylococcus.
- Dicloxacillin is also called antistaphylococcal.
- Daptomycin cannot be used while treating VRSA pneumonia because lung surfactants inactivate it.
- **IN MRSA:** Beta lactams are ineffective except for the 5th generation of Cephalosporins.

Other drugs that can be used to treat MRSA:

- Streptogramins
- Linezolid
- Daptomycin
- Rifampicin
- Tetracycline
- Tigecycline
- Fluoroquinolone - Delafloxacin

Reason for MRSA- altered penicillin-binding protein.

Anti Psuedimonal Drugs

- **Penicillins**
  - Carboxy penicillin
  - Ureido penicillin: piperacillin
- **Cephalosporins**
  - **3rd generation**
    - → Cefoperazone
    - → Ceftazidime (ceftolozane is a derivative of ceftazidime. Ceftolozane combined with tazobactam has anti pseudomonal property)
  - **4th generation**
    - → Cefepime
    - → Cefpirome
  - **5th generation**
    - → Ceftobiprole
  - **3rd and 4th generation**
    - → Cefiderocol
- Carbapenems except Ertapenem
- Aztreonam
- Polymyxin B and colistin are used in resistant cases only.
- **Aminoglycosides**
  - Tobramycin
  - Amikacin
  - Gentamicin
- Fluroquinolones
  - Ciprofloxacin
  - Levofloxacin
- Sulfonamides

Q. Will Vancomycin work on pseudomonas?

Ans. No, it only works on gram-positive bacteria

Important Information

- Ceftriaxone is a DOC in H.influenzae meningitis, epiglottitis, bacteriemia
- If the infection is above the diaphragm, Clindamycin is used, and below the diaphragm, Metronidazole is used because Clindamycin is effective on Actinomyces and microaerophilic streptococcus above the diaphragm, but below the diaphragm, it misses some B.Fragilis
- **Other drugs**: Chloramphenicol, Cephalosporins (second and third generation).

Which drug can attack B. fragilis?

- Cephamycin's (Cefotetan, Cefoxitin, Cefmetazole), Cefoperazone, Carbapenems, Vancomycin, the combination of beta-lactams and beta-lactamase inhibitors, Fluoroquinolone-Moxifloxacin
- If we want to treat anaerobic infection everywhere we can use a combination of beta-lactams and beta-lactams inhibitors, Moxifloxacin, Carbapenems

Prophylaxis

00:31:18

- Prophylaxis or preventive healthcare refers to the treatment given or action taken to prevent the disease.

Disease	Drug of choice
Meningococcal meningitis	Ceftriaxone>Ciprofloxacin> Rifampicin
Rheumatic heart disease	Benzathine penicillin.
Tuberculosis	INH (isoniazid)
Mycobacterium Avium Complex	Azithromycin/ Clarithromycin
Gonorrhea/ Syphilis	Ceftriaxone before and immediately after contact
Recurrent genital herpes simplex	Acyclovir
Malaria	Doxycycline, Mefloquine
Influenza A2 or H1N1	Oseltamivir
Plague	Doxycycline
Cholera	Tetracycline
Pneumocystis Jiroveci pneumonia	Cotrimoxazole
Filariasis	Albendazole+ DEC or Ivermectin

Mnemonics: ESKAPE PATHOGENS 00:34:11

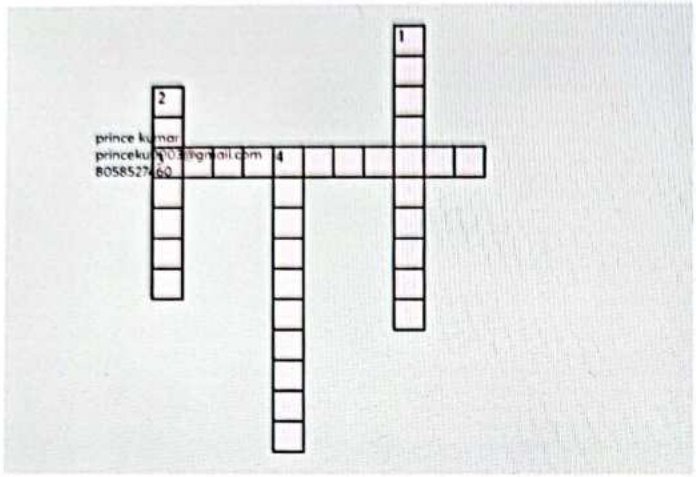
They are very common pathogens.

- **E**- E.Coli
- **S**- Staphylococcus
- **K**- K.pneumonia
- **A**- Acinetobacter
- **P**- Pseudomonas
- **E**- Enterococci: Faecalis, Faecium

CROSS WORD PUZZLES

Crossword Puzzle 1

Identify The Disease Caused By The Following Microbes



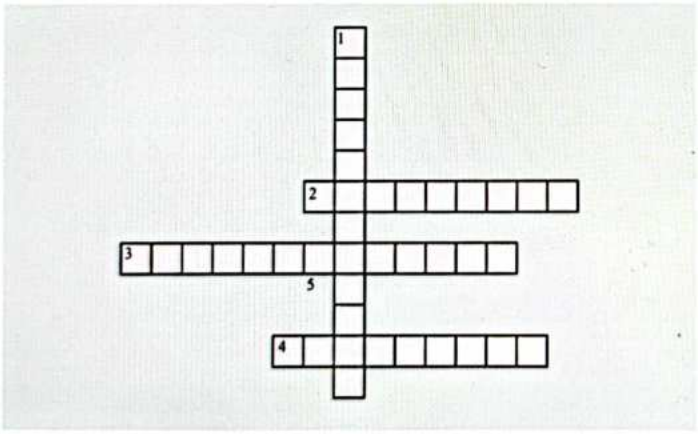
Across

3. Pseudomonas aeruginosa causes _____.

Down

1. Salmonella typhi causes _____.
2. Streptococcus pneumonia causes _____.
4. Corynebacterium diphtheria causes _____.

Crossword Puzzle 2



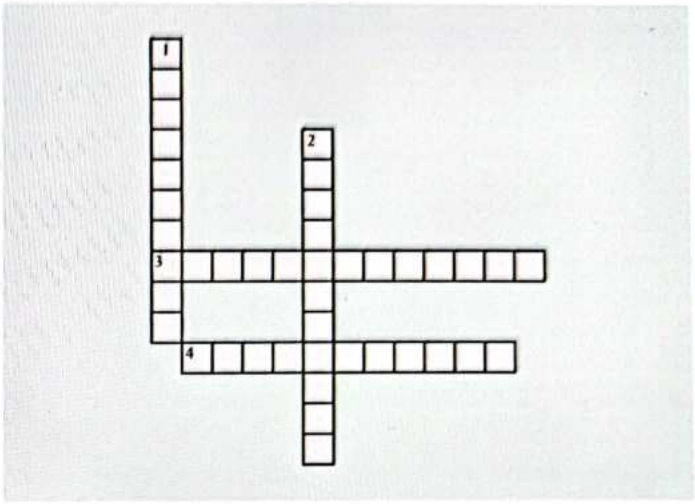
Across

1. Drug to be avoided during pregnancy _____.

Down

2. Prevents the recurrence of Pseudomonas colitis_____.
3. Anti staphylococcal drug _____.
4. _____used to treat MRSA.

Crossword Puzzle 3



Across

3. Cholera caused by _____.
4. Recurrent genital herpes simplex caused by_____.

Down

1. Filariasis caused by_____.
2. Malaria caused by_____.

75 DRUGS FOR URINARY TRACT INFECTION (UTI) AND SEXUAL TRANSMITTED DISEASES (STIs)

Urinary Tract Infection (UTI)

- **Upper urinary tract infection**
  - It infects kidneys and ureters
  - Observed symptoms are loin pain, fever, etc.
- **Lower urinary tract infection**
  - Common symptoms are burning micturition (burning sensation while passing the urine) associated with increased frequency of micturition and fever.

Case 1

Q. A 35 Year old female patient comes with history of fever, abdominal pain, burning and difficulty in micturition, increased frequency of micturition since 2 days.
What is your diagnosis?
How do you proceed in treating this patient?

Patient history

Age	Gender	Symptoms
35 years	female	• Fever, abdominal pain, burning sensation, difficulty in micturition and increased urinary frequency for two days.

Suspected diagnosis: UTI

Approach Towards Treating UTI 00:01:34

For symptomatic relief:

Prescribe Urinary analgesic	Treating urgency (Overactive bladder)	Treating fever
As the patient is suffering from burning micturition i.e. pain during passing urine, we should prescribe the patient with a local analgesic like Phenazopyridine, which is a dye.	To treat the symptoms of overactive bladder we should prescribe the drugs like flavoxate or oxybutynin.	Manage the fever with tablet paracetamol.

For treating infection: In most cases, UTI is caused by gram negative bacteria like *E. coli* and *Klebsiella.*

Starting empirical antimicrobial therapy/urinary antiseptics	Urine culture and sensitivity
• As we are unaware of the causative agent, to subside the infection earlier the patient should be started either on empirical antimicrobial therapy or can be prescribed with urinary antiseptics.	• Collect the urine sample before the patient starts the empirical therapy. • The purpose of culture and sensitivity is to find out the exact causative agent and accordingly start further therapy.

Commonly used Urinary Antiseptics 00:06:10

- **Properties of urinary antiseptics**
  - These drugs get concentrated in the kidney and will not treat infection anywhere else in the body.
  - They will only work at the kidney level hence termed as local antiseptics.
- **Examples of urinary antiseptics**
  - Nitrofurantoin
  - Methanamine

Nitrofurantoin 00:07:06

Mechanism of action

Nitrofurantoin
↓
Enters bacterial cell
↓
Produces reactive intermediates
↓
Damages bacterial DNA
↓
Bacterial death

Important features

- It doesn't show any cross resistance with other antimicrobial agents.
- It is mainly effective against E. coli.

Contraindications

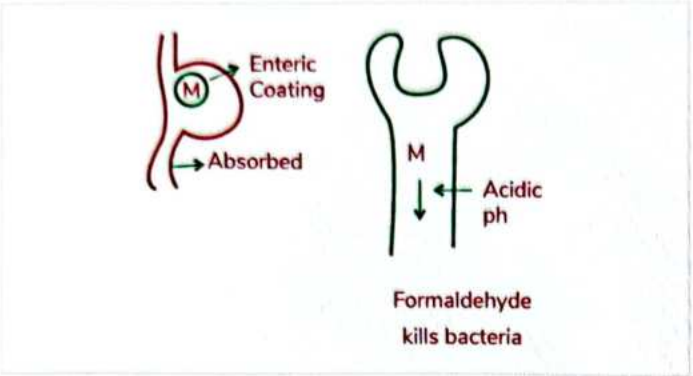
- It is contraindicated in patients with renal failure, neonates

and also in G6PD (glucose-6-phosphate dehydrogenase) deficient patients as it will cause haemolysis in them.

Adverse events

- While on Nitrofurantoin the urine turns brown on exposure to air (and not due to vaginal bleeding) and it should be communicated with the patient while prescribing the drug.

Methenamine 00:09:59



Mechanism of action

Methenamine (Prodrug)
↓
Stomach
↓
Gets absorbed
↓
Enters into the kidney
↓
Under acidic conditions (urine is acidic) the drug gets converted into a toxic compound formaldehyde
↓
Formaldehyde kills bacteria

Important question

Q. Methenamine requires an acidic environment to get converted into formaldehyde, then why doesn't it get converted into formaldehyde in the stomach?

Ans. Methenamine tablets are enteric coated. The enteric coated drugs only get released under alkaline pH, whereas the stomach has acidic pH. Hence the drug gets released only in the intestine and further gets converted into formaldehyde in the kidney where the pH is acidic.

Q. When Methenamine gets converted into formaldehyde and that kills the bacteria, then why we cannot consume formaldehyde directly?

Ans. We cannot consume formaldehyde directly as it's formalin and it's highly gastric irritant and it is toxic to the body.

Empirical Antibiotics to Treat UTI 00:12:10

- Empirical drugs are the drugs, which are prescribed without knowing about the exact causative agent.

Examples of empirical antibiotics used in UTI

- Beta lactam
  - o Penicillin
    - → Amoxicillin + clavulanic acid
  - o Cephalosporins
    - → Oral
      - → Cephalexin
      - → Cefpodoxime proxetil
    - o Intravenous
      - → Ceftriaxone
- Fluoroquinolones
  - o Norfloxacin
  - o Ciprofloxacin
  - o Ofloxacin
- Cotrimoxazole
- Fosfomycin

Specific Antibiotics used in the Management of UTI 00:14:00

- Specific antibiotics are started on receiving the culture and sensitivity report.

Important Question

Q. What is the drug of choice for UTI caused by ESBL (extended spectrum beta lactamase) producing E. coli or Klebsiella?

Ans. Drug of choice for treating UTI caused by ESBL (extended spectrum beta lactamase) producing E. coli or Klebsiella is Carbapenem. If this drug is not available, then the patient should be prescribed beta lactam plus beta lactamase inhibitor.

Q. Which drugs are ineffective against UTI?

Ans. Moxifloxacin and tigecycline are ineffective against UTIs.

UTI in Pregnancy 00:16:25

- Amoxicillin
- Cephalosporins
- Nitrofurantoin
- Cotrimoxazole can also be used in pregnancy, but it should be avoided in the first trimester. The risk associated with this drug is that it can enter the foetus and displace the bilirubin resulting in a baby born with a high bilirubin level.

Drugs for STDs (sexually transmitted diseases) or STIs (sexually transmitted infections) 00:17:40

Causative agents for STIs		
Bacteria	**Protozoa**	**Viruses**
• Syphilis • Gonorrhoea • Chlamydia (lymphogranuloma venereum)	• Trichomonas (trichomoniasis)	• HIV • Hepatitis B • Hepatitis C (rarely) • Herpes simplex • Genital warts

Management of Syphilis 00:19:14

- Depending on the stage of the infection syphilis is treated with different drugs.

Refer Table 75.1

Q. Why Benzathine penicillin cannot be used to treat neurosyphilis?

Ans. Benzathine penicillin is big in size and it cannot pass the brain membrane, hence Benzathine penicillin cannot be used to treat neurosyphilis.

Alternative Drugs to Treat Syphilis

- Alternative drugs are prescribed in patients who are allergic to penicillin.
- Example of alternative drugs,
  - Ceftriaxone
  - Tetracycline
  - Doxycycline

Q. Which drugs are prescribed for managing syphilis in patients who are allergic to penicillin and also have cephalosporin cross resistance?

Ans. Drug of choice under such circumstances is Tetracycline or Doxycycline.

Q. Which drug should be prescribed in a pregnant patient, who is allergic to penicillin?

Ans. We cannot prescribe Tetracycline or Doxycycline in pregnant women as they can affect tooth and bone development in baby and we have to desensitize the patient to penicillin means we have to give smaller doses of penicillin, so the patient can tolerate that.

Management of Gonorrhea or Chancroid 00:24:38

- Various drugs used in the management of gonorrhoea under different circumstances:
  - Ceftriaxone is the drug of choice for treating gonorrhoea
  - Azithromycin is the drug of choice in patients who have gonococcal as well as non-gonococcal urethritis.
  - Spectinomycin is also used in the management of gonorrhoea. It is an aminocyclitol. If patient is allergic or intolerant to beta lactams
  - Spectinomycin used in management of gonorrhoea, when patient have pencillin allergy, or patient is intolerant to penicillin. It is an aminocyclitol.

Q. Why Ceftriaxone is not prescribed in patients who have gonococcal as well as non-gonococcal urethritis infection and what is the drug of choice for such patients?

Ans. Non-gonococcal urethritis is caused by ureaplasma urealyticum, mycoplasma and chlamydia. Mycoplasma are resistant to Ceftriaxone because they lack the cell wall, hence Azithromycin is prescribed in such patients as it is effective against gonococcal as well as non-gonococcal infections.

Q. When Spectinomycin is used for treating gonorrhoea?

Ans. Spectinomycin is used under two circumstances to treat gonorrhoea

1. If the patient is allergic to penicillin
2. If the patient is penicillin intolerant

Management of Other STI Caused by Bacteria 00:26:47

Disease	Drug of choice
Lymphogranuloma venereum	Doxycycline or Azithromycin
Granuloma inguinale	Doxycycline or Azithromycin
Chancroid	Ceftriaxone Doxycycline or Azithromycin can be used as alternative therapy

Protozoan STIs 00:28:00

- While managing the STIs it is essential to treat both the partners to avoid repeated infections.

Trichomoniasis

- The vagina looks like a strawberry.
- For treating trichomoniasis the drug of choice is metronidazole.
- Alternative therapy for trichomoniasis is tinidazole.

Management of Viral STIS

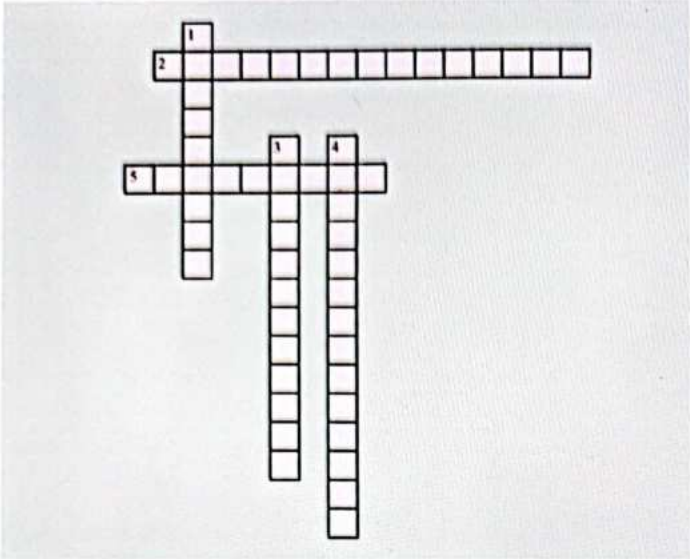
Viral disease	Drug of choice
Herpes	Acyclovir or Valacyclovir
Genital warts	Imiquimod or Trichloroacetic acid

Table 75.1

Syphilis			
Stage	Primary, secondary or early latent	Late latent, uncertain duration, tertiary	Neurosyphilis
Drug of choice	Benzathine penicillin	Benzathine penicillin	Aqueous crystalline penicillin
Dosage	2.4 M.U.	2.4 M.U. weekly	18 to 24 M.U.
Route of administration	Intramuscular	Intramuscular	intravenous
Duration	Single dose	Weekly for three weeks total three injection given	10 to 14 days

CROSS WORD PUZZLES

Crossword Puzzle 1



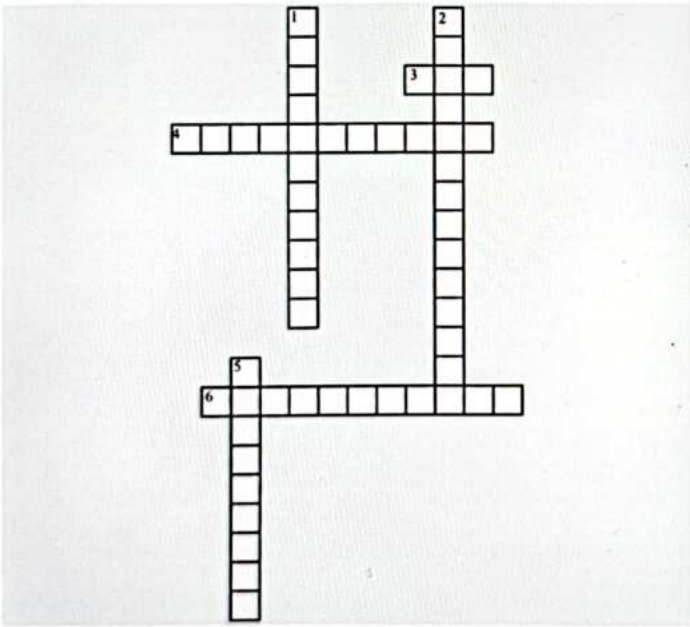
Across

2. Is used to treat burning micturition
5. Drug used to treat Herpes

Down

1. Causative agent for lymphogranuloma venereum
3. Toxic compound formed by Methenamine
4. Drug of choice for UTI with E. Coli

Crossword Puzzle 2



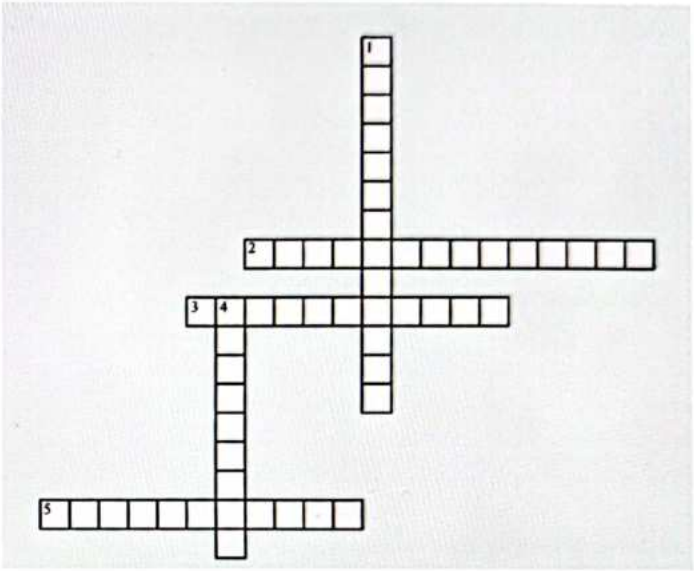
Across

3. It is an antipyretic drug
5. Drug of choice for treating Granuloma inguinale

Down

1. Urine turns brown on exposure to air while on this drug
2. Abbreviation for Sexually Transmitted disease
4. Pathogen responsible for Trichomoniasis

Crossword Puzzle 3



Across

2. Kills the bacteria by damaging its DNA
3. It is termed as prodrug
5. Drug of choice in case of simultaneous gonococcal as well as non-gonococcal infection

Down

1. It is a Fluoroquinolone
4. Drugs that are prescribed without knowing the exact causative agent

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76 ANTI TB DRUGS

- There are multiple cases of tuberculosis in India, and it is known as the TB capital of the world. The treatment of TB goes on for a very long period, at least a minimum of 6 months.
- This is because the various bacteria involved are in different phase , some are slowly multiplying, and some are fast multiplying. The second problem is resistance. If the patient is not completely cured, the bacteria become resistant to the drugs. Nowadays, multidrug-resistant TB and extensively drug resistant TB can be seen, which are very difficult to treat. The treatment of these complex TB conditions can go on for around 1 to 2 years.

Case study

- A 51-year-old female comes to the hospital with a four-week history of cough and fever. A chest radiograph showed a right upper lobe cavitary infiltrate. Sputum cultures yielded acid-fast bacilli M. tuberculosis, susceptible to all anti-microbacterial drugs.

Anti Tuberculosis Drugs 00:02:03

The drugs used to treat tuberculosis affect almost all organs of the body. Anti-TB drugs can be divided into the following:

- First line drugs
- Second line drugs

First-line drugs are used in the beginning.

Four important drugs are present in this category.

1. H- Isoniazid
2. R- Rifampicin
3. Z- Pyrazinamide
4. E- Ethambutol
5. S- Streptomycin (considered a first-line supplement drug).

Second-line drugs are used in resistance cases.

H- Isoniazid

Fullform: Isonicotinic Acid Hydrazide or INH

Mechanism of Action

MOA:

⊖Mycolic acid synthesis

↓

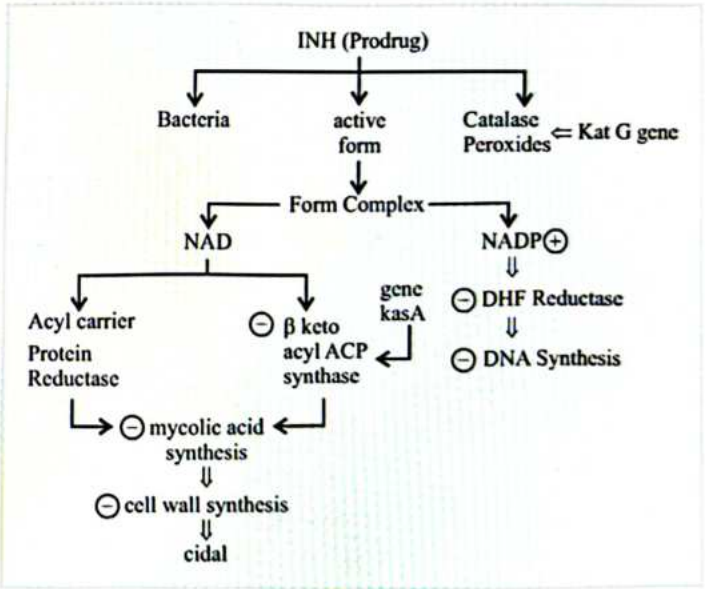
⊖Cell wall synthesis

↓

Tuberculocidal

INH [Prodrug]

- It inhibits mycolic acid synthesis, which is important for making the cell wall of the tuberculosis bacteria. The cell wall is there for not formed as an effect of this drug and is there for tuberculocidal.
- INH is a pro-drug. It enters the bacteria. Catalase-peroxidase enzyme in the bacteria makes it transform into its active form. The active form forms a complex with two important molecules,
  - NADP +, which will inhibit the enzyme called DHF reductase
  - NAD inhibits two important actions: inhibiting acyl carrier protein reductase and inhibiting beta keto acyl ACP synthase.
- When these enzymes are inhibited, that is inhibition of mycolic acid synthesis.
- This leads to the inhibition of cell wall synthesis.
- This is leading to cidal effect.



- Acyl carrier protein reductase is coded by certain genes called INHA genes or INHA proteins. Beta keto acyl ACP synthase is coded by a gene called Kas A.
- Kat G gene is responsible for catalase-peroxidase.
- When an INH drug is used, bacteria will mutate its gene. The enzyme catalase-peroxidase will not be produced in such a case. This will cause INH, when it enters inside, to not become active, and therefore the drug will not work. This major mutation is a Kat G gene mutation.
- Kas A can also undergo minor mutation. This will again lead to a resistance problem.
- INH A will also produce resistance due to overexpression. A high dose of this drug has to be given to overcome this resistance.

Pharmacokinetics of the Drug 00:11:10

Pk = Acetylaton

t1/2 3 hrs ← Slow acetylators = 60%

t1/2 1 hr ← Fast acetylators = 40%

→ Enz. Inhibitor
CYP3A4/5

Enz. Inducer
"CYP2E1"
↓
Generate
↓
Toxic metabolite
↓
Hepato toxic

- For drugs undergoing acetylation, acetylation can happen in two ways.
- Slow acetylators in the body (60% of the Indian population). For slow acetylators the drug is not metabolised fast. The half-life In these cases will be 3 hours.
- Fast acetylators in the body (40% of the Indian population). In such cases, the half-life of the drug will be one hour.
- Drugs undergoing acetylation can produce drug-induced lupus. This is seen majorly in the case of often anti-arrhythmic drugs called procainamide.
- Isoniazid is mainly an enzyme inhibitor and inhibits the enzyme CYP3A4/5.
- It is an enzyme inducer of CYP2E1. It generates toxic metabolite, which causes hepatotoxicity.

Uses 00:14:01

- It is used mainly in cases of Tuberculosis and prophylaxis of TB. Suppose there are four people living in the room, and one of them has TB. The other three are also at risk of contracting tuberculosis. The drug is also given to the rest of the three people in such a case.
- It is used in infections of M Kanasii.

Adverse Effects

- It is an inhibitor of enzymes and an MAO inhibitor.
- It produces peripheral neuropathy. The drug interferes with pyridoxine, which becomes pyridoxine 5 phosphate. This interferes with the drug, and this will lead to the patient having a tingling sensation in the peripheries.
- To treat peripheral neuropathy, the patient is given pyridoxine at 10 mg/day.
- The drug produces hepatotoxicity. INH toxicity is caused when this drug is given at a high dose.

Triad of INH Toxicity

- Metabolic acidosis (not easily treated with Sodium Bicarbonate)
- Seizures (resistant to Barbiturates and Phenytoin and hence treated with benzodiazepines like lorazepam and diazepam)
- Coma

Antidote

- (MCQ) The antidote for INH toxicity is pyridoxine. Normally on use, it becomes pyridoxine 5 phosphates. When INH is given, it becomes INH-pyridoxal. The active form of pyridoxine depletes, leading to a decrease in GABA synthesis. This will lead to glutamate levels going up, and hence CNS excitation. This will again cause the patient to develop seizures.
- Pyridoxine is given intravenously on a gram-to-gram basis, dependent on how much pyridoxine has been taken. If the patient does not know the dose it can be given at 70 mg per kg.

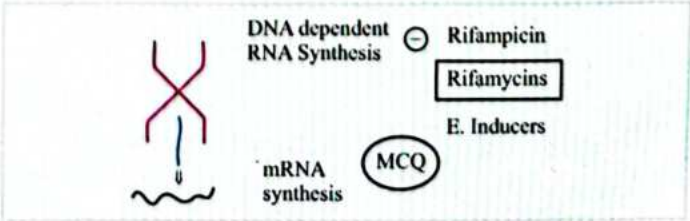
Rare Adverse Effects 00:20:01

- Since it is an MAO inhibitor, it will increase serotonin levels. This can cause psychosis and hallucinations.
- It can also increase the activity of noradrenaline due to MAO inhibition. Therefore the patient will have a risk of seizures.
- The decrease in pyridoxine can also lead to seizures due to a decrease in GABA synthesis.
- The drug can produce gynecomastia.
- Another side effect of this drug is shoulder hand syndrome, characterized by pain and stiffness in the shoulders and hands. The patient will have similar features as that of rheumatoid arthritis.
- The patient may also develop Sideroblastic anemia due to pyridoxine deficiencies. This condition is treatable with pyridoxine or B6.
- In some patients, this has caused memory impairment.

Speciality

- The speciality of the drug is that it can act on intracellular and extracellular bacteria. When the bacteria are outside the cell, it is extracellular bacteria, and when the bacteria are present inside the macrophage, it is intracellular bacteria. For intracellular bacteria, the drug has to go inside the cell and kill it.
- The second speciality is that it is effective in rapidly multiplying bacilli.
- This drug has maximum CSF penetration.
- This drug is effective in acidic and alkaline pH.

R- Rifampicin 00:24:32



The Mechanism of Action

- From the DNA, RNA is obtained. It is DNA-dependent RNA synthesis. The Messenger RNA synthesis is the main result of this process. If it is inhibited, mRNA synthesis does not occur, and the bacteria will not be able to multiply. This blockade is done by rifampicin. The mechanism of action of this drug is that it inhibits DNA-dependent RNA polymerase.
- RNA-dependent RNA polymerase is also observed and is mainly seen in viruses. It is mainly inhabited by a drug called remdesivir.
- Rifampicin belongs to a group of drugs called rifamycin. Rifampicin is an enzyme inducer.

Types of the Drug

Refer Diagram 76.1

- Rifampicin- this is the maximum enzyme inducer.
- Rifapentine- this is a moderate enzyme inducer.
- Rifabutin- this is the minimal enzyme inducer.
  - This drug is used to treat mycobacterium avium complex. The adverse effects of this drug include uveitis, pseudo-jaundice, and arthralgia. This drug has better utility in MAC infection and is preferred more than Rifampicin.
  - If a patient is newly diagnosed with HIV and tuberculosis, he is treated first for tuberculosis. After 2 weeks of being treated, HIV treatment is started.
  - If HIV is treated first, the immunity will boost, which was earlier suppressed. Immune reconstitution inflammatory syndrome (IRIS) will take place in which the immune response will then cause the patient to have a fever, lymph node enlargement, and other symptoms. Therefore after tuberculosis is treated, HIV can be treated to avoid IRIS.
  - If rifampicin is added to a patient having TB, since it is an enzyme inducer, it will induce the metabolism of the HIV drugs.
  - Therefore for newly diagnosed patients, instead of this drug, Rifabutin is used. Rifabutin has less enzyme induction, and therefore the drugs used in HIV are not metabolized and will not become short-acting.
- Rifaximin
  - This drug has very poor oral absorption. It is used to treat irritable bowel syndrome, especially diarrhea-predominant conditions. It is also used in the management of pseudomembranous colitis.

Implications of Rifampicin

- When a woman is on an oral contraceptive pill and has been recently diagnosed with tuberculosis, the treatment for tuberculosis has to be started, and the major drug for treatment is Rifampicin. Since it is an enzyme inducer, the oral contraceptive pills will be metabolized faster, leading to contraceptive failure.
- If the lady becomes pregnant again, the drugs will affect the fetus . A barrier method of contraception is therefore advised in such a case.
- Rifampicin
  - It is an enzyme inducer.
  - It undergoes enterohepatic recycling.

Uses

- It is used to treat tuberculosis, leprosy, MRSA, meningococcal prophylaxis, H influenza, Brucellosis (Doxy + Rifampicin), and Legionella.

Adverse effects

- It causes orange-red discolouration secretions.
- It can cause hepatotoxicity.
- It can cause the cutaneous syndrome, flu syndrome and abdominal syndrome in case of intermittent dosing.

Special effects

- This drug acts on intra and extracellular bacteria,
- It treats sperters and persistors.
- H+R is responsible for producing synergism.

Z- Pyrazinamide 00:39:30

- When does drug enter the bacteria, it acts on an enzyme called pyrazinamidase which is coded by a gene called pnc A gene. It gives rise to pyrazonic acid. This drug inhibits the fatty acid synthase and cell wall synthesis and disrupts the cell membrane of the bacteria and the transport mechanism.

Special effects

- This drug especially acts very well in acidic PH and intracellular bacteria, and inflammatory areas. H+Z+R+E reduces the duration of treatment from 9 months to 6 months; it has exceptional sterilising properties.

Adverse effects

- Pain and Arthralgia. Hyperuricemia is also observed. Hepatotoxicity is also observed. It is the most hepatotoxic first-line drug.

E - Ethambutol (Static) 00:44:06

- This drug inhibits arabinosyl transferase, causes arabinogalactan synthesis inhibition and inhibits cell wall synthesis.

Adverse effect

- Eye toxicity is observed. Retrobulbar optic neuritis is seen, which causes red-green blindness and decreases visual acuity.
- Mild increasing uric acid is also observed.

Uses

- This drug is used to treat tuberculosis and MAC.

Streptomycin 00:46:48

- It is AGs "cidal" and contraindicated in cases of pregnancy.

Special uses

- These drugs are very effective in alkaline pH and extra cellular bacilli. These drugs are given as injections.

A Summary

Refer Table 76.1

- Fast multiplying bacilli (Wall of cavitary lesion)
- Slow multiplying bacilli (Inflammatory site/macrophages)
- Slow and intermittently dividing (persister/spurters) bacilli
- Dormant bacilli → Bedaquilline
- Caseous material → pH neutral and low O_2
  (H+R) = Synergistic Effect
  L = 9 months → 6 months
  = Good sterilizing properly
  E = ↓ Resistance
- Drugs are used in combination because when the bacteria mutates the combination of the drugs can kill the mutation.

Second Line Drugs 00:53:45

- The second-line drugs are used because the first-line drugs made develop resistance. Types of second-line drugs

1. Fluoroquinolones

- These include two major drugs
- Moxifloxacin (this comes with the risk of QT prolongation) and levofloxacin. Ofloxacin and ciprofloxacin are also used but are less effective for treating tuberculosis.

2. Injectables/Second-Line Injectables

- These are known as ACK drugs.
  - Amikacin
  - Capriomycin
  - K-Kanamycin

3. Thioacetazone

- This was one of the earlier drugs for tuberculosis. It is static, and the major adverse effect is that it is hepatotoxic. It is a low-cost drug and has been shown to decrease the resistance problem.

4. Cycloserine

- It is a static drug. It can cause psychosis and seizures.
- Terizodone is made up of two molecules of Cycloserine and has fewer neuropsychiatric adverse effects. It is the preferred drug for genitourinary tuberculosis.

5. Ethionamide/Prothionamide

- This has cross-resistance with INH. These inhibit cell wall synthesis.

6. Para Amino Salicylate

- Drug numbers 5 and 6 may develop the adverse effect of hypothyroidism.

7. Linezolid

- This drug is used for the treatment of drug-resistant TB.

8. Unknown Efficacy Drugs

- Imipenim+ Cilastatin, Amoxicilin+ Clavulanic acid, Meropenim.

9. Clofazimine.

- New drugs for treating tuberculosis

10. Bedaquiline

- The drug inhibits mycobacterium ATP synthesis. This is even effective in cases of dormant bacilli and is bactericidal. It has a very long half-life of 160 to 165 days due to the high volume of distribution. Fatty food increases the absorption of this drug. It is metabolised by the enzyme CYP3A4/5.
- Adverse effects of this drug include QT prolongation and hepatotoxicity. It has cross-resistance with clofazimine.
- This drug is given for 0 to 2 weeks at 400 mg daily. From the third week to 24 weeks, 200 mg is administered thrice weekly. The total dose in a week should be 600 mg.
- It is used only for drug-resistant pulmonary TB. It is not used for DST TB and extrapulmonary TB.

Regime Used to Treat Tuberculosis

B- Bedaquiline
Pa- Pretomanid
L- Linezolid

- It is used to treat MDR and DR TB. All of these drugs are already administered, and safety is ensured. Bedaquiline should not be used in cases of pregnancy.
- Pretomanid belongs to the group bicyclic Nitroimidazole. Examples of drugs from this group include Delamanid as well. These inhibit protein and mycolic acid synthesis and also inhibit cell wall synthesis. The only adverse effect is that they can cause QT prolongation. These are suited for drug-resistant TB.

Diagram 76.1

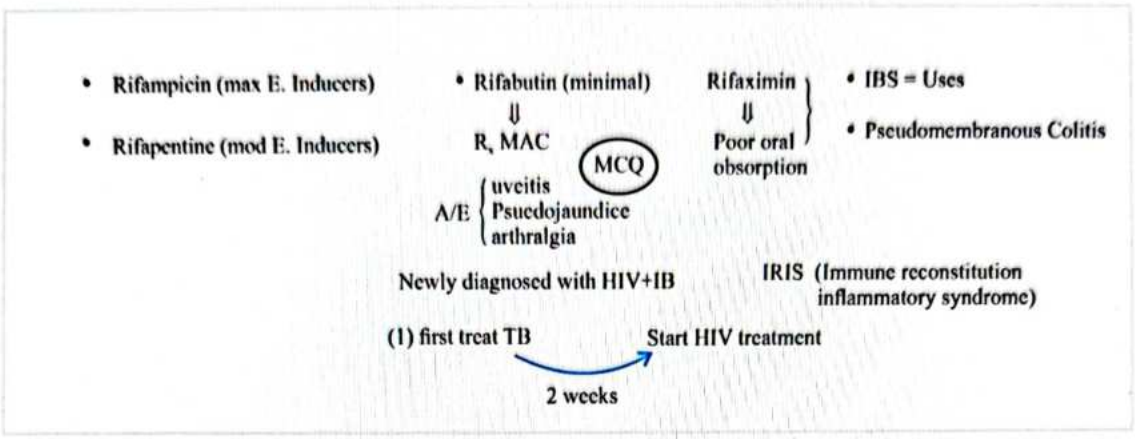
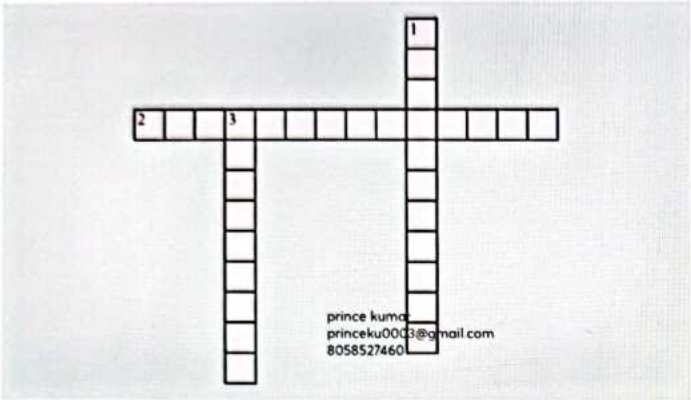


Table 76.1

DRUG	Cidal	Intra/ extra cellular	Hepatotoxic	Reduce dose In renal failure	Pregnancy	Gene mutation
H	✓	Both	✓✓	No	✓	Kat G
R	✓	Both	✓	No	✓	rpo B
Z	✓	Intra acidic pH	✓✓✓	mild	Avoid	pnc A
E	Static	Both	-	Yes	✓	emb B & A
S	✓	Extra alkaline pH	-	Yes	C/I	rpsl

CROSS WORD PUZZLES

Crossword Puzzle



Across

2. Pretomanid belongs to the group bicyclic _____.

Down

1. _____ should not be used in cases of pregnancy.
3. _____ is used to treat mycobacterium avium complex. Bedaquiline has cross resistance with clofazimine.

78 TREATMENT OF LEPROSY AND MYCOBACTERIUM AVIUM COMPLEX

Leprosy 00:00:23

- Leprosy is a chronic, infectious disease-causing skin lesions and nerve damage, mainly affecting skin, eyes, nose and peripheral nerves.
- Causative agent – Mycobacterium leprae.
- Main symptoms - Muscle paralysis, enlarged nerves and eye problems.

Drugs for Leprosy

Bactericidal drugs (Kill the side effects)	Bacteriostatic drugs
• Rifampicin • Ofloxacin • Moxifloxacin	• Dapsone • Clofazimine • Ethionamide • Minocycline • Clarithromycin

- Major drug of choice in leprosy – **Rifampicin, Dapsone, Clofazimine.**
- Other drugs are used in case of drug resistance to the first drug of choice.

Important Information

- MOA of rifampicin: Inhibits DNA dependent on RNA polymerase and has a bactericidal effect on the Leprae bacilli.
- Rifampicin and Ethionamide are both used in tuberculosis
- Bacteriostatic drugs - A drug which prevents the growth and reproduction of the bacteria. But not kill them.

Dapsone 00:03:05

Mechanism of Action:

- Inhibits folate synthase or dihydrofolate synthase.
- Goes into acetylation reactions similar to sulphonamide drugs.

Uses:

- In dermatology, the first drug of choice for Dermatitis and Herpetiformis.
- Leprosy
- Used in the management of malaria.
- Toxoplasmosis

Adverse effects:

- Allergy
- Sulfone syndrome
- **Haemolytic anaemia** (Hb% < 7gm/dl, stop dapsone as it causes anaemia).

Contraindication:

- G6PD deficiency leads to Haemolysis.

Rare Adverse Effects include the following.

- Hepatitis
- Nephritis
- In case of hepatitis and nephritis, it is advised to stop Dapsone and refer the patient to a tertiary centre.

Clofazimine 00:06:51

- It is a **dye.**
- It has anti-inflammatory properties.

Mechanism of actions:

- Its mechanism of action is unclear, but it alters the membrane structure of leprae bacilli.
- It disrupts the bacterial cell's mitochondrial ETC (electron transmission chain).

Uses:

- Used in drug-resistant tuberculosis.
- Leprosy
- Lepra reaction type 2

Adverse effects:

- **Blackish–red discolouration** of the skin, urine, and other body fluids. (Give reassurance to patients for this condition)
- Dry and scaly skin, i.e. Ichthyosis (Apply oil or Vaseline)

Important Information

- Clofazimine is cross-resistant of which MDR – TB (multidrug resistant- tuberculosis) drug?

Answer: Bedaquiline

Treatment of leprosy

00:10:36

Management of Pauci bacillary (involvement of nerves is less)	Management of Multi bacillary (more severe case)
First combination of drugs use – • Rifampicin 600 mg • Clofazimine 300mg For Duration – once monthly under supervision, i.e. in front of the Healthcare worker. **Second combination of drugs use –** • Dapsone 100mg • Clofazimine 50mg For Duration – given daily for 6 months, without supervision.	DOC – Same regime to followed as in the management of Pauci bacillary but for a longer duration, i.e. 12 months

- The treatment given for leprosy is prolonged due to the slow multiplication of bacteria and drug-resistant issues.

Lepra Reaction

00:13:26

Type 1	Type 2
• Hypersensitivity level is type IV. • Drug of choice - Steroids.	• Also known as ENL (Erythema nodosum leprosum). • Hypersensitivity is type III • Drug of choice – Steroids. • In recurring type ENL: Thalidomide • Other drugs – Chloroquine, Clofazimine

MAC (Mycobacterium Avium Complex)

- Groups of mycobacterium intracellular and mycobacterium avium related to tuberculosis.

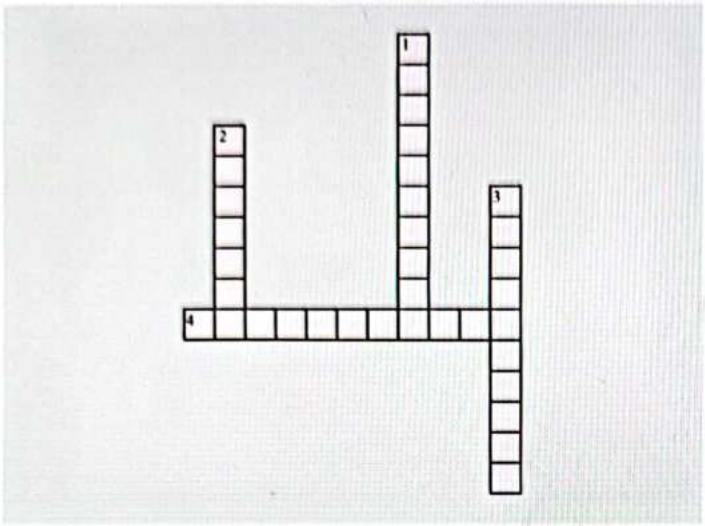
Treatment of MAC (Mycobacterium Avium Complex)

00:15:53

Intensive phase	Maintenance phase	Prophylaxis
R - Rifabutin **E** - Ethambutol (also, a TB drug) **C** - Clarithromycin	Clarithromycin / Azithromycin + Ethambutol / Rifampicin Or 1 FQ (fluoroquinolones)- ciprofloxacin / Moxifloxacin	Clarithromycin/ Azithromycin

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

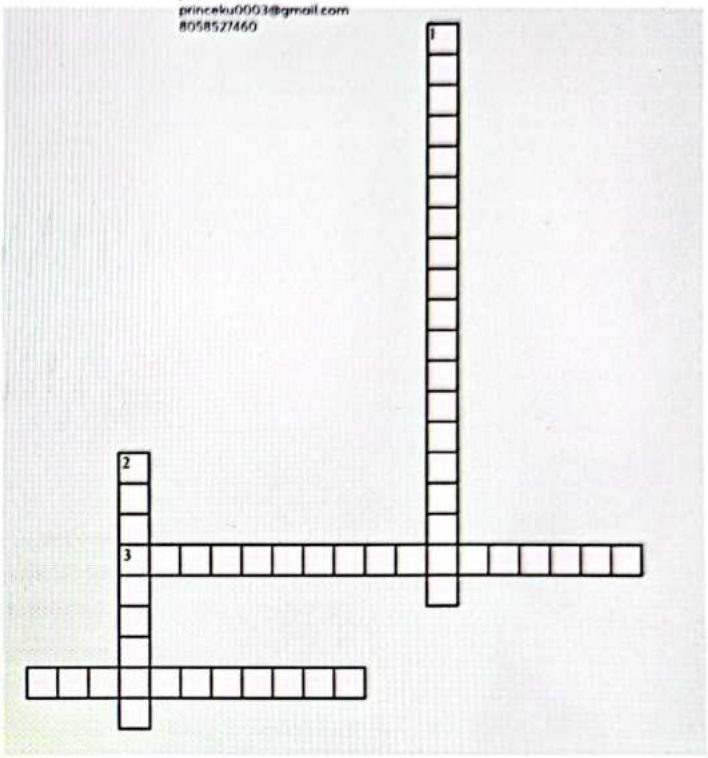
2. _____ also, a TB drug.
4. Cross-resistance for Clofazimine is called _____.

Down

1. _____ is the choice of drug for Dermatitis.
3. _____ is the choice of drug in lepra reaction 1.

Crossword Puzzle 2

prince kumar
princeku0003@gmail.com
8058527460



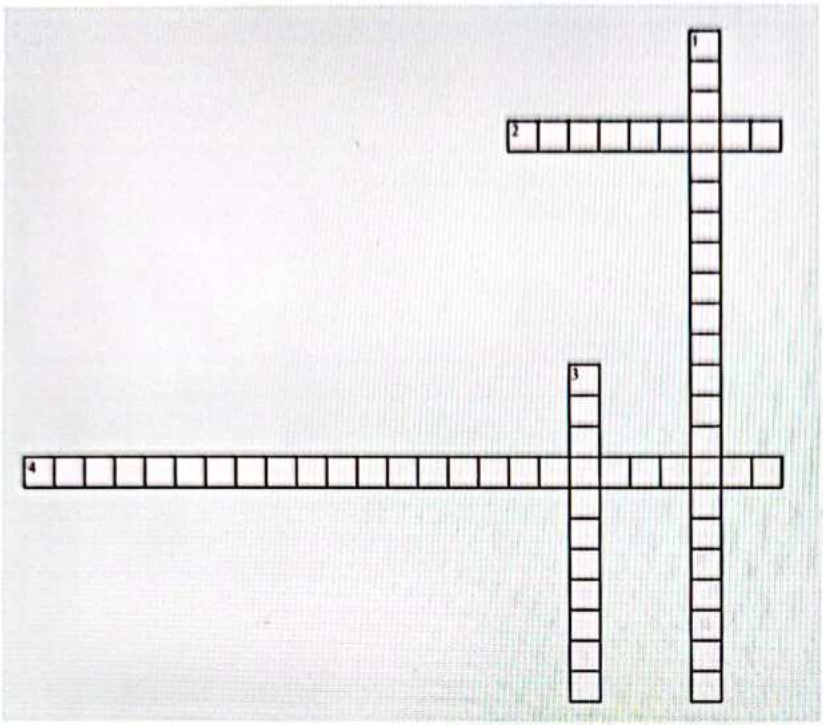
Across

3. The adverse effect of dapsone is _____.
4. Bactericidal drug _____.

Down

1. The causative agent of leprosy is called _____.
2. Inflammation of tissues of the kidney _____.

Crossword Puzzle 3



Across

2. Inflammation of the liver is called_____.
4. Group bacteria related to tuberculosis is called _____.

Down

1. Lepra reaction two is also known as_____.
3. Colour of body fluids due to Clofazimine _____.

79 ANTI VIRAL DRUGS

- Most viral infections are difficult to treat, but certain viruses can be treated. For example, influenza, hepatitis B and C, herpes virus, covid-19, and HIV.
- Certain viruses, such as rabies, mumps, measles, and rubella, cannot be treated but are prevented.

Treatable Viral Infections

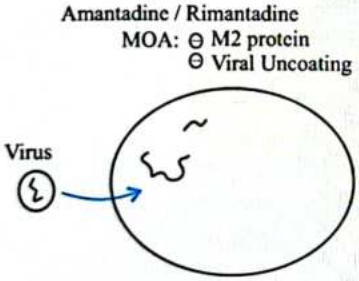
- Influenza
- Hepatitis B and C
- Herpes virus
- Covid-19

Anti-Influenza Drugs

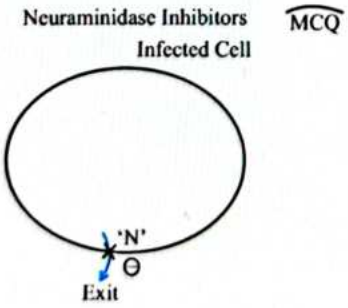
Refer Table 79.1

Important Information

- **Amantadine and Rimantadine** (older drugs) work by inhibiting M2 protein and viral uncoating. These drugs are effective against influenza A only.



- Viral uncoating: When the virus enters to infect a cell containing the DNA or RNA, depending on the virus, it has to remove the coat, and genetic material is released, which is called uncoating. Amantadine and Rimantadine block this step.



- **Neuraminidase inhibitors:** When the virus is inside the cell, it has to exit after the new virus is formed, which is done by neuraminidase. The drug used is Oseltamivir and given orally

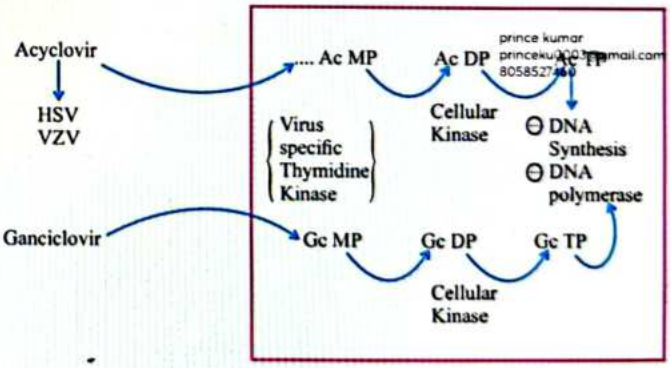
Antiherpetic Drugs

The different herpes viruses are.

- Herpes Virus 1 (HSV1)
- Herpes Virus 2 (HSV2)
- Varicella zoster virus (VZV) [known for chicken pox]
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV) [no treatment]

Acyclovir

- The drug should go into the infected cells of humans and inhibit the virus.
- It is a guanosine analog.
- When taken up by the infected cells, acyclovir is converted into acyclovir monophosphate. This conversion is done by virus-specific thymidine kinase. Hence, non-infected cells are rescued from this drug.
- Acyclovir monophosphate converts into acyclovir diphosphate and acyclovir triphosphate by the cellular kinase enzyme.
- It acts as a fake nucleoside and inhibits DNA synthesis and polymerase enzyme.
- Acyclovir is DOC in herpes virus (HSV1 and HSV2) and Varicella zoster virus (VZV).
- Adverse effects include Nephrotoxicity.



Mechanism of action of acyclovir and ganciclovir

Ganciclovir (Guanosine Derivative)-

- It is used for Cytomegalovirus (CMV).
- It is also activated by virus-specific thymidine kinase.
- Inside the cell, ganciclovir monophosphate converts into Ganciclovir diphosphate and Ganciclovir triphosphate by the cellular kinase enzyme.
- It also inhibits DNA synthesis and DNA polymerase enzyme.
- Adverse effects include nephrotoxicity and bone marrow suppression. Hence, it is required to monitor serum creatinine levels continuously.

Foscarnet

- Foscarnet is a DOC in Acyclovir-resistant HSV1,2 and VZV, and ganciclovir-resistant CMV.
- It directly inhibits DNA synthesis and polymerase without virus-specific thymidine kinase activation.
- Adverse effects include nephrotoxicity and electrolyte abnormality. Hence, renal function tests and electrolyte monitoring should be done properly.

Important Information

- Viruses can mutate virus-specific thymidine kinase. As a result, the enzyme does not work.
- In this condition, Acyclovir will not kill HSV and VZV, and ganciclovir will not work on Cytomegalovirus (CMV).
- Acyclovir and ganciclovir are short-acting. Therefore, these are given as prodrugs in valacyclovir and valganciclovir respectively.

Other Drugs

Refer Table 79.2

Hepatitis B

00:23:23

- It is treated with single-drug therapy.
- The EAT drugs are used for hepatitis B.
- Mnemonic EAT stands for Entecavir, Adefovir, and Telbivudine.
- They all work by inhibiting DNA polymerase.
- The other drugs used are Tenofovir, emtricitabine, and Lamivudine.
- **Tenofovir is available in two formulations.**
  a. Disoproxil fumarate is preferred in HBV-positive pregnant women.
  b. Alafenamide
- The drug of choice for Hepatitis B are entecavir or tenofovir. (Not in combination)

Hepatitis C

- The earlier therapy was Interferon-α.
- Ribavirin was the earliest drug used for hepatitis C that works by inhibiting RNA-dependent RNA polymerase. This drug is also used for respiratory syncytial virus (RSV) infection.
- Combination therapy should be given, such as Sofosbuvir + Daclatasvir ± Ribavirin, for 3-6 months. [99% cure rate]

Important Information

- Palivizumab is preferred to prevent respiratory syncytial virus (RSV) infection.

Direct-Acting Drugs

Target	Drugs
NS5A inhibitors [Name ends with "asvir"]	Daclatasvir Ledipasvir Ombitasvir
NS5B inhibitors or RNA polymerase inhibitors [Name ends with "buvir"]	Sofosbuvir Dasabuvir Deleobuvir
NS3/4A inhibitors (protease inhibitors) [Name ends with "previr"]	Boceprevir Simeprevir Paritaprevir

Covid-19

- Steroids decreases mortality.
- Patients were given low molecular weight heparin or Novel oral anticoagulants (NOVACs) such as dabigatran or "xaban" drugs during the clot formation.
- During the second wave, cytokine storm syndrome was observed in patients. In this condition, patients have been given steroids and tocilizumab [Interleukin6 antagonist].
- Remdesivir was given intravenously and worked by inhibiting RNA-dependent RNA polymerase. It was first approved for Ebola.

Important Information

- Rifampicin inhibits DNA-dependant RNA-Polymerase.

New Drugs

TARGET	DRUGS
Spike protein	Casirivimab +Imdevimab Bamlanivimab +etesevimab Sotrovimab Bebtelovimab [used to treat mild to moderate Covid-19]
Protease inhibition	Nirmatrelvir + Ritonavir

Q. Which drug can prevent lung fibrosis in Covid-19?
Ans.

- Pulmonary fibrosis due to Covid-19 can be prevented by Pirfenidone which is an anti-fibrotic agent.
- Similarly, nintedanib can also be used to treat idiopathic pulmonary fibrosis.

Table 79.1

MOA	DRUGS	USES
Inhibit M2 protein and inhibit viral uncoating	Amantadine and Rimantadine (older drugs)	influenza A only
Neuraminidase inhibitors	Oseltamivir (given orally)	Treatment and prevention of influenza A, B, H5N1, and H1N1 variants.
	Peramivir (given parenterally)	
	Zanamivir (given through the nasal route)	
Inhibits polymerase acidic endonuclease – It inhibits viral replication	Baloxavir (new drug)	

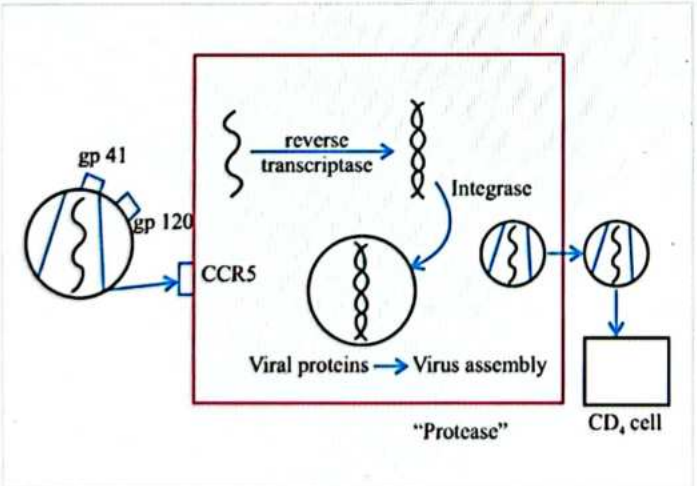
Table 79.2

Virus	Drugs	Properties
HSV1, HSV2, and VZV	Famciclovir (prodrug) ↓ Penciclovir (inside the body)	
	Dacosanal	• Inhibits virus entry. • Used topically for Herpes Labialis
	Idoxuridine and Trifluridine	• Eye drops for herpes keratitis.
Cytomegalovirus (CMV)	Cidofovir	• Used for CMV resistant cases.
	Fomiversen	• It is Antisense oligonucleotide • Silence the RNA expression. • It is used in multidrug-resistant Cytomegalovirus (CMV) infection.

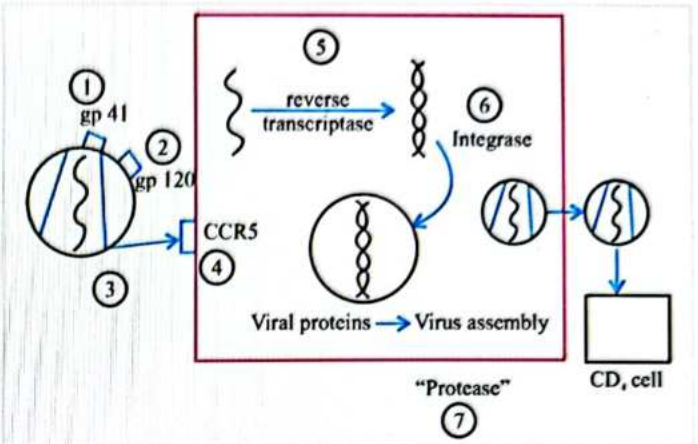
80 ANTI HIV DRUGS

HIV- Human Immunodeficiency Virus 00:00:38

- The HIV virus infects the immune cells, CD4 cells. Once the CD4 cells are destroyed, the immunity decreases and the patient becomes immunocompromised and progresses to Acquired Immunodeficiency Syndrome(AIDS).
- AIDS results in opportunistic infections.
- The Anti-HIV drugs stop the replication of the virus so that the virus does not infect the new CD4 cells and immunity remains intact and opportunistic infections are managed along.
- HIV has two variants, HIV-1(most common) and HIV-2.
- HIV virus is a retrovirus, and it contains a single-stranded RNA.
- For providing attachment it has a glycoprotein called gp 120, and gp 41.
- On CD4 cells, attachment is provided at CCR5.
- The virus fuses and releases the RNA.
- RNA is made into double-stranded DNA by an enzyme called **reverse transcriptase.**
- The nucleus of the CD4 cells has DNA (host) with which the viral DNA gets integrated by an enzyme called integrase. From this, the viral proteins are synthesized, forming virus assembly by the enzyme protease. Once the virus assembly is done, a new virus is synthesized and released into the bloodstream and again it will infect the new CD4 cells.



- When the CD 4 cells are infected, they die and hence the immunity is suppressed.
- These steps can be blocked at gp 41, gp 120, Fusion of virus, CCR5,
- It can also be blocked by inhibiting the enzyme Reverse Transcriptase, Integrase and, Protease



1. gp 41 Blocker

- Enfuvirtide is given as a subcutaneous injection. It is for HIV-1 only.
- It is not given oral
- A/E: Injection site reactions, Nodules

2. gp 120 blocker - Fostemsavir

- When gp 120 is blocked, the virus cannot attach to the CD 4 cells.
- Fostemsavir is used HIV -1 only

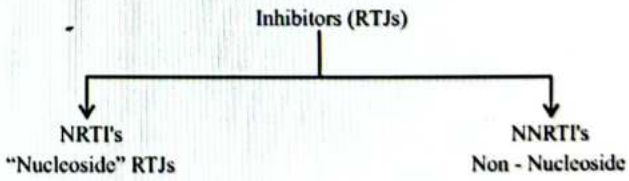
3. Inhibition of HIV fusion and entry 00:10:38

- Ibalizumab is a monoclonal antibody and hence cannot be taken orally.
- It is used in HIV 1 only

4. CCR-5 Blocker

- Maraviroc inhibits HIV 1 only
- Vicriviroc

5. Reverse Transcriptase Inhibitors (RTIs)



NRTIs

- In order to synthesize DNA, purines, and pyrimidines are required.
- Formulations that duplicate pyrimidines and purines are given that get incorporated into viral DNA and the replication stops.
- The normal cells are less affected and hence the chances of toxicity are less.

- Zidovudine
  - Zidovudine is the first anti-HIV drug.
  - Zidovudine enters inside the CD 4 cells and gets converted to zidovudine monophosphate (ZMP) by the enzyme thymidine kinase.
  - Zidovudine monophosphate gets converted to zidovudine diphosphate which gets further converted to zidovudine triphosphate by triple phosphorylation inside the cell.
- Tenofovir
  - Tenofovir is a nucleotide Reverse Transcriptase Inhibitor (RTI) that gets converted to di and triphosphates and not monophosphate as it is already phosphorylated.
- Stavudine is also a thymidine analogue, so it is also derived from thymidine like zidovudine.
- Pharmacodynamic antagonism: If zidovudine and stavudine are given together, they start competing with each other as both require the same enzyme for activation.

a. Zidovudine
- Zidovudine is toxic and causes bone marrow suppression
- Myopathy
- Nail pigmentation.
- Lipodystrophy

b. Stavudine
- Lipodystrophy
- Lactic Acidosis
- Hepatic steatosis

c. Didanosine
- Pancreatitis
- Peripheral Neuropathy
- Stavudine and didanosine should not be combined

d. Zalcitabine

e. Abacavir
- For HIV 1 only
- Cause Hypersensitivity reaction in person with HLA B5701 genetic makeup

f. Lamivudine
- Less S/e and more safe

g. Emtricitabine
- Less S/e and more safe
- A/E:
  - Skin pigmentation in sun exposed area
  - Palms and sole pigmentation

h. NtRTI
- Tenofovir:
  - Available in 2 forms: Disoproxil Fumarate, Alafenamide
  - A/E: Nephrotoxic by decreasing GFR and bone mineral density.

Non Nucleoside Reverse Transcriptase Inhibitors
- These drugs directly inhibit the enzyme reverse transcriptase, activation is not required.
- These drugs have two important generations
- Gen-1
  - Delavirdine
  - Efavirenz: Can produce neuropsychiatric problems. This should not be taken with food because food increases absorption and more the level of drug, more is the adverse effect.
  - Nevirapine: Nevirapine induces its own enzyme and hence it is an autoinducer.
- Gen-2: Effective for HIV 1 only
  - Rilpivirine
  - Etravirine
  - Doravirine

6. Integrase inhibitors
- Dolutegravir
- Raltegravir
- Bictetegravir
- Elvitegravir: Elvitegravir is used with a drug called Cobicistat, a pharmacokinetic booster. Elvitegravir is metabolized with microsomal enzymes, Cobicistat inhibits microsomal enzymes.
- Specialty
  - More efficacy
  - HIV 1 and 2
  - More safe
  - HIV newly diagnosed
  - Post-exposure Prophylaxis
- Integrase inhibitors are the best drugs these days, only problem is their cost.

7. Protease inhibitors 00:33:41
- These drugs inhibit assembly of viral proteins and these end with "navir".
- These are effective for both HIV 1 and HIV 2.
- They are Enzyme inhibitors
- A/E: Metabolic syndrome

Drugs

a. Lopinavir
  - Always used with ritonavir (PK booster)
  - A/E is diarrhea
  - It inhibits Cytochrome P3A4/5

b. Amprenavir
c. Fosamprenavir
d. Saquinavir
e. Nelfinavir
   - Metabolized by CYP2C19
   - No PK boosting
   - Active metabolite
f. Darunavir
g. Atazanavir
   - Less Lipodystrophy
   - Can cause Renal stones and Gall stones
h. Indinavir
   - Also Increase bilirubin

Cobicistat + [pk booster] - Darunavir - Atzanavir

- Tipranavir
  - Hepatotoxic
  - ↑Bleeding

HIV Positive 00:41:41

- HAART (Highly Active Anti-Retroviral Therapy) should be started immediately.
  - A minimum of three drugs (a minimum of two different groups) should be given, to avoid resistance by virus.
  - Life long treatment
- Commonly used regimen
  - 2NRTIs + 1 NNTRI
  - Tenofovir + lamivudine + Efavirenz
- If HIV 1 and 2 are suspected, then Tenofovir + lamivudine + Lopinavir + Ritonavir
- According to WHO guidelines, instead of Protease Inhibitors or NNRTIs, integrase inhibitors should be used. In India, it is still not approved due to increased cost.

Prevention of Opportunistic injections in HIV positive patients

1. TB: INH prophylaxis
2. Cryptococcal infection: Fluconazole
3. P. Jiroveci: Cotrimoxazole

"HIV + TB"
↓
First treat TB (IRIS) —— 2 weeks ——→ Start HIV Treatment

- If a patient has both HIV and TB, then TB (Opportunistuc infection) should be treated first and then after two weeks treatment for HIV should be initiated.
- This is to avoid Immune Reconstitution Inflammatory Syndrome (IRIS).

Prophylaxis of HIV 00:48:21

1. Post exposure Prophylaxis

- < 72 hrs
- Minimum 3 drugs
- 28 days
- Preferred: Tenofovir + lamivudine + Dolutegravir (> 10 yrs , >30 kg)
- >6yrs/ >20 kg: Zidovudine + lamivudine + Dolutegravir
- < 6yrs/< 20 kg: Zidovudine + lamivudine + Lopinavir
- There is no adequate data to give Dolutegravir to less than 6 years.

Important Information

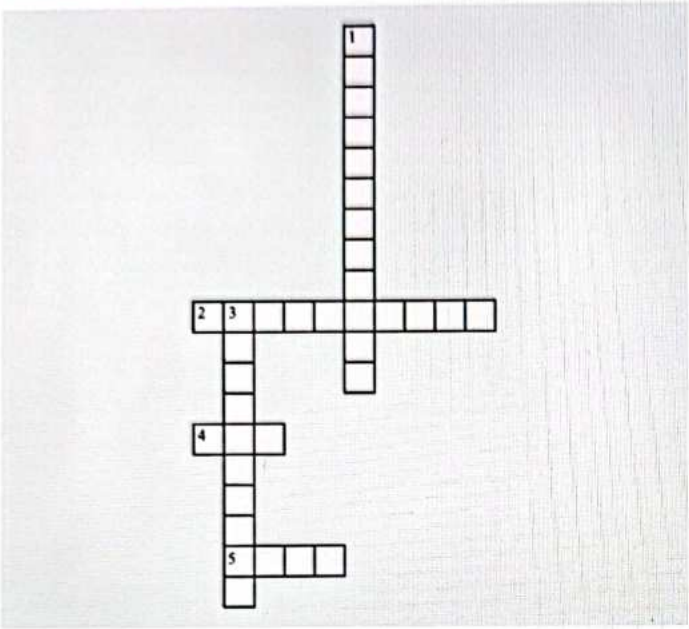
- To prevent mother to child transmission, the preferred drug is Nevirapine and is given for a minimum period of 6 weeks.
- If Nevirapine is not available, zidovudine can be used.
- These two drugs are preferred because these are available as syrup formulations

2. Pre- Exposure prophylaxis

- Tenofovir ± Emtricitabine
- Required in sex workers, men having sexual relations with men.

CROSS WORD PUZZLES

Crossword Puzzle 1



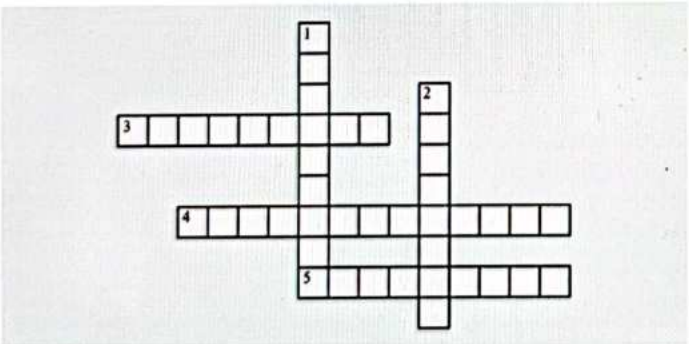
Across

2. is the first anti-HIV drug.
4. virus infects the CD4 cells.
5. results in opportunistic infections.

Down

1. is given as a subcutaneous injection.
3. is a monoclonal antibody.

Crossword Puzzle 2



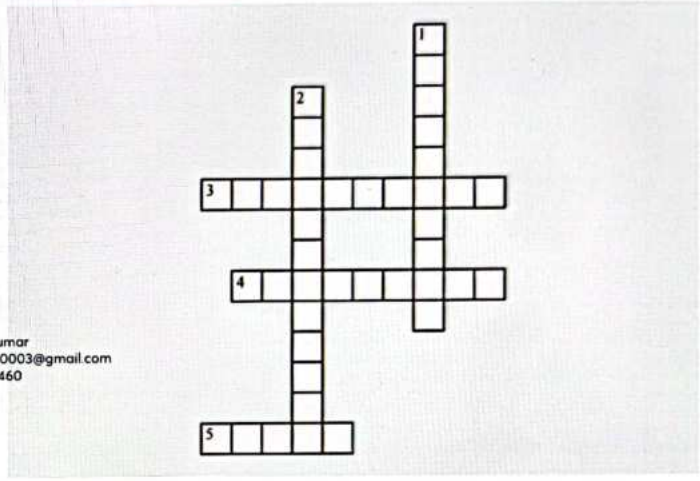
Across

3. is a nucleotide Reverse Transcriptase Inhibitor.
4. can cause skin and palm pigmentation.
5. causes neuropsychiatric problems.

Down

1. is also a thymidine analog.
2. causes hypersensitivity reactions.

Crossword Puzzle 3



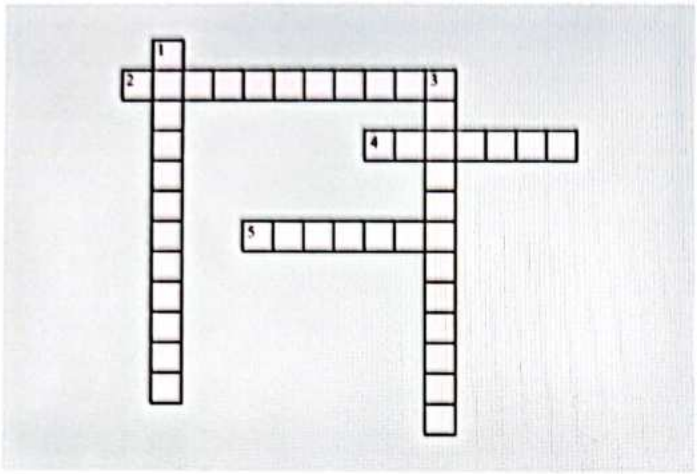
Across

3. is preferred drug for prevention of mother to child transmission
4. inhibitors are the best drugs these days
5. is the Highly Active Anti-Retroviral Therapy.

Down

1. is a pharmacokinetic booster.
2. is used with a drug called Cobicistat.

Crossword Puzzle 3



Across

2. The early stage drug for west African Trypanosomiasis
4. Unicellular protozoa
5. The early stage drug for east African Trypanosomiasis

Down

1. Drug of choice for south African Trypanosomiasis
3. The later stage drug for west African Trypanosomiasis

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81 ANTIPROTOZOAL DRUGS

Protozoa

- Protozoa are unicellular, eukaryotic, heterotrophic organisms.
- The most important ones are
  - Amoebiasis
  - Trypanosomiasis
  - Leishmaniasis
  - Cryptosporidiosis
  - Isosporiasis
  - Cyclosporasis
  - Malaria.

Antiprotozoal Drugs 00:00:36

- It is a group of drugs called Nitroimidazoles.
- Classical drug example – Metronidazole.
  - Remember Nitroimidazoles, they end with Nidazole.

Metronidazole 00:01:05

Mechanism of Action

Metronidazole
↓
produces nitro free radicals.
↓
The nitro free radicals are generated in an anaerobic environment.
↓
Cause DNA damage.
↓
Leads to cell death.

This is the reason it is more effective in treating anaerobes.

Nitroimidazoles: Drugs Ending with 'Imidazole'

- Tinidazole
- Ornidazole
- Secnidazole
- Satranidazole
- Benznidazole

Benznidazole

- The drug of choice for Chagas disease.

Satranidazole

- Specialty – It produces less GI adverse effect and less Disulfiram reaction problem.

Uses of Metronidazole

- **Mnemonic '3G PATA', 3G stands for.**
  - **G** - Giardiasis
  - **G** - Gardnerella Vaginalis
  - **G** - Guinea worm
    → Guinea worms are already eradicated from India.
  - **P** - Pseudomembranous colitis (caused by bacterium Clostridium difficile) and used in pylori (H. pylori).
  - **A** - Anaerobic infections
  - **T** - Trichomoniasis (Has strawberry vagina.)
  - **A** - Acute Necrotizing Gingivitis, Amoebiasis
    → Amoebiasis is caused by Entamoeba histolytica.
    → There are 2 important amoebiasis: Intestinal amoebiasis and Extraintestinal amoebiasis
    → Metronidazole - drug of choice.

- **Giardiasis**
  - Tinidazole has more efficacy than Metronidazole.
  - Usually, they will not administer both drugs.
  - If both are given, Tinidazole is the best option.
  - Resistance for both, then the drug of choice will be Nitazoxanide.

- **Gardnerella Vaginalis**
  - Causes bacterial vaginosis (BV).
  - Drug of choice - Metronidazole.

- **Guinea worm**
  - Drug of choice - Metronidazole.

Protozoal infection	Drugs used
Anaerobic protozoa.	Satranidazole
Chagas disease	Benznidazole
Giardiasis	Tinidazole, Metronidazole, Nitazoxanide
Gardnerella Vaginalis	Metronidazole
Guinea worm	Metronidazole
Pseudomembranous colitis, pylori, and anaerobic infections	Metronidazole
Trichomoniasis	Metronidazole
Intestinal amoebiasis and Extraintestinal amoebiasis	Metronidazole

Adverse Effect of Metronidazole

- GI effects (Nausea, vomiting, and diarrhoea).

- Allergy
- Fixed drug eruption.
- Damage to the central nervous system (CNS).
  - Seizures at high dosage.
  - Long-term use causes peripheral neuropathy.
- Dysgeusia - metallic taste.
- Disulfiram-like reaction.
- Discoloration of urine (cystitis)

Q. Metronidazole should not be used with alcohol.
Ans. It causes a disulfiram-like reaction.

Management of Amebiasis 00:09:30

- Caused by Entamoeba histolytica.
- Very common infection.
- Intestinal amebiasis: Infection is mainly in the intestine. And does not spread to other body parts.
- Extraintestinal amebiasis: If it goes from the intestine and spreads to the brain and the liver is called extraintestinal amebiasis.
- For both intestinal and extraintestinal amebiasis, the drug of action is metronidazole.
- Other drugs used: Emetine and dehydroemetine (older drugs)
- Chloroquine is not the drug of action but can be used in extraintestinal amebiasis.
- Intestinal cyst carriers: to kill the cyst we use Luminal amebicidal agents.
  - Paromomycin, as per the recent guidelines, is the drug of action for the carrier cyst
  - But in India, we still use the drug Diloxanide furoate.
- In the cases of Amebiasis, we combine Metronidazole with Diloxanide furoate.
  - Metronidazole will take care of intestinal amebiasis and extraintestinal amebiasis.
  - Diloxanide furoate will kill the intestinal cyst.

Important Information

Luminal amebicidal agents:

- Paromomycin
- Tetracyclines
- Nitazoxanide
- Quiniodochlor
- Iodoquinol
- Main drugs for intestinal cyst carriers: Paromomycin and Diloxanide furoate.

Management of Leishmaniasis 00:13:25

- If RK-39 dipstick test is positive, then it is Leishmaniasis.
- Three different varieties of leishmaniasis
  - Visceral Leishmaniasis (also called kala-azar)
  - Mucocutaneous Leishmaniasis
  - Dermal Leishmaniasis
- For Visceral Leishmaniasis and Mucocutaneous Leishmaniasis, the drug of choice is Liposomal Amphotericin B Injection. And oral drug of choice is Miltefosine.
- Other drugs used for Visceral Leishmaniasis and Mucocutaneous Leishmaniasis are:
  - Pentamidine
  - Paromomycin
  - Sodium Stibogluconate
- For Dermal Leishmaniasis (also known as Oriental sore)
  - It is a mild sore.
  - Sodium stibogluconate local injection or Paromomycin ointment.

Q. Patient has come down with fever and chills, malaria negative, and RK-39 dipstick positive. What is the drug of choice?
Ans. Liposomal amphotericin B.

Management of Trypanosomiasis 00:16:29

Two important types:

- African Trypanosomiasis
- South American Trypanosomiasis

African Trypanosomiasis

- **East African Trypanosomiasis:**
  - For the early stage, the drug used is Suramin.
  - For a later stage, the drug used is melarsoprol.
- **West African Trypanosomiasis**
  - For the early stage, the drug used is Pentamidine.
  - For a later stage, the drug used is Eflornithine.

South American Trypanosomiasis

- Also called Chagas disease.
- Drug of choice is Benznidazole.
- An alternative drug is called Nifurtimox.

Management of Cyclosporiasis and Isosporiasis 00:18:40

- Drug of action is Co-trimoxazole.
- Co-trimoxazole is a combination of trimethoprim and sulfamethoxazole.

Management of Cryptosporidiosis

- Drug of choice is Nitazoxanide.

Management of Toxoplasmosis

- Caused by Toxoplasma Gondii.
- Drug of choice is Pyrimethamine plus sulfadiazine.
- During the first trimester of pregnancy, the drug of choice is Spiramycin.

Important Information

Toxoplasmosis in pregnancy:

- During the first trimester of pregnancy, the drug of choice is Spiramycin.
  - Spiramycin is a macrolide. And it is safe in pregnancy.
- In 2nd and 3rd trimester.
  - Can administer both Pyrimethamine and Sulfadiazine.
  - Pyrimethamine + sulfadiazine is used as the drug of choice.

Management of Balantidiasis

- Drug of choice is Tetracycline.

Management of Babesiosis

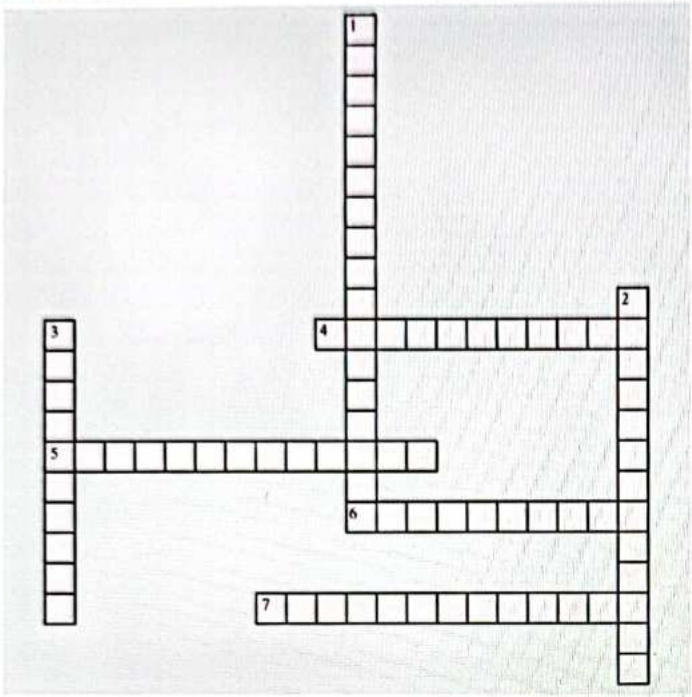
- Whether it is mild, moderate, or severe, the combination of atovaquone and azithromycin is used.
- If not available, the alternative regimen is quinine + clindamycin.

Specific protozoa infection	Drugs used
Amebiasis	Metronidazole Emetine Dehydroemetine Chloroquine
Intestinal cyst carriers	Paromomycin Diloxanide furoate
Leishmaniasis	Paromomycin Liposomal amphotericin B Miltefosine
East African trypanosomiasis	For the early stage - Suramin For a later stage - Melarsoprol
West African trypanosomiasis	For the early stage - Pentamidine For a later stage - Eflornithine
South American trypanosomiasis	Benznidazole / Nifurtimox

Other protozoal infection	Drugs used
Cyclosporiasis	Co-trimoxazole
Cryptosporidiosis	Nitazoxanide
Toxoplasmosis	1st trimester - Spiramycin 2nd and 3rd trimester – Pyrimethamine plus Sulfadiazine
Balantidiasis	Tetracycline
Babesiosis	combination of atovaquone and azithromycin or quinine plus clindamycin

CROSS WORD PUZZLES

Crossword Puzzle 1



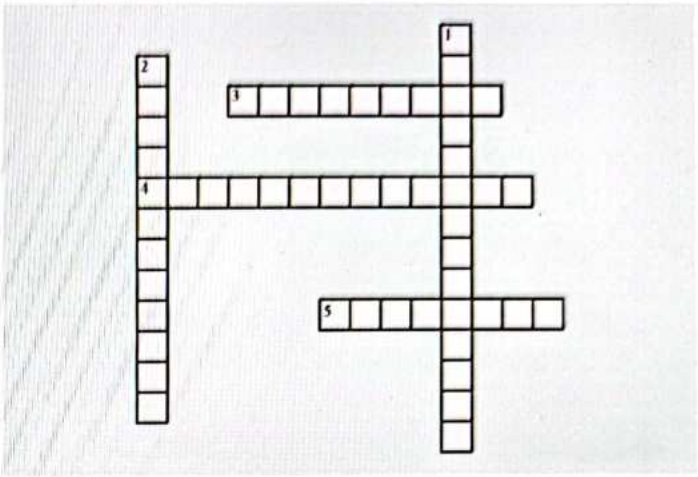
Across

4. Only oral drugs are available
5. The drug of action is Tetracycline
6. Is a macrolide
7. Infection during the first trimester of pregnancy

Down

1. The drug of action is Nitazoxanide
2. Test name called 'RK- 39 dipstick'
3. Caused by Entamoeba Histolytica

Crossword Puzzle 2



Across

3. Patients complain of a metallic taste.
4. Produces nitro free radicals.
5. Reason for Discoloration of urine.

Down

1. Drug of action for Metronidazole
2. Drug for carrier cyst.

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82 ANTI MALARIAL DRUGS

00:05:08

- Malaria is a disease caused by the Plasmodium parasite, transmitted through the bite of an infected mosquito.
- There are two important malarial parasites i.e., Plasmodium falciparum, and Plasmodium vivax.
- Plasmodium vivax causes relapse and Plasmodium falciparum causes recrudescence.
- For the treatment of malarial parasite, Anti-Malarials are used
- In the falciparum type, complicated cerebral malaria can be seen. People traveling in malaria-endemic areas may get prophylaxis.
- Plasmodium vivax and Plasmodium ovale are known to cause relapse.
- The recurrence of a disease or its symptoms following the period of improvement is called relapse.

Case:

- A 25 year old lady residing in Chennai, presents with a 1 week history of intermittent fever, chills, acute abdominal pain and excessive sweating.
- Physical examination reveals an acutely ill patient with a tender abdomen with a soft, tender, slightly enlarged spleen.
- Urine analysis showed tracs of albumin and no bacteremia. A peripheral blood smear showed ring forms of P. falciparum.
- The patient was diagnosed as a case of uncomplicated malaria.

Life cycle of Malaria

Refer Flowchart 82.1

- When a mosquito bites the human, it releases sporozoites into the blood circulation of humans

↓

- Then, sporozoites enter the liver quickly where they multiplied. Before infecting the RBC there is a stage called the Pre-erythrocytic stage.

↓

- Then, the sporozoites mature into tissue schizonts and some sporozoites stay in the liver (seen only with vivax and ovale). These hypnozoites are also called the exo-erythrocytic stage.

↓

- If these hypnozoites are not killed, they can again come back to the tissue schizonts stage and again can cause malaria. Hence, the patient may relapse again.

↓

- Then, these tissue schizonts are released into circulation in the form of merozoites. Merozoites enter the RBC where they divide their number.

↓

- RBC will rupture, and parasites are released into the circulation then finally the patient will have an episode of fever and chills.

↓

- Again, these merozoites infect the new RBC, enter the circulation and the person will again have fever and chill.
- Parasites also form male and female gametes in circulation. When the mosquito again bites the infected person. Mosquito will take the male and female gamete. Fertilization will start in the mosquito. This is called the sexual cycle.
- Then these mosquito releases sporozoites, stored in the saliva of the mosquito.
- When mosquito again bites a non-infected person, then it turns into malaria.

Classification of Anti-Malarial Drugs

00:12:10

- Suppose a person is traveling in an endemic area and exposed to a mosquito bite.
- To prevent the occurrence of malaria there are certain drugs that can prevent malaria at the pre-erythrocytic stage. These drugs are called causal prophylaxis.

Causal Prophylaxis

- **Drugs:** Primaquine, Proguanil, Atovaquone.
- These drugs are given when the patient travels to the endemic areas

Suppressive Prophylaxis

- There are some other drugs that can suppress the clinical manifestation of malaria. These drugs are called suppressive prophylaxis.
- These drugs interfere with the erythrocytic stage, they block the RBC from rupture. So, the fever will not occur.

- **Drugs:** Doxycycline, Chloroquine, Mefloquine

Radical cure drugs

- Hypnozoites are the reason to cause relapse. To prevent relapse, hypnozoites should be killed so that person will not get malaria again.
- Drugs that kill the hypnozoites and the stage is called the Exo-erythrocytic stage.

- **Drugs:** Primaquine, Tafenoquine.
- These drugs decrease the chances of relapse and radical cure. Radical cure is the complete elimination of parasites and

hypnozoites from the body.

- Fever starts from the erythrocytic stage, so it needs to block this stage.
- Drugs that kill the gametes (vivax and falciparum) by decreasing clinical transmission are Primaquine and Tafenoquine.
- Primaquine and Tafenoquine kill all species of gametes.
- Other drugs that can kill the gametes are Artemisinin but its efficacy is low.
- Drugs that kill the vivax gametes are chloroquine and Quinine.

Drugs prevent clinical transmission.

- **Drugs:** Primaquine, Tafenoquine, Artemisinin, chloroquine and Quinine

Important Information

- Primaquine is effective in every stage except the erythrocytic stage. Because it does not have the property to decrease the fever.

Refer Flowchart 82.2

Drugs that act on the erythrocytic stage or the treatment of clinical cure are- 00:15:08

I. **Low efficacy and slow acting**

- Tetracycline (Doxycycline),
- Clindamycin (binds to 50S unit),
- Dapsone (inhibits folic acid synthesis),
- Proguanil,
- Pyrimethamine (inhibits dihydrofolate reductase),
- Sulfonamides (sulfadoxine) combines with other drugs like pyrimethamine.

]II. **High efficacy and fast acting**

Refer Flowchart 82.3

- **Drugs inhibiting heme to hemozoin:**
  - Heme is present in the RBC and this heme is converted into hemozoin. This step is inhibited by certain drugs.
  - If this step is inhibited, then heme increases which are toxic to the parasite.
  - Drugs: Chloroquine, Quinine, Mefloquine, amodiaquine.
  - Mefloquine has neuro psychotic adverse effects (seizures, hallucinations).

Important Information

- Mefloquine is contraindicated in cerebral malaria. Because the patient is already in a confused state and mefloquine further worsens the condition.

- **Drugs causing free radical injury to parasites**
  - Another group of drugs causes free radical injury to parasites
  - Drug: Artemisinin derivatives.

- **Drugs inhibit the electron transport in parasites**
  - Drugs that inhibit the electron transport in parasites, decrease the energy (ATP). As a result, the parasite will not survive.
  - Drug: atovaquone.
  - Atovaquone is used in the management of Babesiosis and atovaquone is used in combination with azithromycin in the treatment of babesiosis (the drug of choice in babesiosis.
  - Atovaquone is also used in the treatment of Pneumocystis jirovecii and Toxoplasmosis.

- **Drugs inhibit the proton pump in the malarial parasite**
  - Drugs: Lumefantrine and Halofantrine.
  - Lumefantrine increases fatty food absorption.
  - Halofantrine is a cardiotoxic drug.

Chloroquine

Pharmacokinetics

- Chloroquine has a high volume of distribution (Vd = 1300 L). The drug will not stay in the blood vessels. It is stored in the tissue and causes retinal toxicity.
- Because of high Vd, chloroquine is given as a loading dose (600 mg) followed by maintenance dose (300 mg). Loading dose depends on Vd, and maintenance dose depends on clearance.

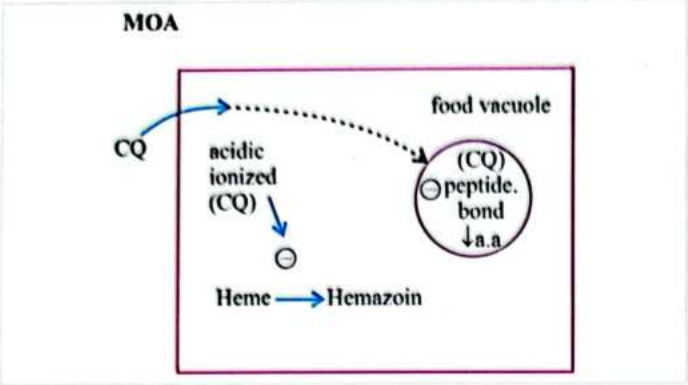
Adverse effects:

- Retinal toxicity-Bull's eye maculopathy (the concentric pattern that damages the retina),
- Corneal micro-deposits
- Nail and mucus membrane pigmentation
- ECG abnormalities (QT prolongation).
- Chloroquine is the safest drug in pregnancy.
- Hydroxyquinine also causes QT prolongation.

Uses of Chloroquine

- Rheumatoid arthritis
- Extraintestinal amebiasis
- Discoid lupus erythematosus
- Lepra reaction (type II lepra reaction)
- Mononucleosis
- Photogenic reaction
- Malaria
- Giardiasis.

Mechanism of action of Chloroquine



- When chloroquine enters the cell where pH is acidic (ionized form). So, chloroquine is trapped inside and inhibits the conversion of heme to hemozoin (major mechanism)
- Inside the parasite, there is a food vacuole in which chloroquine attacks and inhibits the formation of peptide bonds. If there is no peptide bond. So there will be no formation of amino acid.

Quinine

- Quinine is given via the intravenous route in the treatment of complicated malaria or cerebral malaria.
- Quinine is also given via the oral route in the combination with clindamycin to treat malaria in pregnancy (first trimester of pregnancy) in Plasmodium falciparum.

Adverse effects:

- Use of Quinine via IV route pushes the glucose level down (hypoglycaemia), arrhythmia.

Primaquine

- Primaquine acts in the Exo-erythrocytic stage, pre-erythrocytic stage, and Gametocytic stage but it has no action in the erythrocytic stage.

Uses

- Primaquine is used to produce radical cure and decrease relapse.
- For radical cure the drug should be given for 14 days.

Contraindication

- It is contraindicated in patient with G6P6 deficiency that can cause hemolysis.
  - If the patient is G6P6 deficient then NADPH will not produce, free radicals will not neutralize and free radicals destroy the RBC.
  - Primaquine is a drug that generates free radical and damages RBC.
- Primaquine is contraindicated in pregnancy. Because foetus is relatively deficient in G6PD

Tafenoquine

- Tafenoquine has a very long half-life (14-9 days). It is used to treat the radical cure in a single dose.

Artemisinin derivatives

- Artemisinin and its derivatives are natural compounds obtained from artemisinin and used widely as antimalarials.

Drugs:

- Artesunate, Artemether, Arteether, Arterolane and Dihydroartemisinin.
- These drugs are highly efficacious and fast-acting in the case of cerebral malaria.
- These drugs are always given in combination with other drugs. If used alone, it will cause resistance.

Uses

- These drugs are used in the management of cerebral malaria
- It is not used in the management of prophylaxis because it is short-acting person cannot use it repetitively.

Treatment of different types of Malaria 00:20:05

I. Management of Plasmodium vivax and Plasmodium ovale

- Both Plasmodium vivax and Plasmodium ovale cause relapse.
- Chloroquine is used at a dose of 600 mg on day 1 (loading dose). After 8 hours 300 mg, the dose is given as a maintenance dose. On day 2, again 300 mg dose is given. On day 3, again 300 mg.
- It mainly acts in the erythrocytic stage. But it does not kill parasites completely (hypnozoites).
- Primaquine is administered as 15 mg with chloroquine on the 2nd day for 14 days. It is given for 14 days because hypnozoites multiply first, then it will kill hypnozoites.
- The dose in mg/kg is 0.25.

II. Management of Plasmodium falciparum or Plasmodium malariae

- In most countries, Plasmodium falciparum is already resistant to Chloroquine. So, there is no need to administer.
- Combination therapy is used- Artemisinin Combination Therapy (ACT).
- It depends on the patient's traveling history.
- If the patient is in the north-east part of the country, then the regimen will be Artemether+ Lumefantrine and a single dose of primaquine (45mg or 0.75 mg/kg), which decreases the clinical transmission of malaria and kills the gametes.
- In rest of India, Artesunate + Sulfadoxine+ Pyrimethamine and a single dose of primaquine (45mg or 0.75 mg/kg), decrease the clinical transmission of malaria and kill the gametes.

III. If the patient has mixed infections (falciparum and vivax)

- Chloroquine is not used in this case because Chloroquine has no effect on falciparum.
- ACT regimen+(Primaquine*14 days). Because vivax causes relapse.
- Sulfadoxine + Pyrimethamine is avoided in the ACT regimen because these drugs are not effective on vivax.

IV. Management of malaria if the patient is pregnant.

- It depends on the kind of parasite (falciparum or vivax)
- **In the treatment of vivax,**
  - Chloroquine is used in the treatment of malaria in pregnancy, but radical cure cannot be given because primaquine is contraindicated in pregnancy.
  - Radical cure only can be given after delivery, because in pregnancy the foetus is already G6PD deficient. So, there is a chance of haemolysis.
- **In the treatment of falciparum,**
  - First trimester of pregnancy - Clindamycin +quinine
  - II, III trimester- ACT regimen depending on the area of patient.

Important Information

- Plasmodium falciparum can cause complicated malaria or severe malaria or cerebral malaria.

V. Management of complicated malaria or severe malaria or cerebral malaria.

- The drug of choice is Artesunate administered through the IV route. IV quinine cannot be used because it causes hypoglycemia.
- Once the patient becomes stable, then the patient can switch to oral ACT therapy.
- In all trimesters drug of choice is Artesunate.

Drugs combination approved by WHO (ACT Regimen)

- Artesunate+ sulfadoxine+ Pyrimethamine
- Artesunate+ Amodiaquine
- Artesunate+ Mefloquine
  - Mefloquine causes neuropsychiatric symptoms. So, it is contraindicated in patients with cerebral malaria.
- Artemether+ Lumefantrine
- Dihydroartemisinin+ Piperoquine

VI. Treatment of malaria if the person is traveling to a malaria-endemic area.

- Malaria chemoprophylaxis is used in the management of malaria-endemic areas.
- Travelers, military persons, and migrant laborers require prophylaxis treatment.
- **If the duration of journey is less than 6 weeks,**
  - The preferred drug will be doxycycline.
  - Doxycycline starts 1-2 days before travel. Doxycycline should be taken daily during the journey.
  - When the person returns from a journey. He should take doxycycline daily for 28 days. It is done because even if the mosquito bit the person in the last days, doxycycline will suppress the manifestation of fever and chills. This is called suppression prophylaxis.
- **If the journey is longer than 6 weeks.**
  - Then mefloquine is the drug given 1-2 weeks before the journey.
  - Mefloquine is a long-acting drug. So, there is no need to take it daily. Mefloquine is given only once a week during journey.
  - Mefloquine should be taken weekly for 4 weeks after traveling.
- **In pregnant women,**
  - Prophylaxis is given in pregnant women only if the pregnant woman is staying a high malaria endemic area but not in the first trimester.
  - WHO-approved combination Sulfodoxine+ Pyrimethamine (single dose) is given in II and III trimesters.
    → And the gap should be of at least 1 month

Important Questions 00:29:10

Q. Define suppression prophylaxis.
Suppressive prophylaxis is directed against the red blood cell stages of the malaria parasite and must be given for a few weeks to prevent infection.

Q. What is the treatment of vivax in pregnancy
Clindamycin and quinine (first trimester of pregnancy)

Q. What is the treatment if the patient has both infections (falciparum and vivax)
ACT regimen and Primaquine for 14 days

Q. What are the two important malarial parasites
Plasmodium falciparum, and Plasmodium vivax

Q. ACT regimen defines.
Artemisinin Combination Therapy

Q. What is the treatment for malaria if the person is traveling to a malaria-endemic area
The preferred drug will be doxycycline. Doxycycline starts 1-2 days before travel.

Q. Drugs combination approved by WHO (ACT Regimen)
Artesunate + sulfadoxine + Pyrimethamine
Artesunate + Amodiaquine
Artesunate + Mefloquine
Artemether + Lumefantrine
Dihydroartemisnin + Piperoquine

Q. What are the adverse effects of chloroquine
Renal toxicity, Bull's eye maculopathy (the concentric pattern that damages the retina), Corneal micro-deposits, Nail and mucus membrane pigmentation, ECG abnormalities (QT prolongation)

Q. Suggest the drugs that interfere with the erythrocytic stage and block the RBC from rupturing.
Doxycycline, Chloroquine, Mefloquine

Q. Suggest the drugs that kill the hypnozoites.
Primaquine, Tafenoquine.

Q. Define the term "Radical cure"
Radical cure is the complete elimination of parasites and hypnozoites from the body

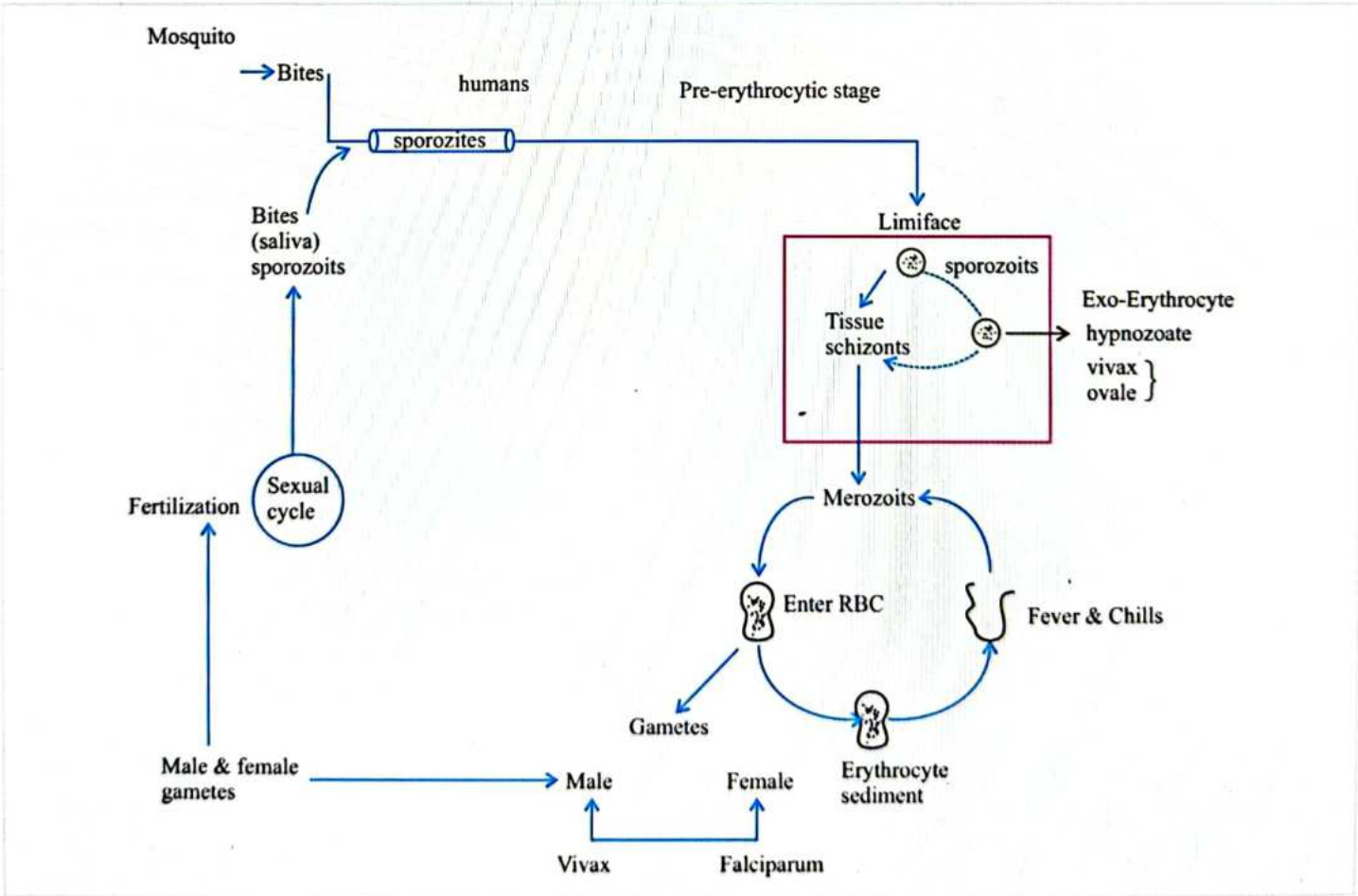
Q. What should be the drug of choice in all trimesters of pregnancy
Artesunate

Q. If the patient is in the north-east part of the country then the regimen will be
Artemether + Lumefantrine and a single dose of primaquine (45mg or 0.75 mg/kg), which decreases the clinical transmission of malaria and kills the gametes

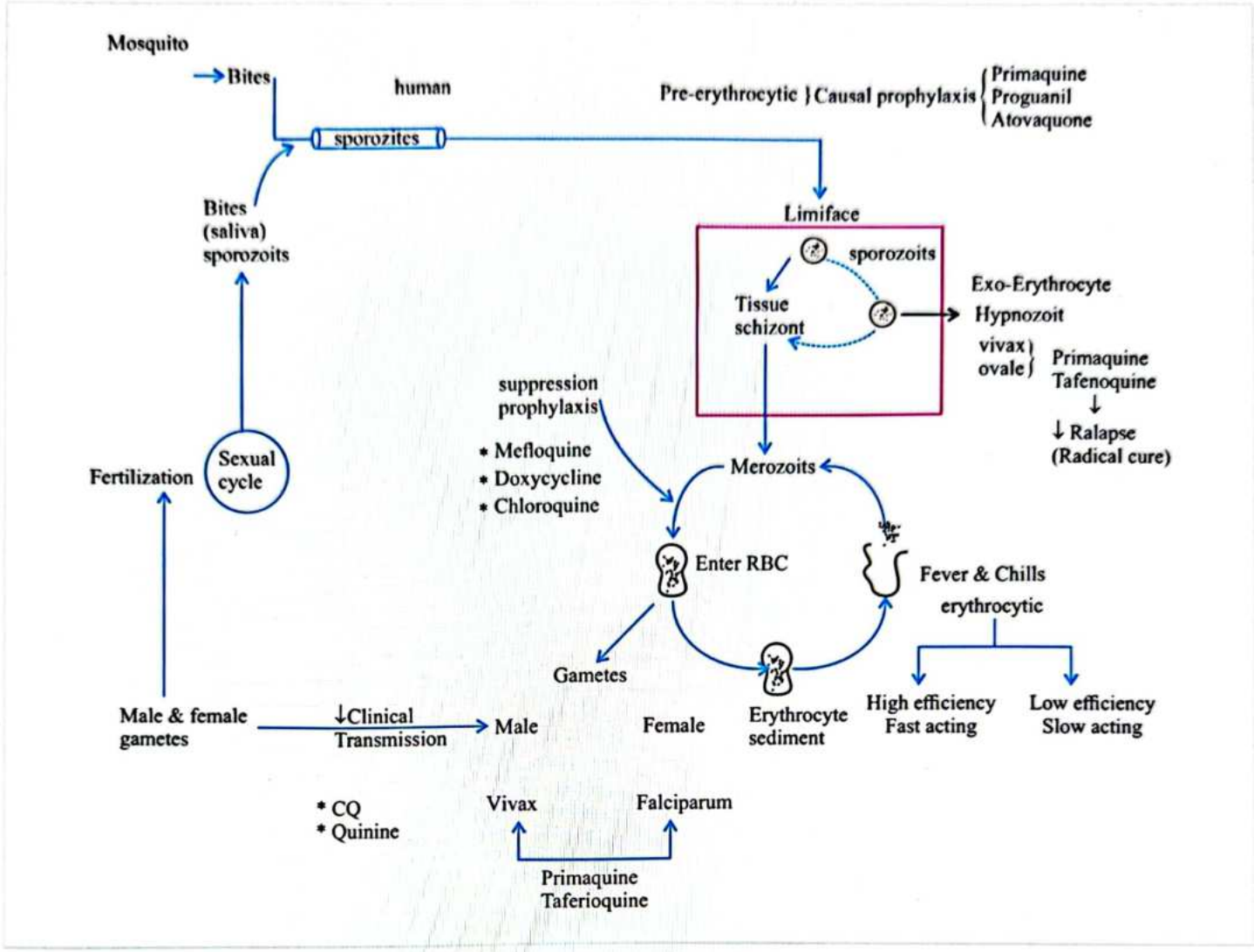
Q. What is the loading and maintenance dose of chloroquine
Loading dose (600 mg) followed by a maintenance dose (300 mg)

Q. Which drug has neuro psychotic adverse effects.
Mefloquine has neuro psychotic adverse effects (seizures, hallucinations)

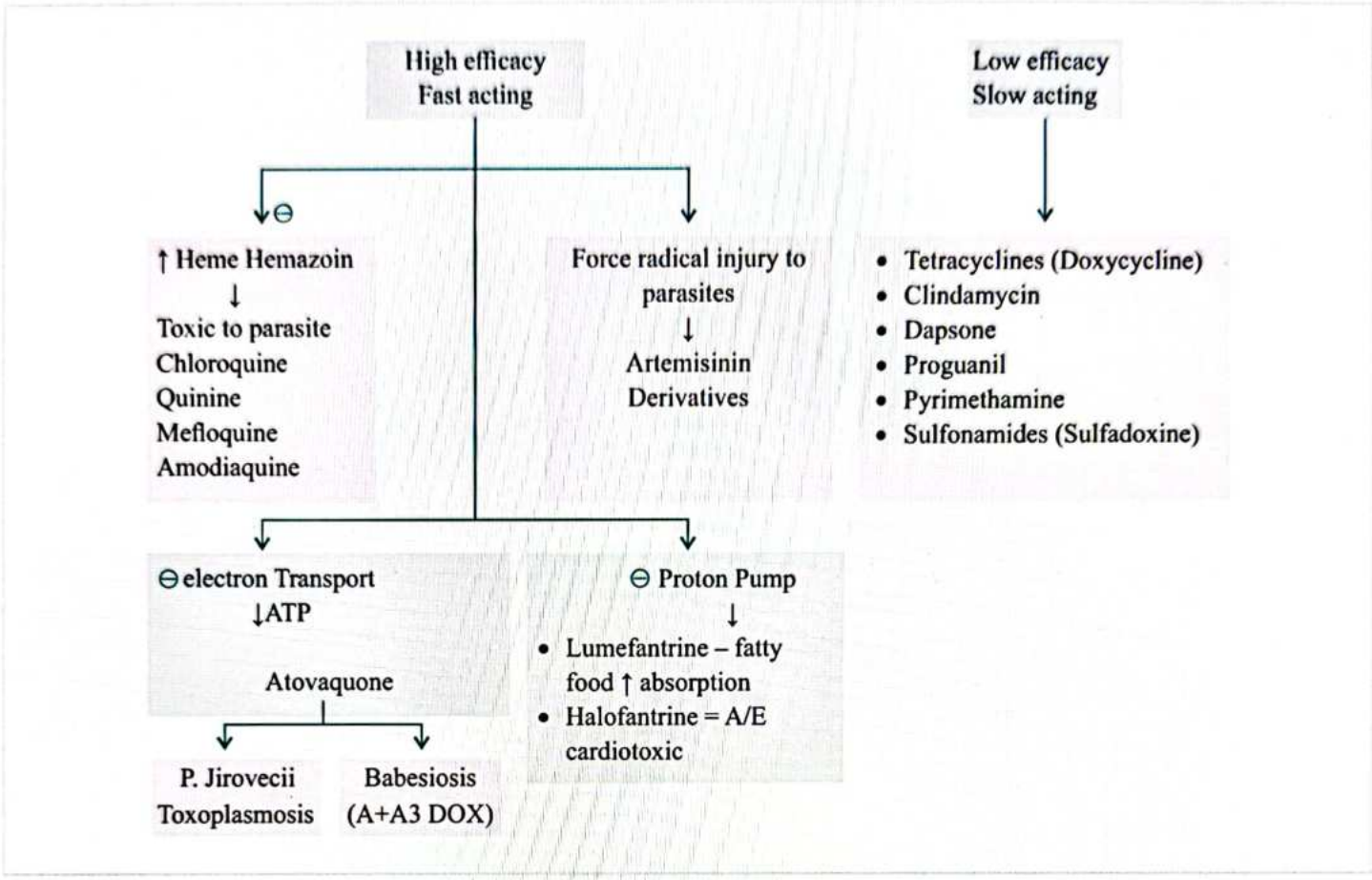
Flowchart 82.1



Flowchart 82.2

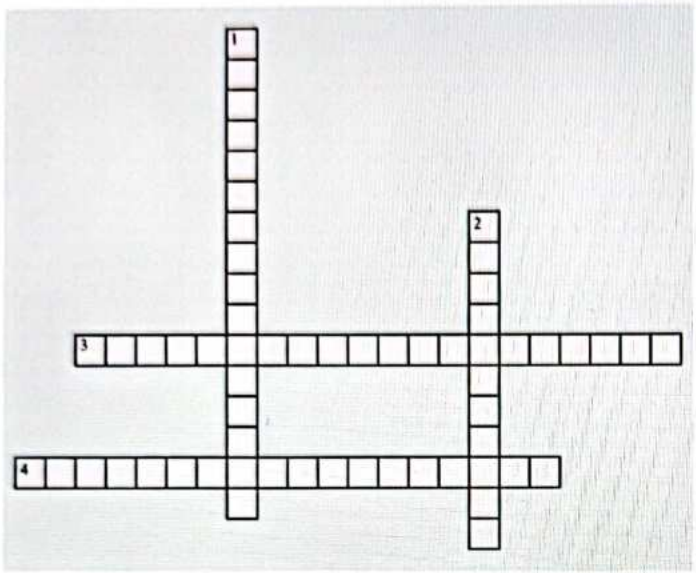


Flowchart 82.3



CROSS WORD PUZZLES

Crossword Puzzles 1



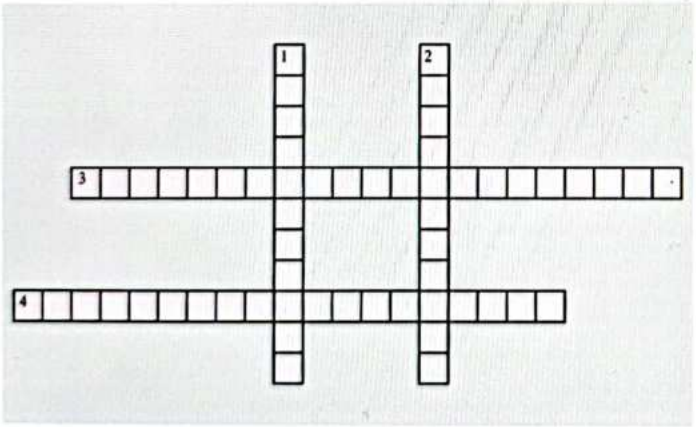
Across

3. _____ is a parasite that causes malaria.
4. _____ is a parasite that causes resistance.

Down

1. _____ is the stage when sporocytes quickly enter the liver, where they multiply.
2. _____ is a drug that interferes with the erythrocytic stage.

Crossword Puzzles 2



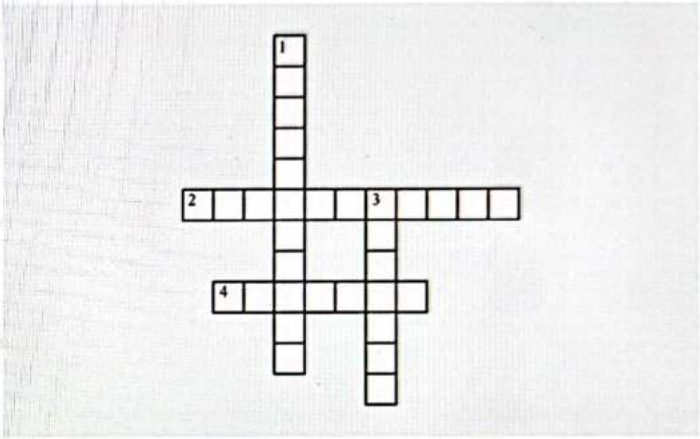
Across

3. _____ is used in the management of cerebral malaria.
4. _____ is used in the treatment of vivax (first trimester of pregnancy).

Down

1. ____ has a very long half-life (9-14 days).
2. In the erythrocytic stage, ____ acts directly.

Crossword Puzzles 3



Across

2. When _____ administered intravenously, it lowers the glucose level.
4. ____ is administered intravenously to treat complicated malaria or cerebral malaria.

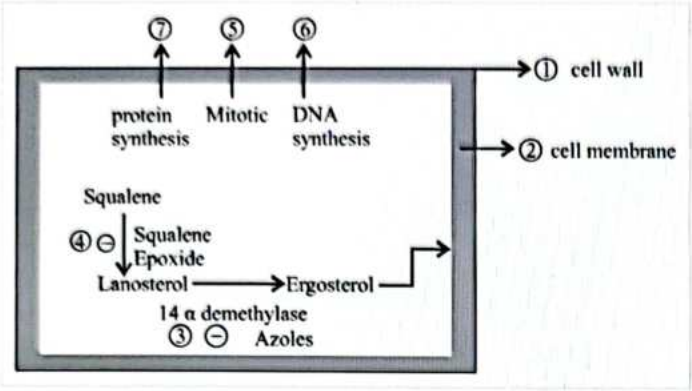
Down

1. ____ has high volume of distribution.
3. ____ has Bull's eye maculopathy as an adverse effect.

83 ANTI FUNGAL DRUGS

Mechanism of Action

00:01:39



- Inside the fungal cell, many metabolic processes take place to keep the cell alive. So antifungal drugs can inhibit any of these functions to stop the proliferation of the infection. Here are some important functions inside the fungal cell:
  - Squalene is converted to lanosterol with help of the enzyme squalene epoxide.
  - This lanosterol is further converted to ergosterol with help of the enzyme 14 α demethylase.
  - This ergosterol is important for cell membrane formation, thus attacking any of the above steps can hinder cell membrane formation.
- So, the functions/sites where the antifungal drugs can attack are:
  - Cell wall
  - Cell membrane
  - DNA synthesis
  - Mitosis
  - Protein synthesis
  - Squalene epoxide
  - 14 α demethylase

Types of Antifungal Drugs

00:05:26

- Antifungal drugs are divided as per their mechanism of action on the fungal cell. There can be nine types of drugs that affect:

Cell Wall

- These drugs inhibit the enzyme 1,3 β Glucan Synthase which is essential to make the fungal cell wall.
- The drugs that inhibit cell wall formation are called Echinocandins.
- Echinocandins are used to treat two types of fungus:
  - Candida - Both Candida glabrata and Candida krusei can be treated.
  - Aspergillus
- The name of the drugs is: (CAM)
  - Caspofungin
  - Anidulafungin: It is safe in both renal and hepatic failure patients as it goes under slow metabolic degradation.
  - Micafungin.

Polyene Antibiotics

- The name of the drugs is:
  - Amphotericin B: It is also called conventional amphotericin
  - Hamycin and Natamycin: These are only used topically as they are highly nephrotoxic.
- **Mechanism of action of amphotericin B:**
  - When amphotericin B enters the cell, it combines with ergosterol and together they create pores in the cell membrane.
  - Now the cellular components will try to come out of the cell and this will kill the cell.
  - This makes amphotericin B a fungicidal agent.
- **Adverse effects of amphotericin B:**
  - **Infusion reaction**: The patient develops chills, rigors, and fever after taking the medicine. To prevent this, amphotericin B can be given slowly or in combination with an antihistamine.
  - **Nephrotoxicity**: As the drug attacks the cell membrane of the fungus, it can also do the same to the human cell. So, the drug causes renal tubular acidosis in humans.
  - **Anemia**: It causes hypochromic normocytic anemia.
  - Hypokalemia and hypomagnesemia
  - **Seizures**: They can occur if the drug is used intrathecally.

Newer Preparations of Amphotericin B

- Due to the adverse effects of the conventional drug, newer drugs were made that target the infection and not the entire body. These are:
  - Liposomal amphotericin B (LAMB): These have less nephrotoxicity as well as fewer adverse effects compared to conventional amphotericin B.
    → They are presently used most commonly.
    → They are costly.
  - Amphotericin B colloid dispersion (ABCD): These have more infusion reactions.
  - Amphotericin B lipid complex
- **Uses of liposomal amphotericin B:** These can be of two types-
  - **Fungal**
    → It is the drug of choice to treat Mucormycosis.

→ It is also the drug of choice for cryptococcal meningitis.
→ Reserved for serious systemic fungal infections.
→ Due to the adverse effects, it is reserved for serious systemic fungal infections.

- **Non-fungal**: It is the drug of choice for visceral leishmaniasis and mucocutaneous leishmaniasis. (Kala-azar)

Important Information

- Treatment of cryptococcal meningitis: Initially I.V. liposomal amphotericin B is given with or without flucytosine.
- After the patient has stabilized, he is given oral fluconazole.

Azoles

00:18:40

- These drugs inhibit the enzyme 14 α demethylase which further inhibits the formation of the fungal cell membrane.
- Azoles are also enzyme inhibitors.
- Types of azoles: These are divided into 3 types –
  - **Topical:**
    → Clotrimazole
    → Luliconazole
    → Miconazole
    → Sertaconazole: This drug is also antipruritic and has anti-inflammatory properties.
  - **Topical and systemic:**
    → Ketoconazole: Topically it is used in shampoos for treating dandruff. Systemically they are given orally to treat Cushing's disease as ketoconazole inhibits steroid synthesis.
    → Adverse effect: This is a microsomal enzyme inhibitor. It can cause gynecomastia.
  - **Systemic:**
    → Itraconazole
    → Fluconazole
    → Voriconazole: Its adverse effect is that the patients may experience visual and auditory hallucinations.
    → Posaconazole
    → Isavuconazole

Important Information

- Posaconazole and isavuconazole can be used to treat Mucormycosis, but itraconazole, fluconazole and voriconazole can't be used to treat Mucormycosis.
- Fluconazole can't be used to treat Candida krusei because it has an intrinsic resistance against the drug.

Squalene Epoxide Inhibitors

- These drugs inhibit the enzyme squalene epoxide.
- The name of the drugs is:
  - Terbinafine and Butenafine: These are used to treat dermatophyte infections.

Mitosis Inhibitors

- These drugs stop the process of mitosis in the fungal cells.
- The name of the drug is Griseofulvin:
  - It inhibits microtubule polymerization.
  - It is given orally to treat the infection caused by dermatophytes.
  - It is also used to treat the infection caused by T.capitis.
  - It is not effective for topical application.
- Special points: Griseofulvin is:
  - Enzyme inducer
  - It has a disulfiram reaction.
  - Fatty food increases the absorption of this drug.

Inhibit DNA Synthesis

- The name of the drug is Flucytosine.
- After entering the fungal cells, flucytosine becomes 5 Fluorouracil (5 FU) which has anticancer properties.
- This conversion doesn't take place inside normal human cells so the humans are not affected.
- The 5 FU inhibits fungal DNA synthesis.
- It is a fungistatic drug.
- Uses: It is majorly used to treat cryptococcal meningitis along with amphotericin B.
- Adverse effects: It can cause bone marrow suppression if it gets activated in human cells.
- It should be given in low doses in patients with renal failure.

Inhibit Protein Synthesis

- These drugs inhibit tRNA synthesis which further inhibits protein synthesis.
- The names of the drugs are Tavaborole and Efinaconazole.
- Uses: These are mainly used to treat toenail fungal infections.

Inhibit Chitin Synthesis

- The name of the drug is Nikkomycin.
- Uses: It is also used to treat the infection caused by dermatophytes.

Topical Antifungal Drugs

00:32:43

- **Polyenes:**
  - Hamycin
  - Natamycin
  - Nystatin

- **Azoles:**
  - Clotrimazole
  - Luliconazole
  - Miconazole
  - Sertaconazole
  - Efinaconazole
- Butenafine and Terbinafine
- **Other topical drugs are**:
  - Whitefield's ointment - It is a combination of salicylic acid and benzoic acid.
  - Ciclopirox olamine
  - Undecylenic acid
  - Tolnaftate

Management of different Fungal Infections

- The fungal infections can be superficial or deep mycotic. Here are some drugs of choice for different types of fungal infections:

Superficial Infections

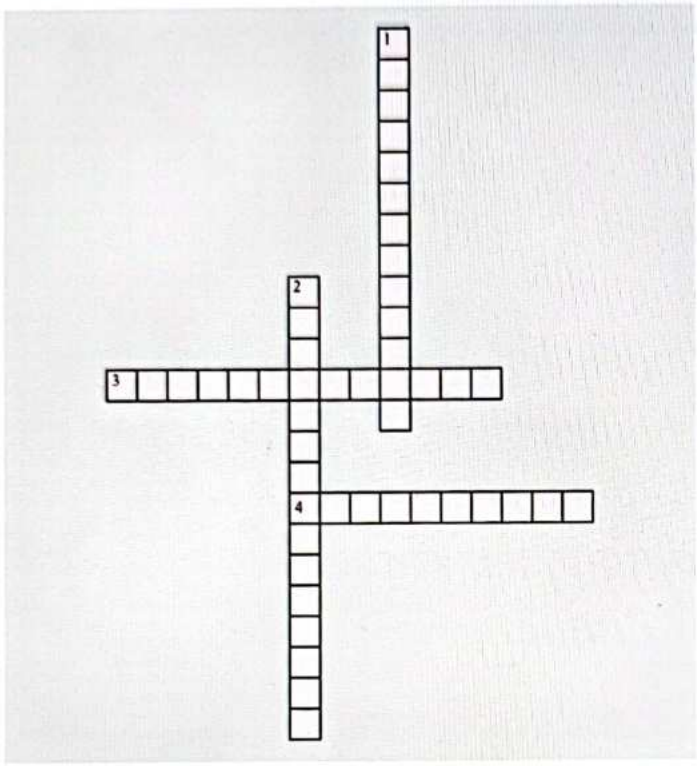
- The diseases are candidiasis, dermatophytes, and P.versicolor.
- The drugs of choice are:
- Oral: Fluconazole, itraconazole, or terbinafine are given.
- Topical antifungals are also given.

Deep Mycotic Infections

- Aspergillosis: This can be of two types-
  - Allergic bronchopulmonary type: Steroids + itraconazole is given.
  - Invasive aspergillosis: Voriconazole is given.
- Blastomycosis and Chromoblastomycosis: Itraconazole is given
- Candidiasis invasive, Cryptococcus, and Coccidioidomycosis: The drug of choice is fluconazole.
- Mucormycosis: The DOC is liposomal amphotericin B. The alternatives are Posconazole and Isaruconazole.
- Histoplasmosis and sporotrichosis: The DOC is itraconazole.
- Fusarium and pseudallescheria: The drug of choice is voriconazole.

CROSS WORD PUZZLES

Crossword Puzzle 1



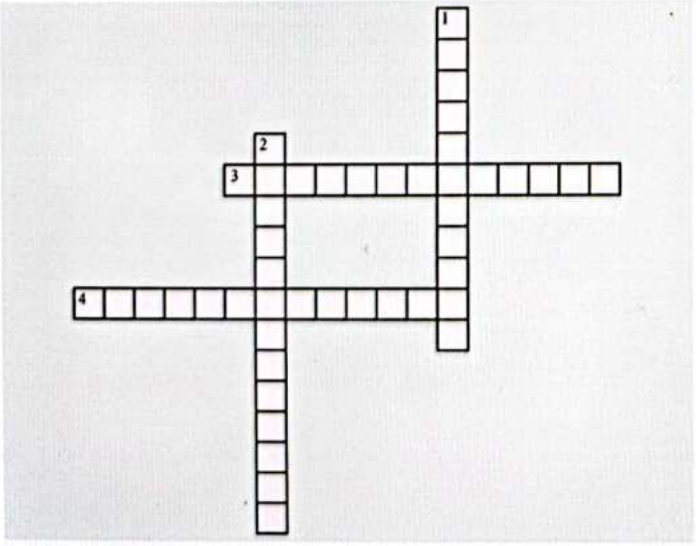
Across

3. _____ can be given to renal and hepatic failure patients.
4. _____ is important for cell membrane formation.

Down

1. The drugs that inhibit cell wall formation are called _____.
2. Squalene is converted to lanosterol with help of the enzyme _____.

Crossword Puzzle 2



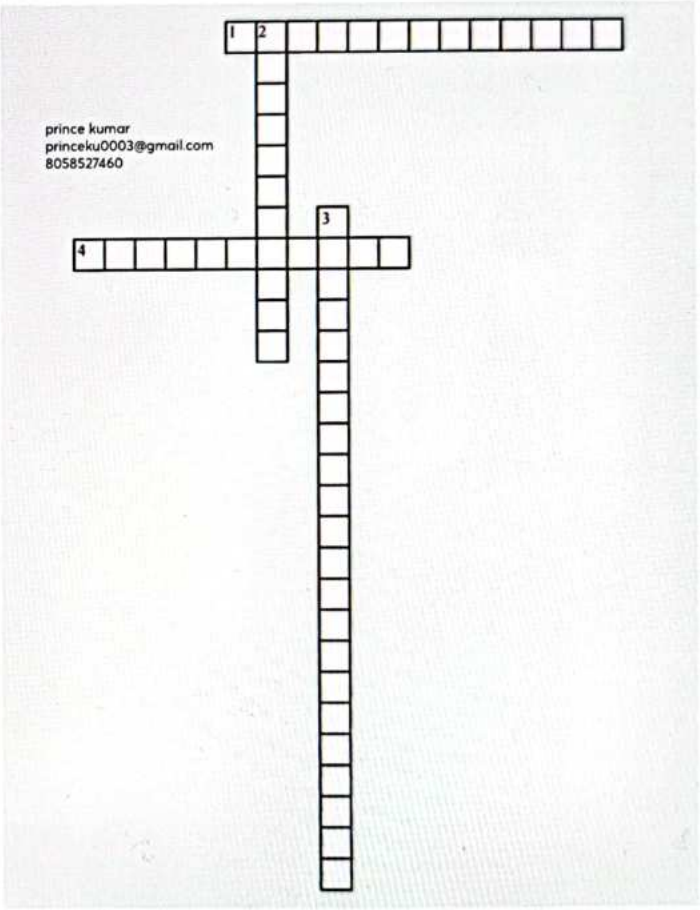
Across

3. _____ has anti-inflammatory properties.
4. _____ has anticancer properties.

Down

1. _____ can't treat Candida krusei because of intrinsic resistance against the drug.
2. _____ is used to treat Cushing's disease.

Crossword Puzzle 3



Across

1. amphotericin B can be given in combination with _____ to prevent infusion reaction.
4. I.V. liposomal amphotericin B is given with _____ to treat cryptococcal meningitis.

Down

2. Natamycin is used only topically as it is highly _____.
3. _____ is the drug of choice to treat Mucor mycosis.

84 ANTI HELMINTHIC DRUGS

- Anti-helminthic drugs are medications used to treat parasitic infections caused by helminths (worms).
- These drugs are designed to kill or remove the worms from the body, either by causing them to detach from the host tissue or by blocking their metabolic processes.
- Anti-helminthic drugs can be used to treat a variety of infections, including intestinal worms, liver flukes, and blood-borne parasites.
- They can be administered orally or through injections and can have varying degrees of effectiveness depending on the type of helminth infection being treated.

Helminths

00:01:40

The following table shows various helminths (Cestodes or worms):

Cestodes	Drug of choice
Taenia solium	Praziquantel
Taenia sagginata	Praziquantel
Fish tapeworm	Praziquantel
H.nana	Praziquantel
Neurocysticercosis And Hydatid cyst	Albendazole

The following table shows different Nematodes and the drug of choice:

Nematodes	Drug of Choice
Ascaris Lumbricoides	Albendazole
Ancylostoma Duodenale	Albendazole
Necator Americanus	Albendazole
Enterobius Vemicularis(Pin Worm)	Albendazole
Trichenella Spiralis	Albendazole
Filariasis	Diethyl Carbamazine [DEC]
Loa Loa	Diethyl Carbamazine [DEC]
Strongyloidosis	Ivermectin
Onchocerciasis	Ivermectin
Cutaneous Larva Migrans	Albendazole/Ivermectin
Visceral Larva Migrans	Albendazole

Important Information

- Ivermectin is used for scabies.
- DEC is used in tropical eosinophilia

The following tables show types of trematodes/ flukes and drug of choice:

Trematodes (Flukes)	Drug of choice
Blood fluke	Praziquantal
Lung fluke	Praziquantal
Bladder fluke	Praziquantal
Liver fluke (Fasciola hepatica)	Triclabendazole

Albendazole

Mechanism of Action

00:05:59

- The main mechanism is to inhibit microtubules
- Second mechanism is to inhibit glucose uptake
- By inhibiting these helminths will be expelled out.

Pharmacokinetics:

- Albendazole is converted into albendazole sulfoxide.
- The advantage of albendazole sulfoxide is it has high Vd and have very good penetration into the cysts.
- Therefore, albendazole is preferred in the treatment of neurocysticercosis and hydatid disease.

Q. Why is the albendazole drug better than praziquantel in neurocysticercosis?

Ans. The following points make the albendazole drug better than praziquantel:

1. Albendazole is cost-effective.
2. It is more efficacy than praziquantel.
3. Duration of therapy with albendazole is short.
4. Penetration to cyst is good.
5. Steroids increase the effect of albendazole.

- Before giving albendazole, you had to start the patient on anti-seizure medications and steroids.
- Ocular cysticercosis cannot be treated with drugs because it can cause blindness to the patient.

Q. Can we give albendazole to a new born baby?
Ans. Albendazole is contraindicated in child less than 1 year.

- Albendazole is one of the medications used in the national deworming programme: the dosage for children between the ages of one and two years is 200 mg. For children more than two years the dosage is 400 mg.
- Because of hepatotoxicity as the adverse effect.

Other Drugs

Drugs	Description
Pyrantel Pamoate	• This drug stimulates nicotinic Cholinergic receptors in the worm which will lead to spastic paralysis. • When there is spastic paralysis the worms cannot hold on and they are expelled.
Piperazine	• It is a GABA Agonist. It will open the chloride channels. • When the chloride channels are opened there will be cell hyperpolarization and it will lead to flaccid paralysis.
Levamisole	• It stimulates the ganglia of worms. • This will lead to tonic paralysis. • It is a modal modulator. Immunomodulator and is used in cancer called Colorectal cancer (levamisole + 5FU is used).
DEC (Diethyl Carbamazine)	• They alter the micro- filarial membrane. • Then Mounting of the immune response takes place. • It is a drug of choice for filariasis and loaloa. Also used in tropical eosinophilia.
Ivermectin	• It stimulates a special channel for glutamate gated chloride channels. • It is effective particularly in Nematodes. • This leads to tonic paralysis.
Praziquantal	• Praziquantal is a drug of choice of cestodes and nematodes. • The mechanism of action increases the calcium influx and this leads to spastic paralysis.
Niclosamide	• It inhibits PFOR (Pyruvate ferrodoxin reductase). It is required for the electron transport chain if we inhibit this chain the energy process is hampered and helminthics is expelled out.

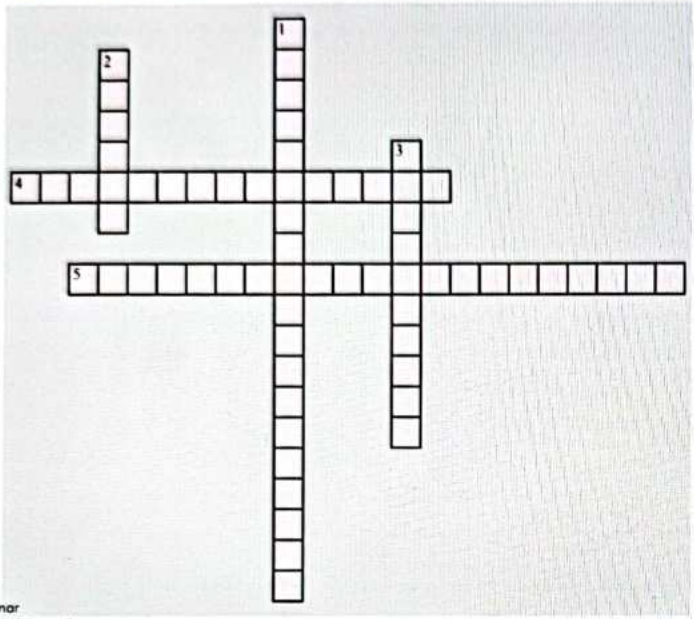
Q. What happens when you're managing a patient of onchocerciasis [river blindness]?
Ans. In this therapy, we can use Ivermectin Or Diethyl Carbamazine.

- But the DOC is ivermectin because the risk of mazotti reaction is more with DEC.
- When we use the drug mostly a reaction occurs called as mazotti reaction. The symptoms of mazotti reaction are fever, rashes, and lymphadenopathy.

Q. How to manage mazotti reaction?
Ans. Stop the drug and give steroids.

CROSS WORD PUZZLES

Crossword Puzzle 1



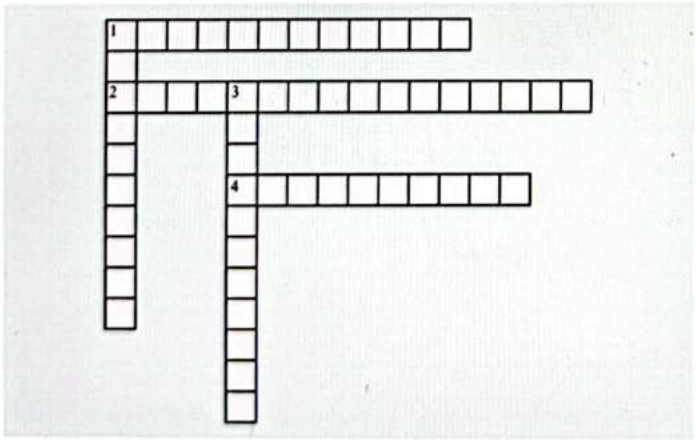
Across

4. found in tropical areas
5. causes damage in tissue organs

Down

1. parasitic roundworm
2. causes severe disfiguring skin lesions
3. swollen lymph nodes

Crossword Puzzle 2



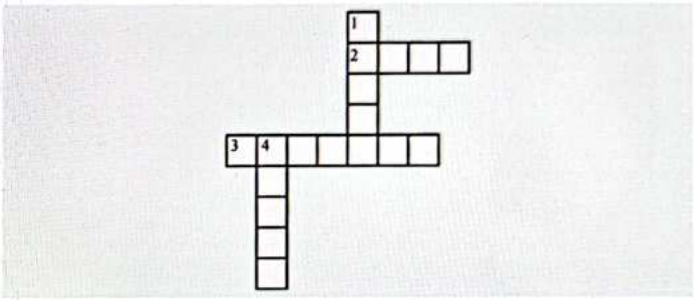
Across

1. Drug of choice of cestodes
2. It stimulates nicotinic cholinergic
4. It is a modal modulator

Down

1. It is in the Gaba agonist
3. It ihibits pyruvate ferroxidin reductase

Crossword Puzzle 3



Across

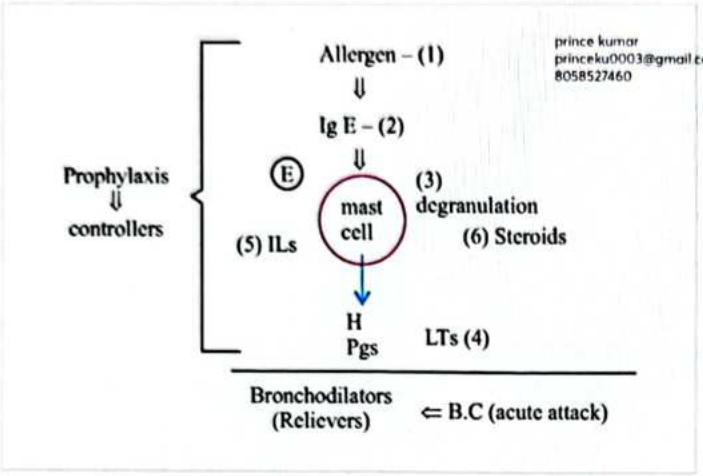
2. drug of choice praziquantal
3. infects the urinary tract of humans

Down

1. parasitic flatworm
4. drug of choice is triclabendazole

85 ASTHMA

Pathophysiology of Bronchial Asthma 00:01:00



- When the patient is exposed to allergens like dust, mite, and pollen, which is responsible for causing Broncho-constriction.
- As a result, the patient will have symptoms like sneezing, coughing, wheezing, and difficulty in breathing (acute attack of asthma).
- When the patient is exposed to an allergen, it activates immunoglobulin (IgE).
- IgE binds to the mast cell receptors which causes degranulation and release of inflammatory mediators (histamine, serotonin, leukotriene, prostaglandin, eosinophils)
- These inflammatory mediators are responsible for the contribution of Broncho-constriction.
- As a result, it increases mucus production. This is called Acute attack of Asthma.
- Drugs used in the treatment of Bronchial asthma are called bronchodilators/relievers.

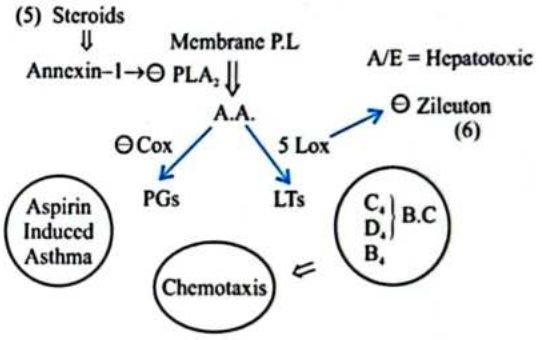
Management of Bronchial Asthma

- **Patient education not to be exposed to the allergen**
- **Block the immunoglobulin IgE with** Omalizumab (only for prophylactic use).
  - Omalizumab is a monoclonal antibody, it can't be given through the oral route, because these are proteins. So, the subcutaneous route is the preferred route.
  - Omalizumab is used in bronchial asthma and allergy.

- **Stabilize the mast cells or Mast cell stabilizers**
  - These Mast cell stabilizers do not allow the mast cells to degranulate. So, inflammatory mediators will not release.
  - Mast cell stabilizers can be given by inhalation route or oral route.
  - Drugs given by inhalation route is Sodium Cromoglycate (only for prophylaxis), Nedocromil.
  - Drugs given by oral route is- Ketotifen

- **Leukotriene receptor antagonist** 00:08:06
  - Montelukast, Zafirlukast (used for allergy, bronchial asthma and prophylactic drugs).
  - Montelukast has steroid-sparing properties.
  - Adverse effects- Increase liver enzymes, Chrug strauss syndrome.

Steroids 00:10:10



Mechanism of Action

- From the phospho-lipid membrane, it releases arachidonic acid by phospholipase A2 (PLA2).
- Arachidonic acid releases two important enzymes- COX (cyclooxygenase enzyme) and LOX (lipoxygenase enzyme).
- COX releases prostaglandins and LOX releases leukotrienes.
- C4, D4, and B4 are leukotrienes and C4 and D4 are responsible for bronchoconstriction.
- B4 is responsible for chemotaxis.
- When inflammation occurs, it causes bronchoconstriction.
- Steroids produce annexin-1, which inhibits PLA2.
- COX inhibitors or COX inhibition can trigger asthma, and arachidonic acid can divert to LOX which produces leukotrienes and cause bronchoconstriction (particularly aspirin-induced asthma).
- LOX enzyme can be inhibited by Zileuton.
- Zileuton causes hepatotoxicity.
- Steroids have anti-inflammatory property and increase β2 response in the lungs.

Routes of Administration 00:13:15

- Inhalation route
  - Beclomethasone, Budesonide, Ciclesonide, and Fluticasone.

- Ciclesonide is soft steroids.
- When steroids are administered through metered dose inhaler or dry powder inhaler. There is a chance that steroids can reach systemic circulation and can cause adverse effects.
- Ciclesonide systemic absorption is less, so these are called soft steroids.
- Steroid inhalers have some adverse effects- Oral candidiasis. It can be prevented by gargles or mouthwash after inhalation.
- If the patient gets oral candidiasis, it can be treated by clotrimazole.

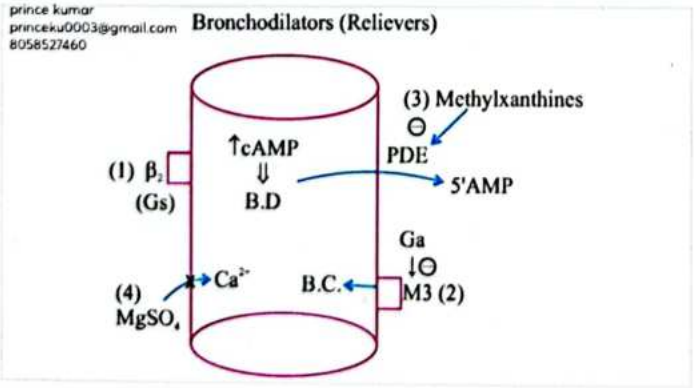
- Oral steroids
  - Prednisolone and methylprednisolone
  - Oral steroids should not be used in the beginning because these are systemic steroids and can cause adverse effects in the long run. Only used for severe persistent asthma cases.

- Intravenous steroids
  - Hydrocortisone and Methylprednisolone.
  - Used in status asthmaticus (acute attack of asthma).

Important Information

- Histamines can't be blocked, because antihistamines are not effective in asthmatic conditions.
- Prostaglandins can't be blocked because some are bronchodilators and some are bronchoconstriction.
- Bronchodilators or Relievers of Bronchoconstriction.
- Drugs that are used to prevent the attack of asthma are called Prophylactic drugs or controllers.

Bronchodilators or Relievers of Bronchoconstriction 00:18:00



- β2 is present in the bronchus which are Gs-coupled receptors, which increase cyclic AMP that result in bronchodilation.
- cAMP is broken down into 5'AMP by the phosphodiesterase enzyme (PDE).

- M-3 receptors (Gq coupled receptor) act by the IP3-DAG pathway- causing smooth muscle constriction or bronchoconstriction.
- It also allows entry of Ca2+ which helps in bronchoconstriction.
- By stimulating β2, it will cause bronchodilation.
- To make it longer-acting, it needs to block the PDE enzyme. These drugs are called methyl xanthine.
- Block the Ca2+ channel with the drug magnesium sulphate (MgSo4) which is a bronchodilator
- or inhibits the M-3 receptor.

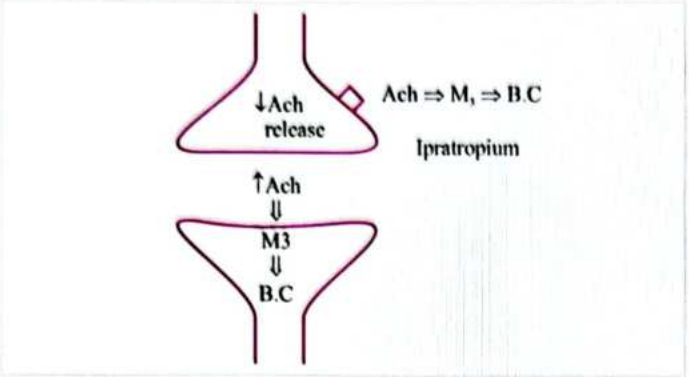
β2 Agonists

- **SABA (short-acting β2 agonist)**
  - For example- Salbutamol, Terbutaline- work only for 4-5 hours. So, the patient needs to take these drugs four times a day.
  - Adverse effects: Salbutamol and Terbutaline are known to cause hyperglycemia and hypokalemia.
  - Salbutamol is known to cause tremors, tachycardia, and tolerance after repeated use.
  - The reason for tolerance is that the β2 receptor undergoes desensitization.
  - Salbutamol can be used to treat hyperkalemia by nebulization.

- **LABA (Longer-acting β2 agonist)**
  - These drugs can work for >12 hours.
  - Drugs: Formoterol (fast onset), Salmeterol (slow onset).
  - These drugs are not used alone for a long period, because they develop tolerance (β-2 undergoes desensitization).
  - These drugs are always used in combination with ICS (Inhaled corticosteroids).
  - ICS increases β2 sensitivity and can be used alone.

Muscarinic Antagonists 00:26:35

- **SAMA (Short-acting Muscarinic Antagonists)**
  - Drug- Ipratropium bromide
  - Ipratropium bromide needs to be given 4 times a day.
  - Mainly used in the management of COPD than bronchial asthma.
  - In COPD, larger bronchioles are affected because of high cholinergic tone, so anticholinergic drugs are used like ipratropium bromide.
  - In bronchial asthma, smaller bronchioles are affected. So, β2 is preferred.
  - **Adverse effect-** it can produce a bitter taste and paradoxical bronchoconstriction.
    → **Two theories to explain paradoxical bronchoconstriction -** Due to the use of preservatives (benzalkonium, EDTA) or by inhibiting presynaptic M2 receptors.



→ Acetylcholine acts as an M3 receptor and causes bronchoconstriction.

→ In the presynaptic terminal, the M2 receptor is present. Its role is to decrease acetylcholine release.

→ Ipratropium bromide blocks the M2 receptor at the presynaptic terminal, then acetylcholine will be released.

→ This acetylcholine acts on the M3 receptor present at the postsynaptic terminal which will cause bronchoconstriction. This is called paradoxical bronchoconstriction.

- **LAMA (Longer-Acting Muscarinic Antagonists)**
  - Advantages- No paradoxical bronchoconstriction, longer-acting.
  - Drugs- Tiotropium bromide, Glycopyrronium bromide, Umeclidinium bromide.
  - Mainly used for the management of COPD.
  - **Adverse effect-** Dry mouth and Urinary retention.

- **Methylxanthines**
  - Drugs: Aminophylline and Theophylline.
  - Theophylline requires therapeutic drug monitoring and the level should be between 5-15 mg/L.
  - Aminophylline and Theophylline work by inhibiting the enzyme PDE and adenosine which are responsible for bronchodilation.
  - Aminophylline and Theophylline increase interleukin-10 (IL-10) release and decrease inflammatory genes.
  - Aminophylline and Theophylline also work by histone deacetylation activation.
  - Aminophylline is given via the I.V. route to treat attacks of asthma.
  - Theophylline is used for mild asthma and severe cases of COPD.
  - Caffeine, Aminophylline, and Theophylline have methylxanthines.
  - **Adverse effects**
    → CNS:
    - Seizures: due to adenosine blockade
    - Behavioural abnormality

    → CVS
    - Arrythmia: due to adenosine blockade and PDE3 inhibitor

    → Renal: It cause diuresis due to adenosine blockade

    → Others: Nausea, Vomiting, Gastritis, Headache due to the blockade, and PDE 4 inhibition.

- **Magnesium Sulphate ($MgSO_4$)**
  - $MgSO_4$ blocks the entry of Ca^{2+}. As a result, it will not cause smooth muscle contraction and bronchoconstriction.
  - $MgSO_4$ can be given either as an IV route or nebulization in the management of acute attacks of asthma.

Status Asthmaticus

00:39:20

- It is the condition when the patient comes with difficulty in breathing and hypoxia.

Management

- **S** - Salbutamol: is used in the form of nebulization.
- **O** - Oxygen: Humidified with 100% oxygen.
- **H** - Hydrocortisone (IV route): increases ß 2 response.
- **I** - Ipratropium bromide: It dilates larger bronchioles and is given in the form of nebulization.
- **T** - Terbutaline: Given via subcutaneous route because it can reach the lower alveoli.
- Asthma - Antibiotics: Because the triggering of status asthmaticus is an infection.
- Acidosis: So, it can be managed by sodium bicarbonate ($NaHCO_3$).
- $MgSO_4$ and Aminophylline are the reserve drugs.

Newer Drugs for the Treatment of Asthma and COPD

00:42:20

- **Interleukin-5 antagonists (IL-5)**
  - **Drugs are** Reslizumab, Benralizumab and Mepolizumab
  - Used in the treatment of severe eosinophilic asthma patients.
  - Given as injection
- **Newer drug for COPD**
  - **M3 antagonist:** Revafenacin
  - **PDE4 inhibitor:** Roflumilast
  - **V.LABA:** Indacaterol and Vilanterol

Important Questions

Q. When the patient is exposed to an allergen, it activates

Ans. Immunoglobulin (IgE)

Q. What are the inflammatory mediators

Ans. Histamine, serotonin, leukotriene, prostaglandin, eosinophils.

Q. Inflammatory mediators are responsible for the
Ans. Contribution of Broncho-constriction

Q. Hydrocortisone (IV route) increases
Ans. ß 2 response

Q. Ipratropium bromide dilates larger bronchioles and given in the form of
Ans. Nebulization

Q. Theophylline requires therapeutic drug monitoring and the level should be
Ans. between 5-15 mg/L

Q. Aminophylline and Theophylline work by inhibiting the enzyme
Ans. PDE

Q. Chrug strauss syndrome is the adverse effect of which drugs
Ans. Montelukast and ZafiRluKast

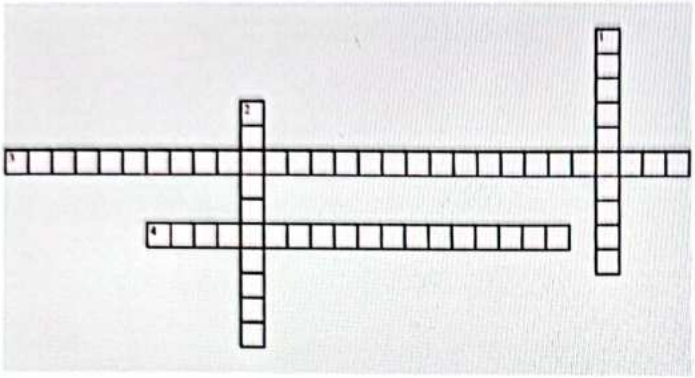
Q. Immunoglobulin IgE can be blocked with
Ans. Omalizumab

Q. MgSO4 blocks the entry of
Ans. Ca2+. As a result, it will not cause smooth muscle contraction and bronchoconstriction

Q. Bronchodilators are also called
Ans. Relievers of Bronchoconstriction

CROSS WORD PUZZLES

Crossword Puzzle 1



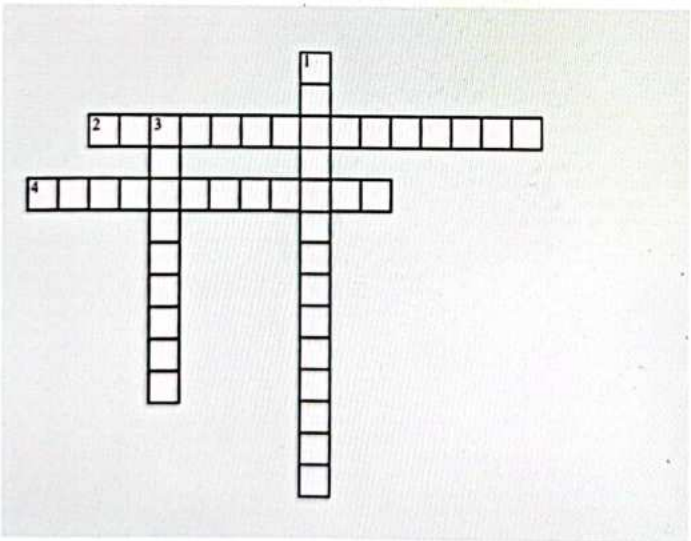
Across

3. ___ is the adverse effect of short-acting muscarinic antagonists,
4. ___ belongs to the class of short-acting muscarinic antagonists (SAMA).

Down

1. _____ is a LABA with a rapid onset of action.
2. _____ can be used to treat hyperkalemia by nebulization.

Crossword Puzzle 2



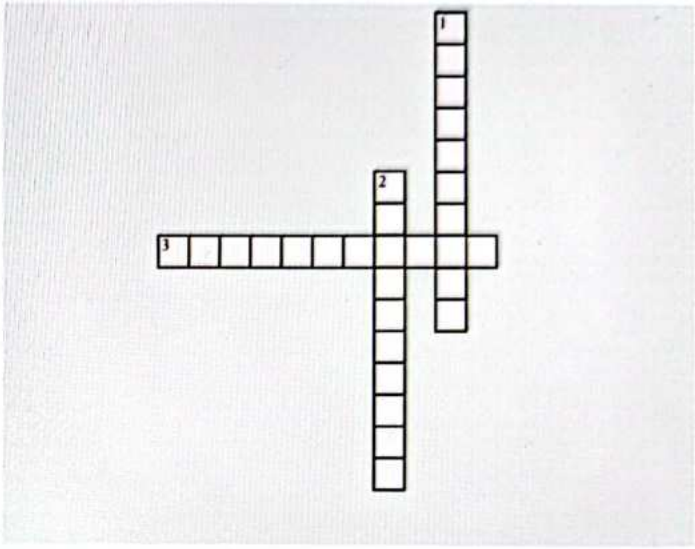
Across

2. ___ can be prevented by gargling or mouthwash after inhalation.
4. _____ is an oral steroid.

Down

1. ___ is the intravenous steroid.
3. ___ is produced by steroids, which inhibit PLA2.

Crossword Puzzle 3



Across

3. _____ is known to cause tremors, tachycardia, and tolerance after repeated use.
4. _____ can cause seizures in the brain due to adenosine blockade.

Down

1. ___ are the drugs that are used to prevent the attack of asthma.
2. ___ inhibits the LOX enzyme.

87 COUGH

Classification

- Dry cough - No sputum production.
  - Dry cough has to be suppressed.
- Productive cough - Sputum production is present.
  - Sputum must be let out.

Drugs for Dry Cough 00:00:26

- **Opioids**
  - Opioids used for dry cough are:
    - → Codeine
    - → Pholcodine
    - → Levopropoxyphene
  - The adverse effects of opioids are:
    - → Sedation
    - → Constipation
    - → Possible abuse
    - → Higher doses can cause respiratory depression and thus aren't used in the paediatric population.

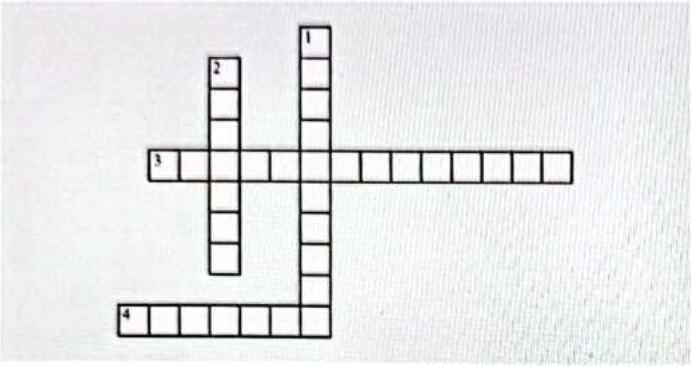
- **NMDA Antagonist**
  - Dextromethorphan:
    - → No/fewer chances of sedation/abuse/respiratory depression
    - → Can be used in children.
    - → The combination of codeine and dextromethorphan cannot be used and is considered irrational.
- **Benzonatate**
  - It is a local anaesthetic.
  - It has two actions:
    - → Brain - Central mechanism to suppress cough.
    - → Lung - Peripheral mechanism to inhibit peripheral Lung stretch receptors

Drugs for Productive Cough 00:05:17

- The sputum must be removed or infection will flare up.
- **Expectorants**
  - They increase the expulsion of sputum from the lung. E.g. Guaiphenesin, Ammonium chloride.
- **Mucolytics**
  - They will convert the thick sputum into thin and watery sputum. E.g. Ambroxol, Bromhexine.
  - These drugs depolymerize the mucopolysaccharide in the sputum.
- **Carbocysteine & Acetylcysteine**
  - They break the disulphide bond in the sputum to convert thick sputum into thin sputum.
  - Acetylcysteine is also the antidote for Paracetamol (PCT) toxicity.
- The cough syrups cannot be exchanged because if productive cough syrup is used for dry cough, it tries to expel the sputum by increasing the cough. Thus, it worsens the condition.

CROSS WORD PUZZLES

Crossword Puzzle 1



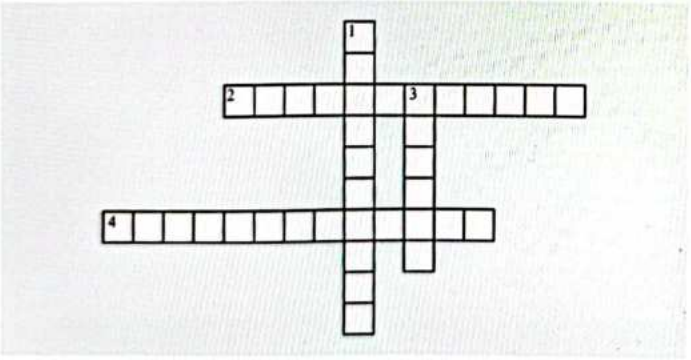
Across

3. _____ is the antidote for Paracetamol (PCT) toxicity.
4. Higher doses of____ can cause respiratory depression.

Down

1. _____ depolymerize the mucopolysaccharide in the sputum.
2. The combination of _____ and dextromethorphan is considered irrational.

Crossword Puzzle 2



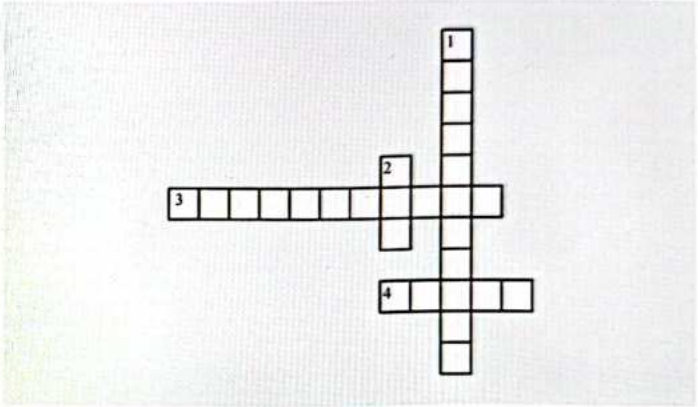
Across

2. ____ increase the expulsion of sputum from the lung.
4. _____ breaks the disulphide bond in the sputum to convert thick sputum into thin sputum.

Down

1. Ambroxol and Bromhexine are _____.
3. Codeine is considered a kind of____.

Crossword Puzzle 3



Across

3. Guaiphenesin is a kind of_____.
4. Benzonatate has a central mechanism in ____ to suppress cough.

Down

1. _____ is a local anaesthetic.
2. ____ cough must be suppressed to be treated.

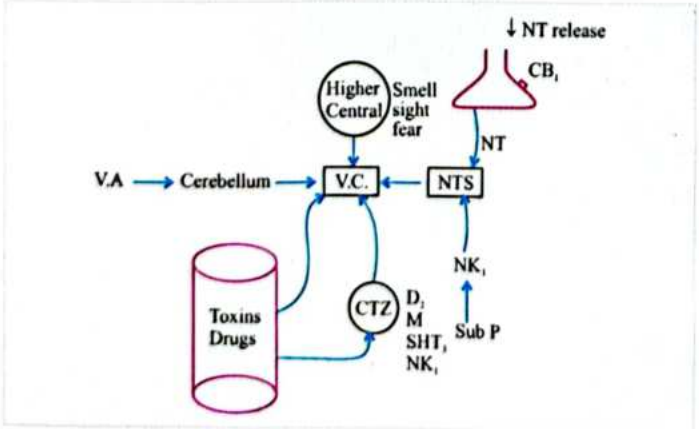
89 ANTI EMETIC DRUGS

These drugs are used to prevent and treat nausea and vomiting. The most common uses of antiemetic drugs include

- Gastroenteritis.
- Motion sickness.
- Morning sickness (first trimester).
- Chemotherapy-induced nausea and vomiting (CINV).
- Postoperative nausea and vomiting.

Pathophysiology of vomiting

- The higher center stimulates the vomiting center in the brain through bad smell, sight, and fear.
- The second stimulus comes from the vestibular apparatus (balance) connected to the cerebellum, which activates the vomiting Center.
- The toxins or some drugs in the blood vessels also trigger the stimulation of the vomiting center.
- There is a zone called the chemoreceptor trigger zone (CTZ) outside the blood-brain barrier. This can also be activated by toxins and drugs, which activate the vomiting Center. The activation of receptors in this zone, including D2, Muscularinic, 5HT3, and Neurokinin1 (NK1), activates the vomiting center.
- The nucleus tractus-solitarius (NTS) is also connected to the vomiting Center.
- NTS can be activated by neurotransmitters released from the nerve terminal can cause nausea and vomiting. This is controlled by the cannabinoid1 (CB1) receptor, which decreases the release of neurotransmitters. Hence, it is suggested to stimulate CB1 to control nausea and vomiting.
- Pain in any condition causes the release of "substance P," which activates NK1.



Anti Ematic Drugs: Targets, Uses, And Effects

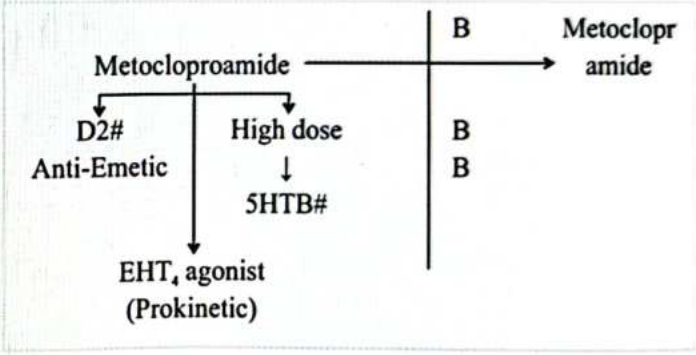
Refer Table 89.1

Mechanism of Action

Metoclopramide- It acts on the peripheral and central regions of the brain.

Periphery-

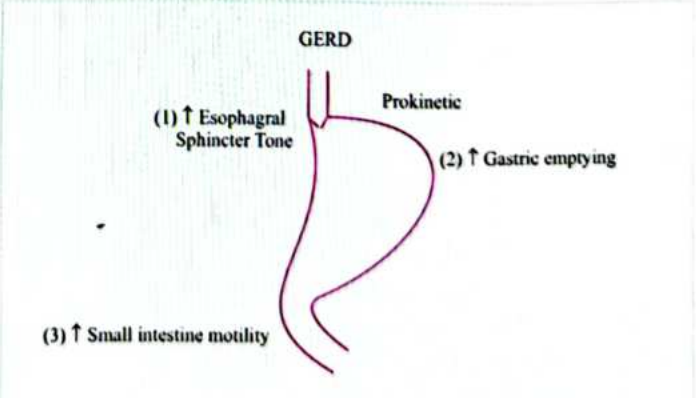
- It enters the brain by crossing the blood-brain barrier. In the periphery, it blocks D2, which is responsible for the antiemetic effect.
- It also has 5HT4 agonistic property that helps in prokinetic properties used to manage GERD (Gastroesophageal reflux disease).
- The drug also produces 5HT3 antagonistic properties at high doses.



Side note-

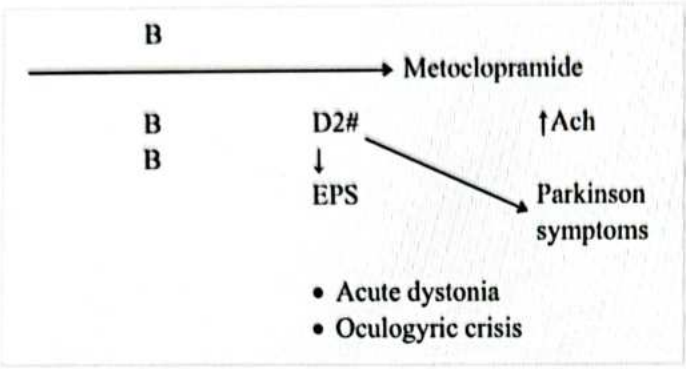
Prokinetic property:

- In GERD patients, the esophageal sphincter does not work properly, and acid reflux back into the esophagus. Metoclopramide increases esophageal sphincter tone, gastric emptying, and small intestinal motility, collectively known as prokinetic properties.



Brain Centre

- When metoclopramide enters the brain, it blocks the D2 receptor in the brain where dopamine and acetylcholine are in balance. But D2 Blockers stop the dopamine action, and acetylcholine becomes higher in concentration, and the patient may develop extrapyramidal symptoms leading to acute dystonia and oculogyric crisis.



- These conditions are usually seen in younger populations, but blocking D2 in the elderly can lead to Parkinson's symptoms.
- In this condition, central anticholinergics such as benzhexol or promethazine are given to manage the levels of acetylcholine.

Important Information

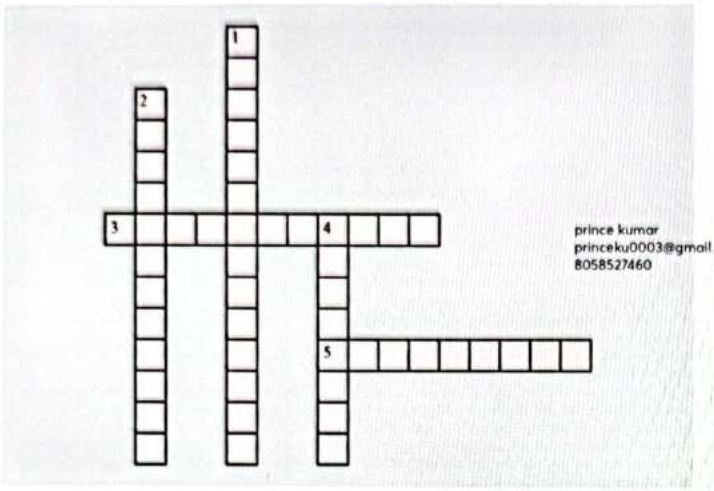
- Due to the central action of metoclopramide, it is not commonly used nowadays.
- Domperidone does not cross BBB, so no risk of extrapyramidal symptoms.
- Hyoscine can be given in two ways; oral tablet or transdermal patch.
  a. The oral tablet is taken 1-2 hours before the journey and works for a shorter journey (4-6 hours).
  b. The patch is applied 6-8 hours before the journey and works for 3 days.
- Recently, the combination of Netupitant and Palonosetron has been approved for early and late CINV.

Table 89.1

Target	Drug	Effect	Use
D2 Blocker	Metoclopramide	Cross BBB	
	Domperidone	Does not cross BBB	GERD, Nausea and vomiting and levodopa-induced nausea and vomiting
	Levosulpiride	cross BBB	GERD
	Amisulpiride		Postoperative nausea and vomiting
Antihistamines (I Gen)	Doxylamine+B6		Morning sickness
	Promethazine Buclizine Meclizine		All are used to prevent motion sickness.
Anticholinergic drugs	Hyoscine (scopolamine)		Motion sickness (DOC)
5HT3 Antagonists	Ondansetron (preferred in child) Granisetron (patch) Dolasetron Palonosetron	QT Prolongation	Early chemotherapy-induced nausea and vomiting(CINV) [DOC]
Neurokinin 1 receptor antagonist	Aprepitant Fosaprepitant Netupitant Rolapitant		Late CINV (DOC)
Cannabinoid 1 Receptor Agonist	Nabilone Dronabinol		Resistant vomiting cases and Anorexia in HIV patients
Adjuvant Drugs	Dexamethasone (steroid)	Decreases inflammation	Vomiting
	Lorazepam (Benzodiazepine)	CNS Suprresant	Resistant Vomiting

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Activates the vomiting center
5. a CNS Suppresant

Down

1. a D2 blocker
2. used to prevent motion sickness
4. Cannabinoid 1 Receptor Agonist

90 CONSTIPATION

Etiology

- In constipation, a patient has difficulty passing stools.
- It's due to two main reasons:
  - Organic cause: It can be due to an obstruction, such as a tumour in the intestine.
  - Functional constipation: The reasons here include a sedentary lifestyle, lack of exercise, fibre deficiency in the diet, and abnormal bowel habits.

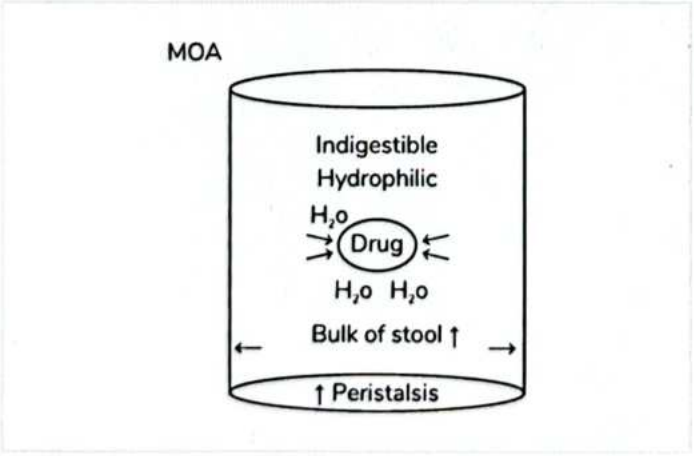
Laxatives And Purgatives 00:02:00

- Laxatives evacuate the formed stools.
- Purgatives evacuate watery stools.
- **Uses:**
  - For functional constipation, a patient must be educated about using fibre in the diet, exercise, and changing lifestyle.
  - Before surgery or endoscopy, the bowel needs to be evacuated.
  - It can be used to decrease the strain if a patient is having hernia or cardiac disease.
  - Diarrhoea is induced to remove the poison.
  - For deworming, purgation is induced.

Bulk-Forming Laxatives 00:04:35

- Drug names are Bran, Ispaghula, Methylcellulose, and Psyllium.
- These are indigestible substances and hydrophilic in nature.

Mechanism of Action



- These indigestible and hydrophilic drugs attract water. There's bulk formation followed by peristalsis. These drugs take one to three days to start working.
- Adverse effects include flatus and abdominal pain.
- These are contraindicated for megacolon patients.

Stool Softeners 00:07:30

- These drugs add fluid or oil to the stool.
- Softening of the stool makes it easier for a person to defecate.
- Examples are Docusates and liquid paraffin.

Liquid Paraffin

- It is a mineral oil and softens the stool.
- Adverse effects include foreign body granuloma as the macrophages ingest liquid paraffin.
- There's a chance of lipid pneumonia as oil can trickle down from the stomach to the oesophagus and to the lungs when person lies down. So, it is avoided at night time.
- It decreases the absorption of vitamins A, D, E, and K.
- Soiling is another adverse effect.

Stimulant/Irritant Purgatives 00:10:50

- They irritate intestinal mucosa and cause peristalsis.
- Watery stools get evacuated easily.

Bisacodyl

- It can be given as an oral drug or a rectal drug.
- Orally it may take 8 hours to work. Rectally, it starts working in one hour.

Anthraquinones

- Drugs include Senna and Cascara Sagrada.
- Adverse effect:
  - They cause pigmentation of the colon, i.e., melanosis coli.

Osmotic Laxatives 00:13:30

- These are Lactulose and Lactitol.
- Besides constipation, they're used in Hepatic encephalopathy.
- In hepatic encephalopathy, ammonia is in high concentration in the blood and enters the brain. Gut bacteria generate ammonia. Rifaximin and Neomycin can be used to kill gut bacteria.
- Another strategy is to use Lactulose or Lactitol. They're broken down into lactic acid upon entering the gut. The environment becomes acidic, and ammonia gets ionized. Thus, they are not absorbed.
- Polyethylene glycol (PEG) is another osmotic laxative. It is given before surgery or endoscopic procedures.

Opioid-Induced Constipation 00:18:35

- Either an addict or a patient undergoing cancer therapy takes opioids for a long time.
- Treatment needs drugs, namely Methylnaltrexone, Naldemedine, Naloxegol, or a combo of Naloxone and Oxycodone in a 1:2 ratio. These are opioid antagonists.

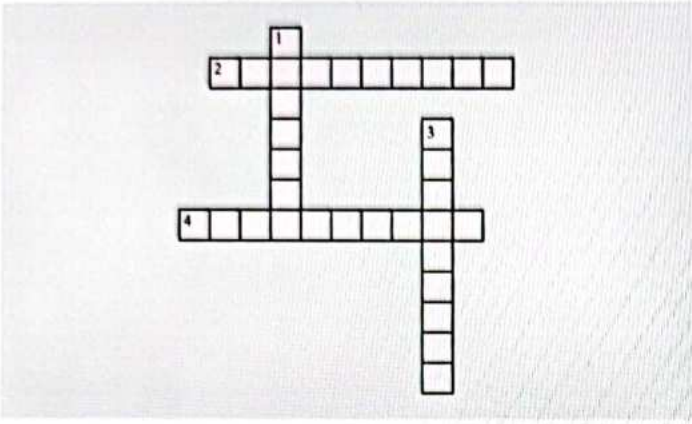
- Another drug is Alvimopan, also an opioid antagonist. It is used for postoperative bowel recovery.
  - **Warning:** It increases cardiovascular deaths.
  - It's only approved for 15 doses.
- A combo of Naloxone and Oxycodone in a 1:2 ratio is used because Naloxone is not absorbed orally and acts locally. Oxycodone is absorbed and gets into the brain, decreasing pain.
- If oxycodone acts peripherally, it can cause constipation in the gut. That's why Naloxone is given, as it acts locally and prevents the effect of oxycodone on the gut.

Irritable Bowel Syndrome (IBS) 00:22:05

- There are constipation-predominant cases of IBS.
- Laxatives and the drug Linaclotide are used in IBS. Another drug is Plecanatide. These drugs stimulate the enzyme guanylyl cyclase. It increases cGMP, which in turn increases Cl- concentration. Cl- draws water.
- Lubiprostone activates prostaglandins and increases the Cl- concentration.
- Prucalopride is a 5HT4 agonist. It increases intestinal motility.

CROSS WORD PUZZLES

Crossword Puzzle 1



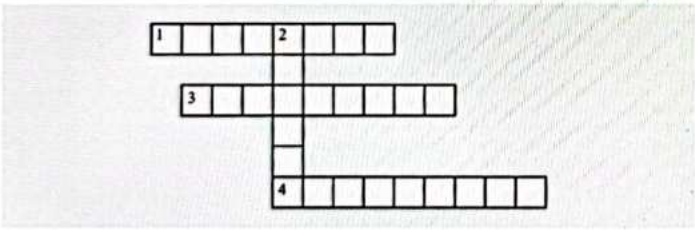
Across

2. _____evacuate watery stools.
4. _____constipation: The reasons here include a sedentary lifestyle, lack of exercise, fibre deficiency in the diet, and abnormal bowel habits.

Down

1. _____cause: It can be due to an obstruction, such as a tumour in the intestine.
3. _____evacuate the formed stools.

Crossword Puzzle 2



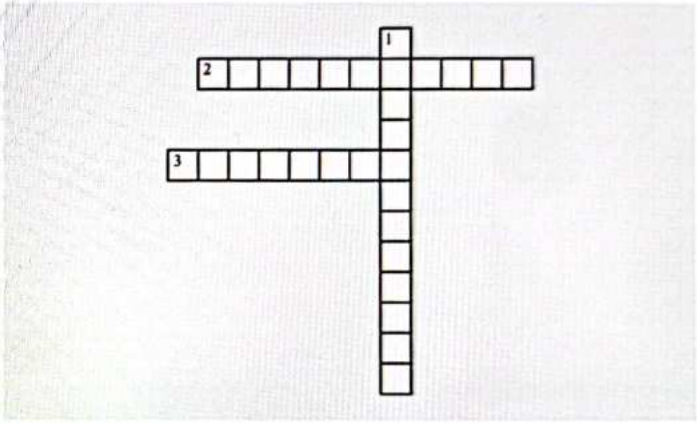
Across

1. Liquid _____ decreases the solubility of vitamins A, D, E, and K.
3. Bulk-forming laxatives are contraindicated for _____ patients.
4. _____purgatives irritate intestinal mucosa and cause peristalsis.

Down

2. Adverse effects include _____ and abdominal pain.

Crossword Puzzle 3



Across

2. Laxatives and the drug _____ are used in IBS.
3. A combo of Naloxone and Oxycodone in a 1:2 ratio is used because _____ is not absorbed orally and acts locally.

Down

1. _____glycol is an osmotic laxative.

91 ANTI DIARRHEA

- Diarrhea is the passage of loose stools.
- Water and electrolytes are lost. So, electrolyte imbalance is the problem.

Management of Diarrhea

Fluid Replacement

ORS

- Oral Rehydration Solution consists of 2.6 gm NaCl, 1.5 gm KCl, 2.9 gm Sodium Citrate, and 13.5 gm of glucose, as per the WHO formula.
- KCl and NaCl replenish the lost electrolytes.
- Sodium citrate treats acidosis.
- Glucose is given to increase sodium absorption. A transporter called SGLT-1 is present in the blood to transport sodium along with glucose.
- ORS is used to manage diarrhea, burns, heat stroke, and cholera.
- Take a sachet, mix it with 1 liter water, and use it within 24 hours.

I.V. Fluids

- Commonly, Ringer Lactate and normal saline are given.

Antimotility Drugs 00:03:10

- These are opioids, namely Loperamide. This drug doesn't cross the BBB (Blood Brain Barrier) and acts in the periphery.
- It decreases the motility of the intestine and secretions.
- It is used in secretory diarrheas and traveller's diarrhea.
- It's contraindicated in infective diarrhea. Bacterial infection can flare up if used. It is because, due to decreased motility, intestines cannot throw out bacteria.
- It's contraindicated in children below four years of age. It can cause toxic megacolon and paralytic ileus in children.
- Another opioid, Diphenoxylate, exists, and the difference is that this drug can cross the BBB and cause Euphoria. That's why it's used along with Atropine, as it also crosses the BBB and causes confusion. This combination is given to decrease the abuse potential of opioids.

Racecadotril 00:07:22

- It is a prodrug and changes to a compound called Thiorphan after metabolism.
- It inhibits the enzyme enkephalinase in the gut.
- Enkephalins are endogenous opioids. So, inhibition of the enzyme causes an increase in Enkephalins in the gut.
- They only decrease secretions in the intestine without affecting motility.
- It can be used in all cases of diarrhea and given to children.

Newer Drugs 00:09:00

Telotristat

- This drug inhibits the enzyme Tryptophan Hydroxylase.
- It is used in Carcinoid syndrome because it decreases serotonin.

Crofelemer

- It blocks the Cl- channels and decreases diarrhea.
- It's used to treat HIV drugs associated with diarrhea.

Clonidine

- It's used in diabetic patients (DMT2) with diarrhea.
- It decreases secretions and motility.

Octreotide

- It is a somatostatin analogue.
- It is used in secretory diarrheas like VIPoma, Carcinoid, etc.

Probiotics

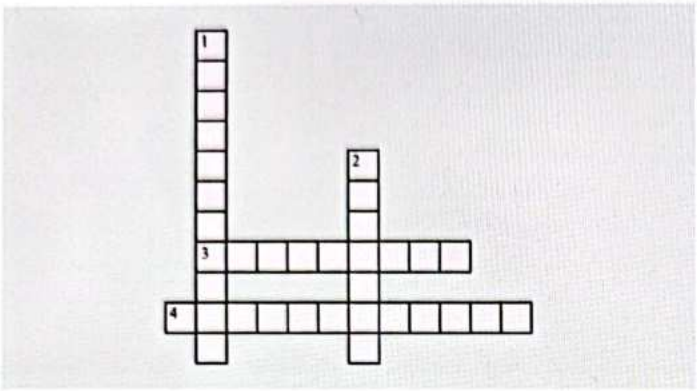
- Probiotic bacteria like Lactobacillus and Bifidobacterium dislodge pathological bacteria and replenish gut flora.
- In pediatric patients, zinc is added to probiotics because it decreases intestinal secretions and restores epithelial damage. It also decreases the severity and duration of diarrhea.

Antimicrobials 00:14:00

- Empirical antibiotics therapy for diarrhea due to bacteria or amoebiasis includes Fluoroquinolone and Metronidazole.
- If a patient's diarrhea is due to Salmonella food poisoning, I.V. Ceftriaxone or oral Ciprofloxacin is used.
- Ciprofloxacin and Rifaximin are the drugs of choice for traveler's diarrhea.
- Cholera patients are given Doxycycline.
- Clostridium difficile: Oral Fidaxomicin and oral Vancomycin are the options.
- Amoebiasis: In combination, Metronidazole and diloxanide furoate (kills amoebic cysts) are given.
- Giardiasis: Tinidazole or Metronidazole can be used.

CROSS WORD PUZZLES

Crossword Puzzle 1



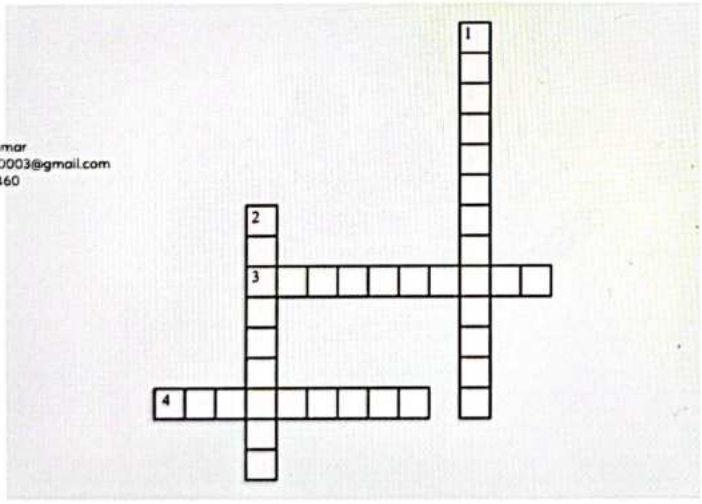
Across

3. Telotristat is used in Carcinoid syndrome because it decreases_____.
4. _____ is a prodrug and changes to a compound called Thiorphan after metabolism.

Down

1. _____drug inhibits the enzyme Tryptophan Hydroxylase.
2. _____are used as anti-motility drugs.

Crossword Puzzle 2



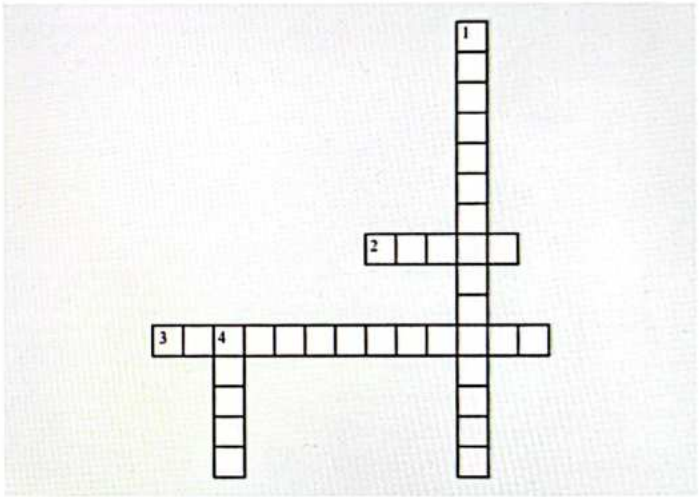
Across

3. _____is used in secretory diarrheas like VIPoma, Carcinoid, etc.
4. In_____ patients, zinc is added to probiotics because it decreases intestinal secretions and epithelial damage.

Down

1. Probiotic bacteria like_____ and Bifidobacterium dislodge pathological bacteria and replenish gut flora.
2. _____ is used in diabetic patients (DMT2) with diarrhea.

Crossword Puzzle 3



Across

2. It can cause toxic megacolon and paralytic_____ in children.
3. Empirical Antibiotics therapy for diarrhea due to bacteria or amoebiasis includes Fluoroquinolone and _____.

Down

1. Empirical antibiotics therapy for diarrhea due to bacteria or amoebiasis includes_____ and Metronidazole.
4. It can cause_____ megacolon and paralytic ileus in children.

92 ANTI PLATELET DRUGS

Classification of Clots 00:00:35

- These drugs prevent clot formation in an artery.
- The major use of these drugs is prophylaxis.
- There are two types of clots;

Refer Table 92.1

Q. Which drug cuts the clot?

Ans: Thrombolytics cut the clots including both arterial clots and venous clots.

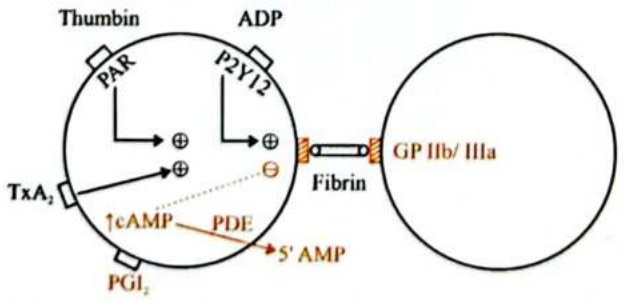
Adverse Effect- Bleeding

Clot Formation: Artery 00:06:15

- In the artery, the endothelium has a smooth lining. This endothelial damage makes the collagen exposed which triggers the secretion of a factor called Von Willebrand factor. As a result, platelets come into action and stick to that place, this is called platelet adhesion.
- Adhered platelets release certain substances called thromboxane A2 that release ADP. Tissues also release thrombin that leads to platelet activation, and more platelets are recruited to the site of damage resulting in platelet aggregation.
- When two platelets come into action they will bind with the help of a protein called GP41 and both are bound together by fibrin.

Platelet Aggregation

- Two platelets come together at a binding site; GP IIb/IIIa allows the attachment of fibrin.
- Platelets are also activated by ADP release and activate the receptor called P2Y12.
- Thrombin activates the PAR receptor that further promotes platelet aggregation.
- Thromboxane A2 (TxA2) also activates platelet aggregation.



- **Opposition**
  - **Prostaglandins I2-** act by increasing cAMP which inhibits platelet aggregation. The cAMP is further broken into 5'AMP with the help of phosphodiesterase.

Target of Platelets Aggregation 00:10:55

- GP IIb/IIIa
- P2Y12
- PAR
- TxA2
- Phosphodiesterase inhibitors

Refer Table 92.2

Important Information

Clopidogrel [Prodrug]

- Activated by CYP2C19 (microsomal enzyme)
- Poor metabolizers cannot convert Clopidogrel into an active state and will fail to work. Hence, it is termed a pharmacogenetic issue.
- Omeprazole + Clopidogrel combination is also not recommended due to the inhibitory action of Omeprazole on CYP2C19.

Important Information

- Dipyridamole causes a Coronary steal phenomenon because it dilates the non-ischemic zone while, in M.I. or angina, the ischemic Zone requires more blood. Therefore, it is not used in MI or angina.
- Aspirin, Clopidogrel, and Dipyridamole only are approved for stroke prophylaxis due to the lesser risk of haemorrhage.

Uses of Antiplatelet Drugs

- **CVS-** Angina, MI, ACS and PCI
- **CNS-** TIA and Stroke
- Peripheral vascular disease

Table 92.1

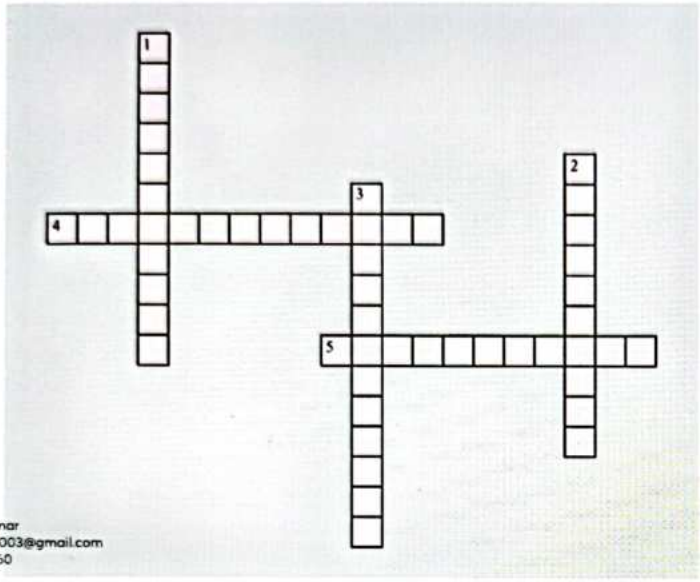
CLOT	LOCATION	EFFECT	DRUGS
Arterial Clot: mainly made up of platelets and some fibrin.	CVS	Angina and Myocardial infarction	Antiplatelet drugs (prevent clot)
	CNS	Transient ischemic attacks (TIA) and stroke	
	Peripheral artery	Peripheral vascular disease (PVD)	
Venous Clot: mainly made up of more fibrin and interrupting of RBCs and WBCs		Venous Thromboembolism • Pulmonary Embolism • Deep vein thrombosis	Anti-coagulants (antithrombotic) (prevent clot)

Table 92.2

Target	Drug	Action	Use
GP IIb/IIIa	Abiciximab (longer acting with short half-life) • Safe in renal failure with no dose reduction • Adverse effects include Bleeding and Thrombocytopenia	High-affinity inhibition of GP IIb/IIIa and vitronectin	• Acute coronary syndrome (ACS) • Myocardial infarction, and • Percutaneous coronary intervention (PCI)
	Tirofiban Eptifibatide [injectables]		PCI and ACS
P2Y12	**Irreversible Antagonists:** • Clopidogrel • Prasugrel (faster) *both are prodrugs • Ticlopidine [adverse effect includes Diarrhoea]		• Myocardial infarction and stroke • Myocardial infarction only (contraindicated in stroke)
	Reversible antagonists: • Cangrelor (I.V.) • Ticagrelor		PCI and ACS M.I. Prophylaxis
PAR	Vorapaxar and Atopaxar		M.I. Prophylaxis
TxA2	TxA2 receptor antagonist; • Terutroban • Low dose aspirin (40-325mg)	Undertrial Inhibits cox 1&2 irreversible leading to decrease in TxA2	For M.I. (162-325mg)
Phosphodiesterase	Inhibitors: • Cilastazole	Increase in cAMP leading to the inhibition of platelet aggregation	Peripheral vascular disease Stroke prophylaxis
	• Dipyridamole	Increases adenosine activity and decreases adenosine uptake	Cardiac stress testing

CROSS WORD PUZZLES

Crossword Puzzle



Across

4. drugs that cut the clot
5. phosphodiesterase inhibitor

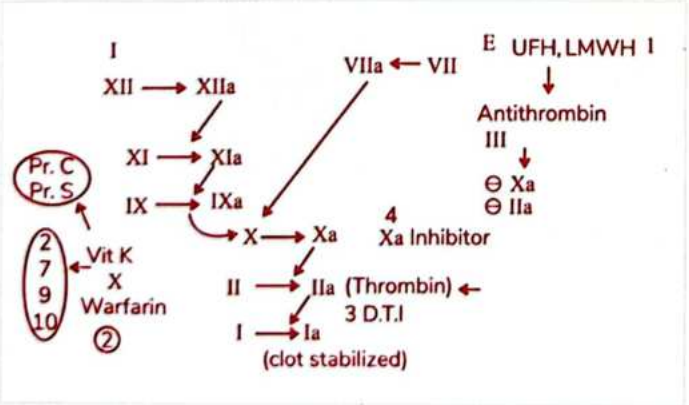
Down

1. P2Y12 antagonists
2. TxA2 receptor antagonist
3. Causes coronary steal phenomenon

93 ANTI COAGULANTS

- Anticoagulants are also called antithrombotics because they prevent the formation of thrombus.
- There's a **Virchow's Triad** consisting of the following factors:
  - Stasis of blood
  - Hypercoagulability
  - Endothelial injury
- The presence of these three factors means there's a chance of clot formation.
- **The factors that can result in the increased formation of thrombus are the following:**
  - It can happen during procedures such as when a catheter is passed through an artery injuring the endothelial cells. These include percutaneous coronary intervention (PCI) and cardiac bypass surgery.
  - Patients with prolonged immobilization are also at risk of thrombosis, for example, in the case of hip surgery. Also, Myocardial infarction (MI) is another factor where unfractionated heparin (UFH) and low-molecular-weight heparin are used to prevent thrombosis.
  - Patients with certain medical conditions like Disseminated Intravascular Coagulation (DIC), Cancer-induced Thrombosis, Atrial Fibrillation, and Heparin-Induced Thrombocytopenia (HIT) can also undergo increased thrombus formation.
  - Prosthetic heart valves are also at risk of thrombosis.
  - In all these conditions, antithrombotics/anticoagulants are used.

Mechanism of Prevention of Clot Formation 00:03:15



- **There are two pathways in thrombus formation.**
  - Intrinsic Pathway
  - Extrinsic Pathway

Intrinsic Pathway

- In this pathway, factor XII gets activated to XIIa.
- From that, factor XI gets activated to XIa.
- There on, factor IX gets activated to IXa.
- IXa activates factor X to Xa.
- Factor Xa activates factor II, which is prothrombin.
- The activated form of factor II is IIa, called thrombin.
- Thrombin activates factor I (fibrinogen) to factor Ia (fibrin).
- There's a formation of a clot and its stabilization.

Extrinsic Pathway

- In this pathway, factor VII gets activated to factor VIIa.
- This factor VIIa also helps in the formation of a clot.

How to stop the clotting mechanism?

- Certain factors are endogenously present in our body to prevent clot formation. These are Protein C and Protein S.
- Antithrombin III is another component that can prevent clots.
- Drugs are still used because they are not fast acting. These need to be activated for fast action in the body.
- Unfractionated Heparin and Low Molecular Weight Heparin activate Antithrombin III.
- Antithrombin III, later on, inhibits the clotting factors Xa and IIa.
- So, the Heparin group of drugs does not act directly but activates endogenously present factors to prevent clotting.
- Vitamin K activates clotting factors 2,7,9, 10, Protein C, and Protein S.
- Antagonising vitamin K helps decrease the effect of clotting factors activated by Vitamin K.
- Warfarin is the antagonist of Vitamin K.
- The Heparin group of drugs all are injections.
- Warfarin is an oral drug.
- Recently, scientists discovered drugs that can directly inhibit thrombin, called Direct Thrombin Inhibitors (DTIs).
- Direct Xa inhibitors were discovered after DTIs.

Activators of Antithrombin III (AT-III) 00:08:27

- AT-III inhibits many factors. Its main action is to inhibit factor IIa.
- AT-III inhibits other factors, namely XIIa, XIa, IXa, and Xa.
  - Unfractionated Heparin (UFH),
  - Low Molecular Weight Heparin (LMWH),
  - Fondaparinux are the drugs involved here.
- **Unfractionated Heparin (UFH) MOA:**
  - Heparin has a Penta saccharide unit and one additional unit.
  - On entering the body, Heparin attaches to Antithrombin III. AT-III gets activated, and it can inhibit factor Xa.
  - The side chain of heparin is the one that inhibits factor IIa.

- **Low Molecular Weight Heparin (LMWH) MOA:**
  - LMWH, the side chain has been cut short. It also binds to ATH-III and inhibits factor Xa. It is not much effective in binding factor IIa.
- **Fondaparinux MOA:**
  - It is a synthetic heparin only with a penta saccharide used. There's no sidechain. It binds to ATH-III and inhibits Xa. It has no effect on factor IIa.

Unfractionated Heparin

- It's a large-sized, ionized drug. It cannot be absorbed orally.
- The drug has a low volume of distribution. It is safe to use during pregnancy.
- Intravenously, UFH has a fast onset of action.
- It is shorter acting.
- The drug is metabolized by an enzyme called Heparinase.
- It is safe to be used in renal failure.
- Subcutaneously, the bioavailability of the drug is unpredictable. It may create toxicity or not work at all.
- **The adverse effects of this drug are the following:**
  - Bleeding: For this reason, aPTT > PT lab monitoring is done.
    - → The antidote for Heparin overdose is Protamine Sulfate. It is obtained from fish sperm.
    - → 1mg of Protamine Sulfate neutralizes 100 units of UFH.
    - → The antagonism between UFH and Protamine sulfate is called chemical antagonism. It is because Heparin is one of the strongest acids, and Protamine Sulfate is a base. So, the acid combines with a base to neutralize it.
  - Hypersensitive reactions
  - Alopecia
  - Mild hyperkalaemia
  - Osteoporosis
  - Heparin Induced Thrombocytopenia
    - → The drug can produce a condition called Heparin Induced Thrombocytopenia. In this case, whenever UFH is used, platelet factor 4 combines with it and activates IgG. This IgG activates platelets. There's thrombus formation. The patient may undergo myocardial infarction, stroke, or limb ischemia.
    - → Later, the platelets are consumed, and the patient ends up with thrombocytopenia.
    - → The problem is the clot which needs to be prevented. Drugs like Argatoban (drug of choice for heparin induced thrombocytopenia), Bivalirudin, and Fondaparinux are given for that.

- A pneumonic to remember the adverse effects of **Heparin is "ABOUT."**
  - **A-Alopecia, Allergy**
  - **B-Bleeding**
  - **O-Osteoporosis**
  - **U-Under-secretion of aldosterone causes elevated K+ levels.**
  - **T-Thrombocytopenia**
- Heparin is used in emergency conditions like Deep Vein thrombosis (DVT), Pulmonary Embolism, cardiac surgeries, Percutaneous Coronary Intervention (PCI), etc.
- It is also used in Disseminated Intravascular Coagulation (DIC).
- **The drawbacks of UFH are the following:**
  - It cannot be given subcutaneously.
  - It requires lab monitoring.
  - Its various adverse effects.

Low Molecular Weight Heparin

- The name of LMWH all end with "parin." They are
  - Enoxaparin
  - Dalteparin
  - Nardoparin
  - Tinzaparin
- **Advantages of LMWH over UFH:**
  - Bioavailability subcutaneously is very good.
  - No need for lab monitoring.
    - → In this case, the right dosage amount can be predicted, which is not the case with UFH.
    - → There's no need for lab monitoring due to its predictable anticoagulant profile.
    - → The anti-factor Xa (anti-Xa) assay can be done, but it's not required.
  - Less chances of HIT and osteoporosis.
  - The drug is longer acting.
- LMWH is a drug of choice for cancer-induced thrombosis.
- Antitode for LMWH is protamine sulphate

Fondaparinux

- Fondaparinux is a Heparin derivative and works on Xa only.
- Lab monitoring is not required.
- There is no antidote for this drug.
- Uses:
  - Heparin Induced Thrombocytopenia.
  - Venous Thromboembolism.

Idraparinux

- It is a synthetic Heparin.
- It binds to AT-III and inhibits factor Xa only.
- All of these drugs are injections.

Vitamin K+Antagonist 00:29:41

- These include Warfarin, Dicumoral, and Acenocumoral.
- **Mechanism of action**
  - The activation of factors 2,7, 9, 10, protein S, and protein C.
  - The activation is done by vitamin K Reduced [R]. After

activation, Vitamin K gets oxidized, and the cycle continues. The enzyme involved in this cycle is epoxide reductase.

- The drug Warfarin is an inhibitor of the enzyme epoxide reductase.
- Warfarin stops the activation of the clotting factors, but it takes days, not hours. It's slow acting.
- The enzyme inhibition by Warfarin is competitive. If Vitamin K+ concentration is increased, Warfarin gets thrown off.
- So, the antidote for Warfarin toxicity is Vitamin K.
- **Pharmacokinetics:**
  - Warfarin in an oral drug with a very good absorption rate.
  - It has two isomers: R and S forms. The S form is 5.4 times more potent than its R form.
  - CYP3A4 metabolizes R Warfarin.
  - CYP2C9 metabolizes S Warfarin.
  - The drug follows saturation kinetics.
  - It has a slow onset of action.
  - It has more drug interactions.
  - Half-life is 40 hours.
  - It's safe to administer in renal failure.
- **The adverse effects of Warfarin are the following:**
  - Bleeding: International Normalized Ratio (INR) is used for monitoring the patient. The normal is between 2-3 N. For example, it can be used for a person with prosthetic heart valves but can be maintained between 2.5 and 3.5 in this case.
    → The antidote for Warfarin in the case of bleeding risk is Vitamin K. However, it takes time to act. Giving Four Factor Prothrombin Complex to the patient can help. It contains preactivated factors 2,7,9,10 and anti-clots proteins C and S.
    → If the complex isn't available, Fresh Frozen Plasma can be administered. Or another way is to perform a blood transfusion.
  - Purple Toe Syndrome. It is due to the mobilization of cholesterol emboli.
    → Arranging factors in ascending order, starting from the one with the short half-life to the one with the last, factor 7, protein C, factor 9, protein S, factor 10, and factor 2 is the order. The shortest for factor 7 is 6 hours, rising up to 60 hours for factors 10 and 2.
  - Skin necrosis. When Warfarin is administered to a patient, different factors with different half-lives start disappearing as per their half-life; factors 10 and 2 with the longest half-life remain and result in skin necrosis.
    → Arranging factors in ascending order, starting from the one with the short half-life to the one with the last, factor 7, protein C, factor 9, protein S, factor 10, and factor 2 is the order. The shortest for factor 7 is 6 hours, rising up to 60 hours for factors 10 and 2.
    → That's why giving UFH or LMWH with Warfarin is a must to inhibit factors 10 and 2. Heparin/LMWH is given for five days and then stopped. This method is Heparin Bridging.
  - Warfarin is not safe during pregnancy. It is teratogenic. The blockage of K+ causes inhibition of bone protein osteocalcin. The baby will have bone abnormalities. The condition is called Fetal Warfarin Syndrome or Contradi Syndrome, or Chondrodysplasia punctata. There's nasal bone hypoplasia. The patient will have stippled epiphysis.
- **Uses of warfarin:**
  - Venous Thromboembolism (VTE). Two conditions exist here, Deep Vein Thrombosis and Pulmonary Embolism. It is used for prophylaxis.
  - Atrial fibrillation.
  - Prosthetic heart valves.

Direct Thrombin Inhibitors 00:43:30

- They can be given as an injection called parenteral drugs or can be given orally.

Parenteral Direct Thrombin Inhibitors

- **These have two important types:**
  - The first type includes the drugs that bind to both the substrate and catalytic site of thrombin, such as Hirudin (obtained from leeches), Lepirudin, Bivalirudin, Desirudin, etc. aPTT must be done for these drugs.
  - The second drug type only binds to the catalytic site of factor IIa. The drug's name is Argatroban. Both aPTT and PT should be monitored.

Oral Direct Thrombin Inhibitors

- The oral DTI is Dabigatran. They're called NOACs (Novel Oral Anti-coagulants) and DOACs (Direct-acting Oral Anti-coagulants).
- **Dabigatran uses:**
  - Venous thromboembolism prophylaxis.
  - Hip surgery prophylaxis.
  - Atrial fibrillation to prevent thrombus formation.
- The antidote for this drug is Idarucizumab.
- Lab monitoring is not required for this drug.
- These drugs are not used in patients with prosthetic heart valves; there is a chance of clot formation, and a patient may have a stroke. The best drug for that still is Warfarin.

Direct Xa Inhibitors 00:49:50

- **Examples:**
  - Apixaban
  - Betrixaban
  - Edoxaban
  - Revorxaban, etc.
- These are also NOACs and DOACs.
- **Uses:**

- Venous thromboembolism prophylaxis.
- Hip surgery prophylaxis.
- Atrial fibrillation

- **Contra-indicated:** Prosthetic heart valves.
- The antidote for these drugs is Andexanet alfa.
- Lab monitoring is not required.

Summary

00:52:20

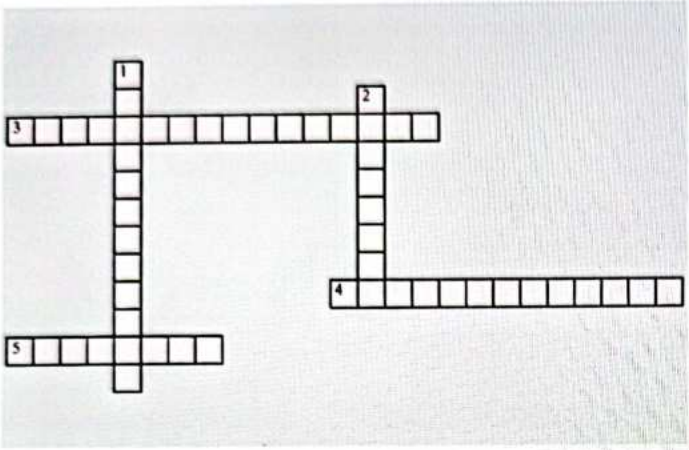
Antidote	Injections	Oral	Antidote
Protamine Sulphate	UFH	Warfarin group	Vitamin K
	LMWH	NOACs: • Direct Xa inhibitor • Dabigatran	• Andexanet alfa for Direct Xa inhibitor • Idarucizumab for Dabigatran
No antidote	Fondaparinux		
No antidote	Parenteral DTIs		

- **Drugs that require lab monitoring are tabled below:**

Drug Name	Lab Monitoring
UFH	aPTT> PT
Warfarin	INR
Parenteral DTIs	aPTT, PT

CROSS WORD PUZZLES

Crossword Puzzle 1



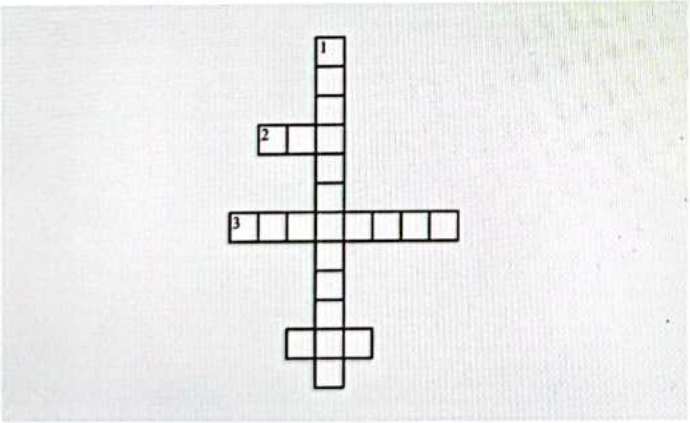
Across

3. _____ is an antidote for UFH and LMWH.
4. The antidote for direct Xa inhibitors is_____.
5. Vitamin K is an antidote for _____.

Down

1. _____ is an antidote for parenteral DTIs.
2. _____ is a drug of choice for prosthetic heart valves.

Crossword Puzzle 2



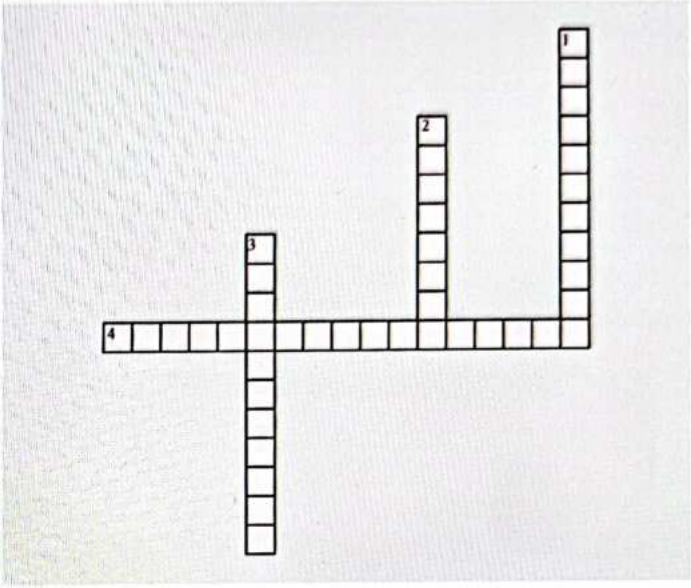
Across

2. In the intrinsic pathway, the factor ____gets activated to XIIa.
3. Antagonising vitamin K helps _____the effect of clotting factors activated by Vitamin K.
4. In the extrinsic pathway, the factor _____gets activated to factor VIIa.

Down

1. III Unfractionated Heparin and Low Molecular Weight Heparin activate_____.

Crossword Puzzle 3



Across

4. Warfarin can cause _____due to the mobilization of cholesterol emboli.

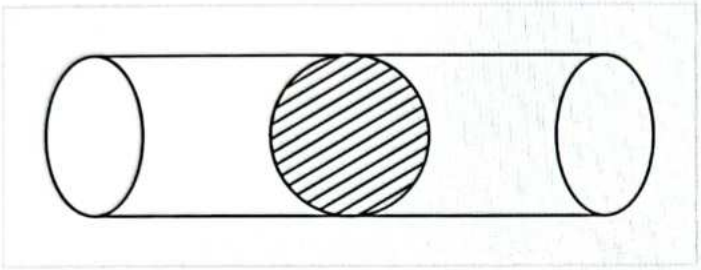
Down

1. The antidote for Warfarin in the case of bleeding risk is_____.
2. _____follows saturation kinetics.
3. The blockage of K+ causes inhibition of bone protein _____.

94 THROMBOLYTICS AND FIBRINOLYTICS

Fibrinolytics

- Consider an artery or a vein where there are chances of clot formation to block circulation. Fibrinolytics are used to cut this clot.



Uses of fibrinolytics

- The management of MI i.e., STEMI (ST-elevation MI).
- Ischemic stroke
- Pulmonary Embolism
- Deep vein thrombosis (DVT)
- Peripheral Artery Occlusion

How does it work? 00:01:10

- The clot is cut through an enzyme that is already present in our body called Plasmin.
- Consider a clot where the cells are tightly bound by fibrin.
- For activation of plasmin, drugs are used to convert plasminogen to plasmin.
- Plasmin cuts the clot and releases it.
- Since the conversion takes time, Fibrinolytics are used to enhance this conversion process.
- These drugs are:
  - Streptokinase - it is obtained from bacteria.
  - Urokinase - It is obtained from recombinant human kidney cells(urine).
- The major drawbacks of these drugs are allergic manifestation, which is why their usage has been reduced.
- Plasmin must be activated from plasminogen at the site of the clot. But these drugs activate plasmin everywhere in the body and not just near the clot. This decreases the fibrinogen level, resulting in an increased risk of bleeding.
- Thus, newer fibrinolytic drugs have been discovered.

Newer fibrinolytic drugs 00:04:47

- **Alteplase**
  - It is a Recombinant Tissue Plasminogen Activator (TPA).
  - The advantage of this drug is:
    - → Less risk of bleeding
    - → Activate plasminogen bound to fibrin i.e., the site of the clot
    - → Inactivated immediately by Plasminogen Activator Inhibitor-1(PAI-1)
    - → Thus, it is short acting. It cannot be given repeatedly and must be given through IV infusions.
  - Uses of this drug:
    - → STEMI
    - → Ischemic Stroke
    - → Venous Thromboembolism (VTE) i.e., DVT and pulmonary embolism.

- **Reteplase.**
  - It is mainly used in MI.
  - It is given as a 2-bolus injection (30 min apart).

- **Tenecteplase**
  - It is used for the management of MI and pulmonary embolisms.
  - It is given as a single Bolus.
- The major drawback of all these drugs is bleeding.

Contraindications of Fibrinolytics/Thrombolytics 00:07:56

- Non-ST-Elevation MI (NSTEMI)
- Head
  - If the patient had an intracranial haemorrhage.
  - If the patient had head trauma less than 3 months ago
  - If the patient has an ischemic stroke less than 3 months ago.
- Uncontrolled Hypertension
- Bleeding disorder/ Bleeding tendencies
- Major surgeries less than 3 weeks ago.

Antifibrinolytics 00:09:48

- They are:
  - Tranexamic Acid
  - Epsilon Amino Caproic Acid (EACA)

- Method of Action:
  - They do not allow the conversion of plasminogen to plasmin.
  - They bind to plasminogen and plasmin individually, inhibiting the conversion process.

- Thus, fibrin is not cut and the clot is stabilized. As a result, the bleeding stops.

- Uses:
  - Menorrhagia
  - Post Dental extraction
  - Postpartum Haemorrhage
  - Antidote for fibrinolytic overdose.

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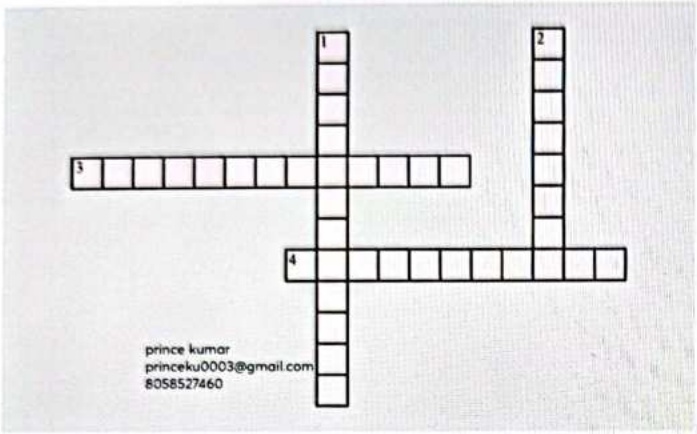
Important Information

- Tranexamic Acid and Epsilon Aminocaproic Acid (EACA) are antidotes for fibrinolytic overdose.
- Plasmin must be activated from plasminogen at the site of the clot.
- The major drawback of Streptokinase and Urokinase is allergic manifestations.
- The major drawback of all the newer fibrinolytics is bleeding.
- Antifibrinolytics do not allow the conversion of plasminogen to plasmin.

CROSS WORD PUZZLES

Crossword Puzzle 1



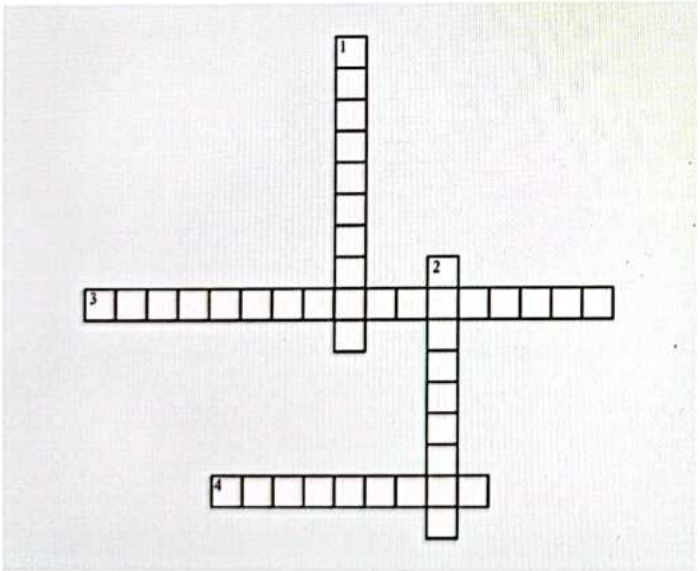
Across

3. The major drawback of _____ is allergic manifestations.
4. Plasmin must be activated from _____ at the site of the clot.

Down

1. Epsilon Amino Caproic Acid (EACA) is an antidote for _____ overdose.
2. The major drawback of all the newer fibrinolytics is _____.

Crossword Puzzle 2



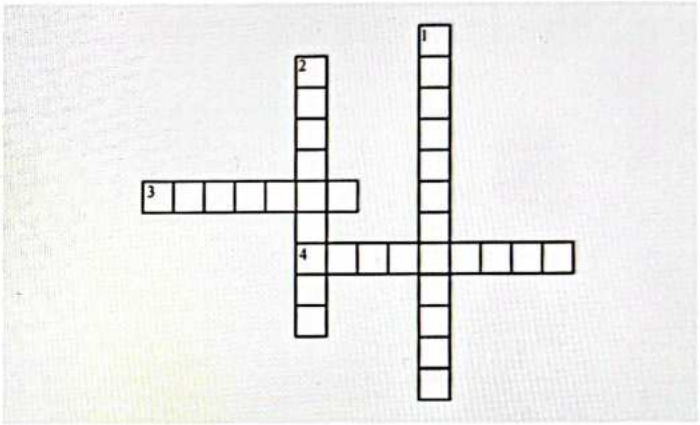
Across

3. _____ do not allow the conversion of plasminogen to plasmin.
4. _____ is given as 2 bolus injections, 30 min apart.

Down

1. _____ Acid is an antidote for fibrinolytic overdose.
2. _____ is a Recombinant Tissue Plasminogen Activator (TPA).

Crossword Puzzle 3



Across

3. Clots are cut through an enzyme that is already present in our body called _____.
4. _____ is short-acting and must be given through IV infusions.

Down

1. _____ is given as a single Bolus.
2. _____ is obtained from recombinant human kidney cells (urine).

95 DRUGS FOR DYSLIPIDEMIA

Definition

- It is a condition where lipid abnormality of high cholesterol causes atheromatous plaques in arteries leading to the rupture of the blood vessel and embolize to other parts.
- This may result in stroke, peripheral arterial occlusion, or erectile dysfunction. It also increases the risk of myocardial infarction.
- When atheromatous plaques are formed in coronary arteries, which supply blood to heart muscles, it is called atherosclerotic cardiovascular disease.
- It leads to angina and myocardial infarction.

- The aim of the therapy is to:
  - Decrease total cholesterol.
  - Decrease LDL (Low-density lipoprotein).
  - Decrease VLDL (Very-low-density lipoprotein).
  - Decrease Triglycerides.
  - Increase HDL (High-density lipoprotein).

Classes of Drugs Available for Dyslipidemia

Statins 00:02:55

- It is a common word for HMG CoA reductase inhibitors, which hampers the cholesterol biosynthesis in the body.

- The drugs are:
  - Rosuvastatin- Long lasting.
  - Atorvastatin- Safe in patients with renal dysfunction without dose reduction.
  - Simvastatin- Prodrug.
  - Lovastatin- Prodrug.
  - Pitavastatin- Most potent, that is it works at the lowest dose.
  - Pravastatin.
  - Fluvastatin.

Mechanism of Action 00:05:52

HMG CoA
↓ HMG CoA reductase ⊖
Mevalonate
↓
Cholesterol
↓ Cholesterol in liver
↓
↑ LDL receptor
↓
LDL is taken from periphery
↓
↓ LDL

Pleiotropic effects of statins 00:08:00

- Atheromatous plaque stabilization.
- Decreases plaque rupture.
- Anti-inflammatory effect.
- Increased nitric oxide in the endothelium.
- Antioxidant effect.
- Lower platelet aggregation.

Pharmacokinetics 00:10:00

- Cytochrome 3A ⅘ metabolize statins in the liver.
- Cytochrome 3A ⅘ inhibitors increase the levels of statin.
- High levels of statin the risk of myopathy.
- Pravastatin, Fluvastatin, and Rosuvastatin are highly productive and independent of Cytochrome 3A ⅘ for metabolism.
- The absorption of statins increases with food.
- Statins are taken at night because HMG CoA reductase is active between 12-2 AM.
- Rosuvastatin and atorvastatin are longer acting and can be given at any time.

Adverse effects of statin 00:12:40

- The adverse effect can be expressed using a mnemonic HMG.

H	M	G
• Headache • Hepatotoxicity (indicated by increased levels of liver enzymes) • High glucose (increases the risk of the development of diabetes).	• Myopathy (leads to Rhabdomyolysis, Myoglobinuria and Renal failure)	• Upset GI tract upset • nausea • diarrhea.

Contraindications 00:15:35

- Pregnant women
- lactating mothers
- Children

Important Information

- Some statins have been approved for children, including:
  - Pravastatin for children older than 8 years.
  - Atorvastatin, lovastatin, or simvastatin for children older than 11 years.

Uses of statins 00:17:10

- Familial dyslipidemia
- Prophylaxis of MI and stroke
- Diabetes mellitus with dyslipidemia
- Metabolic syndromes

High-intensity statins 00:18:00

- Reduce LDL by more than 50 percent.
- Atorvastatin (40-80 mg) and Rosuvastatin (20-40 mg) are the high-intensity statins used in high-risk patients.

Fibrate 00:19:50

- They include Fenofibrate, Benzafibrate, Clofibrate, and Gemfibrocil.

Mechanism of action 00:20:40

Fibrates stimulate Peroxisome Proliferator Activator Receptor-alpha (PPAR-alpha).

↓

The activated receptor promotes the synthesis of lipoprotein lipase

↓

Increases the metabolism of VLDL to triglycerides.

↓

Triglycerides → free fatty acids → energy

- Metabolism of TGs → primary mechanism of fibrates,
- Additionally, they also reduce total cholesterol and LDL, and increase HDL.

Fibrates for dyslipidemia in diabetic patients 00:22:20

- PPAR gamma is a nuclear receptor involved in glucose sensitization in peripheral tissue and insulin-producing cells in the pancreas.
- The agonists, such as pioglitazone, of the receptor are some drugs used to treat diabetes.
- Saroglitazaar stimulates PPAR-alpha and PPAR-gamma, making it a preferred drug for dyslipidemia in diabetic patients.
- It was recently discovered in India and has been approved for clinical use.

Uses of fibrates 00:23:20

- Treat genetic conditions like familial chylomicronemia syndrome (FCS) that result in hypertriglyceridemia.

Important Information

- Statins are prescribed for dyslipidemia with triglyceride levels between 70 and 500 mg/dl.
- Fibrates are given when the level exceeds 500 mg/dl, which is called severe hypertriglyceridemia.

Adverse effects 00:23:55

- Myopathy
- Risk of gallstone by increasing the lithogenicity of bile juice.
- Among the fibrates, clofibrate poses the highest risk of gallstone.

Drug interaction

- **Is combining fibrates with statin safe?**
  - Combining statin with fibrate increases the risk of myopathy. However, studies have shown that fenofibrate with statin is the safest option as it does not interfere with the metabolism of statin and the risk of myopathy is the least compared to the combination with other fibrates.

Niacin 00:26:00

- Niacin is a vitamin known as vitamin B3.

Mechanism of action

- The liver senses high levels of FFA caused by lipid breakdown by Hormone-sensitive lipase and absorbs it to synthesize VLDL, IDL, and LDL.
- Niacin inhibits HSL, reducing fat reserves turnover from adipose tissue and reducing FFA supply to the liver. As a result, it reduces the levels of LDL and VLDL.
- Another mechanism of niacin in reducing lipids is a reduction in the synthesis of apolipoprotein.

Advantages

- Increases HDL (Maximum among other drugs).
- Decreases Apolipoprotein A

Adverse effects 00:28:40

- Cutaneous vasodilation that causes skin flushing.
- Pruritus (Avoided by using sustained release Niacin or aspirin).
- Myopathy
- High levels of uric acid
- Increased risk of diabetes mellitus
- Dyspepsia

Drug interaction 00:30:30

- The combination of niacin and statin increases the risk of myopathy and the range of side effects caused by niacin does not attract the risk-benefit analysis for the combination.

Contraindications 00:30:50

- Niacin has failed the preclinical studies for the safety of its use in pregnant animals with dyslipidemia. Hence, researchers have concluded that niacin doses required for treating dyslipidemia are hazardous to pregnant women.

Bile Acid Binding Resins 00:31:50

- They include Colestipol, Cholestyramine, and Colesevelam.

Mechanism of Action

- Cholesterol is required to synthesize bile acids
- The bile acids are secreted from the liver into the intestines.
- When Resins are taken, these charged resins are not absorbed from the intestine. They bind with bile acid and will get excreted through intestines.
- This leads to an increased amount of cholesterol used to synthesize bile acids.
- Cholesterol is taken up from the periphery due to a reduced amount in the liver leading to decrease in LDL, VLDL and Total cholesterol.

Uses

- The drugs are safe for all dyslipidemia patients, including pregnant women, lactating women, and children, as they do not enter the bloodstream and pass through placenta.

Contraindication 00:34:41

- Due to the side effect of rise in triglycerides, colestipol and cholestyramine are not safe for patients with hypertriglyceridemia.

Adverse effects

- Patients may complain of bloating and constipation.

Ezetimibe

- Inhibits intestinal cholesterol absorption from the food, increasing the cholesterol biosynthesis in the liver to compensate for the lack of external supply of the nutrient.
- Ezetimibe is the drug to augment the treatment of patients with a high risk of myopathy, as higher doses of statins are harmful.

Important Information

- Statins are the most efficient in reducing LDL.
- Fibrates are the most effective drugs to reduce triglycerides.
- Niacin is the most effective enhancer of HDL.

Newer drugs 00:39:10

Proprotein Convertase Subtilisin–Kexin Type 9 (PCSK-9) inhibitors

- Monoclonal antibodies that inhibit the enzyme PCSK-9.
- Alirocumab and evolocumab are the members of the class.
- Used for familial hyperlipidemia and prophylaxis of atherosclerotic cardiac disease
- PCSK9 destroys LDL receptors in the liver and promotes LDL absorption, decreasing its level in the blood.

Lomitapide

- Inhibits microsomal triglycerides transport proteins

Mipomersen

- Antisense oligonucleotide
- Inhibits the translation of mRNA for the synthesis of apo B100, a lipoprotein.

Icosapent

- Inhibits the synthesis and release of VLDL from the liver.

Important Information

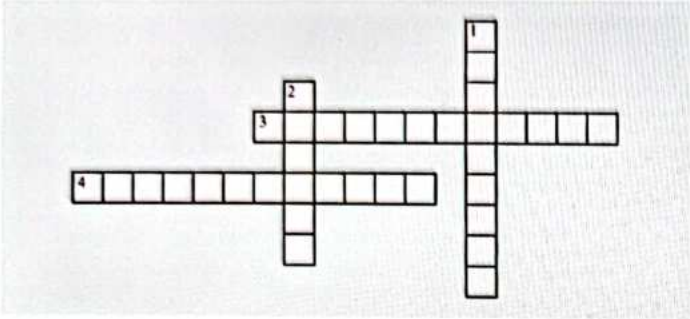
- Lomitapide, Mipomersen and Icosapent are all approved in the treatment of Familial hyperlipidemia.

Bempedoic Acid

- Inhibiting ATP citrate lyase that catalyzes the conversion of citrate to acetyl CoA, the initial reaction of cholesterol synthesis.
- The drug has been approved for atherosclerotic cardiovascular disease and familial hyperlipidemia.

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. The safest drug for-dyslipidemia patients with renal dysfunction.
4. Most preferable fibrate drug for diabetic patients with dyslipidemia

Down

1. The drug that inhibits absorption of cholesterol from intestine
2. The most commonly prescribed drug for dyslipidemia and related cardiovascular diseases.

96 COLONY STIMULATING FACTORS

- They are used as drug preparations since there is a risk of bone marrow separation, reduction in WBC, RBC, platelet count, etc. during anti-cancer therapy.

Classification

- Granulocyte-monocyte colony-stimulating factor (GM-CSF) Analogue
  - Sargramostim & Molgramostim: They are used to treat leukopenia due to anti-cancer drugs.
- Granulocyte colony-stimulating factor(G-CSF) Analogue
  - Filgrastim
  - Pegfilgrastim (Adding a peg makes the drug act longer)
  - Lenograstim
  - We use them in cases of Febrile Neutropenia, Agranulocytosis, leukopenia due to antI-cancer drugs.
- Erythropoietin: It is secreted from the kidney. The preparation of erythropoietin is:
  - Epoetin
  - Darbepoetin
  - It is used for:
    - → Anemia in CKD patients.
    - → Anemia due to drugs:
- Anti-cancer drugs
- Zidovudine (causes bone marrow separation)
  - Erythropoietin increases reticulocyte count. This makes the blood thicker and more viscous. This causes adverse effects:
    - → Increased risk of thrombus formation
    - → Risk of hypertension
- Peginesatide: It is a peptide where 'ESA' stands for Erythrocyte Stimulating Agent
  - This agent is used to treat anemia in CKD patients.

Platelets 00:05:30

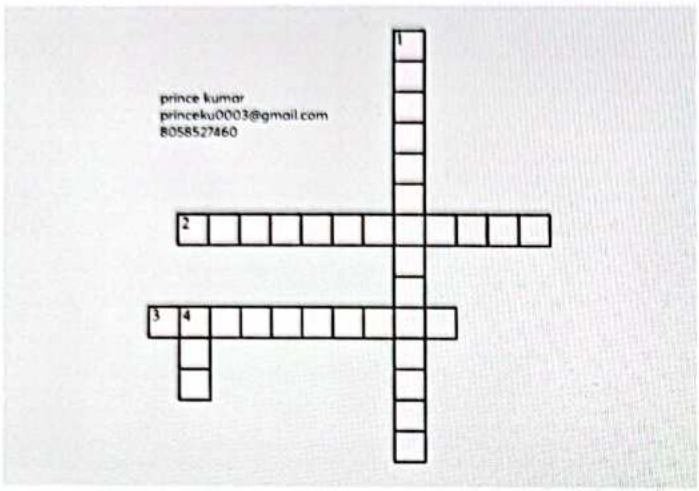
- Use of anti-cancer therapy can lead to a decrease in platelet count. We can increase this count through:
  - Interleukin (IL) -11 analogue - Oprelvekin
    - → It is used to treat thrombocytopenia due to anti-cancer drugs.

Idiopathic Thrombocytopenic Purpura (ITP)

- Drugs used in Idiopathic thrombocytopenic purpura
  - Romiplostim - Given through IV
  - Eltrombopag - Given oral
- These both stimulate thrombopoietin receptors i.e., thrombopoietin receptor agonists.

CROSS WORD PUZZLES

Crossword Puzzle 1



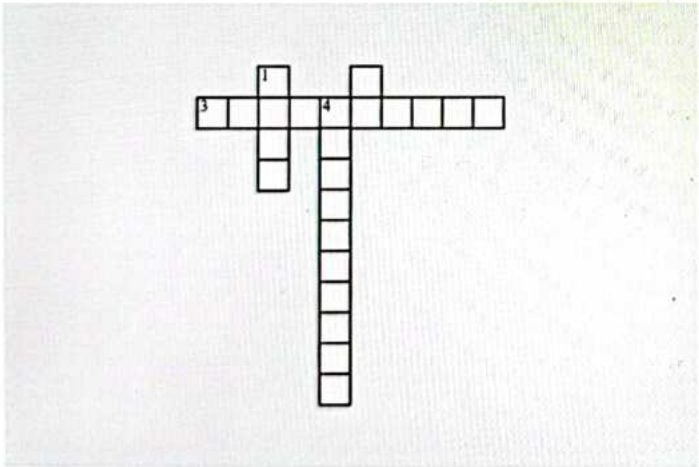
Across

2. Erythropoietin increases _____ count.
3. _____ is used to treat thrombocytopenia due to anti-cancer drugs.

Down

1. Drugs used in Idiopathic thrombocytopenic purpura stimulate _____ receptor.
4. Adding a _____ makes the drug act longer.

Crossword Puzzle 2



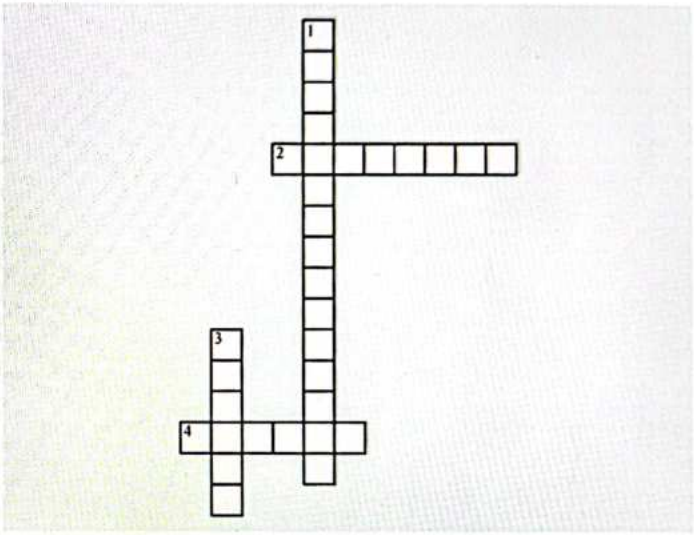
Across

3. The name of the Interleukin (IL)-11 analogue is _____.

Down

1. Eltrombopag is given through ___.
2. Romiplostim is given through ___.
4. Sargramostim & Molgramostim are used to treat _____ due to anti-cancer drugs.

Crossword Puzzle 3



Across

2. Erythropoietin can lead to an increased risk of ____ formation.
4. Peginesatide is an agent used to treat ____ in CKD patients.

Down

1. Darbepoetin is a kind of _____.
3. Erythropoietin is secreted from the _____.

97 HEMATINICS

- These nutrients are the compounds that are required for forming blood Components.
- This is mainly required for Hematopoiesis.
- Hematinics are usually given to treat anemia.

Type of Hematinics

Major Hematinics	Minor Hematinics
• Fe	• Cu
• B12	• Pyridoxine
• Folic acid	

Iron (Fe) Preparation of Iron 00:01:05

Oral Iron Therapy

- Ferrous sulfate (33% of elemental iron)
- Ferrous Fumarate (33% of elemental of iron)
- Ferrous gluconate (12% of elemental of iron)
- Colloid ferric hydroxide (50%)
- Carbonyl Iron (Highly purified iron preparation)

Pharmacokinetics

- Iron is given orally into the gut, in the stomach (Acidic). Ferric is converted into ferrous ⇒ Absorbed.
- Iron absorption is maximum in the duodenum.
- Iron should be given on an empty stomach.

Q. Can combine Ferrous with Vit. C?

Ans: Yes. This combination is rational because Vit. C helps in maintaining acidic pH.

Important Information

- Do not combine Iron and PPI as they make the environment alkaline and impair iron absorption.
- Don't give milk + iron = Complex formation because they cannot absorb iron.

Uses

- Iron Deficiency anemia
- Reason to continue Iron even if the HB levels are normal
  - Iron is absorbed in the gut and stored as Ferritin in the intestines. It is also circulated in the body in the form of Transferrin. It will deliver iron for Hematopoiesis and to store in the reticuloendothelial system.
  - The hemoglobin levels become normal with treatment of iron, due to the diversion of iron from the synthesis of RBC.
  - But the stores are not replenished. Hence iron should be continued to replenish the stores.
- ↑ Demand ⇒ Pregnant Women, Children, Lactation women
- Chronic blood loss (Menorrhagia, Ulcer, Fistula, Hookworm infection)

Adverse effect:

- Gastritis
- Teeth discoloration
- Diarrhea, Constipation
- Black stool

Parenteral Iron Therapy 00:11:38

Indications

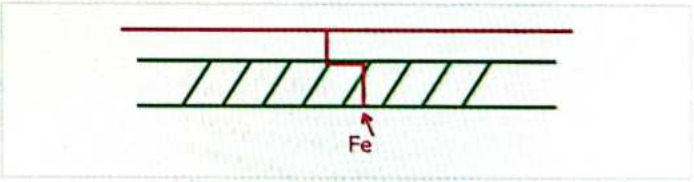
- Intolerant to oral iron therapy
- Malabsorption
- Severe iron deficiency anemia
- Chronic Kidney Disease ⇒Anemia ⇒ Drug given Erythropoietin + Iron Inj.

Preparation

- Iron dextran (I.V./I.M.)
- Iron sorbitol citric acid complex (I.M. Only, not given by I.V.)
- Ferrous sucrose (Less allergy)
- Ferric carboxy maltose (Less allergy)

Drug Administration Techniques

- Z-track technique
- Iron has been given by the intramuscular (I.M.) route. It will form a track, and the drug can go back to the skin, causing Skin Staining.



- The Z-TRACK method of I.M. injection prevents leakage of irritating and discoloring medications (such as iron dextran) into the subcutaneous tissue.
- To avoid skin staining.

Formula to Calculate Parenteral Iron

- To calculate Parenteral Iron = 4.4 × Body wt. × Hb Deficient

Iron Poisoning 00:19:15

Presentation

- Nausea
- Vomiting
- Hematemesis
- GI Hemorrhage

Tips for managing iron poisoning

- Airway
- Breathing
- Circulation
- Gastric lavage
- ↓ Iron absorption (Using sodium bicarbonate, Egg yolk)

Antidote

- Desferroxamine (I.V., I.M.)

Absorption

- Iron - Duodenum
- Folic Acid- Jejunum
- B12- Terminal part of ileum with the help of intrinsic factor

Vitamin B12 00:22:10

- Vitamin B 12, also known as cobalamin, is a water-soluble vitamin in metabolism.
- B12 more in Non-vegetarian diet.

B12 Deficiency

Symptoms

- Megaloblastic anemia
- Neuropathy (Paresthesia)
- Glossitis
- Knuckle pigmentation

Preparation

- Cyanocobalamin
- Methylcobalamin
- Hydroxocobalamin

Uses

- Megaloblastic anemia (Folic acid + B12)
- Pernicious anemia
  - In pernicious anemia, Intrinsic Factors are deficient.
  - In Ileum IF + B12 ⇒ B12 absorb.
  - If B12 is not absorbed orally, it can be given by I.M. route with Hydroxocobalamin.
- Cyanide Poisoning.
  - Hydroxocobalamin is used to treat. It combines with cyanide to form cyanocobalamin which is water soluble and is excreted easily in urine.
- DM Neuropathic pain
- Tobacco amblyopia

Folic Acid 00:29:30

Uses:

- Nutritional deficiency
- Megaloblastic anemia
- Along with anti-epileptics + phenytoin
- ↓ Risk of neural tube defect

Dose of folic acid in Pregnant Women

- Low risk (400 ug/day)
- High risk (4000 ug/day)

Folinic Acid 00:31:25

- Folinic acid also called as N5 Formyl Tetrahydro furoic acid / Citrovorum / Leucovorin

Uses

- In methotrexate Toxicity.
- In Cancer ⇒ FOLFOX (Folic acid Fluorouracil Oxaliplatin). Used in colorectal cancer.

Pyridoxine (B6) 00:33:38

Uses

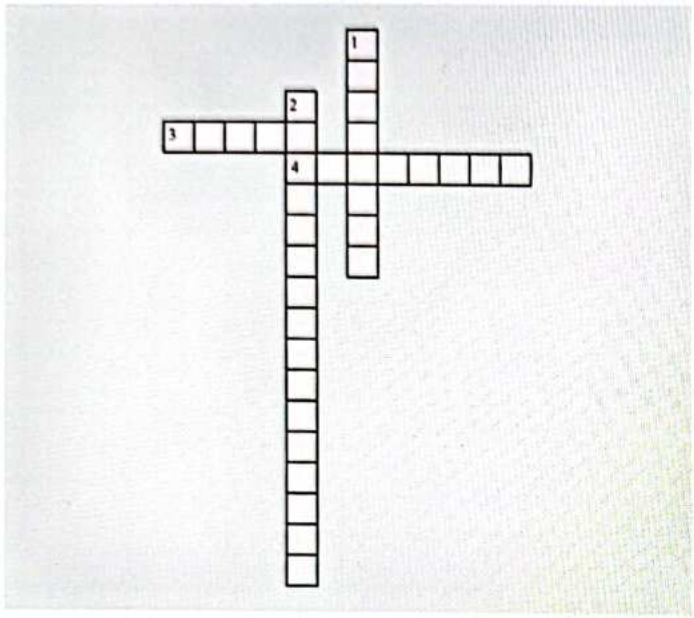
- INH overdose
- INH-induced peripheral neuropathy
- INH ⇒ Sideroblastic anemia
- Doxylamine + B6 = Morning Sickness

Drug interaction

- L-Dopa + B6
  - L-Dopa is metabolized by an enzyme called peripheral decarboxylase into dopamine. This enzyme activity is increased by B6. This leads to excess dopamine and less L-Dopa enters the brain.

CROSS WORD PUZZLES

Crossword Puzzle 1



Across

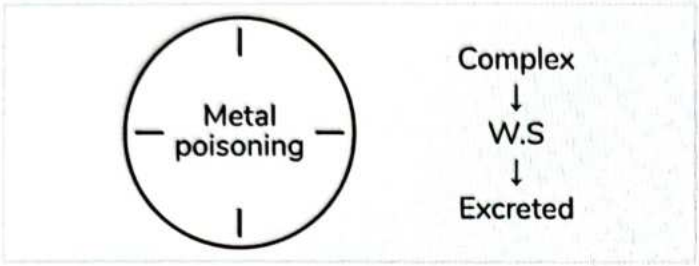
3. Iron should be given Stomach is
4. Iron absorption is maximum in the

Down

1. Highly purified iron preparation
2. Antidotes for Cyanide Poisoning is _ adverse effect is Non-cardiogenic pulmonary oedema.

98 CHELATING AGENTS

- They are the drugs used in cases of metal poisoning such as iron poisoning, lead poisoning, arsenic poisoning etc.
- The term 'chela' stands for crab. This is because when there is metal poisoning, the drugs attack the metal like a crab to form a water-soluble complex that can be excreted from the body.



- **Desferroxamine or Deferoxamine** - Iron chelator
  - It is given through either IV or IM.
  - It is used for acute iron poisoning.

- **Deferiprone & Deferasirox** - Iron chelators
  - They are given orally.
  - They are used particularly for chronic iron overload. Patients with Thalassemia major have to undergo repeated blood transfusions and these patients suffer from chronic iron overload.

- **Dexrazoxane** - Iron chelator
  - It is used to prevent anthracyclines - induced cardiotoxicity.

- **Dimercaprol or British Anti-Lewisite (BAL)**
  - **It is used in:**
    - → Arsenic poisoning (particularly)
    - → Mercury poisoning
    - → Gold poisoning
    - → Bismuth poisoning
  - It is not used in cases of iron and cadmium poisoning. This is because the iron and BAL form a complex that is toxic for the patient.

- **Disodium Edetate (EDTA)**
  - It chelates calcium and is used in cases of hypercalcemia.
  - The adverse effects include hypocalcemia if the drug was given to treat some metal poisoning and not hyperkalemia.

- Calcium disodium edetate (Ca EDTA)
  - **It is used for:**
    - → Lead poisoning
    - → Zinc poisoning
    - → Manganese poisoning
  - It is not used in mercury poisoning.
  - There is no risk of hypocalcemia since there is calcium already attached in the drug.

- **Penicillamine**
  - It is used for chelating copper in cases of Wilson's disease (excessive copper), Copper poisoning, Mercury poisoning.
  - It was used for Remote Arthritis (RA) previously but not anymore due to invention of better drugs.

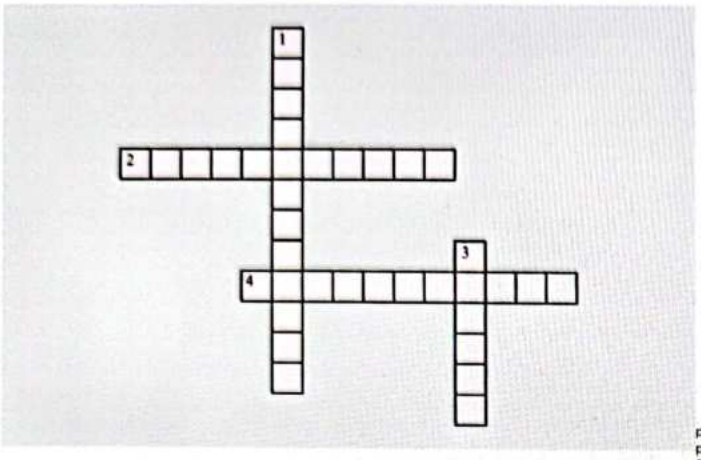
- **Succimer or Dimercaptosuccinic Acid**
  - **It is used for (LAM) i.e.,**
    - → Lead poisoning
    - → Mercury poisoning
    - → Arsenic poisoning

Important Information

- Deferiprone & Deferasirox are used particularly for chronic iron overload.
- Dimercaprol or British Anti-Lewisite (BAL) is not used in cases of iron and cadmium poisoning.
- The adverse effect of Disodium Edetate (EDTA) is hypocalcemia if the drug was given to treat some metal poisoning and not hyperkalemia.
- The copper excessive condition is called Wilson's Disease.
- Penicillamine is used for chelating copper.

CROSS WORD PUZZLES

Crossword Puzzle 1



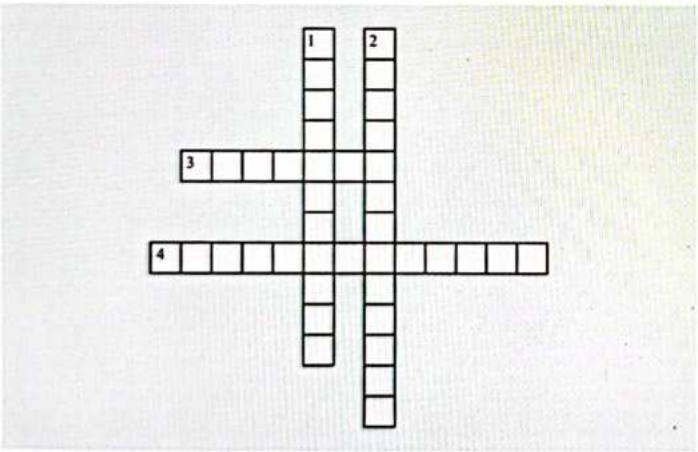
Across

2. _____ is not used in cases of iron and cadmium poisoning.
4. _____ is used particularly for chronic iron overload.

Down

1. The adverse effect of Disodium Edetate(EDTA) is _____.
3. The copper excessive condition is called _____'s Disease.

Crossword Puzzle 2



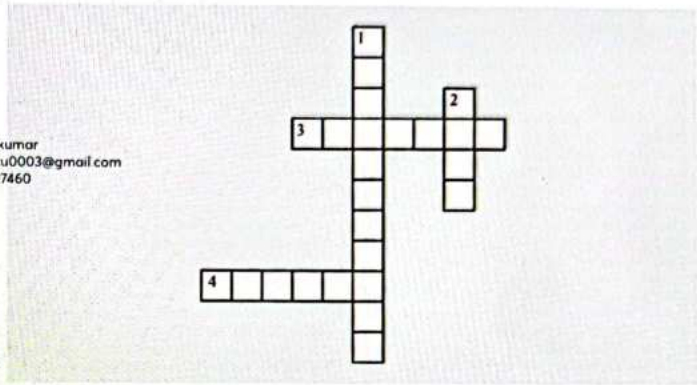
Across

3. Succimer is used for Lead, Mercury, and _____ poisoning.
4. _____ was used for Remote Arthritis(RA) previously

Down

1. Deferiprone is used particularly for _____ overload.
2. _____ is used for chelating copper.

Crossword Puzzle 3



Across

3. Ca EDTA is not used in ____ poisoning.
4. There is no risk of hypocalcemia when ____ is used.

Down

1. _____ is used to prevent anthracyclines-induced cardiotoxicity.
2. The term 'chela' stands for ___.

99 ANTI CANCER DRUG

- Cancer is an abnormal proliferation of cells.
- Cancer cells undergo uncontrolled proliferation or division, while normal cells have controlled division.

Modalities of Treatment for Cancer

- Surgery
- Radiotherapy
- Chemotherapy (Anti-cancer drugs)
  - Anti-cancer drugs cannot differentiate between normal and cancerous cells and target the division of both normal and cancerous cells.

Common Adverse Effects of Anti-Cancer Drugs 00:03:00

- Since hair follicles are also dividing, reversible alopecia is seen with anti-cancer drugs.
- The mucosa of the mouth regenerates daily; after administering anti-cancer drugs, the mucosa is not able to regenerate, and the mucosa becomes inflamed. This is called Mucositis. This is prevented by Palifermin (Keratinocyte growth factor).
- Due to bone marrow suppression, immunity comes down, and the patient is prone to opportunistic infections.
- The management of decreased WBC is done with
  - GM CSF (Granulocyte-Monocyte Colony Stimulating Factor) analogue.
  - Sargramostim and molgramostim stimulate bone marrow to produce wbc's
  - G-GCF (Granulocyte-Colony Stimulating Factor)-Filgrastin, Pegfilgrastim (longer acting) and Lenograstin.
- Decreased RBC production results in anemia. Treated by stimulating Erythropoietin.
  - Darbepoetin and Epoetin are used to treat anemia due to anti-cancer drugs.
- Thrombocytopenia is treated with Oprelvekin.

Bone Marrow-Sparing Anti-Cancer Drugs 00:09:10

- Some anticancer drugs do not suppress the bone marrow and only kill the cancer cells.
- These drugs are
  - Vincristine
  - Bleomycin
  - L-asparaginase

GIT 00:09:45

- In GIT, the cells are also killed, and serotonin is released, resulting in nausea and vomiting.
- Chemotherapy-induced nausea and vomiting (CINV), if occurs within 24 hours of starting chemotherapy, is considered early CINV.
- Drug of choice is 5HT3 antagonist
  - Ondansetron
  - Palonosetron
- Late CINV happens within 1 to 5 days of starting chemotherapy.
- Neurokinin 1 receptor antagonists are the drug of choice.
  - Aprepitant
  - Fosaprepitant
  - Netupitant
  - Rolapitant
- To prevent CINV, the best combination is a 5HT3 blocker, neurokinin 1 receptor antagonist, and dexamethasone given prior to chemotherapy. The steroids decrease the inflammatory process.
- The drug of choice for cancer-induced diarrhea is loperamide.

Gonads 00:13:36

- In males, stops the multiplication of the cells and leads to oligospermia and in the females, there is decrease in Oogenesis ultimately leading to infertility.
- Anticancer drugs are contraindicated in pregnancy as they are teratogenic.

Radioprotector

- Amifostine is used to decrease radio sensitization during radiotherapy.

Tumor Lysis Syndrome 00:15:25

- In leukemia or lymphoma, plenty of WBCs are killed, and there is the release of purine.
- The patient experiences hyperuricemia, known as tumor lysis syndrome.
- The treatment is started with allopurinol; in resistant cases, the overall drug of choice is Rasburicase. This drug immediately converts uric acid to allantoin, which is water-soluble.
- Allopurinol only blocks the synthesis; it cannot bring down the levels of uric acid.

Hypercalcemia

- In hypercalcemia of malignancy, the levels of calcium shoot up suddenly.

- Calcitonin, Furosemide is a loop diuretic, and zoledronate is a bisphosphonate, used to manage hypercalcemia of malignancy.

Anticancer Drugs 00:19:06

- The types of Anti-cancer drugs:
  - Cytotoxic drugs
  - Hormonal agents
  - Targeted therapy

Cytotoxic Drugs (Non-Targeted Drugs)

- The two types are
  - Cell cycle non-specific
  - Cell cycle specific
- G0 phase do not multiply like in the brain and heart.
- G1S is the normal phase: Etoposide
- S is the synthesis phase: Anti-metabolites (Purine antagonist, Pyrimidine antagonist, Folate antagonist and Hydroxyurea)
- G2M is the mitotic phase: Bleomycin, DNA topoisomerase 1 & 2 inhibitors.
- In cancer cells, these checkpoints are not there, so they keep on replicating.

Cell Cycle-Specific Drugs

- The drugs that interfere with DNA synthesis are known as anti-metabolites.
- Methotrexate also acts on the S phase.
- Drugs that act on the G2 to M phase include:
  - Anticancer antibiotic bleomycin.
  - DNA topoisomerase I and II inhibitors.
- Mitosis means cell division. During cell division, microtubules contract and pull the DNA to the opposite end, and the cell divides.
- Microtubule Inhibiting agents (VEEET mnemonic). These drugs act on the M phase and interfere with microtubules, and damage them.
  - **V** - Vinca alkaloids: these are obtained from a plant.
  - **E** - Estramustine: It is used in prostate cancer.
  - **E** - Epothilones: it is used in breast cancer.
  - **E** - Eribulin
  - **T** - Taxanes

Cell Cycle Nonspecific Drugs 00:25:25

DNA Alkylating Agents

- These drugs enter the cells and produce highly reactive carbonium ions.
- These ions bind at the N^7 guanine residue.
- They cause cross-pairing and mismatch in the DNA.
- The damaged DNA can proliferate and can lead to secondary cancers. This leads to cell death or the damaged DNA can proliferate and lead to secondary cancer.
- Drug Resistance in Cancer Cells:
  - The cancer cells have a p-glycoprotein efflux pump that resists the drugs, and hence in most cancers a combination of drugs is used to avoid drug resistance.

Mechlorethamine 00:30:12

- Mechlorethamine was used to treat Hodgkin's lymphoma but it caused skin blisters.
- MOPP regimen is not used nowadays. (Mechlorethamine, Oncovin, Prednisolone and Procarbazine)
- The new regimen for Hodgkin's lymphoma is ABVD
  - Adriamycin, Bleomycin, Vinblastine and Dacarbazine
  - Adriamycin is also known as doxorubicin or hydroxydaunorubicin.

Melphalan

- It is used to treat Multiple myeloma.

Busulfan

- It is used to treat Chronic myeloid leukemia
- Adverse effect: Pulmonary fibrosis and Sinusoidal obstruction syndrome.

Chlorambucil

- It is oral drug of choice for Chronic lymphocytic leukemia

Cyclophosphamide 00:35:40

- It is a product that needs to be converted to the active form by cytochrome 2B6 which gives rise to 4-hydroxy cyclophosphamide.
- This is converted to Aldophosphamide which in turn gives rise to Phosphoramide mustard and Acrolein.
- The phosphoramide mustard component produces an anti-cancer effect.
- Acrolein is another component that causes hemorrhagic cystitis, resulting in pain in the supra-pubic region.
  - MESNA (mercapto-ethanesulphonate) binds to acrolein and prevents this problem.
- Cyclophosphamide is one of the highly emetogenic drugs.

Uses of Cyclophosphamide

- It is used in autoimmune disorders and is the drug of choice in Wegener's granulomatosis and steroid-dependent nephrotic syndrome.
- It is also used in the treatment of rheumatoid arthritis but is not the first-line drug.

- Cyclophosphamide is mainly used as an anticancer drug, in the treatment of non-Hodgkin's lymphoma.
- The regimen used for non-Hodgkin's lymphoma is R CHOP.
  - **R** - Rituximab (CD20 blocker)
  - **C** - Cyclophosphamide.
  - **H** - Hydroxydaunorubicin
  - **O** - Oncovin (Vincristine)
  - **P** - Prednisolone
- Also used in breast cancer. The regimen is called CMF
  - **C** - Cyclophosphamide.
  - **M** - Methotrexate
  - **F** - 5 fluorouracil

Ifosfamide

- It is a less emetogenic drug.
- It causes more hemorrhagic cystitis and is highly neurotoxic.
- Ifosfamide produces metabolite chloroacetaldehyde which is why it is highly neurotoxic.

Nitrosoureas

- The drugs are
  - Carmustine
  - Lomustine
  - Semustine
- These are highly lipid soluble so they easily cross the blood-brain barrier and are hence used in the treatment of brain tumors.
- Being lipid soluble, these can easily cross the bone marrow and result in sustained neutropenia.

Streptozocin

- It is used in experiments to induce diabetes in rats (as it damages the pancreas) and in certain cancers.

Procarbazine 00:44:10

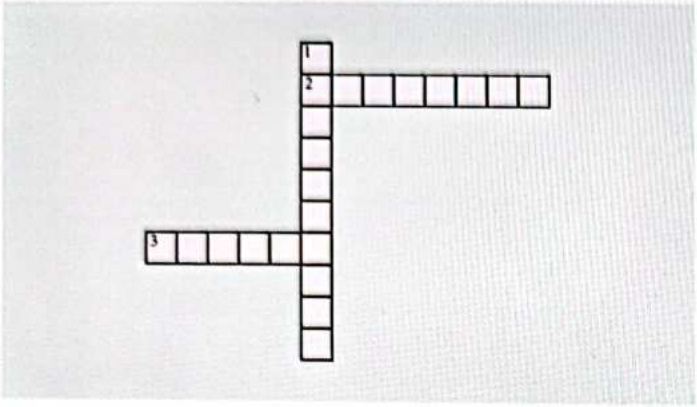
- Procarbazine is a MAO inhibitor.
- It should not be consumed with alcohol, as it causes a disulfiram like reaction.
- Procarbazine is also known to produce secondary leukemia.
- Procarbazine and dacarbazine are used in the treatment of Hodgkin's and non-Hodgkin's lymphoma.

Temozolomide

- It is used in the treatment of brain tumor, glioblastoma multiforme.

CROSS WORD PUZZLES

Crossword Puzzle 1



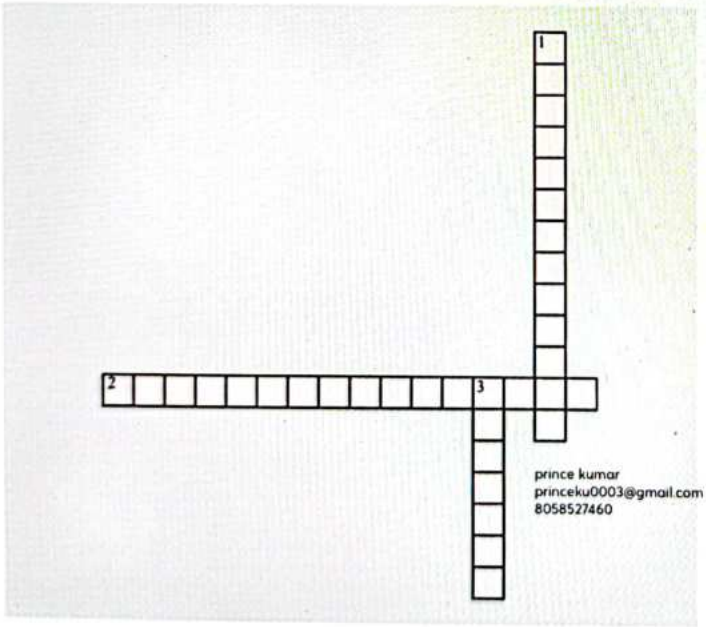
Across

2. _____ due to cancer treatment is reversible.
3. _____ is an abnormal proliferation of cells.

Down

1. _____ drug is used to prevent Mucositis.

Crossword Puzzle 2



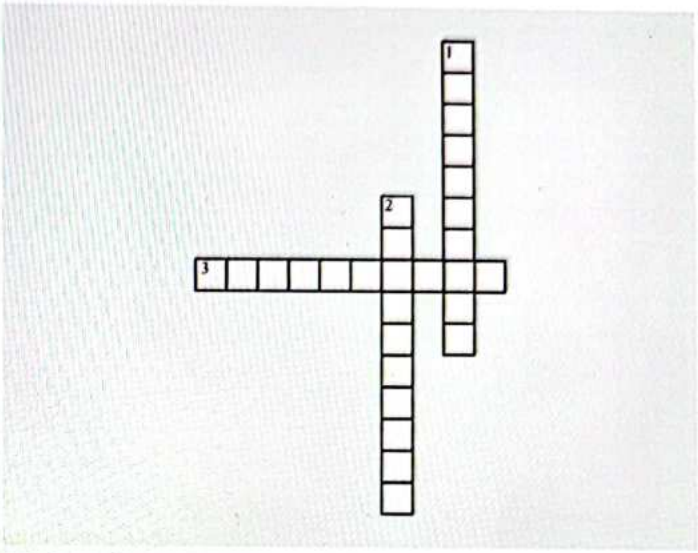
Across

2. _____ is treated with Oprelvekin.

Down

1. _____ is longer acting G-CSF analogue.
3. _____ are used to treat anemia due to anti-cancer drugs.

Crossword Puzzle 3



Across

3. _____ 1 receptor antagonists are the drug of choice for late CINV.

Down

1. _____ is the drug of choice for cancer-induced diarrhea,
2. _____ is used to decrease radio sensitization during radiotherapy

100 PLATINUM COMPOUNDS

- In platinum compounds, the major drugs are cisplatin, carboplatin, and oxaliplatin.
- All they end with platin, so they are platinum compounds.

Mechanism of action 00:00:52

- Platinum compounds are also called platinum coordination complexes
- When these drugs enter into the inside cells they are broken down and release highly reactive moiety and bind to N7 guanine residue of DNA.
- They cause cross-pairing in the DNA, it leads to DNA damage that will lead to cell death.

Cisplatin 00:02:45

- Cisplatin is the most widely used anti-cancer drug.

Mechanism of action

- It binds to N7 guanine residue of DNA.
- They cause cross-pairing in the DNA, it leads to DNA damage that will lead to cell death.

USES (Mnemonic HE GOT Bladder Cancer)

- **H-** Head and neck cancer
- **E-** Esophageal cancer
- **G-** Gastric cancer
- **O-** Ovarian cancer
- **T-** Testicular cancer
- **B**ladder cancer

Adverse Effects 00:04:17

- It is also the most emetogenic anticancer drug.
- It also causes ototoxicity.
- The drug causes nephrotoxicity. To prevent this kidney damage,
  - Forced chloride diuresis can be done.
    - → In order to induce diuresis faster, mannitol is combined with sodium chloride.
    - → So, in the presence of chloride, cisplatin can't stay for longer periods in the kidney.
    - → Thus, cisplatin is thrown away.
  - Amifostine
    - → Is a radio protector and is also used in the management of platinum nephrotoxicity.
- It is also neurotoxic
  - Produces mainly peripheral neuropathy.
  - In peripheral neuropathy, the patient has a tingling and numbness sensation.
  - These adverse effects will remain even after stopping the drug usage.
  - By stopping the drugs, the adverse effect should stop but it will remain even after stopping the drug usage. That effect is called the coasting effect.
- Cisplatin can decrease the major electrolytes like potassium, calcium and magnesium.

Oxaliplatin

- Oxaliplatin is used to treat a cancer called colorectal cancer.

Anti-Cancer Antibiotics 00:07:42

- Antibiotics are obtained from some organisms to kill the other organism.
- If they are killing the cancer cells they are called anticancer antibiotics.

Bleomycin

- It is a (G2 and M-phase) specific drug.

Mechanism of action

- All anticancer antibiotics damage DNA strands.
- It induces or releases free radicals.
- These free radicals break DNA strands.

Advantages

- Bleomycin is bone-marrow sparing drug.
- It is used in testicular cancer treatment.
  - BEP regimen, where B stands for bleomycin, E stands for etoposide and P for platinum.
- It is used in Hodgkin lymphoma and the regimen is ABVD.
  - B stands for Bleomycin.

Adverse Effects

- Pulmonary fibrosis.
  - In the lung there are two types of cells,
    - → Type-1 pneumocytes and
    - → Type 2 pneumocytes.
  - It causes necrosis of type-1 pneumocytes and type 2 pneumocytes will undergo hyperplasia.
- Dermatitis.
  - Dermatitis is seen like flagellate.
  - It is called flagellate dermatitis which is seen in the back buttocks and everything.

Important Information

- The other anti-cancer drug that starts with B also causes this pulmonary fibrosis is Busulfan.

Other Anticancer Antibiotic Drugs 00:11:56

Anthracyclines

Mechanism of action

- They intercalate into DNA and they form breaks in DNA.
- They induce free radicals, free radical injury to the DNA.
- They also inhibit an enzyme called DNA topoisomerase II.
- All these lead to DNA damage and result in cell death.

Anthracycline Drugs

- Daunorubicin
  - Also called Rubidomycin.
- Doxorubicin
  - Also called as Adriamycin (or) Hydroxy doxorubicin
  - Used in the treatment of both Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL).
- Idarubicin
- Valrubicin
  - Majorly used in the management of bladder cancer.

Adverse Effect

- Cardiotoxicity
  - Because of free radicals that are iron free radicals.
  - To prevent the cardiotoxicity, iron chelator is used that is Dexrazoxane (Iron chelator)
  - It will chelate iron and prevent free radical injury to the heart.
- **Radiation recall syndrome**
  - Using anticancer therapy along with drugs, sometimes there is a need for radiation therapy. In a few more cases after surgery, radiation therapy was given.
  - When radiation is given they induce mucosal damage, skin will become bright, itching, all those are due to radiotherapy.
  - Once the patient has undergone radiotherapy, and lesions are gone and again when given these drugs the patient will get the same lesions back that is called radiation recall syndrome that is seen in anthracyclines.

Actinomycin D 00:16:20

- It is also called Dactinomycin.
- **Mechanism of action**
  - It intercalates in DNA and here instead of damaging the DNA, it inhibits RNA synthesis.

Mitomycin-C

- It also causes DNA damage.

Use

- It is used to prevent tracheal stenosis to prevent adhesion.
  - When doing surgery, the tissues will proliferate and stick and there is stenosis.
  - After surgery by putting/ applying mitomycin-c topically the cells will not proliferate and they do not stick, thus they will prevent tracheal stenosis.
- Also used to prevent nasal stenosis.
- In nasal and tracheal stenosis, mitomycin-c is used to prevent adhesion.
- Also used during strabismus surgery to prevent scarring.
- It is also used for laryngotracheal stenosis.
- Mitomycin is majorly used in ENT problems.

Mithramycin 00:18:50

- It is not used as an anticancer drug but it is used in complications of hypercalcemia.

Mitoxantrone

- **Adverse effect**
  - Bluish discoloration of sclera, nails and eyes.

Miscellaneous 00:20:11

L-Asparaginase

- It is a bone marrow sparing drug.
- It does not produce adverse effects because it is an enzyme.

Mechanism of action

- L-asparaginase is an enzyme that breaks L-asparagine.
- Aspargin is required for photosynthesis.
- Cancer cells have to multiply rapidly, where they require amino acids from outside so they can synthesize proteins and can multiply fast. So, they lack an enzyme called L-asparagine synthase. This enzyme is deficient in cancer cells.
- Since it is deficient then they will take L-asparagine from the environment nearby.
- This L-asparagine goes into the cancer cell and starts multiplying.
- But in normal cells, they can synthesize their own L-asparaginase.
- When L-asparaginase enzyme is given, this enzyme will go and cut the L-asparagine, when it cuts the supply of L-asparagine to the cancer cells stops.
- If the L-asparagine does not go to the cancer cells, then they cannot synthesize, they cannot divide, and they cannot multiply.
- So, cancer multiplication stops.
- Normal cells have time, they can synthesize L-asparaginase. So, they are not affected much.

Adverse effects

- It can cause allergies.
  - Allergy: when we are using enzymes, they can induce allergy in patients.
- It can cause pancreatitis.
- It can cause increased coagulation.
- It is used in the treatment of children with ALL.

Use

- It is used in the treatment of children with ALL.

Tretinoin 00:23:48

- It is also called All Trans Retinoic Acid.
- In short form it can be represented as ATRA.
- The stage is called M3 stage.
- It is used in Acute promyelocytic leukemia.
- **In case of normal cells**
  - The immature cells myelocyte i.e., myeloblast will become the mature ones.
  - The cells are not differentiated, they are undifferentiated and they multiply. Hence, they are called acute promyelocytic leukemia.
  - These normal cells have nuclear receptor, and the nuclear receptors possess RAR α which binds on RXR, that is leading to differentiation of cells.
  - So, the myeloblast will become mature and come to circulation.

- **In case of cancer cells**
  - In PML and acute promyelocytic leukemia, the PML will bind with RAR α and it inhibits the differentiation of the cells, and now the cells stuck in the blastic or promyelocytic stage.
- It is called a differentiating agent. It will tightly bind to RAR α and RXR. The cancer cells will undergo differentiation. This is the reason it is called a differentiating agent.
- It will bind with PML and RAR α, it will degrades.
- Once degradation occurs, the cells will also undergo differentiation.

Use

- ATRA and anthracyclines (e.g. doxorubicin). This combination has a very good efficacy of 95%.

Arsenic Trioxide

- Used in AML (stage M3).
- **Mechanism of action**
  - It causes DNA damage, similar to that of L-asparaginase.

Thalidomide 00:28:15

- In the past, it was withdrawn from the market, due to its adverse effect of teratogenicity.
  - It is given for morning sickness in pregnancy, phocomelia is the adverse effect seen.
  - Due to this reason it was contraindicated in pregnancy.
- Later it was found to have immunomodulatory and anticancer properties.

Use

- Nowadays, it is used in
  - Multiple myeloma
  - Recurrent ENL
    → Thalidomide is the drug of choice in this condition
  - HIV associated mouth ulcers.
  - Bechet's disease

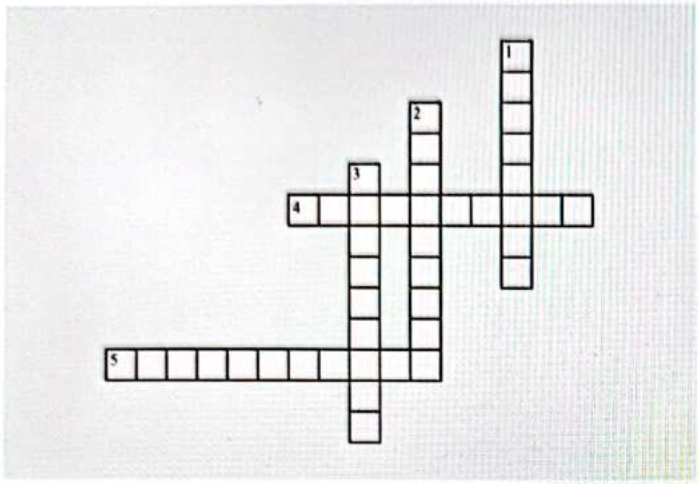
- **Adverse effect**
  - Teratogenic (contraindicated in pregnant women)
  - Sedation
  - Peripheral neuropathy
  - Constipation

Lenalidomide 00:30:54

- It is also used in multiple myelomas.
- It causes less adverse effects than thalidomide.
- Lacks teratogenicity.

CROSS WORD PUZZLES

Crossword Puzzle 1



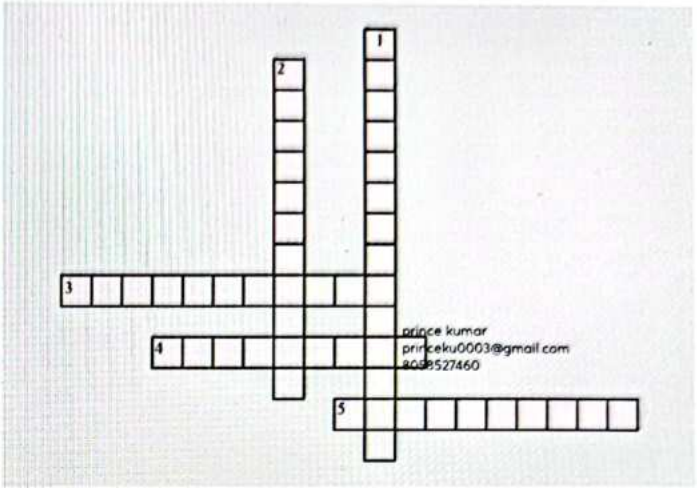
Down

1. ..... effect, is an effect where adverse effects will remain after stopping the drug usage.
2. .....is a G2 and M phase specific drug.
3. ..... is the most widely used anticancer drug.

Across

4. ..... is used in the management of cisplatin nephrotoxicity.
5. ..... drug is used to treat colorectal cancer.

Crossword Puzzle 2



Down

1. ..... are the drugs which inhibit an enzyme DNA Topoisomerase II.
2. ..... the drug is used in the management of HL and NHL.

Across

3. ..... is used to prevent tracheal stenosis.
4. ..... is also called all trans retinoic acid (ATRA).
5. ..... is the iron chelator used to prevent cardiotoxicity.

101 CELL CYCLE SPECIFIC DRUGS

- The cell cycle, or cell-division cycle, is the series of events that take place in a cell that cause it to divide into two daughter cells.
- These events include the duplication of its DNA (DNA replication) and some of its organelles and subsequently the partitioning of its cytoplasm, chromosomes and other components into two daughter cells in a process called cell division.
- Drugs that specifically act on different phases (S, M, G1S, G2M) of cell cycle are cell cycle specific drugs.

Synthesis-Phase (S-Phase) Specific Drugs 00:00:31

- S-phase (Synthesis Phase) is the phase of the cell cycle in which DNA is replicated, occurring between G_1 phase and G_2 phase.
- DNA synthesis requires purine and pyrimidine. When fake purine and pyrimidine are introduced DNA synthesis stops.
- The drugs in S phase are
  - Antifolate
  - Purine antagonist

Antifolate Drugs 00:01:12

- **Methotrexate:** It is used to calm the immune system, to help stop it attacking its own body's cells.
- **Pemetrexed:** It is used in mesothelioma and non-small cell lung cancer.
- **Pralatrexate:** It is used in peripheral T cell lymphoma.

Mechanism of Action of Methotrexate (MTX) 00:02:40

Methotrexate enters the cancer cells

↓

Methotrexate converts to Methotrexate polyglutamate

↓

Inhibits Dihydrofolate (DHF) reductase

↓

Inhibits Tetrahydrofolate (DHF) reductase

↓

Decrease the DNA synthesis

Methotrexate enters the cancer cells

↓

Inhibits Thymidylate synthase

↓

Decrease the DNA synthesis

- It increases the extracellular adenosine, so it acts like an anti-inflammatory and immunosuppressant. Used in treatment of Rheumatoid arthritis.

Cause of Cell Resistance to Methotrexate 00:05:35

- The gene amplification increases the target gene count, leading to treatment resistance to methotrexate.
- As entry to methotrexate is prohibited, methotrexate polyglutamate is not formed.
- Eventually, enzyme thymidylate synthase will not bind to methotrexate.
- By any chance if Methotrexate comes inside it will be thrown out.

Use of Methotrexate 00:06:32

- Methotrexate is used in high doses in case of Osteosarcoma.
- Ut is helpful in case of Crohn's disease (Inflammatory bowel disease).
- As it suppresses the immune system, it is helpful in preventing Autoimmune disease.
- Also used in the case of NHL (Non-Hodgkin's Lymphoma).
- Also used in cases of Choriocarcinoma.
- In case of Ectopic pregnancy, it is used to abort the pregnancy.
- Rheumatoid arthritis due to anti-inflammatory properties.
- Methotrexate is used in treatment of Psoriasis.

The Adverse Effect of Methotrexate 00:09:01

- Bone marrow suppression
- High dose causes pancytopenia
- Normal does Megaloblastic anaemia
- Hepatotoxic (monitor LFT)
- GI mucosal damage (bloody diarrhoea)
- Alopecia

Important Information

- **Pancytopenia:** A condition in which there is a lower-than-normal number of red and white blood cells and platelets in the blood.
- **Megaloblastic anaemia:** It is a form of macrocytic anaemia, a blood disorder that happens when your bone marrow produces stem cells that make abnormally large red blood cells.
- **Hepatotoxic:** Chronic liver injury
- **Alopecia:** Alopecia areata is a disease that happens when the immune system attacks hair follicles and causes hair loss

Management of Methotrexate Toxicity 00:11:30

- Normal cells given folinic acid/Citovorum/ leucovorin to prevent the harm of Methotrexate.
- Glucarpidase enzyme metabolise excess methotrexate hence prevent toxicity.
- Forced alkaline diuresis will be done as the methotrexate is acidic.

Purine Antagonist 00:14:31

- Purine antagonists are substances that interfere with the production of adenosine and guanosine triphosphate, essential components of DNA.

Refer Table 101.1

Mechanism of Action of 6-Mercaptopurine and 6-Thioguanine

- As these both are purine antagonists these will act by inhibiting the synthesis of Purine i.e Adenine, Guanine, De Novo purine and DNA.
- A part of 6-mercaptopurine is metabolised by xanthine oxidase and made inactive. When 6-mercaptopurine is used along with Allopurinol in the treatment of Hyperuricemia, a decreased dose should be given since Allopurinol inhibits xanthine oxidase which in turn leads to 6-mercaptopurine toxicity

Pyrimidine Antagonist 00:23:01

- Pyrimidine antagonists belong to the group of antimetabolite anticancer drugs and show structural resemblance with naturally occurring nucleotides.
- Their action is accomplished through incorporation as a false precursor in DNA or RNA or through inhibition of proteins involved in nucleotide metabolism.
- The example of pyrimidine antagonist are
  - 5 Fluorouracil
  - Cytarabine
  - Gemcitabine
  - Azacytidine
  - Decitabine

5 Fluorouracil

5 fluorouracil is a pro drug which binds with folinic acid and is converted to FdUMP (active form)

↓

Promotes conversion of dUMP to dTMP

↓

In general, this process is inhibited by Thymidylate synthase

↓

But here the binding of folinic acid is crucial as it increases inhibition of Thymidylate synthase

↓

In this way it acts as pyrimidine antagonist

↓

Decreases DNA synthesis

Uses of 5 fluorouracil

- It is used in treatment of colorectal cancer.
  - FOL FOX (FOL = Folinic acid, F = 5 Fluorouracil, OX = oxaliplatin)
  - FOL FIRI (FOL = Folinic acid, F = 5 Fluorouracil, IRI = Irinotecan)

Adverse effects

- Hand foot syndrome: It is a skin reaction that affects the palms of your hands and the soles of your feet. It's a common side effect of some types of chemotherapy. Symptoms include redness, swelling and sometimes pain.

Important Information

- Capecitabine and Tegafur, after metabolism, gives rise to 5 fluorouracil and also causes Hand foot syndrome.
- Flucytosine gives rise to 5 fluorouracil.

Cytarabine 00:26:30

- Cytarabine is given as a continuous IV infusion.
- It can be used to treat both Myeloid and Lymphoid leukaemia.
- Adverse effects of cytarabine are:
  - Patient will have Cerebral ataxia.
  - Non-cardiogenic pulmonary edema.

Important Information

- Ataxia: It is poor muscle control that causes clumsy voluntary movements.
- Flucytosine, capecitabine, tegafur all metabolise and form 5 Fluorouracil.

Gemcitabine

- It is used in treatment of pancreatic cancer

Hydroxyurea 00:28:40

Mechanism of Action

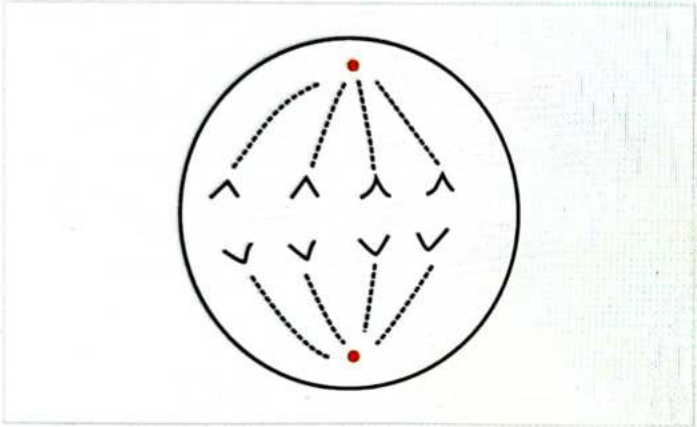
- Hydroxyurea acts by inhibiting the ribonucleotide reductase which is responsible for conversion of ribonucleic acid to deoxyribonucleic acid.

Uses

- **Polycythaemia Vera:** The type of blood cancer in which bone marrow is made to make too many red blood cells.
- **Essential thrombosis**: The bone marrow produces too many of the cells that form platelets, and these platelets often don't work properly.
- **Sickle cell anaemia:** A serious medical condition in which the red blood cells are damaged and change shape.

M- Phase Specific 00:31:40

- Cell division occurs during M phase, which consists of nuclear division (mitosis) followed by cytoplasmic division (cytokinesis).
- These are called Microtubule damaging agents.



- In the centromere, the microtubules will integrate and disintegrate. By doing this they will pull the DNA apart and there is mitosis. These drugs will damage the microtubules and prevent cell division. These drugs will either stabilize or destabilize.

Vinca Alkaloids

- Vinca alkaloids are used to destabilise microtubules.

Vincristine (Oncovin)

- It has bone marrow sparing properties.
- It's used in childhood tumours (wilm's tumour), lymphoma.
- Adverse effects: peripheral neuropathy and SIADH

Vinblastine

- Vinblastine doesn't have bone marrow sparing property
- It is used in Hodgkin's lymphoma

Vinorelbine

- When non-small cell lung cancer (NSCLC) has spread to nearby tissues or to other parts of the body, vinorelbine is used both alone and in combination with other drugs to treat the disease.

Taxzanes

- These act by stabilising microtubules. The main two taxanes are Paclitaxel and Docitaxel.

Paclitaxel

- Cremphor derived- Patient receiving this may develop anaphylactic reaction, to prevent steroids are given
- Nab (Albumin bound Nano - particle).
- Paclitaxel used in solid tumours and its adverse effects is peripheral neuropathy.

Docetaxel

- It is used in the treatment of breast cancer.

Estramustine

- It has two forms and is used in treatment of Prostatic cancer.
  - Oestrogen
  - Normustine

Eribulin

- Eribulin is used in the treatment of breast cancer.

Epothilones - Ixabepilone

- Epothilones are used in the treatment of breast cancer.

G1 - S Phase Specify Drug 00:40:35

- The first growth period of the cell cycle during interphase, in which the cell grows and cytoplasmic organelles are replicated.
- Etoposide is a G1 -S Phase specificity drug.

G2 - M Phase Specific Drug 00:40:40

- During the second gap phase, or G-2 start subscript to end subscript phase, the cell grows more, makes proteins and organelles, and begins to reorganise its contents in preparation for mitosis.
- Bleomycin - It is the most common G2-M specific drug.
- G2 - M Specific drugs are inhibitors of DNA Topoisomerase, these are

Inhibitor of DNA Topoisomerase I

- Irinotecan (A/E - Diarrhoea)
- Topotecan

Inhibitor of DNA Topoisomerase II

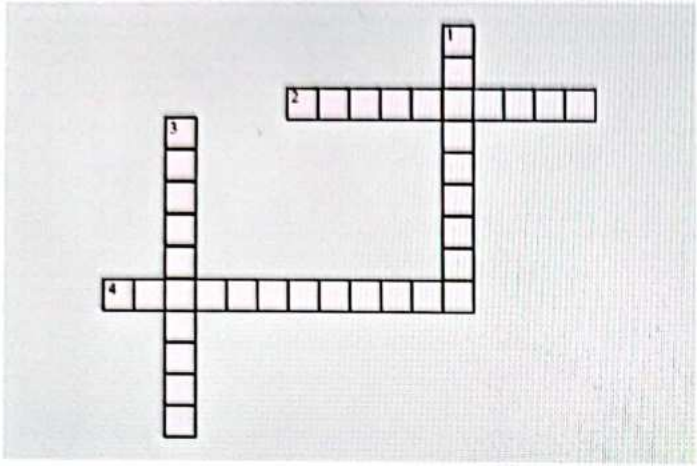
- Etoposide
- Teniposide
- DNA Topoisomerase II inhibitors are used in treatment of testicular cancer.

Table 101.1

Drugs	Action
1. 6 -Mercaptopurine	Management of leukaemia
2. 6 - Thioguanine	Thioguanine is an antimetabolite
3. Cladribine	Drug of choice for Hairy cell leukaemia
4. Pentostatin	Inhibits adenosine deaminase (Decrease in T cell and B cell production). Used to treat Hairy cell leukaemia.
5. Fludarabine	Treats chronic lymphocytic leukaemia (CLL)
6. Clofarabine	Used to treat acute lymphoblastic leukaemia
7. Nelarabine	Treatment of acute T-cell lymphoblastic leukaemia

CROSS WORD PUZZLES

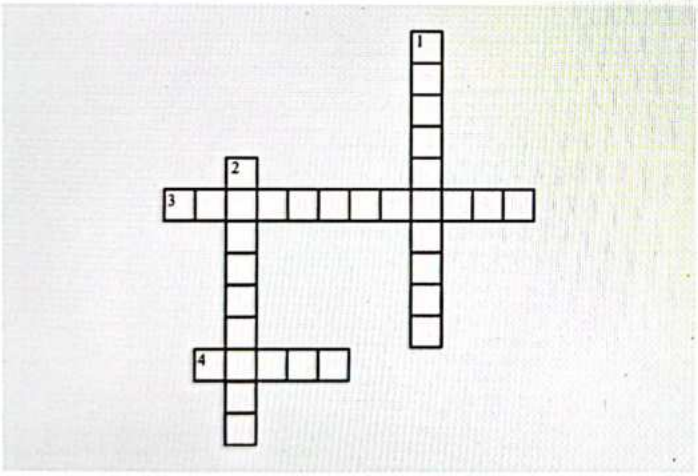
Crossword Puzzle 1



Hints

1. Antifolate drugs
2. Pyrimidine antagonist
3. Hairy cell leukaemia
4. Purine antagonist

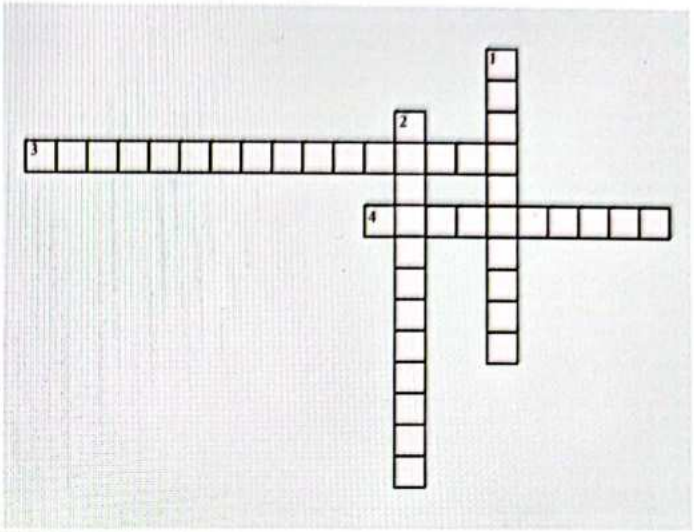
Crossword Puzzle 2



Hints

1. Inhibitor of DNA Topoisomerase I
2. Inhibitor of DNA Topoisomerase II
3. It Has two forms and is used in treatment of Prostatic cancer.
4. Destabilize microtubules

Crossword Puzzle 3



Across

3. Skin reaction that affects the palms of your hands and the soles of your feet.
4. Drug of choice of hairy cell leukemia.

Down

1. Antifolate drug used in non-small cell lung cancer
2. Used in peripheral T cell lymphoma

102 HORMONAL AGENTS

- Some of the hormonal agents are used in the treatment of cancer.
- Prostate cancer, breast cancer, they depend on hormones for their proliferation.

Corticosteroids 00:00:16

- Corticosteroids decrease T cells more than B cells. (T cells > B cells)
- Corticosteroids are used in two important conditions.
  - Leukemia
  - Lymphoma
- In these two conditions, corticosteroids decrease T cells and B cells.

Preparations of corticosteroids used as anticancer drugs

- Prednisolone
- Dexamethasone

Advantages of corticosteroids in cancer patients

- When corticosteroids are used in cancer patients, they have
  - Antiemetic effect.
    - → This effect is beneficial in cancer patients.
    - → E.g. In CDME, dexamethasone is used to suppress vomiting.
  - Mood elevating property.
    - → As most of the cancer patients are suffering from depression, this property will be very good in such cases.
  - Manage hypercalcemia which is seen in malignancies.
  - Decrease cerebral edema.
    - → Many times, malignancies will be associated with inflammations and edema. So, that dexamethasone is used to decrease cerebral edema.

Hormonal agents to treat prostate cancer 00:02:38

Androgen Receptor Antagonist

- These drugs end with glutamide.
  - Flutamide
  - Nilutamide
  - Bicalutamide

GnRH Agonist

- They should continuously decrease testosterone secretion.

GnRH Antagonist

- They also decrease release of testosterone secretion. Examples include:
  - Abarelix
  - Degarelix

Estrogen preparations used in prostate cancer

- In olden days, it was thought that estrogens were producing negative feedback FSH and LH, decrease of FSH and LH and decrease the synthesis of testosterone.
- Thus, estrogens are also used in prostate cancer in early days.
- Estrogen preparations used as anticancer agents are:
  - Estramustine (combination of estrogen and normustine)
  - Fosfestrol

Others

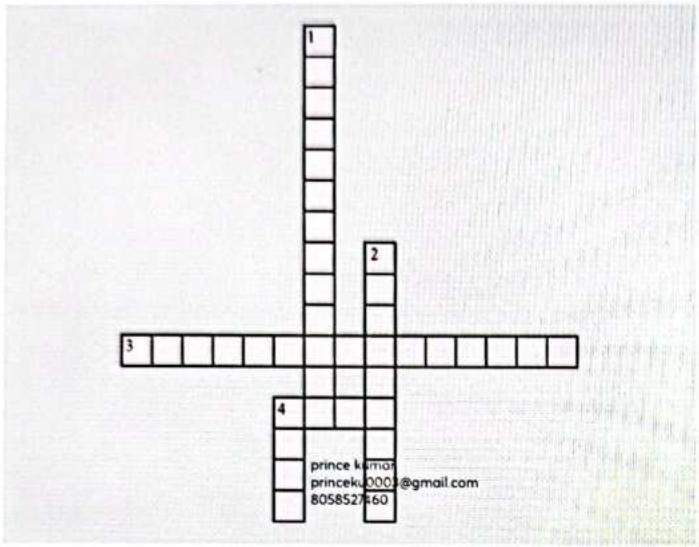
- Recently, one more drug is used for prostate cancer by inhibiting androgen synthesis.
  - 17α Hydroxylase inhibitors- Abiraterone

Hormonal agents to treat breast cancer 00:05:35

- Breast cancer can be seen by pre-menopausal and post-menopausal women.
- For both premenopausal and postmenopausal women with breast cancer.
  - Initial therapy is SERM, examples:
    - → Tamoxifene
    - → Toremifene.
- In postmenopausal women, who are resistant to Tamoxifen. These people can be treated with aromatase inhibitors.
- Aromatase inhibitors have two class of drugs which includes:
  - Irreversible blockers
    - → Exemestane
    - → Formestane
  - Reversible inhibitors
    - → Letrozole
    - → Anastrozole
- If still, the patient is not responding to aromatase inhibitors. In such cases of aromatase inhibitor resistant breast cancer patients, the modality of treatment is with SERD (Selective estrogen receptors degraders).
- Example of SERD is Fulvestrant

CROSS WORD PUZZLES

Crossword Puzzle 1



Down

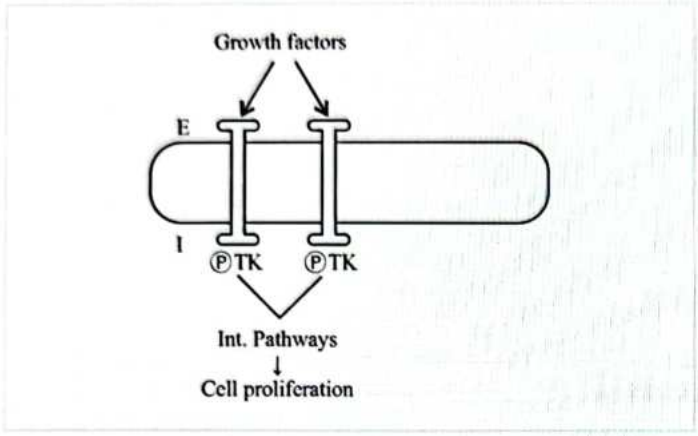
1 ..... to treat cerebral edema in cancer patients.
2 ..... an androgen receptor antagonist.
4 ..... are used to treat aromatase inhibitor resistant breast cancer patients.

Across

3 .....decrease T cells more than B cells in cancer therapy.
5 .....is the initial therapy for pre and postmenopausal women to treat breast cancer.

103 TARGETED THERAPY

00:01:03



- The tyrosine kinase receptors have intrinsic tyrosine kinase properties.
- Whenever the growth factors bind to the receptors, the receptor will go under dimerisation and they will phosphorylate the tyrosine kinase.
- This will activate the intermediate pathways which will send a signal for cell-proliferation.
- Thus, the growth factors are the stimulus for cancer proliferation.

So, we can target the following areas to stop cancer proliferation:

- **Blocking the growth factor:** This is done by using MAbs (Monoclonal antibodies).
  - MAbs are not given orally, instead parenteral as antibodies are proteins.
  - For example, the growth factor for breast cancer is Her2/neu is blocked by MAbs, then they can't bind to the receptors.
  - The MAbs to block Her2/neu is Trastuzumab, thus it is used to treat breast cancer.

- **Blocking the tyrosine kinase:** This is done by using tyrosine kinase inhibitors.
  - These can be given orally.
  - The name of the drugs usually ends with 'nib.'

- **Blocking the intermediate pathways.**

Important Information

- The drugs that block tyrosine kinase and the intermediate pathway are called small molecule inhibitors.

Monoclonal Antibodies

00:06:00

1. Epidermal growth factor (EGF) receptor:

- Cetuximab is used in the treatment of metastatic colon cancer and head and neck cancer.
- Panitumumab is used in the treatment of metastatic colorectal cancer.

2. Her2/neu: It is a type of EGF.

- Trastuzumab is used for the treatment of breast cancer. Adverse effect: It is cardiotoxic.
- Pertuzumab is another drug for breast cancer.

3. Vascular endothelial growth factor (VEGF) receptor:

- Bevacizumab is used to treat-
  - Colorectal cancer
  - Angioproliferative retinopathy
  - Renal cell cancer
  - NSCLC (non-small cell lung cancer)
  - Ranibizumab is used to treat wet age-related macular degeneration.

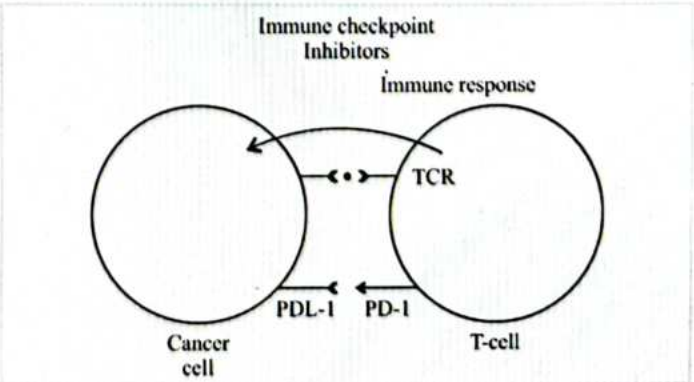
4. Platelet-derived growth factor (PDGF) receptor:

- Olaratumab is used to treat soft tissue sarcoma.

5. CD Factor Blocking Mabs

- CD52 blockers: It is blocked by alemtuzumab and is used to treat CLL and multiple sclerosis.
- CD20 blockers: It is blocked by rituximab and is used to treat **(mnemonic: no match)**
  - **No in Non-Hodgkin** Lymphoma (NHL)
  - **Multiple** sclerosis and myasthenia gravis.
  - **A**rthritis (Rheumatoid arthritis)
  - **T**TP (thrombotic thrombocytopenic purpura)
  - **C**LL
  - **H**emolytic anaemia (autoimmune)

6. Immune Checkpoint Inhibitors



- These are also a type of Mabs.
- T-cells have a TCR (T-cell receptor) where the antigen is presented.
- The cancer cells express PDL-1 (programmed death ligand 1) which will combine with PD-1 (programmed cell death 1) which is present on T-cells.
- If PDL- 1 and PD-1 bind, the immune cells will not kill the cancer cells.
- So, blocks were discovered for PDL-1 so that PD-1 can't bind to it and the cancer cells get killed.
- These drugs can be used to treat many types of cancers. These are:

a) PD-1 Inhibitor: The drugs are-
- Pembrolizumab
- Nivolumab
- Cemiplimab
- **Uses:** Here are the various uses of these drugs-
  → Melanoma
  → Renal cell cancer (RCC)
  → Hodgkin's lymphoma and
  → Various other tumours.

b) PDL-1 inhibitors: The drugs are-
- Atezolizumab
- Durvalumab
- Avelumab
- **Uses:** These are used to treat the same conditions as PD-1 inhibitors.

c) CTLA-4 inhibitor: The drug is
- Ipilimumab which is used to treat melanoma, RCC and various tumors.

Small Molecule Inhibitors 00:20:34

1. Tyrosine Kinase Inhibitors:

a. BCR-ABL TK Inhibitor:
- It is also an inhibitor of cKIT TK. The drugs are -
- Imatinib: It is the drug of choice for CML and GIST (gastrointestinal stromal tumour). It is also used to treat ALL.
- Dasatinib and Nilotinib are used in case of Imatinib resistance.

b. EGF TK inhibitor: The drugs are -
- Erlotinib
- Geftinib
- Afatinib
- These all are used to treat NSCLC.

c. Her2/neu TK inhibitor: The drugs are
- lapatinib and neratinib.
- They are used to treat metastatic breast cancer and are given orally.

d. VEGF TK inhibitor: The drugs are -
- Sorafenib: It is used to treat hepatocellular cancer.
- Sunitinib: It is used to treat Imatinib-resistant GIST.
- Regorafenib: It is used to treat colorectal cancer and sunitinib-resistant GIST.

e. ALK TK inhibitor: The drugs are -
- Alectinib and crizotinib: These are used to treat NSCLC.

2. JAK 1/2 Inhibitors: The drug is Ruxolitinib.
- It is used to treat polycythemia vera.

a. BRAF Inhibitors: The drugs are vemurafenib and dabrafenib.
- These are used to treat melanoma.

3. Proteosome Inhibitors: The drugs are -
- Bortezomib
- Ixazomib
- Carfilzomib
- These all are used to treat multiple myeloma. The treatment follows a regimen: Bortezomib + Lenalidomide + Dexamethasone

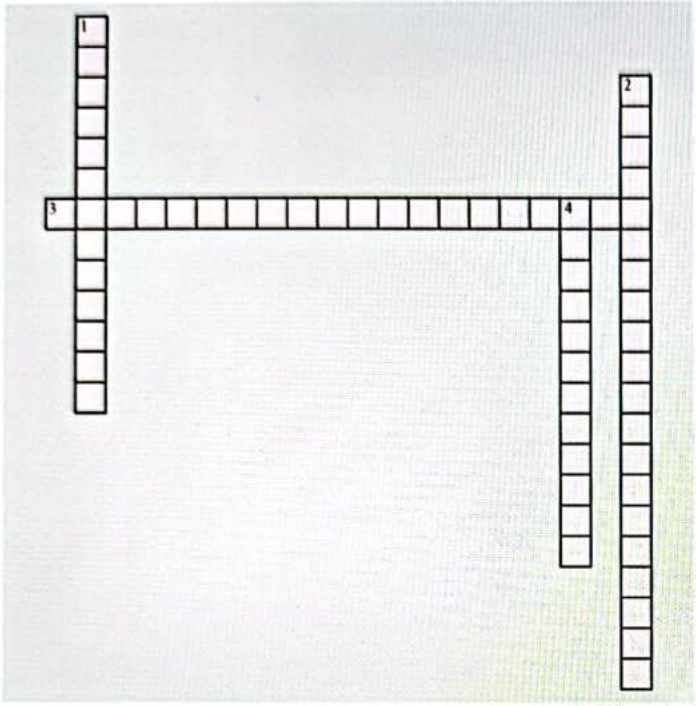
4. Cycline-Dependent Kinase Inhibitors: These are -
- CDK 4/6 inhibitors: The drug is palbociclib and is used to treat breast cancer.

5. PARP (Poly ADP ribose polymerase) Inhibitors: The drug is Olaparib.
- It is used to treat breast cancer and ovarian cancer.

6. Histone Deacetylase Inhibitors: The drugs are -
- Vorinostat: It is used to treat CTCL (cutaneous T-cell lymphoma).
- Panabinostat: It is used to treat multiple myeloma.
- Romidepsin: It is used to treat CTCL or PTCL (peripheral T-cell lymphoma).

CROSS WORD PUZZLES

Crossword Puzzles 1



Across

3. MAbs stands for _____.

prince kumar
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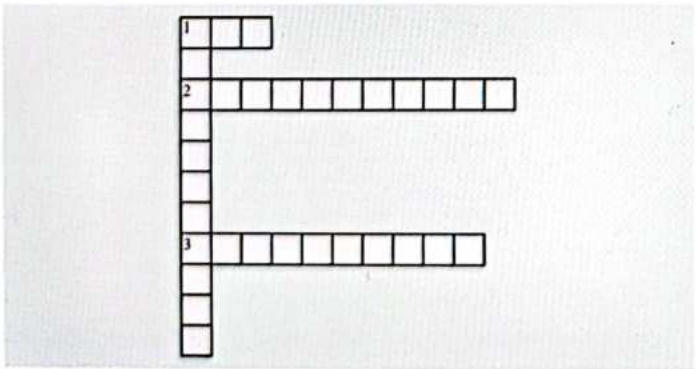
Down

1. Drugs that block tyrosine kinase and the intermediate pathway are called _____ inhibitors.
2. Panitumumab is used in the treatment of _____ cancer.
4. _____ pathways send a signal to cancer cells for self-proliferation.

Crossword Puzzles 2



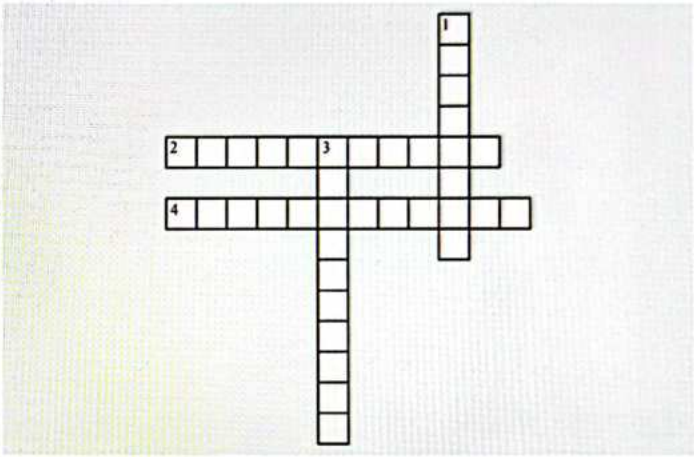
Across

1. Alemtuzumab is used to treat multiple sclerosis and _____.
2. _____ is used to treat wet age-related macular degeneration.
3. An example of a platelet-derived growth factor (PDGF) receptor blocker is _____.

Down

1. The adverse effect of trastuzumab is that it is _____.

Crossword Puzzles 3



Across

2. _____ is used to treat polycythemia vera.
4. The treatment regimen of multiple myeloma includes Bortezomib, _____, and Dexamethasone.

Down

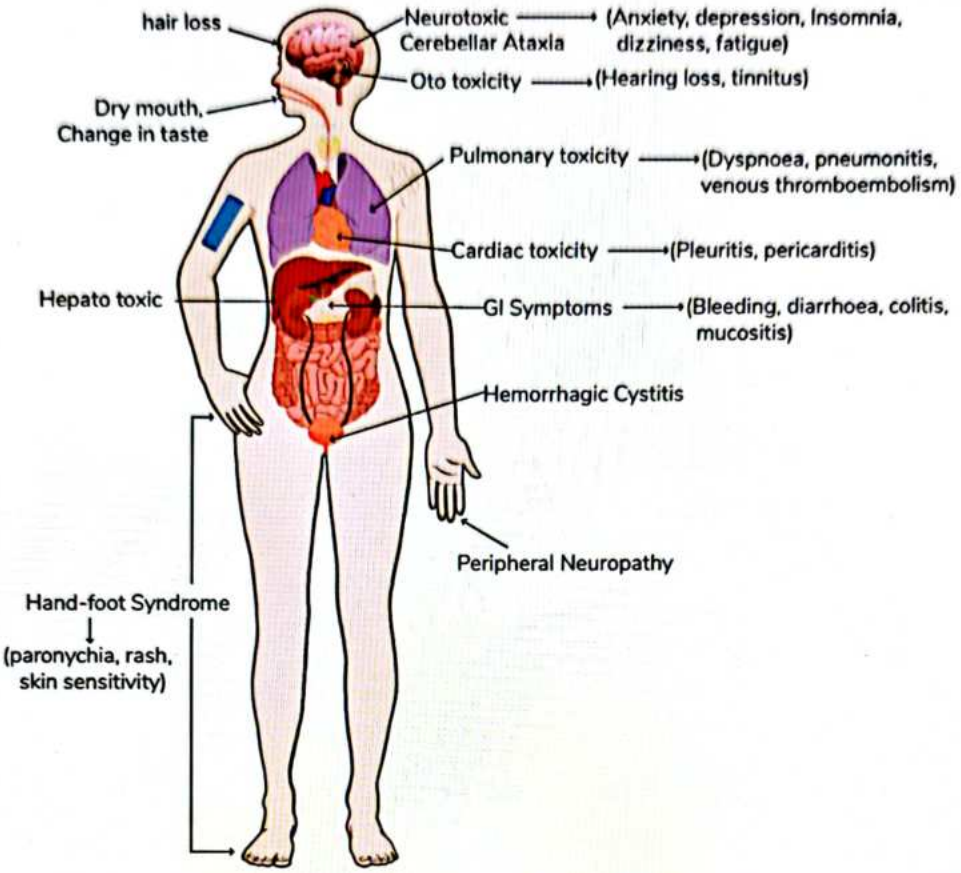
1. _____ is the drug of choice for CML and GIST.
3. An example of a CTLA-4 inhibitor is _____.

104 ADVERSE EFFECTS OF ANTICANCER DRUGS

00:00:10

The most common adverse effects associated with anticancer drugs are listed in the table given below:

Drugs	Adverse effects
Cisplatin	Ototoxicity
Cisplatin, Cyclophosphamide, and Chlorambucil	Nausea and Vomiting.
	Mucositis
Bleomycin	Flagellate Dermatitis.
Bleomycin and Busulfan	Pulmonary toxicity.
Trastuzumab and anthracyclines	Cardiotoxicity
Cytarabine	Non-cardiogenic pulmonary oedema.
Methotrexate	Gastrointestinal bleeding in the stomach.
	Diarrhoea
Cyclophosphamide and ifosfamide	Haemorrhagic cystitis in the bladder due to acrolein (a metabolite of cyclophosphamide).
5 Fluorouracil, capecitabine, Tegafur and pemetrexed	Hand-foot syndrome.
Anthracyclines	Radiation recall syndrome.
Vinca alkaloids and Taxanes	Peripheral neuropathy.
Cisplatin	Kidney damage (nephrotoxicity).
Methotrexate (MTX), 6-Mercaptopurine	Hepatotoxicity
Nitrosoureas →	Sustained neutropenia. (cause bone marrow suppression)
Ifosfamide →	Neurotoxic (brain)
Cytarabine →	Cerebellar ataxic

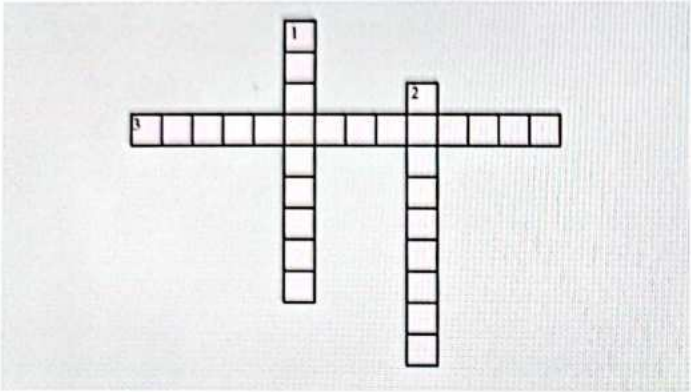


Important Information

- The drug of choice for Early Chemotherapy induced nausea vomiting is Setron and for Late Chemotherapy induced nausea vomiting pitant (neurokinin 1 receptor blockers) for late CINV.
- Mucositis is prevented by palifermin (keratocyte growth factor).
- Dexrazoxane is used to treat cardiotoxicity.
- Antidote for methotrexate is folinic acid/leucovorin and glucarpidase.
- Loperamide treats Anticancer drug-induced diarrhoea.
- Haemorrhagic cystitis is prevented by MESNA (sodium 2-mercapto ethane sulfonate).
- Nephrotoxicity is prevented by Amifostine and Forced chloride diuresis.
- Vincristine, Bleomycin, L-asparaginase are Bone-marrow sparing drugs.
- If there is bone marrow suppression, we use Filgrastim, Sargramostim, erythropoietin or IL 11 analogues to correct it.

CROSS WORD PUZZLES

Crossword Puzzle 1



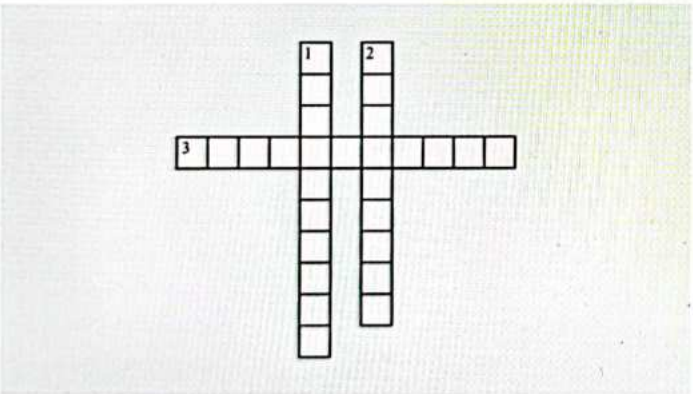
Across

3. Trastuzumab and anthracyclines' adverse effect is _____.

Down

1. _____ adverse effect Flagellate Dermatitis.
2. _____ adverse effect is Otoxicty.

Crossword Puzzle 2



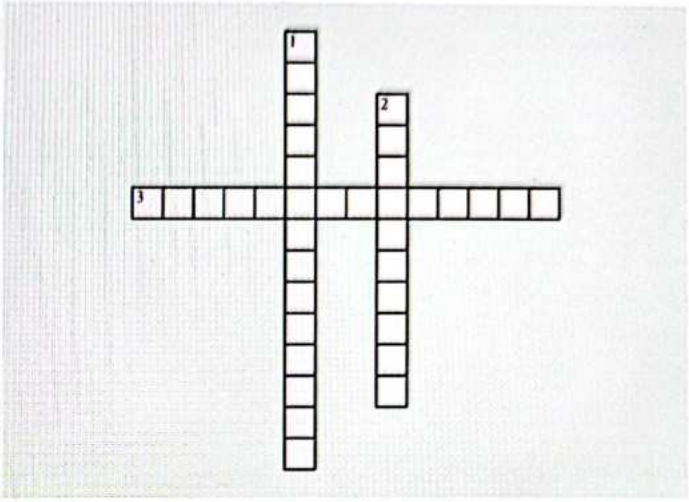
Across

3. _____ is used to treat cardiotoxicity.

Down

1. _____ adverse effects Non-cardiogenic pulmonary oedema.
2. _____ is prevented by palifermin (keratocyte growth factor).

Crossword Puzzle 3



Across

3. _____ and Texans Peripheral neuropathy.

Down

1. Adverse effect of _____ Radiation recall syndrome.
2. _____ adverse effect is Non-cardiogenic pulmonary oedema.

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105 IMMUNOMODULATORS

Definition

- Immunodulators are substances that modify the immune system.
- They are mainly of two types;
  - Immunostimulants
  - Immunosuppressants.

Immunostimulants 00:02:40

- As the name suggests, Immunostimulants increase immunity.
- Examples:
  - BCG Vaccine is given locally as intravesical therapy for treating superficial bladder cancer to increase immunity and destroy cancer cells.
  - Interleukin-2 (IL2) analogue, also called Aldesleukin and is used in managing renal cell cancer and melanoma.
  - Levamisole is an antihelminthic drug used to treat colorectal cancer in combination with 5-fluorouracil.

Immunosuppressants 00:05:00

- Immunosuppressants suppress immunity. They are used in the following conditions.
  - Autoimmune diseases
  - Organ transplant
  - Graft versus host disease (GVHD)
  - Medicated Stents
  - Allergy

Problems of Using Immunosuppressants

- Patients are prone to opportunistic infections.
  - For example, steroids used during the Covid-19 pandemic resulted in Mucormycosis.
- Chances of cancerous growth such as lymphomas or leukaemia.

Immunity can be suppressed in Two ways

- Decreasing the T-cell activation (suppress cell-mediated immunity)
- Decreasing the B-cell activation (suppress humoral immunity)

Decreasing T-Cell Activation 00:07:40

- T-cells undergo activation when an antigen-presenting cell (APC) interacts with T-cells.
- As a result, interleukin-2 (IL-2) is released, which acts on the same T-cell through the IL-2 receptor, which causes the T-cells to proliferate and boost immunity.
- It is a three-step process:

Step 1: Activation of T-cell by APC

- When the antigen is presented to the T-cell, the T-cell receptor (TCR) on the cell takes this and activates Cd3.
- CD 80/86 from APC activates CD28 in T-cells. Therefore, it is also known as a co-stimulator.
- **Blocking the Step:**
  - Cd3 - Muromonab (used in acute organ rejections)
  - CD80/86 - Abatacept and Belatacept (used in an autoimmune disorder called rheumatoid arthritis)

Step 2: Release of IL-2

- Activation of CD3 activates IP3, which releases the calcium (Ca^{2+}). This released calcium activates calcineurin.
- Calcineurin phosphorylates nuclear factor-activated T-cells (NFAT) that move inside the cell and cause gene transcription to produce IL-2.
- **Blocking the Step** - Calcineurin
  - Combination of cyclosporine and cyclophilin.
  - Tacrolimus, a macrolide derivative, bonds with the FK binding protein (FKBP) to inhibit the action of calcineurin.

- Adverse effects of Calcineurin inhibitors:

Cyclosporine	Tacrolimus
• Hyperglycemia • Hyperkalemia • Neurotoxicity • Nephrotoxicity • Hepatotoxicity • Hypertension • High uric acid • Gum hyperplasia • Hirsutism. } Less seen with Tacrolimus	• Neurotoxicity • Nephrotoxicity • Hyperglycemia. } More with Tacrolimus

Step 3: T-Cell Proliferation

- The released IL-2 acts on the same T-cells through the IL-2 receptor, also known as CD25. As a result, the JAK-STAT pathway is activated through phosphorylation, leading to the activation of M-ToR (Mammalian Target of Rapamycin).
- M-ToR then commands to increase Nucleic acid synthesis for increasing T-cell proliferation.
- **Blocking the Step-**
  - **IL-2 receptor blockers**- Daclizumab and Basiliximab; used in acute organ rejection.
  - **JAK inhibitors**-Tofacitinib and Barcinitib.

- **M-ToR inhibitors-** Sirolimus (used in medicated stents), Temsirolimus, and Everolimus (cancer).
- **Nucleic Acid Synthesis Inhibitors-** Mycophenol mofetil (MMF) inhibits IMP dehydrogenase (purine synthesis inhibition lead to decrease T cells), and Leflunomide inhibits dihydro Orotate dehydrogenase (pyrimidine synthesis inhibition lead to decrease T cells)
- **Cell Proliferation-** Anticancer drugs such as methotrexate, Drug of choice for Rheumatoid arthritis, psoriasis cyclophosphamide (Drug of choice for Wegener's granulomatosis), and azathioprine.
- It is prodrug. it is used as Immunosuppressent in Rheumatoid arthritis , Myasthenia gravis.
- After metabolism it become anticancer drug 6 Mercaptopurine used in anticancer therapy.
- Corticosteroids are also used to decrease T-cells, monocytes, eosinophils, basophils, IL1, IL2, IL6, and TNFα

Decreasing B-Cell Activation 00:30:45

- **Belimumab:** Inhibits the B-lymphocyte stimulator used to treat systemic lupus erythematosus (SLE).
- **Rituximab:** Blocks CD20 used to treat rheumatoid arthritis, myasthenia gravis, and Non-Hodgkin lymphoma (NHL).
- **Ocrelizumab:** Blocks CD20, which is used to treat multiple sclerosis.

Other Targets to Suppress Immunity 00:32:45

- Various other targets and their blockers along with their uses, are discussed in the table given below:

Refer Table 105.1

Clinical Cases 00:36:55

Case-1

- **A 45-yr. old patient needs to undergo a liver transplant.**
  - **Organ Transplant Regimen**
    - **→ Induction Regimen:**
      - This step uses three drugs: Cyclosporine or Tacrolimus, or Sirolimus, and Prednisolone (steroid) along with Mycophenol mofetil (MMF).
    - **⇒ Maintenance Regimen:**
      - Sirolimus, and steroid along with Mycophenol mofetil (MMF)
    - **→ Antirejection Regimen:**
      - High-dose I.V. steroids and Muromonab CD3 blocker or Antithymocyte globulin (ATG); against CD and HLA antigens. Furthermore, MMF can be added if the rejection is not controlled.

Case-2

- **A 55-year-old woman with rheumatoid arthritis needs treatment.**
  - The common drugs used in this case include rituximab, abatacept, belatacept, anakinra, tofacitinib, barcinitib, leflunomide, methotrexate, etc.

Case-3

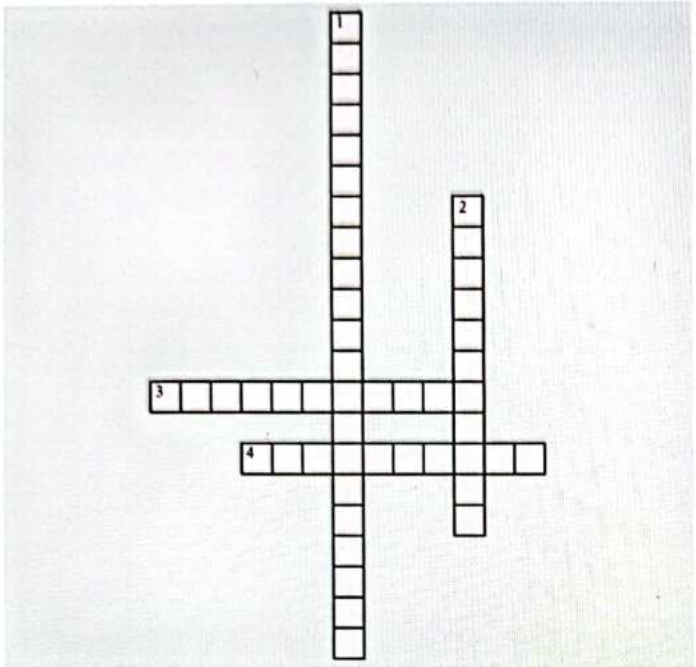
- **A 60-year-old male patient was placed with a coronary stent due to CAD. the stent is medicated to prevent stent blockade**
  - Sirolimus can be used in the medicated stent to prevent blockade.

Table 105.1

Targets	Blockers/inhibitors	Use for treatment
Tumour Necrosis Factor-alpha (TNFα)	Infliximab (I) Certolizumab (CE) Adalimumab (A) Golimumab (G) Etanercept (E) (Mnemonic- ICE AGE)	Rheumatoid arthritis
IgE	Omalizumab	Allergies and bronchial asthma
CD6	Itolizumab	Psoriasis
Many CD factors and HLA	Anti thymocyte globulin (ATG)	Acute graft rejection
CD2	Alefacept	Psoriasis
CD3	Muromonab	Acute organ transplant rejection
CD20	Rituximab and Ocrelizumab	Multiple sclerosis
CD25	Basiliximab and Daclizumab	Acute organ transplant rejection and maintenance therapy of the graft
IL-1	Anakinra	Rheumatoid arthritis
IL-1β	Canakinumab	CAPS (cryopyrin-associated periodic syndrome) and Systemic Juvenile Idiopathic Arthritis.
IL-4	Dupilumab	Atopic dermatitis
IL-2	Basiliximab and Daclizumab	Acute organ rejection
IL-5	Mepolizumab, Reslizumab, and Benralizumab	Severe eosinophilic asthma
IL-6	Sarilumab and Tocilizumab	RA and cytokine storm syndrome
IL-17	Ixekizumab, Brodalumab, and Secukinumab	Plaque psoriasis
IL-12/23	Ustekinumab	Plaque psoriasis

CROSS WORD PUZZLES

Crossword Puzzle



Across

3. Used in the management of renal cell carcinoma
4. An IgE blocker

Down

1. Used to treat acute graft rejection
2. Used to treat CAPS

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106 GENERAL ANESTHESIA

- It is a reversible phenomenon.
- There is reversible loss of consciousness and sedation.
- Patient will have amnesia.
- Patient will have analgesia.
- Patient becomes immobile (muscle relaxation)
- Reflex also decreases.
- Use:
  - Surgery
  - Electroconvulsive therapy
  - Status epilepticus

Drugs 00:02:20

- **Inhalation:**
  - Gas: N_2O, Xenon, Cyclopropane
  - Volatile liquids: Ether, Halothane, Desflurane, Isoflurane, Sevoflurane, Enflurane.
- **IV:**
  - Faster acting: Thiopentone, Propofol, Etomidate
  - Slower acting- Benzodiazepines, Opioids, Ketamine

Pre-anesthetic medications 00:05:20

- In case of surgery is to be done, then pre-anesthetic medications are given to patients to decrease anxiety and to cause anterograde amnesia, like benzodiazepines are given.
- To decrease secretions and reflex vagal bradycardia, glycopyrrolate is given as it doesn't cause a blood-brain barrier so it can be used easily.
- To decrease HCl secretions H_2 blockers and PPIs (proton pump inhibitors) are given.
- Anti-emetic drugs and opioid analgesics are given before surgery.
- Once the patient is ready, anesthesia is given which is called induction of anesthesia.
- Maintenance of anesthesia is to be done until the surgery is done.

Mechanism of action of general anesthesia 00:09:22

- Inhaled general anesthetics increase the GABA activity.
- They also act as glycine agonists.
- Therefore, there is CNS depression.
- They are also shown to produce potassium channel opening.
- Drugs like ketamine and nitrous oxide decrease the activity of glutamate and they are NMDA antagonists.

Inhaled General Anesthetics 00:11:05

Techniques of inhalation

- Anesthetic machines are used for drug delivery.
- There is an open system and a closed system of delivery.
- In an open system patient inhales the anesthetic and exhales it. In a closed system, the patient inhales and exhales anesthetic and exhaled anesthetic is rebreathed again.

Important Information

- During rebreathing process, exhaled carbon dioxide is absorbed using soda lime.
- Remaining anesthetics will again be consumed.
- Inhaling anesthetics are supplied in cylinders, and their cylinders have different colors.
- There is pin index, when anesthetic cylinders are fit into the Boyles machine. The pin index should be matched. If it does not match cylinder may not fit. This is done to avoid miscommunication.
- To avoid mistakes, there is a pin index and color coding for the cylinder.

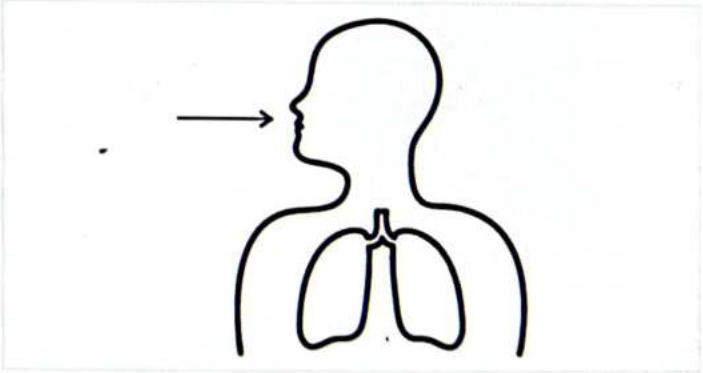
Stages of general anesthetics

- **1ST STAGE-** Stage of analgesia (pain comes down)
- **2nd STAGE-** Stage of delirium (confusion)
- **3rd STAGE-** Stage of Surgical anesthesia (airways, breathing, and circulation are maintained)
- **4th STAGE-** Medullary paralysis
- **5th STAGE-** Death

These stages are demonstrated in ether

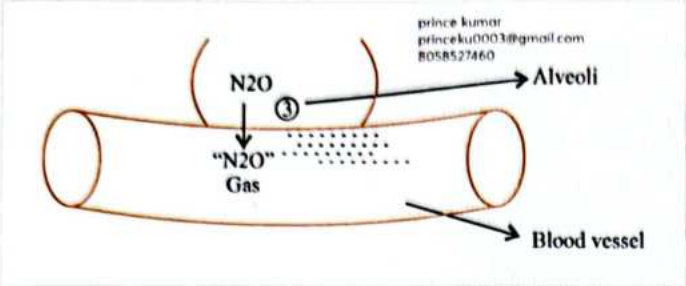
Pharmacokinetics of inhaled general anaesthetics

- When a general anesthetic is inhaled, it will come to the lung and will reach the alveoli, where exchange occurs.



- N_2O which is gas, is given with partial pressure using the Boyles machine. If the partial pressure is high, induction of anesthesia is faster. Pressure should not be too high as alveoli may rupture.
- In the ventilation process, if ventilation is fast induction is also faster.

- In alveolar exchange, nitrous oxide moves into the blood vessel, it can occur only if alveoli are healthy.



- Some of them get dissolved in the blood and some are free, from the heart they reach out to the brain, free one is easy to go inside the brain, and a dissolved one has to get free to go inside the brain.
- Blood gas coefficient is there to know the drug dissolution, if this coefficient is low that means the drug is less dissolved and more in free form.
- Blood gas coefficient is inversely proportional to induction.
- **Distribution:**
  - Nitrous oxide will enter the brain faster because the brain has more blood flow, it also enter the liver, kidney, adipose tissue, and skeletal muscle.
  - They have to come back from the brain, liver, and kidney again. It takes time to come back from adipose tissue and skeletal muscle because of less blood flow.
  - If it stays in adipose tissue, it is called tissue binding. Recovery of the patient will not be faster. This phenomenon is given by a coefficient called Oil gas coefficient.
  - Oil gas coefficient: Time to recover from GA
  - Oil gas coefficient is inversely proportional to the recovery time from GA.
- Minimum alveolar concentration
  - Minimum alveolar concentration (MAC) is the minimum concentration of the GA drug to be present in alveoli to achieve immobility in 50% population.
  - MAC is inversely proportional to potency.

Agent	MAC	OIL GAS	BLOOD: GAS
Nitrous Oxide	105	1.4	0.47
Desflurane	7.0	19	0.48
Sevoflurane	2.0	53	0.63
Diethyl ether	1.9	65	12
Enflurane	1.7	98	1.9
Isoflurane	1.2	98	1.4
Halothane	0.75	225	2.3
Methoxyflurane	0.16	825	13

- Metabolism = No/ minimal metabolism
  = Halothans (20% Hepatic metabolism)
- Elimination = Lungs [Exhaled air] [reverse order]

Individual Drugs 00:37:00

Nitrous Oxide

- **Second gas effect:** Nitrous oxide is given with halothane; nitrous oxide enters alveoli and occupies a lot of space. Suddenly it enters the blood vessel and a vacuum is created. Therefore, halothane also comes and enters the alveoli. This is called the second gas effect.
- **Diffusion hypoxia:** Once the surgery is over, nitrous oxide anesthesia is stopped. Then nitrous oxide will come out of the blood vessel and immediately occupy the alveoli, due to this oxygen cannot enter and the patient may suffer from hypoxia. This can be prevented by giving oxygen before stopping nitrous oxide.
- **Advantages:** Analgesic, non-toxic, second gas effect.
- **Disadvantages:** Poor anesthesia, poor MR, diffusion hypoxia, it can decrease B_{12} levels, and it is avoided in air-filled spaces surgery.

Halothane

- **Advantages-** Potent anesthetic, a bronchodilator, can be used in bronchial asthma, controlled hypotension, uterine relaxant (can be given in pregnancy), can be used in children.
- **Disadvantages-** Poor analgesic, poor MR, CVS suppressant, contraindicated in pheochromocytoma, halothane sensitizes the heart to adrenaline which causes arrhythmia, can cause hepatitis in 1:1000 patients, it can produce malignant hypothermia (DOC for management: Dantrolene Na).

[Halothane] + N_2O] → Second gas effect
↓ ↓
- Anaesthetic poor anaesthetic
- Poor analgesia good analgesic

Ether

- **Ether: Pungent odour**
  - Inflammable = cautery not used
  - Irritant vapours
  - Good MR & analgesea

Enflurane

- Causes Seizures

Isoflurane

- Pungent odour
- Maintains CVS stability
- Preferred in
  - Cardiac patients
  - IHD

Desflurane

- Desflurane "Day Care Surgery"

↓

Fast induction

↓

Fast recovery

Sevoflurane

- Used for induction & maintenance
- Preferred in children
- Not used in closed system

Sevoflurane + Sodalime

↓

Compound A

↓

Nephrotoxicity

Xenon

- Rare, insert gas
- Expensive
- MOA
  - NMDA antagonist
  - TREK channel agonist
- Fastest induction [lowest BG co-efficient]
- Fast recovery

Conclusions:

- All are non-inflammable and non-explosion except ether.
- All produce hypotension.
- All produce respiratory depression and muscle relaxation except nitrous oxide and halothane.
- Most of them are bronchodilators.
- No hepatotoxicity except halothane.
- All are used in closed systems except sevoflurane.
- All can cause malignant hyperthermia except nitrous oxide.

Preferred

- Cardiac patient = Isoflurane
- Children = Sevoflurane
- Pregnancy = Halothane
- Day care surgery = Desflurane
- Not used for induction = Isoflurane & Desflurane and ether

Intravenous Anesthetic

01:02:02

Thiopentone Sodium

- Drug is used for induction of anesthesia.
- Used in truth serum for narcoanalysis.
- Used in status epilepticus.
- It does not have analgesic and muscle relaxant properties.
- **Pharmacokinetics:**
  - Highly lipid soluble - Faster onset of action.
  - Ultrashort acting due to redistribution phenomenon.
  - Supplied as a highly alkaline solution.
  - If it is given accidentally, it can cause ischemia and gangrene.

Benzodiazepines

- Midazolam, Lorazepam, and Diazepam can be used as pre-anesthetic.
- They decrease anxiety.
- They can produce anterograde amnesia.
- They are known to produce very good sedation.
- They are good muscle relaxants.
- They decrease BP.
- They don't have analgesic properties.

Propofol

- It is a milky white powder.
- It is a phencyclidine derivative.
- It contains soyabean oil and lecithin.
- It is used for starting induction and maintenance of anesthesia.
- It is preferred for **day care surgery**.
- It is also used in intravenous regional anesthesia.
- It is used for sedation in ICU.
- The drug has a **euphoric effect** (feel-good effect).
- It is a potent anti-emetic and anti-pruritic.

Ketamine

Dissociation anaesthesia

↓

Sedation
Amnesia
Immobility
↑ Sympathetic activity

- ↑BP } → Prefer in Hypotension shock
- ↑CO } → C/I = HTN emerge, Stroke, IHD
- ↑ICP → C/I: Head Injury
- ↑IOP

Hallucinations [Emergence delirium]

MNEMONIC

K = Kids preferred
E = Emergence Delirium
T = Thalamo-cortical junction (dissociation)
A = Analgesic
M = Meals (can be given in full stomach)
I = Increases all pressure
N = NMDA
E = Excellent in asthma

Etomidate

- Inhibits Steroid Synthesis
- It can cause adrenal suppression.

Opioids Analgesics

- Opioids that are used are synthetic.
- **Fentanyl** - 100 times potent than morphine.
- **Sufentanil** - 1000 times potent than morphine.
  - It is highly plasma protein bound, so it has a long duration of action.
- **Remifentanil** - It is metabolised by plasma esterase.
  - It is very short acting.
  - Can be preferred in day care surgery.
- **Alfentanil** - It is total intravenous anesthesia.
- Synthetic opioids may cause muscle rigidity.
- There may be chest wall rigidity.
- This can lead to wooden chest syndrome.

Patient recovery after surgery 01:19:38

- Induction → maintenance (Surgery) → Surgery done → (Stop anaesthesia → Recovery)

- Balanced anaesthesia
  - Anaesthesia
  - Analgesia
  - MR

"G.A" + Opioids + peripheral SKMR } Reverse: Neostigmine Pyridostigmine
↓ curium curonioum

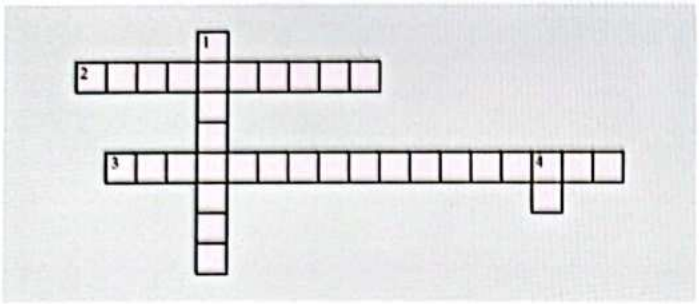
Respiratory Depression
↓
"Naloxone"

Post - op { Paralytic Ileus, Urine retention } Pyridostigmine Bethanechol

Post up Shivering → DOC Pethidine

CROSS WORD PUZZLES

Crossword Puzzle 1



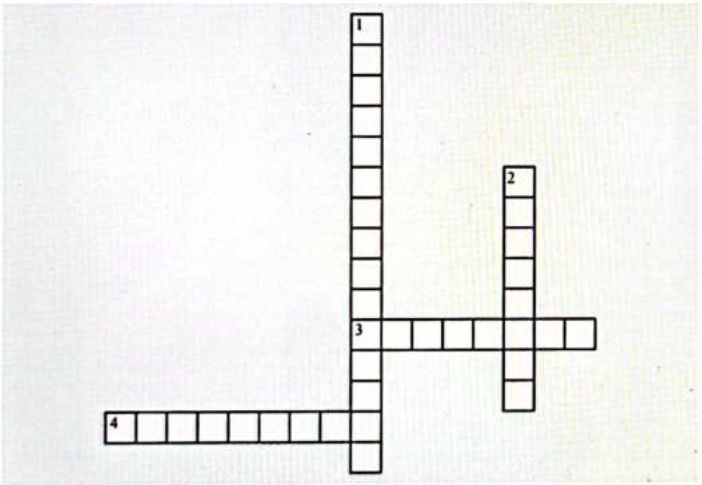
Across

2. General anesthesia phenomenon is_____
3. _____is used in truth serum for narcoanalysis.

Down

1. _____ is preferred for daycare surgery.
4. _____ anesthetics are faster acting.

Crossword Puzzle 2



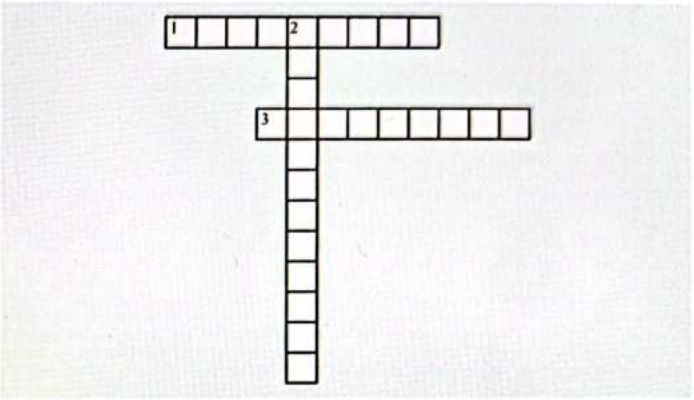
Across

3. _____ is a phencyclidine derivative.
4. _____ causes adrenal suppression.

Down

1. _____can decrease anxiety and they can produce anterograde amnesia.
2. _____ drug has a euphoric effect (feel-good effect).

Crossword Puzzle 3



Across

1. Blood gas coefficient is inversely proportional to_____.
3. Drugs like ketamine and nitrous oxide decrease the activity of_____.

Down

2. _____is inhalation anesthetic.

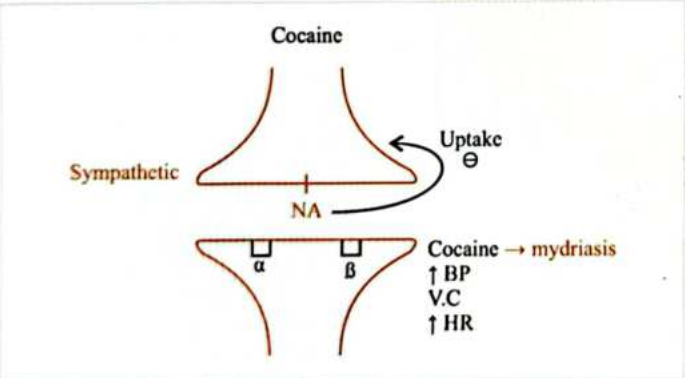
107 LOCAL ANESTHESIA

Aesthesia means sensation, whereas anaesthesia refers to loss of sensation.

Local Anaesthesia vs General Anaesthesia 00:01:30

Local Anaesthesia	General Anaesthesia
• Local area is anesthetized. • Site: Periphery • The person remains conscious. • No vital monitoring is required. • Not effective for a non-cooperative patient. • Cannot perform major surgery with local aesthesia. • Minor surgeries can be performed. • In poor health conditions, it is better.	• Whole body is anesthetized. • Site: CNS • Person loses consciousness. • Vital monitoring is required. • Effective for non-cooperative patients • Major surgery can be performed with general anaesthesia. • Minor surgery can also be performed. • Not appropriate in case of poor health.

Local Anaesthesia 00:05:15



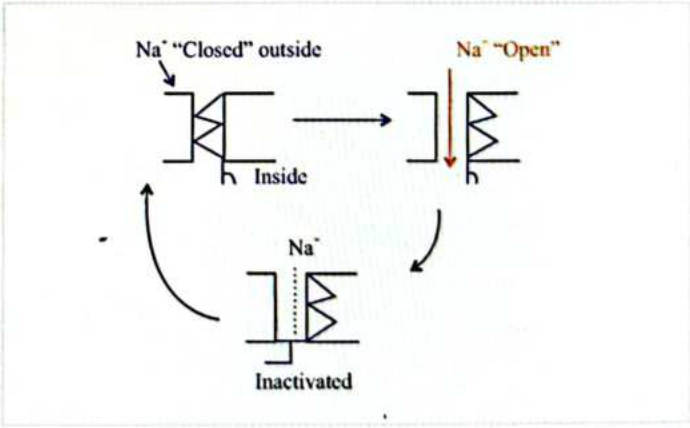
- Procaine: BP
- Lignocaine: M.C. used (Lidocaine) L.A.
- The first discovered local anaesthetic was cocaine.
- Cocaine inhibits the activity of noradrenaline, as a result:
  - Blood pressure increases
  - Vasoconstriction occurs
  - Heart rate increases
- Cocaine can cause mydriasis.
- Procaine – decreases blood pressure
- Lignocaine/Lidocaine – most commonly used anaesthetic

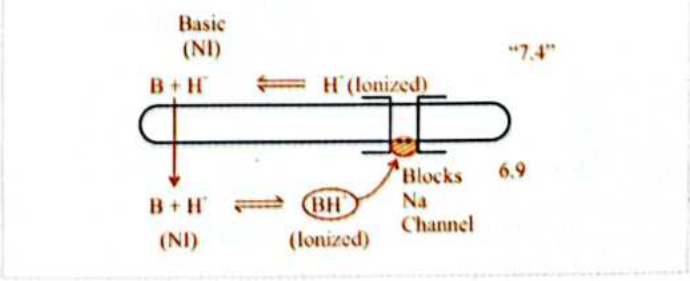
Chemical Nature of Local Anaesthesia 00:08:05

Ester Derivatives	Amide Derivatives
Drugs: • Cocaine • Procaine • Chlorprocaine • Benzocaine • Tetracaine	Drugs: • Lignocaine • Bupivacaine • Prilocaine • Dibucaine
Metabolised by plasma esterases. These are short-acting.	Metabolized by liver enzymes. These are long-acting.
Hypersensitive reactions are seen.	Less or no hypersensitivity.
No PPB (plasma protein binding).	Binds to α1 acid glycoprotein.

Mechanism of Action 00:12:00

Blocks Na channels
(Inactivated channels > Open channels)
↓
Decreased sensation from the periphery
↓
Local anaesthesia





Pharmacological Actions of Local Anaesthesia

System	Effect
LOCAL	• Decreased sensation • Order of blockade: o Small diameter > large diameter o Myelinated > unmyelinated o B fibres > C fibres > Aδ fibres > Aα fibres > Aβ fibres > Aγ fibres o ANS > Sensory > Motor • For example: The tongue is anesthetized first bitter taste is affected, then sweet and sour, followed by the salty taste. • Reverse order of Sensory blockade/ Functions regain order: o Pain > cold > warmth > touch > pressure
CVS - Myocardial suppressant	• Lignocaine: o Class 1B antiarrhythmic o Used to treat Ventricular tachycardia • Procainamide: o Class 1A antiarrhythmic o High dose can cause arrhythmias • Bupivacaine: Highly cardiotoxic
BLOOD VESSEL	• Decrease sympathetic outflow, as a result, vasodilatation and decrease blood pressure (hypotension) • Cocaine increases the sympathetic activity, increases blood pressure and causes mydriasis
CNS	• CNS is stimulated followed by CNS depression • Inhibits GABA. CNS is excited, which results in seizures (high doses) • Early neurological symptom to know local anaesthesia overdose "circumoral numbness"
RESPIRATORY SYSTEM	• High dose: Depressant
OVERDOSE	• Results in seizures • Treatment: Lorazepam and Diazepam • Antidote: 20% Intralipid

Individual Drugs

00:29:52

Drugs	Effects
Cocaine	• Naturally occurring • Ester • Metabolised by liver enzymes, not by esterases • Abused: o Sniffed o Causes nasal perforation o Ischemia (due to vasoconstriction)
Procaine (1st synthetic local Anaesthetic)	• Procaine and Benzocaine metabolized to PABA
Chloroprocaine	• Shortest acting local anaesthetic
Prilocaine	• Metabolized to o-toludine that can cause methemoglobinemia • It can be treated with methylene blue
Lignocaine aka Lidocaine	• Most commonly used local anaesthetic • Anti arrhythmic (class 1B)
Bupivacaine	• Most cardiotoxic • Avoid in IVRA • Levobupivacaine – less cardiotoxic
Ropivacaine	• Labour analgesia

Factors Affecting Local Anaesthesia

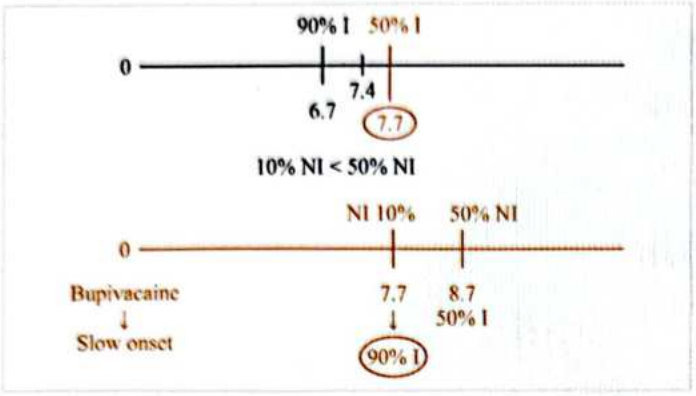
00:36:30

1. PPB (plasma protein binding) – Highly PPB is long-acting
2. Lipid solubility – Increases blockade in nerves
3. Addition of vasoconstrictor – LIGNOCAINE + ADRENALINE (1:50,000 to 1:2,00,000)
   This combination should not be used in end arteries (Tip of Fingers, Toes, Tip of nose, Penis)

Advantage	Disadvantage
It acts longer locally	Adrenaline increases heart rate
Bloodless field for surgery	Adrenaline increases BP
Less systemic absorption of Local Anaesthesia	Containdications: • Ischemic heart disease • Left ventricular failure • Uncontrolled hypertension

4. Inflammation
- At the place of inflammation and pus, there is acidic pH, so LA is ionized hence their activity decreases.
- Also at the place of inflammation, vasodilation occurs and it increases absorption of LA

5. P_{ka}



- Lignocaine has P_{ka} = 7.7 (Fast onset)
- Bupivacaine has P_{ka} = 8.7 (Slow onset)
- At blood pH (7.4)
  - Bupivacaine is more ionized, slow onset
  - Lignocaine easily crosses cell membrane, has fast onset

Important Drug Interactions 00:50:00

1. **Lignocaine + adrenaline** (as explained earlier)
2. **Lignocaine + Propranolol**

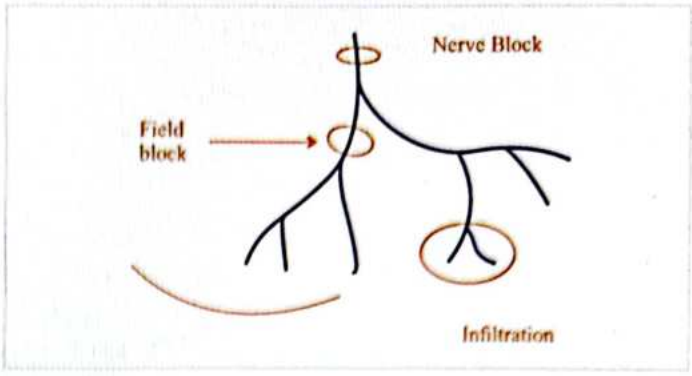
- The liver metabolizes lignocaine
- Propranolol is vasoconstrictor, so decreases hepatic blood flow
- Hepatic clearance = Hepatic blood flow X Hepatic extraction ratio
- So when both are given in combination less dose of lignocaine is to be given.

Uses of Local Anaesthesia 00:51:45

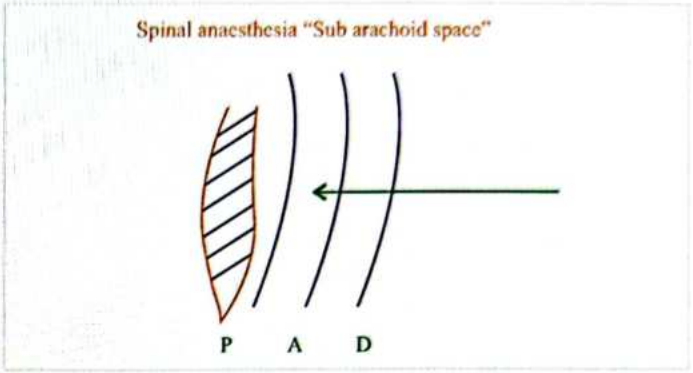
- Anti-arrhythmic
- Local anaesthetic

Types of Local Anaesthesia

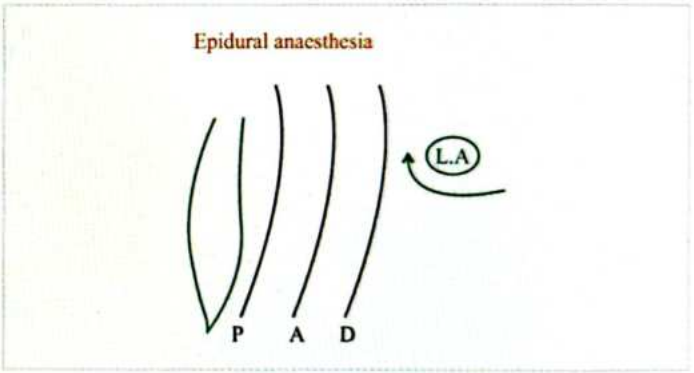
- Surface anaesthesia
- Infiltration anaesthesia
- Conduction block:
  - Field block
  - Nerve block



- Spinal anaesthesia – in subarachnoid space at level L_2–L_3



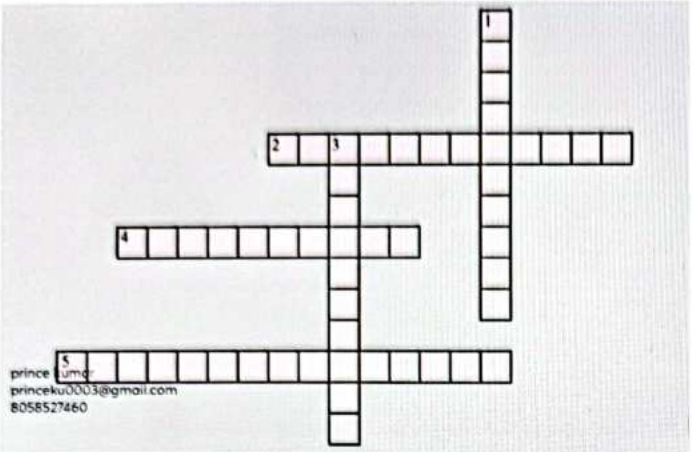
- Epidural anaesthesia



- Intravenous regional anaesthesia
  - Never use bupivacaine for intravenous anaesthesia because it is highly cardiotoxic drug.

CROSS WORD PUZZLES

Crossword Puzzle 1



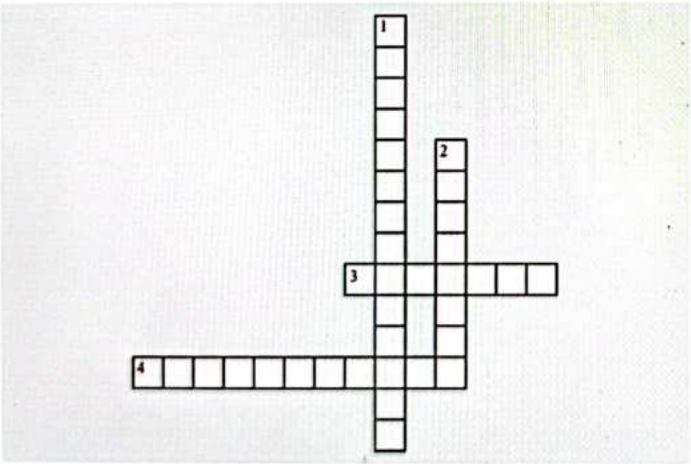
Hints

1. LA which act as vasoconstrictor
2. Site of spinal anaesthesia
3. LA which has slow onset
4. LA which has fast onset
5. Which LA is less cardiotoxic as compare to Bupivacaine

Answers Key

1. Propanolol
2. Subarachnoid
3. Bupivacane
4. Lignocaine
5. Levobupivacaine

Crossword Puzzle 2



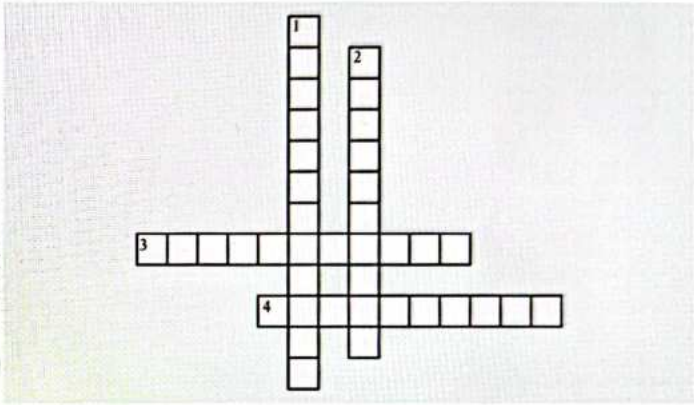
Hints

1. Shortest acting local anaesthetic
2. 1st synthetic local Anaesthetic
3. Naturally occurring Anaesthetic
4. Labour analgesia

Answers Key

1. Chloroprocaine
2. Procaine
3. Cocaine
4. Ropivacaine

Crossword Puzzle 3



Hints

1. class 1B antiarrhythmic
2. class 1A antiarrhythmic
3. Fast onset anaesthetic
4. Slow onset anaesthetic

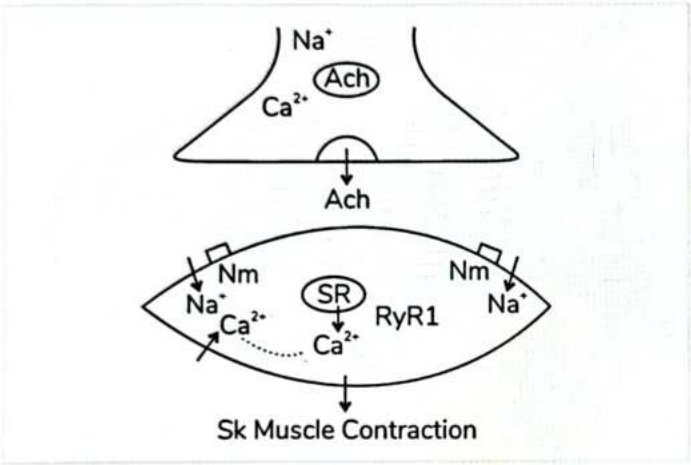
Answers Key

1. Lignocaine
2. Procainamide
3. Lignocaine
4. Bupivacaine

108 SKELETAL MUSCLE RELAXANTS

- Three types of patients are taken into consideration who would require the administration of skeletal muscle relaxants. They are:
  - A patient who had muscle spasms while running.
  - The patient needs to be intubated.
  - A patient who needs adequate muscle relaxation during general anesthesia.

Normal Muscle Physiology



- Acetylcholine (Ach) is stored in the nerve cells.
- On the entry of sodium and calcium ions, this Ach gets released into the neuromuscular junction.
- On the muscle cells, Nm receptors are present which are ion receptors.
- Nm receptors allow Na+ and Ca+2 ions to enter the muscle cell.
- Inside the muscle, the sarcoplasmic reticulum is present which has a RyR1 (Ryanodine receptor 1) receptor which also releases Calcium ions inside the muscle cell.
- These accumulated calcium ions inside the muscle cells cause skeletal muscle contraction.

Classification of Skeletal Muscle Relaxants 00:03:45

Peripheral Skeletal Muscle Relaxants

- Different skeletal muscle relaxants work at different sites of the neuromuscular junction to stop muscle contractions. Here are some of the types:
  - **Botulinum toxin**: It reduces the release of Ach from the nerve cells.
  - **Succinylcholine**
    - → It acts on the Nm receptors and repeatedly stimulates them. This repeated stimulation will eventually cause rapid desensitization of the receptors and thus stop the muscle contractions.
    - → Initially, there will be a release of sodium and calcium causing initial fasciculations but soon the receptors will stop. This will lead to flaccid paralysis of the muscle.
    - → It is also known as a depolarizing skeletal muscle relaxant.
    - → It is a very short-acting muscle relaxant as it is metabolized by pseudocholinesterase.
  - **d-Tubocurarine**
    - → It is also known as the competitive skeletal muscle relaxant.
    - → This is because it works as the Nm receptor antagonist and blocks them. Thus, they compete with the Ach (Nm receptor agonist) to stop muscle contraction.
    - → It is also known as a non-depolarizing skeletal muscle relaxant.
  - **Dantrolene sodium**: This drug blocks the RyR1 receptor.
- When it comes to reversing the effects of competitive muscle relaxants after general anesthesia anticholinesterase drugs are used.
- Examples are neostigmine and pyridostigmine.
- These drugs inhibit the cholinesterase enzyme (ChE) which is responsible for breaking down acetylcholine and thus the concentration of Ach increases.
- As the Ach increases, it competes with the d-Tubocurarine and attaches to the Nm receptors.
- The effects of succinylcholine can't be reversed by the above-mentioned drugs as succinylcholine is a depolarizing drug and is metabolized by pseudocholinesterase and not ChE.
- Dantrolene sodium doesn't affect the heart muscles as they have RyR2 receptors.

Disadvantages of Peripheral SKMR 00:10:50

- They decrease the tone of the muscles.
- They also decrease the voluntary power of the muscles.
- These drugs cause respiratory depression, i.e. respiratory muscles are paralyzed. Thus, these drugs can't be used for routine patients.
- These drugs are only used for anesthetic practices and in ICUs.

Central Skeletal Muscle Relaxants 00:15:00

- CNS has polysynaptic reflexes which inhibit the neuromuscular junction in case of any strenuous activity.
- The muscles will now undergo spasms to prevent further injury.
- So, the drugs that suppress the CNS are called central skeletal muscle relaxants.

- These drugs decrease the tone of muscles.
- However, they don't affect the voluntary power of the muscles.
- Adverse effect: These cause sedation due to suppression of the CNS.
- The different types of central SKMR are
  - Ω2 - Agonist drug called Tizanidine.
  - GABAb Agonist drug called Baclofen.
  - Drug that increases GABAa activity is called Diazepam.
  - The drug that increases GABA activity in the brain is called Thiocolchicoside.
  - The Mephenesin derivatives drugs are called Carisoprodol and Chlorzoxazone.

Important Information

- Baclofen is also prescribed to treat hiccups.

Uses of Central SKMR 00:18:00

- Acute muscle spasms.
- Backache and Torticollis.
- Anxiety and tension.
- Spastic neurological conditions like cerebral palsy and multiple sclerosis.
- Electroconvulsive therapy.
- Tetanus

Peripheral SKMR 00:19:55

Direct

- These drugs act directly on the muscle to stop the spasms. For example - Dantrolene sodium and quinidine.
- **Dantrolene sodium**: This is the drug of choice for two conditions –
  - **Neurolept malignant syndrome**: In this condition, the D2 receptors are blocked due to the usage of typical antipsychotics like haloperidol and thus cause muscle rigidity.
  - **Malignant hyperthermia**: Some individuals have hyperactive Ryanodine receptors and they start to release more calcium whenever anesthetics or muscle relaxants are given. (For example - succinylcholine or halothane). This increases muscle contraction and rigidity and thus the temperature of the body goes up.

Indirect 00:24:05

- These drugs act on the receptors and not the muscles.

Depolarizing SKMR

- These are succinylcholine and Decamethonium.
- **MOA of Succinylcholine**
  - When Succinylcholine attaches with the Nm receptors the Na+ ions and Ca2+ ions will enter the cell leading to muscle contraction. This is called initial fasciculations.
  - This leads to exit K+ from the cell causing hyperkalemia.
  - Stimulation of Nm receptors repeatedly leads to rapid desensitization leading to flaccid paralysis.
- **Uses**: Depolarizing SKMR are used in the following condition -
  - **Intubation**
    - → Succinylcholine is used as it is very short-acting (Onset is 1 - 1.5 mins and duration is 5 mins) as it is quickly metabolized by pseudocholinesterase.
    - → If a patient has atypical pseudocholinesterase, Succinylcholine will become longer acting leading to 'succinylcholine induced' apnea.
    - → This is treated by ventilatory support, FFP and recombinant form of typical pseudocholinesterase.
    - → This problem is detected by Dibucaine number (Normal - 80, Heterozygous - 50 - 60, Homozygous - 20 - 30).
    - → Alternate drug: Rocuronium is used for intubation in such patients.
- **Adverse effects of succinylcholine**
  - Hyperkalemia. That's why it is contraindicated in muscle or nerve injury.
  - Also due to the initial fasciculation, the patient will experience muscle soreness after the recovery.
  - It increases the IOP.
  - It increases intragastric pressure.
  - It causes malignant hyperthermia in certain individuals.

Non- Depolarizing SKMR 00:34:45

- Ach (agonist) & dTC (antagonist) both compete to bind with same receptor (N_N), whichever is more will bind to the receptor.
- Thus also called as competitive neuromuscular receptors.
- To overcome this antagonism:
  - Neostigmine & Pyridostigmine are used → inhibits choline esterase → Increases Ach
- Depending on the chemistry, these are divided into two types

Isoquinolone derivatives

- **d-Tubocurarine**: It causes histamine release which causes a fall in blood pressure.
  - It can also cause ganglionic blockade as ganglions have Nm receptors.
  - That's why it is no longer commonly used.
- **Metocurine**: It also causes histamine release.
- **Atracurium**: After metabolization, it gives rise to the metabolite laudosine which is responsible for seizures.
  - It causes histamine release.
- **Mivacurium**: It is metabolized by pseudocholinesterase and thus it is the shortest-acting drug of the group.
  - It is used for intubation.

- It causes histamine release as well.

- **Cisatracurium**: This doesn't release laudosine and no risk of seizure.
- **Doxacurium**: It is the longest-acting drug of the group with a half-life of 2 hours.
  - It has no/less histamine release.
- **Gantacurium**: It is still an investigational drug.
  - It also has no/less histamine release.

Steroidal derivatives

- There is no histamine release. For example, these are:
  - **Pancuronium**: It causes vagal blockade which leads to tachycardia.
  - **Pipecuronium**
  - **Rapacuronium**: It has a rapid onset of action, so earlier used for intubation.
    → However, it is no longer used for intubation as it causes bronchoconstriction.
  - **Rocuronium**: It is used for intubation.
  - **Vecuronium**

Important Information

- The preferred reversal agent for rocuronium and vecuronium is Sugammadex.

Hoffman's Elimination

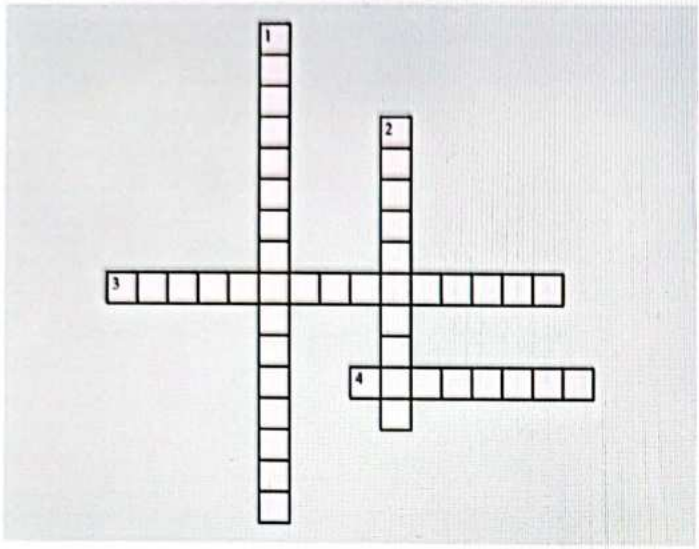
- Atracurium and cisatracurium go under spontaneous molecular rearrangement.
- Due to this, these drugs don't depend on the liver or kidney for their clearance from the body making them safe for patients with renal or liver failure.

Uses of Peripheral SKMR 00:46:25

- General anesthesia
- Intubation
- Assisted ventilation
- Convulsions and trauma during ECT
- Severe cases of tetanus
- Status epilepticus (rarely)

CROSS WORD PUZZLES

Crossword Puzzle 1



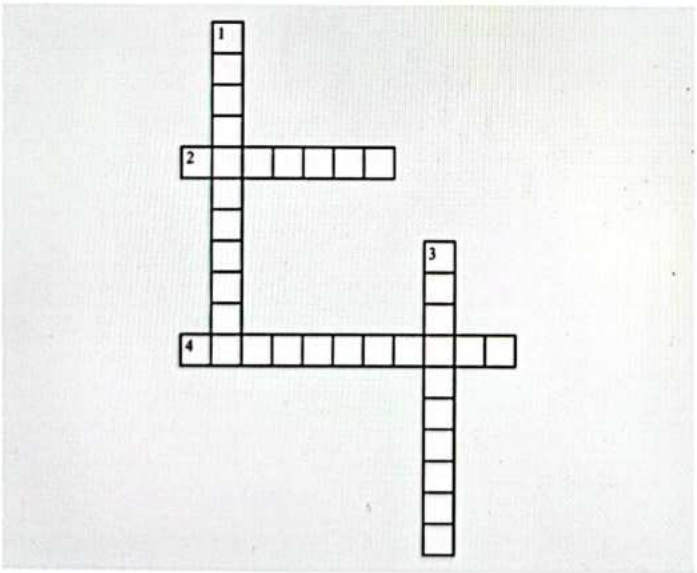
Across

3. _____ causes rapid desensitization of Nm receptors.
4. _____ is used to treat hiccups.

Down

1. _____ blocks the RyR1 receptors.
2. _____ skeletal muscle relaxants work on the neuromuscular junction.

Crossword Puzzle 2



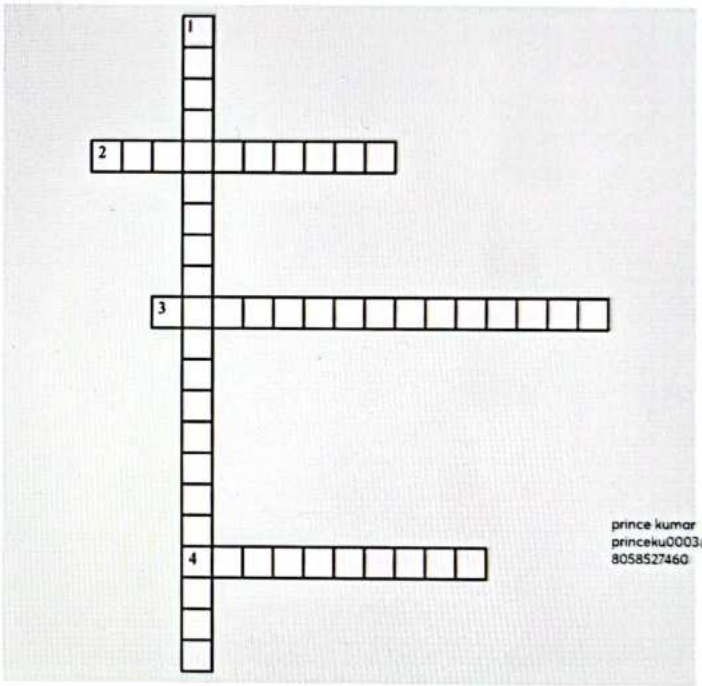
Across

2. _____ skeletal muscle relaxants can be used.
4. _____ and pyridostigmine are used to reverse the GA effect of the competitive SKMR.

Down

1. d-Tubocurarine is also known as the _____ skeletal muscle relaxant.
3. _____ skeletal muscle relaxants decrease the voluntary power of the muscles.

Crossword Puzzle 3



Across

2. The preferred reversal agent for rocuronium and vecuronium is _____.
3. _____ increases GABA activity in the brain.
4. _____ is used for intubation in patients with chances of suffering from malignant hypothermia.

Down

1. _____ happens in individuals who have hyperactive Ryanodine receptors.

109 PRESCRIBING DRUGS DURING PREGNANCY

Principles of Prescribing 00:00:55

- Non-drug therapy: Try to avoid prescribing medicine as much as possible. For example, if the patient has a headache, first tell her to apply Vicks or steam inhalation for a runny nose.
- Use drugs only if needed: For example, to cure a viral infection, there is no need to prescribe antibiotics. Instead, treatment can be done symptomatically.
- Prescribe time-tested drugs: It is safer to prescribe drugs whose adverse effects and usage is well known for years.
- Avoid newer drugs: Clinical trials don't involve pregnant patients so we don't know the effect of newer medicines on a pregnancy.
- Use local route over systemic route: For example, in case the patient is asthmatic, prescribe inhalation drugs instead of oral steroids.
- Use shorter-acting drugs over longer-acting drugs.
- Use the lowest effective dose to avoid adverse effects.
- Try to avoid drugs in the 1st trimester.

USFDA Categories 00:04:25

- These are the category of drugs to be prescribed during pregnancy which is given by the USFDA (United states food and drug administration):

  A-Very safe drugs
  B-Safe drugs
  C-May be safe drugs
  D-Not safe drugs
  X-High risk of teratogenicity

Drugs For Hypertension 00:05:40

- These are the drugs which are safe to prescribe to a hypertensive pregnant patient:
- The mnemonic is let me do care HTN Pregnancy.
  - Labetalol: It is for pregnancy-induced hypertension.
  - Methyldopa: For patients who were hypertensive before pregnancy.
  - DHPs: Like Nifedipine which should be used as a sustained release (SR) drug.
  - Clonidine
  - Hydralazine
  - Prazosin
- **Avoid:** These are the drugs which are not safe for pregnancy:
  - ACE inhibitors
  - ARBs
  - Renin-inhibitors
  - All the above three categories of drugs can cause renal agenesis.

- In case of a hypertensive emergency in a pregnant woman, the drug of choice is IV Labetalol.
- If labetalol is not available, then hydralazine is given intravenously.
- In the case of eclampsia, the drug of choice is magnesium sulphate.

Drugs For Epilepsy 00:09:30

- The drugs for epilepsy that are safe in pregnancy are:
  - Levetiracetam (preferred drug)
  - Lamotrigine
- **Avoid:** Due to high teratogenicity, these drugs are avoided:
  - Valproate
  - Phenytoin
  - Carbamazepine

Drugs For Mania and BPD

- These drugs are preferred for mania and bipolar disease are:
  - Atypical antipsychotics.
- **Avoid:** These are drugs to be avoided:
  - Valproate (Highest teratogenicity)
  - Carbamazepine
  - Lithium: It can cause Ebstein's anomaly.

Anticoagulants In Pregnancy 00:11:25

- These are the pregnancy-safe anti-coagulants:
  - Unfractionated heparin (UFH)/ Low molecular weight heparin (LMWH): These are bigger in size and thus are unable to cross the placenta.
- **Avoid:** Warfarin as it can cause fetal warfarin syndrome.

Pregnant Woman with Prosthetic Heart Valves

- If a pregnant woman has prosthetic heart valves, then prophylactic drugs should be given:
  - During the 1st trimester: LMWH should be given.
  - During 2nd trimester: Warfarin can be given as its risk decreases after 1st trimester. LMWH is not continued because firstly it has to be injected and secondly, its long-term use can cause osteoporosis.
  - During the 3rd trimester: Warfarin can be given.
  - After the end of 36 weeks: The patient is again shifted to LMWH till delivery as warfarin is a longer-acting drug which increases the chances of bleeding during the delivery.

Drugs For Endocrine Diseases 00:16:24

Gestational DM

- Insulin is the drug of choice.

Hyperthyroidism

- For 1st-trimester - The drug given is propylthiouracil
- **Avoid:** Carbimazole/methimazole as they can cause aplasia cutis congenita of the scalp, omphalomesenteric duct anomalies, etc.
- 2nd and 3rd trimester: Now the preferred drugs are carbimazole or methimazole. Propylthiouracil is discontinued as it is shorter acting, has less efficacy, and causes hepatotoxicity.
- Also, avoid radioactive Iodine 131 in all trimesters.

Skin Infection Antibacterial Drugs For Pregnancy

00:19:00

- The safe drugs are (PCM):
  - Penicillin
  - Cephalosporin
  - Macrolides
- **Avoid:** They are (FAST):
  - Fluoroquinolones: They can cause cartilage damage.
  - Aminoglycosides: They can cause ototoxicity.
  - Sulfonamides: If the drug is taken in the 3rd trimester, the drug can reach the fetus and cause bilirubin displacement resulting in jaundice during birth.
    → These are also contraindicated during the 1st trimester in patients with G6PD deficiency as the fetus will carry the risk of hemolysis.
  - Tetracycline: They can cause damage to bones and teeth discolouration.

Drugs For Some Common Diseases

00:22:30

Tuberculosis

- In the 1st line of drugs, avoid the drug Pyrazinamide.
- **Absolutely contraindicated:** Aminoglycosides i.e., Streptomycin.

HBV

- If it is an HBV pregnancy, the safe drug which can be given is Tenofovir disoproxil fumarate (TDF).

Malaria

- If it is due to P.vivax then Chloroquine is given.
- **Avoid:** Primaquine can cause hemolysis in G6PD deficient patients.
- So, the radical cure should be done after the delivery.
- If it is due to P.falciparum, in the 1st-trimester Quinine + Clindamycin is given.
- For 2nd and 3rd trimesters, ACTs (Artemisinin-based combination therapies) can be given.
- In the case of cerebral malaria, the drug of choice is IV Artesunate in all the trimesters.

Toxoplasmosis

- In the 1st trimester, Spiramycin is preferred.
- In the 2nd and 3rd trimester, Sulfadiazine + Pyrimethamine is given.

Analgesic And Antipyretic

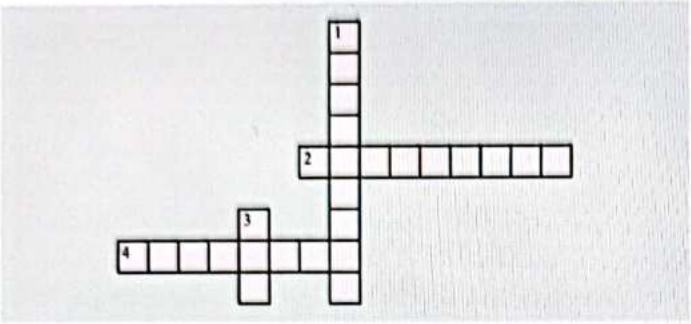
- Paracetamol is given.
- **Avoid:** Indomethacin as it causes premature closure of PDA (patent ductus arteriosus).

Peptic Ulcers

- H2 blockers are preferred over PPI (proton pump inhibitors).
- Antacids can also be given.

CROSS WORD PUZZLES

Crossword Puzzle 1



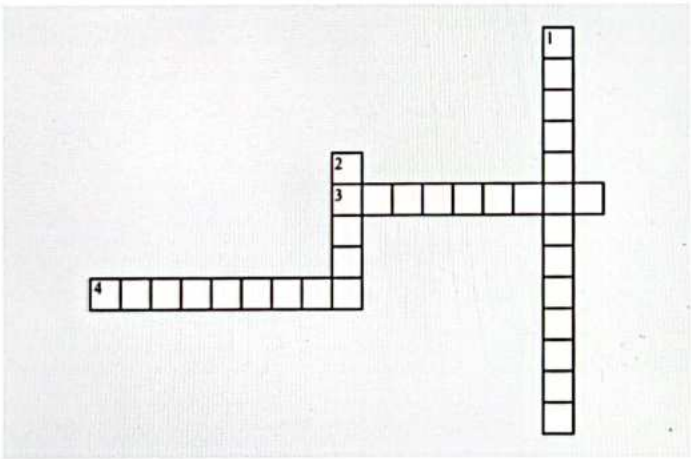
Across

2. _____ is given to treat pregnancy-induced hypertension.
4. According to USFDA, A is categorized as _____ drugs.

Down

1. Release Nifedipine should be used as a _____ drug.
3. One should try to avoid prescribing drugs in the _____ trimester.

Crossword Puzzle 2



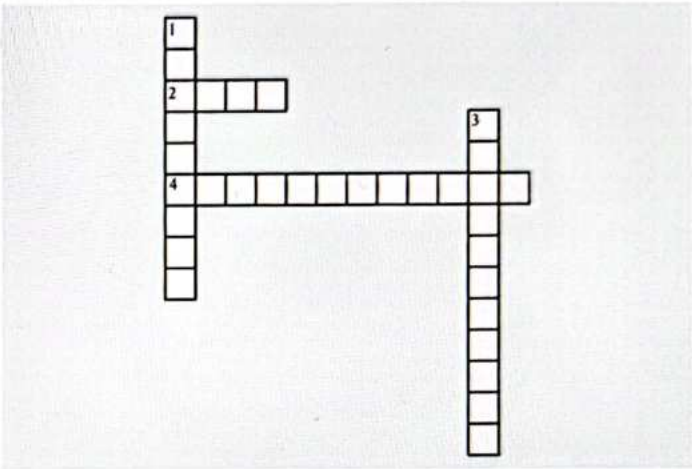
Across

3. Magnesium sulphate is the drug of choice for _____.
4. _____ is given intravenously for a hypertensive emergency.

Down

1. _____ is the DOC for epilepsy treatment.
2. ACE inhibitors can cause _____ agenesis during pregnancy.

Crossword Puzzle 3



Across

2. After the end of 36 weeks, the patient is shifted from warfarin to _____ till delivery.
4. Long-term usage of LMWH causes _____.

Down

1. _____ has the highest teratogenicity.
3. In P. falciparum malaria, in the 1st-trimester quinine and _____ is given.