CONTENTS

PHARMACOLOGY

LIST OF IMPORTANT TOPICS

TOPIC	MUST KNOW		DESIRABLE TO KNOW
GENERAL	pH, pKa, ionization Bioavailability First pass metabolism Vd PPB Prodrugs CYP substrates, inducers, inhibitors	First and zero order kinetics TDM Receptors types and examples DRC Pharmacogenetics Clinical trials Drug labels Orphan drugs Essential drugs	Enzyme inhibition (competitive, non-competitive and uncompetitive) Types of antagonists Pharmacovigilance
ANS	AChE inhibitors OP Poisoning Glaucoma Sympathetic receptors location	Catecholamines table Beta blockers Anticholinergics	Alpha blockers Rabbit practicals
AUTACOIDS	Antihistaminics PCM and aspirin poisoning	DMARDs Gout Migraine	PG actions Other NSAIDs
CVS	Digoxin New drugs for CHF Drugs decreasing mortality in CHF	JNC 8 guidelines for hypertension New antianginal drugs Statins	Pulmonary hypertension Antiarrhythmics
KIDNEY	K sparing diuretics		Free water clearance Vasopressin antagonists
ENDOCRINE	Oral hypoglycemic agents Somatostatin GnRH agonist and antagonist New antidiabetic drugs	Osteoporosis SERM OCPs Mifepristone	Antithyroid drugs Adverse effect of steroids SPRM Anti-androgens

TOPIC	MUST KNOW		DESIRABLE TO KNOW
👉 CNS	Short acting BZD Parkinsonism Antiepileptic drugs	Antipsychotic names and adverse effects SSRI and SNRI TCA poisoning Lithium and mania	Newer hypnotic drugs MAO inhibitors Opioids Multiple sclerosis
👉 ANAESTHESIA	Local anaesthetics mechanism and special points SCh and NDMRs MAC and Bid gas partition coefficient	Colour coding of cylinders Pin index system Xenon Halothane Ketamine	Spinal anaesthesia Neurolept analgesia
👉 HEMATOLOGY	Anticoagulants specially new	Anti platelets Fibrinolytics	Iron deficiency anemia Growth factors
👉 RESPIRATORY	Bronchodilators	DOC for different asthma types	Theophylline
👉 GIT	Peptic ulcer	Crohn's and Ulcerative colitis	Metaclopramide, domperidone IBS
👉 ANTI MICROBIALS	Important points (Review of Pharmacology 12th edition) Tuberculosis with RNTCP Malaria Antifungal	Mechanism of drug resistance Beta lactams Aminoglycosides Fluoroquinolones HIV Hepatitis C	Tetracyclines Macrolides Cotrimoxazole Leprosy
👉 ANTICANCER	CCS and Non-specific drugs General and specific adverse effects of anticancer drugs (Specially chemo-man cartoon)	Monoclonal antibodies Tyrosine kinase inhibitors Newer anticancer drugs	Tetracyclines Macrolides Cotrimoxazole Leprosy
IMMUNOLOGY	Cyclosporine Tacrolimus	Monoclonal antibodies Thalidomide	
SPECIAL TOPICS	New drugs approved in last 12 months (uses only) Anti-obesity drugs	Erectile dysfunction - Anti-smoking drugs T/t of HIT T/t of hyperkalemia	

LEARNING OBJECTIVES

UNIT 1: GENERAL PHARMACOLOGY

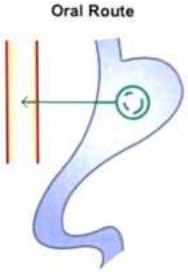
- Pharmacokinetics – Absorption
  - Medium
  - Bioavailability
  - Bioequivalence
- Pharmacokinetics – Distribution
  - Lipid solubility
  - Dialysis
  - Loading dose
  - Maintenance dose
- Pharmacokinetics – Metabolism
  - Enzymes
  - CYP 450
- Pharmacokinetics – Excretion
  - Glomerular filtration
  - Tubular reabsorption
  - Tubular secretion
  - Order of Kinetics
- Pharmacodynamics
  - Intrinsic activity
  - Signal transduction mechanism
  - Ionotropic receptors
  - Enzymatic receptors
  - GPCR
  - Intracellular receptors
  - DRC
- Pharmacogenetics
  - G6PD deficiency
  - Acetylation
  - Sch induced apnea

- Therapeutic Drug Monitoring
- Clinical trials
  - Phases of clinical trials
  - Control and Blinding
- Plasma conc. vs Time graph
  - C(max), T(max) and AUC
- Steady state
- Numericals in pharmacology
- ADR and Pharmacovigilance
  - National pharmacovigilance program of India
- Drugs in pregnancy and lactation
  - Teratogenic drugs
  - Lactation
- Type of enzyme inhibitors
  - Competitive, Non-competitive and Un-competitive
- Type of Drug Antagonism
  - Physiological
  - Pharmacological
- Combined effect of drugs
  - Addition
  - Synergism
  - Potentiation
- Practicals in general pharmacology
- Details of enzymatic receptors
- Spare receptors
- Receptor regulation
- Drugs with peculiar names
  - Orphan drugs
  - Essential drugs
  - Me-too drugs

1 PHARMACOKINETICS (ABSORPTION)

⏱ 00:03:53

- Drug: It is a substance that is used to / intended to be used to modify or explore the physiological function or pathological state for the benefit of the recipient.
  - Pharmacokinetics: Effect of the body on drug
  - Pharmacodynamics: Effect of drug on the body
- Pharmacokinetics ⏱ 00:09:18
  - Aka ADME study
    - → **A**bsorption
    - → **D**istribution
    - → **M**etabolism
    - → **E**xcretion



How to remember

ADME study

Routes of Drugs Administration

Local	Systemic	

(Applying directly at the site)
• Topical
• Intraocular
	Enteral
	• Oral
	• Rectal
	(1st pass metabolism)
		Parenteral
		• Injectable
		  ○ IV
		  ○ IM
		  ○ SC
		  ○ ID
		• Non-injectable

Injection	Angle	Imp. point
I.V.	25°	Titration possible
I.M.	90°	Z-track technique
S.C	45°	Self-administration
I.D.	Almost 0° (<15°)	possible, Hypodermal used for Allery testing, BCG

Non - Injectable parenteral

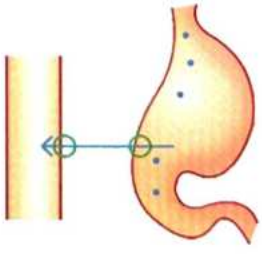
i. Sublingual
- Fast
- No 1st pass metabolism
- Termination possible
- Self-administration possible

ii. Intranasal
- Drugs used
  - Desmopressin
  - Calcitonin
  - Esketamine

iii. Transdermal
- Across the skin
- Advantage
  - Sudden peaks are avoided as the drug is slowly absorbed.

iv. Inhalation
- Through mouth or nose directly into lungs
- E.g.: Salbutamol

ABSORPTION ⏱ 00:22:51



- Absorption means movement of drug from the site of administration to blood.
- Absorption depends upon the following factors

00:24:08

- Lipid solubility
  - → Single most important factor
  - → Lipid soluble drugs are absorbed
  - → Water-soluble drugs are not absorbed.
- Form of drug

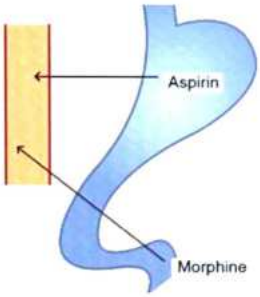
$$H_2O \rightleftharpoons H^+ + OH^-$$
$$HX \rightleftharpoons H^+ + X^-$$

  - → Ionized form of the drug is water-soluble, so not absorbed.
  - → Non-Ionized form of the drug is lipid-soluble, so absorbed.
- pH: When the medium is same, the drug will cross the membrane

Refer Table 1.1

Important Information

- When medium is same, drug will cross the membrane.
- Acidic drug can cross in acidic medium, Basic drug can cross in basic medium



How much drug will cross in different media? 00:31:14

- It depends on the following factors
  - I. Nature of drug: Acidic or Basic
  - II. pH of medium
  - III. pKa : It is the pH at which 50% of the drug is ionized and 50% is non-ionized.
- E.g.: Acidic drug with pKa = 6.0

pH	Lipid soluble	Water soluble
3.0	99.9%	0.1%
4.0	99%	1%
5.0	90%	10%
6.0	50%	50%
7.0	10%	90%
8.0	1%	99%
9.0	0.1%	99.9%
10.0	0.01%	99.99%

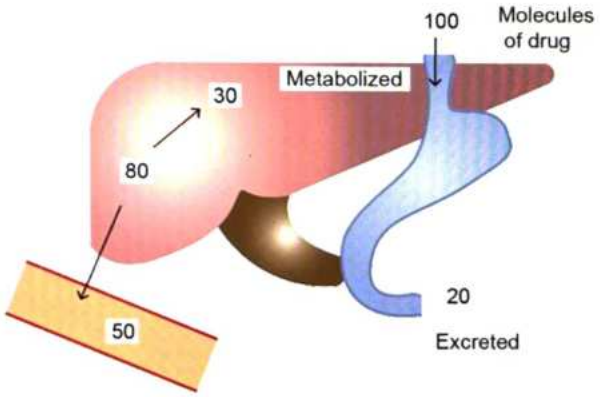
- Henderson Hassel Bach equation 00:39:40

$$pH = pKa + \log\left(\frac{\text{ionized}}{\text{Non-ionized}}\right)$$

  - According To Henderson Hasselblach eq, Acidic drugs are absorbed from the stomach and basic drugs are absorbed from the intestine.
  - But in reality, almost all drugs are absorbed more from the intestine as compared to the stomach because of
    - → More surface area of the intestine
    - → Longer stay time in intestine

Bio availability 00:47:11

- It is the fraction of the given dose which reaches systemic circulation



- It depends on 2 factors

I. Absorption
  - ↑absorption → ↑Bioavailability
  - ↓ absorption → ↓ Bioavailability
  - Bioavailability of a drug given by I.V. route is 100%

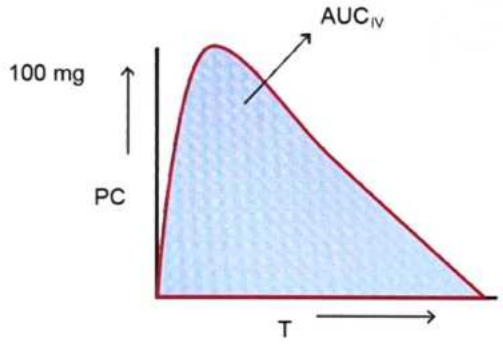
II. First Pass metabolism (FPM)
  - ↑ FPM → ↓ Bioavailability
  - ↓ FPM → ↑ Bioavailability

Important Information

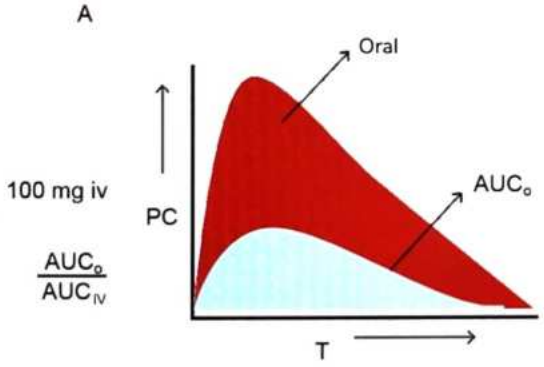
- Bioavailability α 1/FPM
- Bioavailability α Absorption

How to calculate Bioavailability? 00:54:12

- To calculate the BA of a drug by any route, first we need to give the drug (100 mg) by I.V. route to know the 100% BA. Then, we plot a graph.



- Now we give the same dose (100 mg) of drug by oral route and plot the graph.



- Thus, gives us the bioavailability, which is

$$\text{Bioavailability (\%)} = \frac{AUC_{oral}}{AUC_{I.V}} \times 100$$

Previous Year's Questions

Q. Fluoroquinolone with highest oral bioavailability?

(NEET Jan 2019)

A. Levofloxacin
B. Gemifloxacin
C. Ciprofloxacin
D. Norfloxacin

Bioequivalence 00:59:00

- 2 brands of the same drug are compared
  - If the two brands of the same drug have almost similar bioavailability (± 20%), these are called bioequivalent
  - Most of the drugs are bioequivalent except phenytoin.
    → So, in case of phenytoin, we don't change the brand as different brands will give different plasma concentration, which may lead to side effects.

Table 1.1

Drug	Medium	Form	Solubility	Cross
Acidic	Acidic	Non-ionized	Lipid soluble	√
Basic	Basic	Non-ionized	Lipid soluble	√
Acidic	Basic	Ionized	Water soluble	×
Basic	Acidic	Ionized	Water soluble	×

2 PHARMACOKINETICS (DISTRIBUTION)

DISTRIBUTION

00:00:12

- Amount of drug going to the tissues.
- It depends on the ability of a drug to cross membranes. This ability depends upon lipid solubility.
- So, the Distribution of the drug depends upon:

I. Lipid solubility

- Lipid soluble drugs → Higher distribution
- Water soluble drugs → Low distribution

II. Plasma protein binding (PPB)

- ↑ PPB → ↓ Distribution
- ↓ PPB → ↑ Distribution

Plasma proteins	Albumin	α_1 Acid glycoprotein
Bind to	Acidic drugs	Basic drugs
Examples	• Aspirin • Barbiturates • Methotrexate • Dr[illegible]ich form salt with cations	• Drugs ending with '-ine' ○ Atropine ○ Morphine ○ Amphetamine • Drugs which form salt with anions

Important Information

- Acidic drugs bind to Albumin
- Basic drugs bind to α_1 Acid glycoprotein
- Percentage of binding is different for different drugs.

- **Importance of Plasma Protein Binding** 00:05:23

a. Distribution: If PPB ↑, the volume of distribution ↓↓.

b. Displacement Interaction
   - It is the displacement of drugs from binding sites simultaneously in both the plasma and the tissues, and due to decreased binding in both areas, the free drug concentration in the plasma will increase leading to overactivity of the displaced drug.
   - Suppose if we give 100 molecules of warfarin to a person and it has 99% PPB, then 99 molecules are already bound to protein and only 1 molecule is free which is producing the action.
   - Now we start sulphonamide therapy in this patient due to an infection. Sulphonamides also have high PPB and have the tendency to bind at the same place where warfarin binds. So, there would be competition between warfarin and sulphonamides.

c. Duration of action: The drugs with ↑ PPB have a long duration of action, because the binding site acts as a storage area and gradually the drug will be released from those sites.

d. Disease state: In disease states like Nephrotic syndrome, where Albumin is lost, the drugs which bind to albumin (for example Acidic drugs), will have more free molecules. So, drug toxicity happens. Therefore, we reduce the dose of these drugs.

e. Dialysis: The drugs which can be removed by dialysis should have
   I. Low volume of Distribution
   II. Low plasma protein binding
   - These drugs include
     - **M** - **M**ethanol
     - **L** - **L**ithium
     - **A** - **A**spirin
   - Dialysis is not effective in
     - **A** - **A**mphetamines
     - **V** - **V**erapamil
     - **O** - **O**P/ Opioid
     - **I** - **I**mipramine (TCA)
     - **D** - **D**igoxin
     - Dialysis - **D**iazepam (BZD)

How to remember

- MLA has to go for dialysis.
- For ineffective drugs, Avoid dialysis

f. Filtration: If a drug has more PPB, then it has less filtration.

Previous Year's Questions

Q. High plasma protein binding of a drug results in?
(NEET Jan 2019)

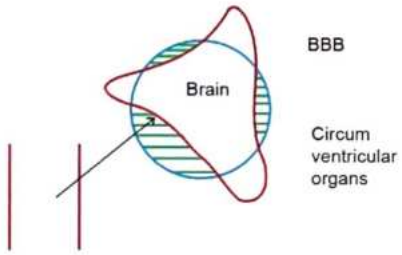
A. Decreased glomerular filtration
B. High volume of distribution
C. Lowers duration of action
D. Less drug interaction

III. Barriers

00:19:15

a. Blood Brain Barrier (BBB)

- Brain is bound on all sides by the blood which forms a barrier, that has to be crossed by a drug to reach the brain.
- There are certain areas in the brain where the BBB is deficient. These areas are called circumventricular organs.
- These include
  - Chemoreceptor Trigger zone (CTZ)
  - Area postrema
  - Post. Pituitary
  - Organum vasculosum
  - Lamina Terminalis



- Chemoreceptor Trigger Zone (CTZ)
  - When CTZ is stimulat[illegible]gs to vomiting.
  - Anti-emetic drugs do not cause vomiting, instead, they are used to prevent vomiting.
  - Another class of drugs having anti-emetic property → Antipsychotic drugs. For E.g.: Haloperidol

b. Blood Placental Barrier (BPB)

- Present b/w the mother and baby
- The drugs which produce adverse effects to the baby if given during pregnancy are known as Teratogenic drugs. For E.g.: Thalidomide
- Thalidomide can cause Sea Limbs or Phocomelia
- There are 2 drugs which do not cross the placenta at all
  - Insulin
  - Heparin
- Rest almost all drugs can cross the placenta to a varying degree, but we cannot stop them all during pregnancy.
- We avoid only those drugs in pregnancy, which can cross the placenta and cause fetal malformations.

Previous Year's Questions

Q. A 28-year-old female with Grave's disease was taking medication for hyperthyroidism during pregnancy. She delivered a child with congenital anomaly" aplasia cutis congenita". Mostly likely drug implicated for this teratogenic effect is?
(AIIMS June 2020)

A. Carbimazole
B. Levo - Thyroxine
C. Methylthiouracil
D. Liothyronine

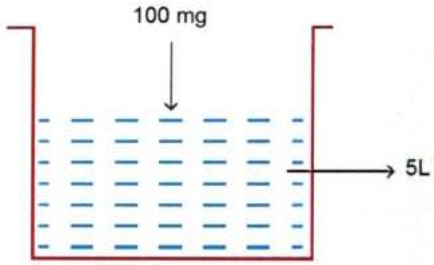
Volume of Distribution (V_d)

00:27:45

$$V_d = \frac{\text{Amount of drug given by I.V}}{\text{Plasma concentration}}$$

- Distribution of drug to tissues is considered only after the drug has reached the blood circulation. The part of drug which does not reach the circulation is not considered, due to bioavailability.

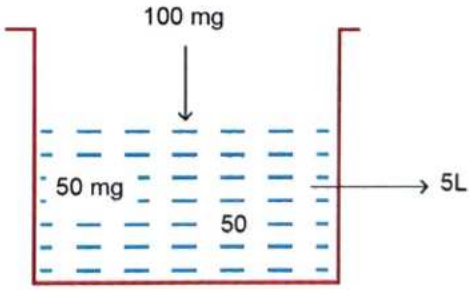
- **Case 1**



$$PC\frac{100}{5} = 20 \text{ mg/L}$$

$$V_d = \frac{100}{20} = 5 \text{ L}$$

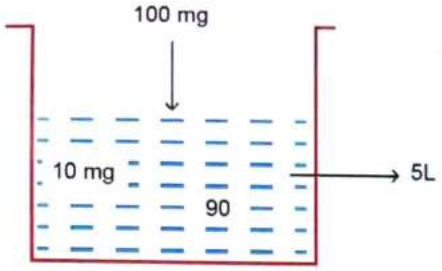
- **Case 2**



$$PC\frac{50}{5} = 10 \text{ mg/L}$$

$$V_d = \frac{100}{10} = 10 \text{ L}$$

- **Case 3**



$$PC \frac{10}{5} = 2 \text{ mg/L}$$

$$V_d = \frac{100}{2} = 50 \text{ L}$$

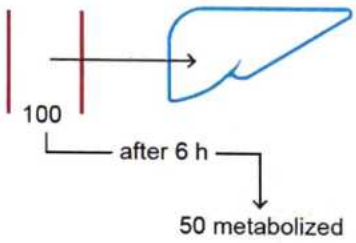
- Chloroquine: Highest volume of distribution (Vd > 1300 L) so chloroquine is mostly distributed to the liver, very less is left in blood for action on RBCs.
- So, we give a high initial dose of chloroquine for the preferred action. This initial dose is called Loading dose.
- Loading Dose (LD): High initial dose of a drug that is given to cover the distribution, so that the desired action can take place.

  LD = Vd x Target plasma Conc.

- **Maintenance Dose (MD)**
  - Dose of drug that is given to maintain the effect of the drug for a prolonged period.
  - Maintenance dose does not depend upon distribution, it depends only upon metabolism. That is, whatever dose is used up.

    MD = Clearance x Target plasma conc.

MAINTAINANCE DOSE



3 PHARMACOKINETICS (METABOLISM)

ELIMINATION

- It is the method of stoppage of action of the drug.
- It includes Metabolism and Excretion.
- Elimination and excretion are different

METABOLISM (AKA BIOTRANSFORMATION)

- Usually: Active drug → Inactive
- But in case of Diazepam: Active drug (Diazepam) → Inactive (Oxazepam)
- In the case of Prodrugs: Inactive drug → Active

Important Information

- All - ACE inhibitors (except captopril, Lisinopril)
- Prefer - Proguanil, PPI, Prednisone
- Doing - Dipivefrine
- M - Methyldopa, Minoxidil, 6 – MP
- D - Levodopa
- In - Irinotecan
- Clinical - Carbimazole, Clopidogrel, cyclophosphamide
- Subject - Sulfasalazine, Sulindac

How to remember

- All prefer doing MD in clinical subjects

Previous Year's Questions

Q. Which of the following is not a prodrug?
(AIIMS June 2020)

A. 5 fluorouracil
B. Primidone
C. Proguanil
D. Sulindac

Aim of Metabolism: To make the drug water-soluble.

00:08:50

Phase I reactions (Catabolic)	Phase II reaction (Anabolic)
• Oxidation • Reduction • Hydrolysis • Cyclization • Deamination	• Aka conjugation reactions or synthetic reactions o Glucuronide conjugation o Glutathione conjugation o Glycine conjugation o Acetylation o Methylation o Sulfation

- Purpose of Phase I reactions: To expose the functional group on the drug.
- Purpose of Phase II reactions: To make the drug water-soluble.
- The only Phase II reaction, which is Microsomal: Glucuronidation. Rest all are non-microsomal
- Enzymes
  - Drug metabolizing enzymes can be of 2 types

Microsomal Enzymes	Non-microsomal
• Present inside microsome i.e., inside the smooth Endoplasmic reticulum (SER) • Can be induced or inhibited.	• Outside microsome • Cannot be induced or inhibited.

- Case 1

Refer Table 3.1

- Case 2: When we add Rifampicin (Enzyme inducer)

Refer Table 3.2

- Case 3: When we add Cimetidine (Enzyme inhibitor)

Refer Table 3.3

- Important examples

Inducers	Inhibitors
• **G** - Griseofulvin	• **V**it - Valproate
• **P** - Phenytoin	• **K** - Ketoconazole
• **R** - Rifampicin	• **C**an't - Cimetidine
• **S** - Smoking	• **C**ause - Ciprofloxacin
• **C**ell - **C**BZ	• **E**nzyme - **E**rythromycin
• **P**hone - **P**henobarbitone	• **I**nhibition - **I**soniazid

How to remember

- **Inducer**: GPRS cell phone
- **Inhibitors**: Vit K can't cause Enzyme Inhibition

- Theophylline
  - Used for Bronchial asthma treatment.
  - The dose required is higher in smokers because smoking is an enzyme inducer.

- Most anti-epileptic drugs are enzyme inducers, except Valproate → inhibitor

- Most anti-microbial drugs are enzyme inhibitors, except
  - Griseofulvin
  - Rifampicin

  } Inducers

- Microsomal enzymes can be
  - CYP mediated enzymes
  - Non- CYP enzymes

- E.g.: Glucuronidation, Rest All phase II reactions are non-microsomal

- All phase II reactions are non-CYP mediated

CYP enzymes ⏱ 00:32:00

- Cytochrome P 450 enzymes
  - P stands for Pigment
  - 450 stands for 450nm → This pigment absorbs max. light at a wavelength of 450nm.

- Nomenclature
  - CYP 3A4.1
    - → **3** - family
    - → **A** - Sub-family
    - → **4** - Isoform
    - → **1** - Gene

- Most of the enzymes are metabolized by CYP 3A4 and CYP2D6.

- CYP enzymes are also involved in endogenous metabolic reactions like Bile acid formation & cholesterol metabolism

- CYP are microsomal enzymes so prone to drug interactions.

- Important examples of drugs metabolised by CYP3A4
  - **C** - Cyclosporine, CCB
  - **T** - Tacrolimus
  - **S** - Statins
  - **C** - Cisapride, Astemizole, Terfenadine } Withdrawn from market because they cause QT prolongation on ECG
  - **A** - Amiodarone
  - **N** - "-navirs" (Protease inhibitors)

How to remember

CT SCAN

- CYP2D6
  - **2** - β blockers
  - **D** - Depression Rx → TCA, SSRI, SNRI
  - **6** - Anti-arrhythmic drugs (except Amiodarone)

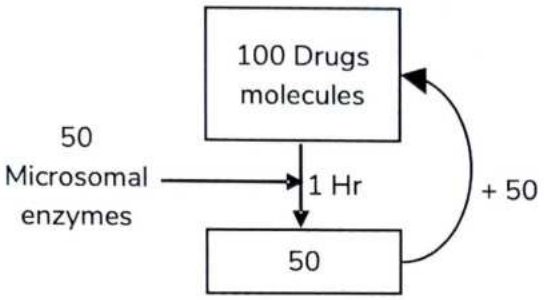
- CYP2C9
  - **C** - Clotting antagonist → Warfarin

- CYP2C19
  - CI → Clopidogrel → Clopidogrel turns active
  - Clopidogrel is converted to active form by CYP2C19
  - PPI are inhibitors of CYP2C19.
  - Therefore, PPIs are avoided with Clopidogrel

- CYP1A1
  - Theophylline
  - Procarcinogens

Table 3.1

Warfarin



Heparin

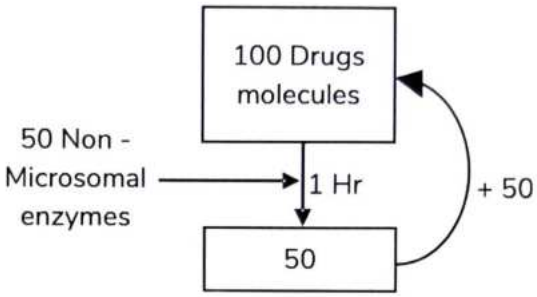
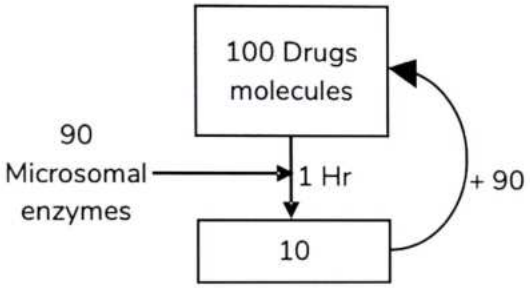


Table 3.2

Warfarin

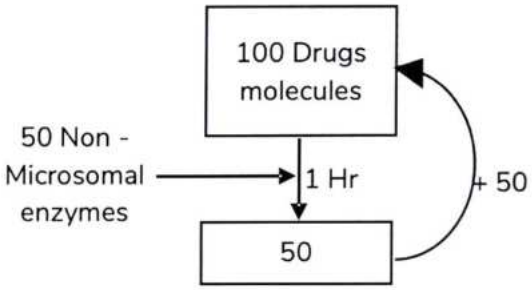
- 50 ME → 90 ME



Dose has to be increased

Heparin

- 50 NME → 50 NME

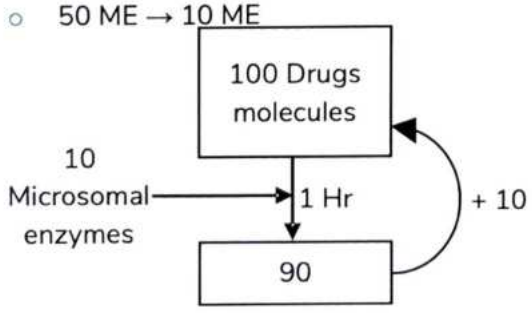


Dose Change not required

Table 3.3

Warfarin

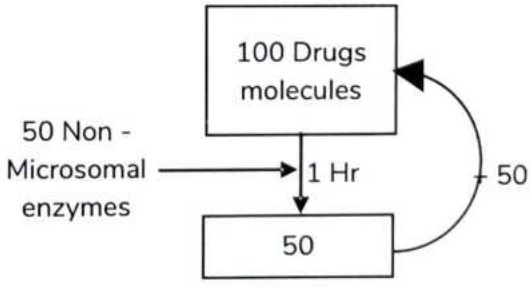
- 50 ME → 10 ME



Drug dose to be decreased

Heparin

- 50 NME → 50 NME

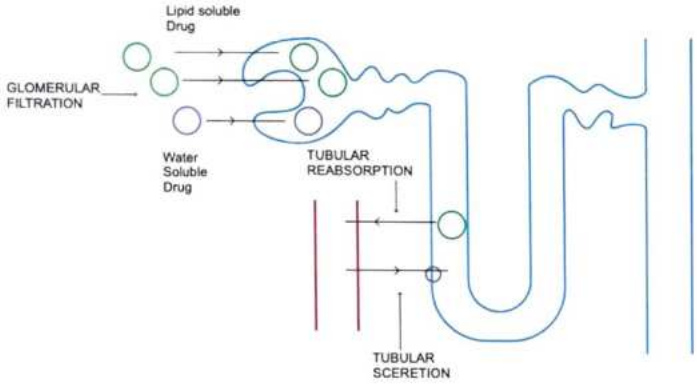


Dose Change not required.

4 PHARMACOKINETICS (EXCRETION)

EXCRETION

- Most of the drugs are excreted through the kidney.
- But there are some drugs that are excreted through sweat. For E.g. Lithium
- The structural and functional unit of the kidney is Nephron.
- Steps in excretion via the Kidney are
  I. Glomerular filtration
  II. Tubular reabsorption
  III. Tubular secretion



Glomerular filtration

00:01:30

- Lipid soluble drugs are easily filtered because they can easily cross the membrane.
- Water-soluble drugs can also be filtered through the pores in the glomerular membrane.
- The major factor affecting the filtration of a drug is its plasma protein binding.

$$\text{Filtration} \propto \frac{1}{\text{PPB}}$$

- Normal GFR = 125 ml/min
  = 125 x 60 = 7.5 L/hr
  = 7.5 x 24 = ~ 180 – 200 L/day
- Normal output of urine = 2 L/day, Rest all is reabsorbed.

Tubular reabsorption

00:40:10

- 99% of the glomerular filtrate is reabsorbed, so the drugs are also reabsorbed
- But the tubular membrane does not have pores (unlike glomerular membrane)
- So, water- soluble drugs are not reabsorbed, they are excreted.
- So basically, metabolism occurs to make the drug water-soluble and thus get excreted.

Important Information

- If drug and media are same: Drug is absorbed
- If drug and media are different: drug is not absorbed

Previous Year's Questions

Q. A patient on Lithium therapy developed hypertension. He was started on thiazides for hypertension. After few days, he developed coarse tremors and other symptoms suggestive of lithium toxicity. Explain the likely mechanism of this interaction?

(NEET Jan 2020)

A. Thiazides inhibits the metabolism of lithium
B. Thiazides act as an add on drug to lithium
C. Thiazides increase the tubular reabsorption of lithium
D. Thiazides cause loss of water thereby increased lithium levels.

- Therefore, for Acidic drug poisoning (E.g. Aspirin) Rx by making urine alkaline (by adding ($NaHCO_3$). This is called Forced Alkaline diuresis.
- For basic drug poisoning (E.g. Amphetamine), we Rx by making urine acidic (by adding NH_4Cl). This is called Forced Acidic diuresis.

Tubular secretion

00:10:45

- Tubular secretion takes place via pumps or transporters in proximal tubules
- These transporters can be
  →Organic Anion Transporter
  →Organic cation Transporter

- These transporters are saturable, so one drug can be transported at one time.
- Penicillin is short-acting (d/t rapid tubular secretion). We add probenecid to penicillin to make it long-acting.
- Probenecid has a higher affinity for transporter and thus prevents penicillin secretion, which makes the penicillin long - acting.

Drugs enter urine Via: 1.Glomerular filtration2. Tubular secretion

- Some parts of the drug can be reabsorbed by tubular reabsorption
- Remaining part of the drug is expelled in clearance.

- Scenario 1
  - If 100 molecules of a drug are filtered through glomerular filtration and 150 molecules are expelled out in clearance.
  - Here, clearance is more than glomerular filtration, which is due to Tubular secretion.
  - So Tubular reabsorption may or may not be present.

- Scenario 2
  - If 100 molecules of a drug are filtered through glomerular filtration and 50 molecules are expelled out in the clearance

  - In this case, clearance is less than glomerularfiltration, which is due to tubular reabsorption.
  - Tubular secretion may or may not be present.

Calculations ⏱ 00:16:50

- Formulae

I. $Vd = \frac{\text{Amount of drug given by I.V.}}{\text{Plasma Concentration}}$

I. Loading dose = Vd x Target plasma conc.
II. Maintenance dose = Clearance x Target Plasma conc.

Previous Year's Questions

Q. For plasma level monitoring lithium Estimation is done?

(AIIMS June 2020)

A. Immediately after the dose
B. 8 hours after last dose
C. 12 hours after last dose
D. 24 hours after last dose

VI. Rate of Elimination ®
  - It is the rate at which a drug becomes inactive.

$$\frac{\text{Amount of drug eliminated}}{\text{Time}}$$

  - It does not tell about the duration of action of the drug, so it is an incomplete parameter.

VII. Clearance (CL)

$$\frac{\text{Rate of elimination}}{\text{Plasma Conc.}}$$

  - It is a complete parameter
  - Renal clearance = $\frac{UV}{P}$

I. Half-life ($t_{½}$)
  - It is the time in which the plasma conc. of a drug becomes half
  - Ques.: Half-life of drug is 2 hrs. How much drug is left after 8 hrs?

$t_{½}$ = 2 hrs
100
↓ $t_{½}$ = 2 hrs
50
↓ $t_{½}$ = 2 hrs
25
↓ $t_{½}$ = 2 hrs
12.5
↓ $t_{½}$ = 2 hrs
Answer: 6.25%

- The drugs which follow first-order kinetics, have a constant half-life. As majority of the drugs follow First order Kinetics, so half-life is constant for majority of the drugs.
- $t_{½} \propto$ Volume of Distribution (Vd)
- $t_{½} \propto \frac{1}{\text{Clearance}}$

  Therefore, $t_{½} = 0.693 \times \frac{Vd}{\text{Clearance}}$

- Dose of a drug cannot be calculated from half-life. But dosing interval can be known.

Previous Year's Questions

Q. All of the following are advantages of enteric coated tablets except?

(AIIMS June 2020)

A. It increases the half-life of the drug
B. It protects acid labile drugs from gastric pH
C. It increases the absorption of drugs that are preferentially absorbed distal to stomach
D. It protects stomach from irritant drugs

Order of Kinetics ⏱ 00:27:50

First order Kinetics

- Fraction is constant

	R	CL	t ½
100			
↓ 1hr	50/hr	½	1hr
50			
↓ 1hr	25/hr	½	1hr
25			
↓ 1hr	12.5/hr	½	1hr
12.5			
↓ 1hr	6.25/hr	½	1hr
6.25			

- Rate of elimination ∝Plasma conc.
- Clearance = constant
- Half-life = constant

- Majority of drugs follow first order kinetics.
- Drugs which follow zero order kinetics are:
  - **Zero** - **Zero** order kinetics
  - **W** - **W**arfarin
  - **A** - **A**lcohol/ Aspirin
  - **T** - **T**heophylline
  - **T** - **T**olbutamide

  Power - **P**henytoin

How to remember

- Zero WATT Power

- The order of kinetics followed by a drug depends upon Enzyme saturation.
  - If enzymes are abundant → Follow 1st order Kinetics
  - If Enzymes are limiting factors→ Follow zero-order kinetics
- So, zero-order kinetics occurs due to the saturation of the enzyme. Therefore, aka saturation Kinetics.

Zero order Kinetics

- Amount is constant

	R	CL	t ½
100			
↓ 1hr	20/hr	0.20	2.5 hr
80			
↓ 1hr	20/hr	0.25	2 hr
60			
↓ 1hr	20/hr	0.33	1.5 hr
40			
↓ 1hr	20/hr	0.50	1 hr
20			

- Rate of elimination does not depend on plasma conc. It is constant.
- $\text{Clearance} \propto \frac{1}{\text{Plasma Conc.}}$
- Half Life ∝ Plasma conc.

- For Example: Aspirin has dose-dependent actions

  I. Anti-platelet action (Low dose)
  II. Fever
  III. Pain
  IV. Inflammation (High dose)

- If Aspirin is used for anti-inflammatory action → It follows zero order kinetics, because the number of enzymes are limiting. When conc. decreases, it follows 1st order kinetics
- So, zero order kinetics is also called Pseudo-zero order kinetics.

5 PHARMACODYNAMICS

Pharmacodynamics means the effect of a drug on the body.

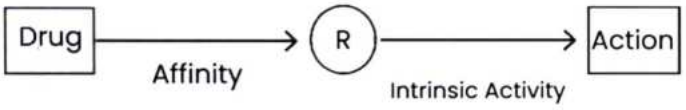
Mechanism of action of drugs (MOA) 00:00:52

1. Physical mechanism
- Physical presence of drug produces action.
- For e.g.: Charcoal is given orally in case of poisoning.
- It goes to the stomach and absorbs the poisonous substance.

2. Chemical mechanism
- Example: Antacids which are alkaline substances, they react with the acid in the stomach and neutralize it.

3. Enzymatic mechanism
- Enzyme inhibitor drugs are used to inhibit the action of an enzyme.

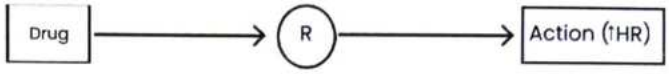
4. Receptor mechanism
- It is the most important mechanism
- Receptor is a substance that is used to receive the drug in the body, and upon binding to the drug it produces action.



- Affinity → The ability of a drug to bind to the receptor is called affinity.
- Intrinsic activity → The ability of a drug to produce action after binding to a receptor is called intrinsic activity
- Affinity is present for every drug.
- Intrinsic activity can be different for every drug

- Based on intrinsic activity, we have four types of drugs
  I. Agonist → Max. Intrinsic activity
  II. Partial agonist → Submaximal I.A
  III. Inverse agonist → Negative I.A
  IV. Antagonist → No action
- Antagonist has no action of itself but it prevents the action of other drugs.

Signal Transduction Mechanism

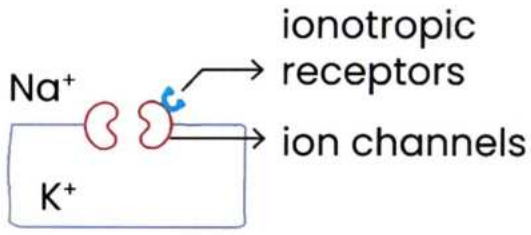


When a drug binds to the receptor, a signal is generated that gets converted into action by a mechanism called Signal Transduction Mechanism.

Classification of receptors based on signal transduction mechanism

00:11:12

I. Ionotropic receptors
- Ionized substances can't cross the membrane, therefore for the movement of an ion in the cell, special gates are presently known as ion channels.



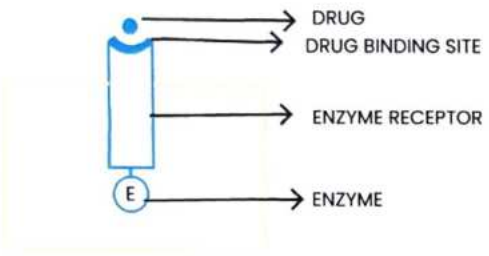
- The receptors present on these gates are called ionotropic receptors.
- Normally these gates are closed.
- When the gate opens, the ions move from high conc. to low conc.
- Na^+ and Ca^{2+} are more outside the cell, when the gate opens, they move inside.
- K^+ is present more inside the cell, when the gate opens it moves out.
- These are the fastest acting receptors.

- They are present in
  I. Brain
     - Major inhibitory in Brain → GABA(A)
     - Major stimulatory in Brain → NMDA / AMPA
  II. N_N, N_M receptors in nerves
  III. $5HT_3$ receptors

II. Enzymatic receptors

00:16:00

- These are big receptors with two ends
  - Intracellular end → Enzyme is present
  - Extracellular end → Drug binds
- Binding of drug activates the receptor which activates the enzyme. The enzyme then produces the action.
- So, without drug entering the cell,the drug can produce action.
- These include Tyrosine kinase receptors.



- These receptors are present for
  I. Cytokines
  II. Hormones
    - Prolactin
    - Insulin
    - Growth Hormones

Previous Year's Questions

Q. Drug acting via tyrosine kinase receptor is?

(NEET Jan 2020)

A. TRH
B. TSH
C. Insulin
D. MSH

- Enzymatic receptors can be divided into 3 types

a. Intrinsic Tyrosine Kinase activity

- Receptor itself has an enzyme: Tyrosine kinase
- Present for Insulin

b. No intrinsic Tyrosine Kinase activity

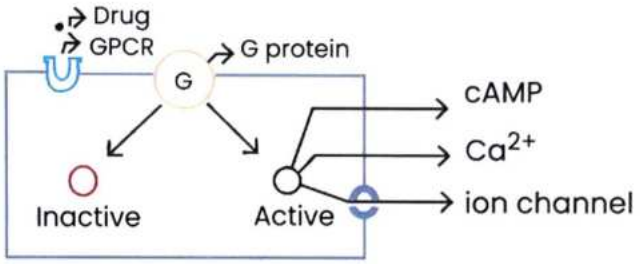
- Tyrosine kinase enzyme not present on the receptor.
- When the drug binds to receptors outside the cell, JAK-STAT proteins are activated inside the cell.
- These proteins recruit the Tyrosine kinase from the cytoplasm.
- Present for
  - Cytokines
  - Prolactin
  - Growth Hormone

c. Guanylate cyclase activity

- Drug binds outside and activates the enzyme guanylate cyclase present on the inside.
- The enzyme↑ the production of cGMP which produces the action.
- Present for Nitric Oxide (NO).

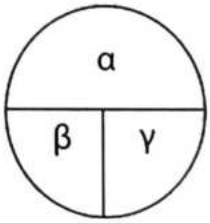
III. G-Protein coupled receptors

00:20:49



- G – Protein is present near the receptor in the cell.
- When the drug binds to the receptor, the receptor activates the G-protein which breaks into 2 components: Active and Inactive
- Active component produces one out of 3 actions
  - cAMP activity
  - Ca^{2+} levels
  - Ion channels
- cAMP has a different effect on different organs
  - In the heart, it has a stimulatory effect.
  - In bronchus, it has an inhibitory effect.
- ↑ Ca^{2+} can cause vasoconstriction
- Ach acts on muscarinic receptors. This leads to the opening of K^+ channels in the heart. K^+ goes out and causes bradycardia

- G' in GPCR stands for GDP/GTP bound protein.
- G protein has 3 subunits →α, β, Υ



- GDP binding site is α. The function of GDP is to stabilize the protein.
- When the protein is activated, GDP is removed and GTP binds. Now, the protein becomes unstable and breaks into 2 components
  - Active component with α
  - Inactive component with βΥ
- GPCR is of 3 main types
  - G_s: Stimulates Adenylate cyclase, Therefore↑cAMP

- G_i: Inhibits Adenylatecyclase, therefore ↓cAMP
- G_q: Activate Phosphatidylinositol phosphate(PIP_2) to inositol triphosphate (IP_3) and Diacylglycerol (DAG). This IP_3 will ↑ Ca^{2+}.

PIP_2
↓
IP_3 + DAG
↓
↑ Ca^{2+}

- α- component has GTPase activity. This GTPase enzyme breaks the GTP after the action has been produced.
- So, G-protein binds to GDP and adds βγ component. Thus, G-protein becomes stabilized again.

IV. Intracellular receptors

00:32:12

- These are present inside the cell, so the drug must cross the cell membrane and enter the cell to bind to the receptor.
- To cross the membrane, the drug must be lipid soluble. So only lipid-soluble drugs can work.

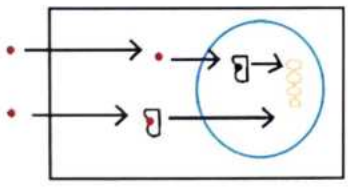
Previous Year's Questions

Q. Which of the following drugs act through intracellular receptor?

(AIIMS Jun 2020)

A. Thyroxin
B. Glycogen
C. Epinephrine
D. Parathyroid hormone

- These receptors are of 2 types
  - Cytoplasmic
  - Nuclear



- These are the slowest acting receptors.
- Examples

Cytoplasmic	Nuclear

• Corticosteroids
  ○ Glucocorticoids
  ○ Mineralocorticoids
• Vit. D
	• Sex Hormones
	  ○ Estrogen
	  ○ Progesterone
	  ○ Testosterone
	• Vit. A
	• T_3, T_4-thyroid hormones

Q. Which of the following drug acts via Nuclear receptors?
A. Hydrocortisone
B. Calcitriol
C. Estrogen
D. All of the above

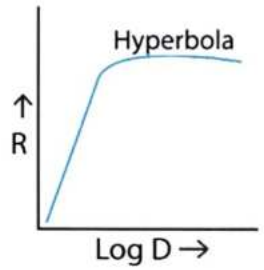
- **Nuclear receptor superfamily**
  - It is the term used for all the intracellular receptors. It includes cytoplasmic and nuclear receptors.
  - Estrogen receptors are purely nuclear, but progesterone and testosterone are both nuclear and cytoplasmic
  - Some drugs and the receptors on which they act are

Ionotropic	Enzymatic	GPCR	Intracellular
• Nicotine	• Insulin • Interleukins	GHRH • Salbutamol • Somatostatin • Oxytocin • Vasopressin	• Estrogen

DOSE RESPONSE CURVE (DRC)

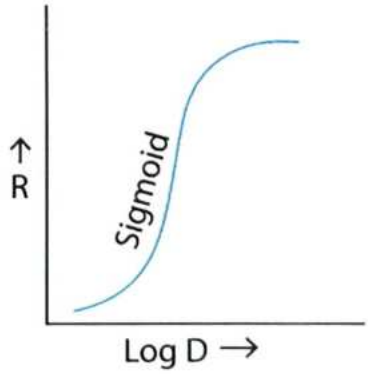
00:43:56

- The shape of DRC is Hyperbola.



- But since, it is a curved line, we cannot compare different drugs.
- So, to compare different drugs, we take another graph called Log DRC.

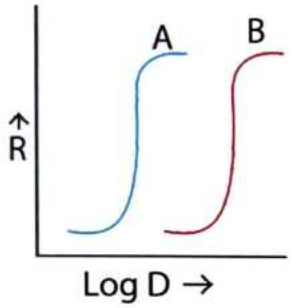
Log DRC



- We take log dose on the x-axis instead of dose.
- This gives us an S-shaped curve (Sigmoid)
- The middle portion of the sigmoid curve is a straight line, which is clinically the most relevant part.
- Log DRC gives us three parameters:
  I. Potency
  II. Efficacy
  III. Slope

I. Potency

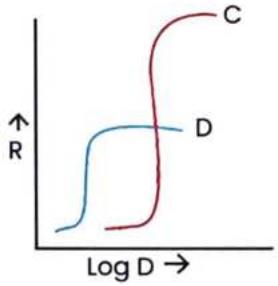
- Potency means power, i.e. which drug is more powerful.
- The drug which produces the response at a lower dose is more potent than another drug which produces the same response at a higher dose.



A is more potent than B. So, curve on left side is more potent.

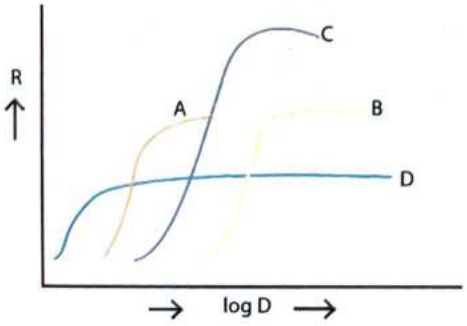
II. Efficacy

- It is the maximum response produced by a drug



C is more efficacious than D. So higher curve is more efficacious.

Q. Which is :a. Most efficacious drug?
b. Most potent drug?



a. Ans is C
b. Ans is D

Q. Which is more relevant clinically -Potency or Efficacy?
For e.g. Patient with BP of 150 mmHg and we have to reduce it to 120 mmHg. We give 2 drugs - A and B.

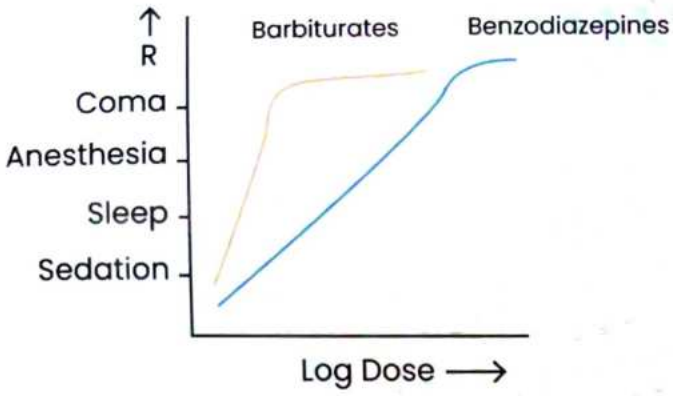
Dose	Reduction in BP (in mmHg)	
	A	B
10 mg	10	0
20 mg	20	10
40 mg	20	20
80 mg	20	30
160 mg	20	30
180 mg	20	30

- A is producing action at the lowest dose, so A is more potent
- B is producing more action than A, so B is more efficacious
- But in this patient, we have to reduce from 150 to 120 (30), which is done by drug B. So we choose drug B based on efficacy. Therefore, clinically efficacy is more important than potency.

- **Efficacy v/s Effectiveness**
  Efficacy is the max. response that we can get, usually measured under ideal conditions.
  - It is tested in clinical trials.
  - Efficacy is fixed for a drug.
    → Effectiveness is the actual response we get from the drug in real-time scenario.
  - It is tested under clinical conditions.
  - Effectiveness is variable. It can be different in different patients.

III. Slope

- Slope is related to the safety of the drug.
- Drug with a steeper slope is less safe than a drug with a more flatter slope.
- Clinically Benzodiazepines are preferred over Barbiturates for insomnia because Benzodiazepines are safer than Barbiturates.



DRC can be of two types 00:59:00

I. Graded DRC

- If we plot grades of response on the y-axis, we get graded DRC.
- It includes the DRC read till now.

II. Quantal DRC

- Sometimes grades of response cannot be put on the y-axis because the response is either all or none, there is no in-between.

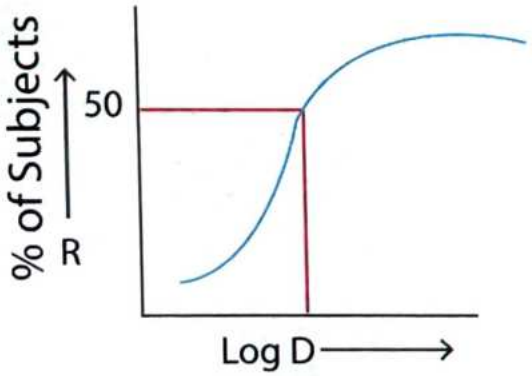
Previous Year's Questions

Q. Which of the following drugs act by inhibiting DNA replication?

(NEET Jan 2020)

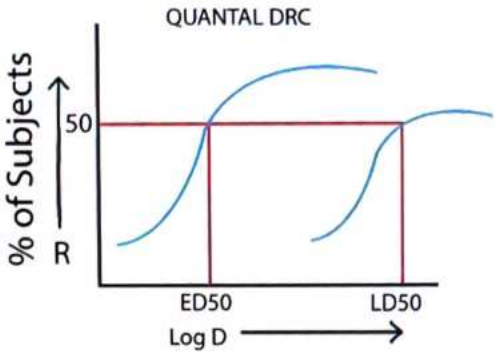
A. 6 Mercaptopurine
B. Actinomycin D
C. Mitomycin C
D. Asparaginase

- So, we plot the quantity of people with that response on y-axis. This gives us Quantal DRC.



- **ED50:** The dose at which 50% of the people get the desired response, is called Ed50.

LD50: Similarly, LD50 is the lethal dose at which half of the subjects died.



Therapeutic index = $\frac{LD50}{ED50}$

- Therapeutic index is the margin of safety for a drug.

6 PHARMACOGENETICS

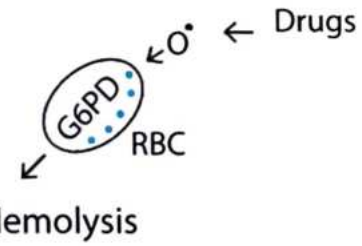
- **Definition:** When the effect of a drug is different for different people because of their genetic makeup, this condition is called pharmacogenetics.

- **Pharmacogenomics** →When the effect of a drug changes with mutation or change in one single gene, it is called pharmacogenomics.

- **CYP polymorphism**
  - Accordingto the level of CYP enzyme in a person, the drug may be metabolized more or less.
  - CYP 2D6 has max. level of genetic polymorphism.
  - CYP 2C19 activates clopidogrel. So, if a person has low CYP 2C19, this results in poor metabolism of clopidogrel.
- Apart from CYP polymorphism, there are three special pharmacogenetic conditions

I. G6PD deficiency 00:04:00

- It is an X-linked recessive disease.
- G6PD enzyme is present in RBCs.
- It protects the RBC from free radical damage.



- When G6PD is present <60% of the moral level, we call it G6PD deficiency.
- In G6PD deficiency, free radicals will damage the RBC and hemolysis will occur.
- Drugs that cause hemolysis in pts. with G6PD deficiency are
  - Primaquine
  - Tafenoquine
  - Sulfonamides (Cotrimoxazole, Dapsone)
  - Nitrofurantoin
  - Furazolidone

II. Succinylcholine induced apnea 00:08:40

- Sch is a muscle relaxant
- It is the shortest acting MR (< 5 min) because it is metabolized by Pseudocholinesterase.
- Sch is used for Endotracheal intubation.
- Some people have an abnormal enzyme called Atypical pseudocholinesterase which takes a longer time to break the Sch.
- So Sch will work for a longer time and relaxes other muscles of respiration also.This leads to apnea.

III. Acetylation 00:15:00

- N-acetyl transferase (NAT) enzyme is required for Acetylationreaction.
- The level of this enzyme is diffrent for different people. So, the metabolism of drugs will be different in different people.
- Isoniazid is metabolized by NAT enzymes. If this drug is given to slow acetylators it will not be metabolized enough and will accumulate leading to side effects like peripheral neuropathy.
- When given to fast acetylators, it is metabolized quickly to compounds which may increase in concentration and lead to hepatotoxicity.
- The drugs which are metabolized by acetylation are
  - [illegible]ulfonamides (Dapsone)
  - H- Hydralazine
  - I - Isoniazid
  - P - Procainamide
- All these 4 drugs can cause SLE as an adverse effect

How to remember

- SHIP drugs

7 THERAPEUTIC DRUG MONITORING (TDM)

00:08:40

- Before going to TDM, we discuss how we normally adjust the dose of a drug:
  - Suppose we give 100 mg of drug A for treatment of HTN.
  - A patient comes with 160 mmHg blood pressure, and we want to reduce it to 120 mmHg.
  - We give the drug A to the patient and call back the patient after a few days to check his BP. If the BP becomes very low, means the dose is high and so we reduce the dose. If the BP is high, this means the dose is low and so we increase the dose.
  - So, we adjust the dose acc. to the response but this is not possible everywhere.
  - For example, in the case of Epilepsy, we cannot measure the effect of the anti-epileptic drug via the response as the next seizure may not happen soon.
  - So, we require Therapeutic Drug Monitoring.

- **Definition**
  - Therapeutic Drug Monitoring means adjusting the dose of a drug according to its plasma concentration.

- **MDT v/s TDM**
  - MDT means Monitoring Drug Therapy
  - TDM means Therapeutic Drug Monitoring
  - MDT is a broad term. It means adjusting the dose of the drug by any method.
  - TDM is a part of MDT.

- TDM is not done for every drug because:
  - We cannot take a blood sample for every drug from every person.
  - It is costly.
  - The plasma concentration of a drug must be measured by sophisticated methods like: HPLC or spectrophotometry. These instruments are very costly.
  - Requires a skilled person to measure it.
  - Availability is an issue.

Criteria for doing TDM 00:06:50

I. Response of a drug is not monitorable

- Anti-hypertensive drugs
- Anti-diabetic drugs
- Anti-coagulants

} TDM not required

II. Narrow Therapeutic index

- Drugs with a wide therapeutic index are safe and don't require TDM. For e.g. penicillin.
- Narrow TI → Aminoglycosides (Gentamicin)

Previous Year's Questions

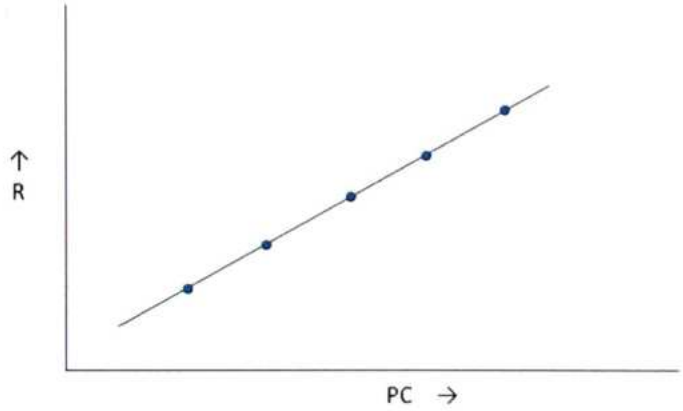
Q. A patient suffering from infective endocarditis was given high dose of penicillin and gentamicin. Which of the following statements is correct regarding these drugs? (INICET Nov 2020)

A. Therapeutic drug monitoring should be done for both drugs as these have narrow therapeutic index
B. Therapeutic drug monitoring should be done for penicillin as it can cause severe anaphylaxis
C. Therapeutic drug monitoring should be done for gentamicin as it has narrow therapeutic index
D. Therapeutic drug monitoring is not required for any drug as both have wide therapeutic index.

III. Inconsistent Pharmacokinetics

- Giving the same dose of a drug produces different response in different people.
- So, we need to adjust dose acc. To plasma level of drug.

IV. Linear relationship between plasma concentration and response



- So, at higher PC, there will be toxicity and at lower PC, there will be inconsistency
- Therefore, we need to maintain the dose in a narrow range.
- So TDM is required

Important Information

- For Prodrugs. TDM is not useful. Prodrug produces an active metabolite. We don't know how much active drug is produced from the prodrug and how much inactive drug is still present in the plasma. which can be converted to the active drug. So TDM not done.

Compliance 00:16:05

- TDM can also be used to check compliance.
- We can measure the plasma conc. of the drug and check whether pt. is taking the drug regularly are not.
- Drug which requires TDM are:
  - A - Aminoglycosides (Gentamicin)
  - Drug - Digoxin
  - Possessing - Phenytoin
  - Very - Valproate
  - Low - Lithium
  - Therapeutic - Tricyclic antidepressants
  - Index - Immunosuppressants: Cyclosporine, Tacrolimus

Important Information

- A Drug Possessing Very Low Therapeutic index

8 CLINICAL TRIALS

Pre-clinical studies

- Done in animals.
- We see whether the drug is safe or not and whether it is effective or not.
- To check for effectiveness, we make animal models. For example, for testing an anti-hypertensive drug we make the animal hypertensive, for testing an anti-diabetic drug we make the animal diabetic.
- We check the safety of the drug by doing extensive lab testing after giving the drug.
- Pre-clinical studies are done under specific guidelines, called CPCSEA guidelines.

CPCSEA stands for "Committee for Purpose of Control and Supervision of Experiments on Animals".

Clinical trials 00:04:03

- Now we do testing of the drug in humans. This is called clinical trials.
- Clinical trials are done under GCP guidelines (Good Clinical Practice guidelines).
- We divide clinical trials into various phases
  - Phase I
  - Phase II
  - Phase III
  - Phase IV
- Before starting the clinical trials, we have to go to a licensing authority
  - USA: FDA
  - India: DCGI (CDSCO)

INDA- Investigational New Drug Application

- We write this application to DCGI (Drug Controller General of India) to ask permission to start the clinical trial.
- We submit the animal data and all the information regarding the drug.

Phase I 00:0[illegible]

- Small number of healthy people enrolled.
- We can't do efficacy testing because of healthy volunteers.
- Healthy volunteers have good immunity so we can come to know about the toxic effects of drugs too.
- But for drugs that are already known to be toxic, for example, anti-cancer drugs → their phase I trial can be done in patients too.
- So, we can test whether the drug is safe or not.
- But if the drug has never been given to humans before, we calculate the human equivalent dose from the animal data.
- Maximum tolerable dose (MTD) can be found. This is the main aim of Phase-I trials.

Important Information

- **Major aim of phase-I clinical trials:**
  - MTD > Dosing > Pharmacokinetics of drug > Safety
- **Not done → efficacy**

Phase II 00:15:25

- Done in patients. Small number of patients are taken (up to 500).
- Efficacy is tested for the 1st time.
- Divided into 2 phases
  - Phase II a → Proof of Concept trial
  - Phase II b → Dose Ranging studies
- Unicentric study i.e., patients are taken from a single center.
- Safety of drugs can also be found.
- Efficacy is not yet confirmed.

Phase III 00:18:25

- This is also known as Pivotal Study.
- Large number of patients (up to 5000) are enrolled.
- Multicentric study.
- Efficacy is confirmed.

Previous Year's Questions

Q. Identify the true statement regarding clinical trials? (NEET Jan 2019)

A. Phase I is done to determine efficacy in patients.
B. Healthy volunteers are recruited for the first time in phase II
C. Randomized controlled trials in patients are done in phase II
D. Phase IV in Pharmacokinetics is done in animals.

New Drug Application (NDA)

- We ask permission from DCGI to market the newly developed drug.
- We sent the Phase-I, II and III trial data and all the information regarding the efficacy and safety of the drug.

Phase IV 00:24:30

- This is also known as Post Marketing Study.
- Main aim is to know the Rare adverse effects of the drug.
- These adverse effects can be known only when the drug is given to a larger number of people.
- Long term side effects can also be known, which appear after the drug has been used for a long period of time.
- Maximum number of patients are assessed in phase IV.
- So, the sequence of new drug development is:

INDA
↓
Phases I
↓
Phase II
↓
Phase III
↓
NDA
↓
Market
↓
Phase IV

- Maximum risk of failure is seen in Phase II.

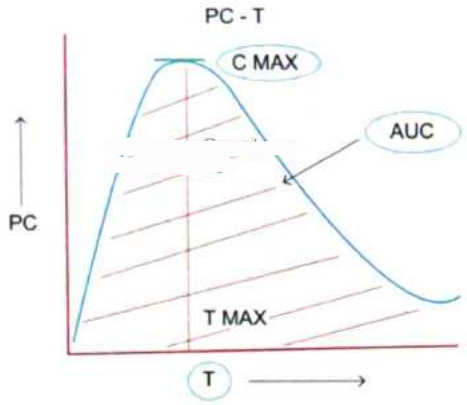
Phase 0 trial 00:35:30

- This is also known as Micro dosing study.
- Done in humans.
- Not mandatory for every drug.
- We use subtherapeutic dose, i.e very less dose (usually 1/100th of human dose or maximum upto 100mg)
- We cannot know the safety of the drug because, at such a low dose, adverse effects are not seen.
- We attach the drug with a radioligand and monitor it in the body → this helps us study the pharmacokinetics of the drug.

Blinding and control 00:38:50

- We give the newly developed drug to the study group.
- Blinding means unawareness of treatment.
- Control group gets placebo treatment. For life-threatening diseases, we use standard drugs.
- Placebo effect is mostly due to endorphins.
- Placebo does not work in all subjects every time
- **Single blind study**
  - Only the subject (patient) is unaware of the treatment.
  - Done in Phase-II
- **Double blind study**
  - Both the investigator and subject are unaware of the treatment.
  - This eliminates the investigator bias.
  - Done in phase III.
  - These are considered the best studies.
- Phase-I are open label studies. This means no blinding is done.
- No blinding is done because we don't test the efficacy in Phase-I trial.
- **Triple blind study**
  - When subject, investigator and statistician all are unaware of the treatment.
- Placebo is very similar to drug and has the same shape size and color but it does not have the active ingredient that produces the action.
- Excipients are the additional substances, other than the active ingredient, that are added to the actual drug to add properties like taste etc.
- Sham surgery → Surgery in which nothing useful is being done and only consists of opening and closing is called sham surgery. It is similar to placebo.

9 PLASMA CONCENTRATION V/S TIME GRAPH

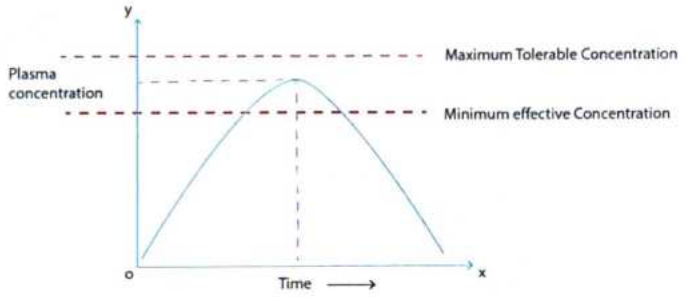


Tmax: Time in which the plasma concentration becomes maximum ⏱ 00:00:05

- Tmax tells about how quickly the drug is absorbed
- It tells about the rate of absorption of the drug
- If a drug has Tmax of 12 hours, we won't use this drug in emergency
- In an emergency, we will use a drug with shorter Tmax

Cmax: Maximum plasma concentration obtained with a particular dose

- We will choose the dose in such a manner, that the Cmax lies between 2 limits: Minimum effective concentration and Maximum tolerable concentration.



AUC: Area under the curve represents the extent of absorption

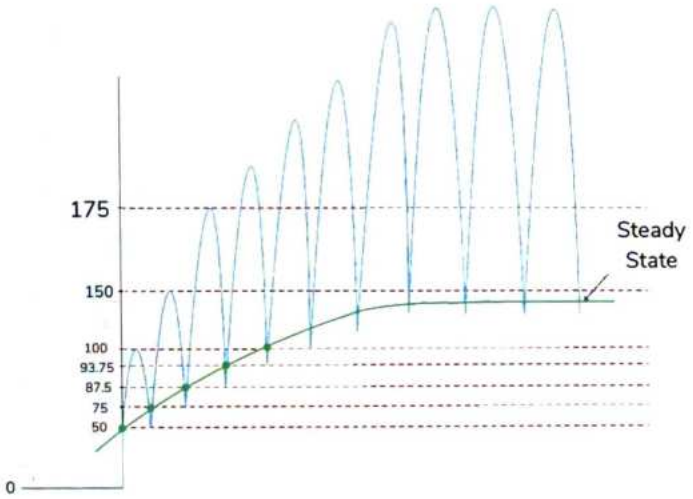
- It means how much drug has entered the body.

10 STEADY STATE

Steady state: It is the state at which the rate of drug administration is equal to rate of drug elimination ⏱ 00:01:50

Importance of steady state

- Steady state concentration is maintained and monitored for drugs used in long term drug therapy which require Therapeutic dose monitoring.
- Intermittent administration: We give the drug either once a day or twice a day and then we stop.
  - For example: we are giving 100 molecules of drug A after every half-life. At the beginning, the plasma concentration is 0.



  - The average plasma level keeps increasing gradually and then it becomes stable. This is now in steady state as the rate of administration becomes equal to the rate of elimination.

Steady state plasma concentration (SSPC) ⏱ 00:05:50

- It depends upon the dosing rate
- It is directly proportional to the dosing rate
- It will become stable after 4-5 half-lives
- If we are giving the same dosing rate, the average plasma concentration remains constant, but the maximum and minimum plasma concentration which is seen as peak and trough on the graph show variation
- This variation between peak and trough depends upon how frequently we give the dose

Important Information

- SSPC obtained depends on → Dosing rate
- Time to reach SSPC → 4-5 half lives
- Variation between peak & trough depends on → Frequency

Loading dose ⏱ 00:10:42

- Amiodarone: Anti-arrhythmic drug with a half-life of 20 days. Time to SSPC is 4-5 half-lives, so the time taken is almost 3 months.
- If we can't wait for 3 months, we give a high initial dose at the beginning to quickly achieve the steady state. This high initial dose is called the loading dose.
- The basic purpose of the loading dose is to attain a steady state quickly.

11 NUMERICALS IN PHARMACOLOGY

Q1. 20 grams of Soframycin cream contains?

- Framycetin sulfate: 1% w/w (weight by weight)
- Methyl paraben: 0.8% w/w
- Propyl paraben: 0.04% w/w

Calculate the amount of Framycetin in this preparation in mg.

Ans

1% w/w means 1g of Soframycin is present in 100g of cream.

So, 100 g of cream contains 1 g of Soframycin.

20 g of cream contains $\frac{1}{100} \times 20 = 0.2$ g

$= 200$mg

So, 20 g cream contains 200 mg Soframycin

Q2. How will you prepare 100 ml of normal saline from 10ml of 15% saline solution?

Ans

Normal saline is 0.9% NaCl i.e., 100ml of solution contains 0.9g of NaCl.

So 15% saline means 15g NaCl present in 100ml solution

1g present in $\frac{100}{15}$ ml

0.9 g present in $\frac{100}{15} \times 0.9 = 6$ ml

∴ 6 ml + 94 ml distilled water = 100 ml solution

Q3. Calculate the required volume in ml for oral administration from 30ml cefadroxil suspension containing 250ml/5ml for a child. The weight of the child is 10 kg and he is suffering from tonsillitis. The dose is 40mg/kg/day orally in 2 divided doses, not to exceed 2g per 24 hours

Ans

Dose is 40mg/kg/day in 2 divided doses

Child's weight = 10kg

∴ Dose = 40x10 = 400mg/day in 2 dose

∴ Dose is = 200mg twice a day (BD)

Now we have 250mg per 5ml

250 mg present in = 5ml

1 mg present in = $\frac{5}{250}$

∴ 200 mg present in $\frac{5}{250} = x \times 200 = 4$ ml

∴ Dose will be 4ml BD

Q4. A solution of Adrenaline contains Adrenaline in a dose of 1:10000. If you want to inject 1 mg of Adrenaline, how much volume should be injected?

Ans

1:10000 means 1g Adr. Is present in 10000 ml solution

1000mg is present in → 10000 ml solution

1 mg is present in → $\frac{10000}{1000} = 10$ ml

∴ We need to inject 10 ml

Q5. Calculate the required volume in ml for intravenous injection from a vial of 30ml. The vial contains chloroquine base 40mg/ml for a patient weighing 40kg at a dose of 3mg/kg body weight suffering from malaria?

Ans

Dose required = 3 mg/kg

Weight = 40 kg

∴ Total dose required = 3 x 40 = 120 mg

40mg/ml means 40 mg present in 1ml

1mg present in $\frac{1}{40}$

120mg present in $\frac{1}{40} \times 120 = 3$ ml

Q6. A vial contains Benzyl Penicillin-G5 lac units per ml after reconstitution. Calculate the required volume in ml for intramuscular injections from this vial for a child weighing 5 kg at a dose of 20000 units per kg?

Ans

Total dose = 20000 x 5 = 100000 units

5 lac unit present in 1 ml

1 lac unit present in $\frac{1}{5}$ ml = 0.2 ml

Q7. A plain insulin vial contains 40 units/ml. How much volume should be taken from this vial to set up an infusion in 500 ml normal saline at a rate of 1ml/min to provide the dose of 0.1 unit/kg/hour for a patient with Diabetic Ketoacidosis weighing 60 kg?

Ans

0.1unit per kg x 60 x $\frac{1}{60}$ = 0.1 unit/min

0.1 unit = 1 ml

Total = 500 ml = 500 x 0.1 = 50 units

If 40units present in 1ml

1 unit present in $\frac{1}{40}$

50 units present in $\frac{1}{40} \times 50 = 1.25$ml

Q8. A vial contains lignocaine 2%. How much volume should be taken from this vial for setting up an infusion in 500ml normal saline at the rate of 1ml/min to provide the dose of lignocaine 0.20mg/min for a patient with ventricular tachycardia, whose weight is 60kg?

Ans

Dose to give = 0.2 mg/min
Infusion rate = 1ml/min
Total bottle should contain = 500x0.2 = 100mg
2g is present in 100ml
2000 mg present in 100 ml
1mg present in $\frac{100}{2000}$
100mg present in $\frac{100}{2000}$ x100 = 5ml

Q9. A 70 kg patient needs to be started on nitroglycerine infusion. The 5 ml ampule contains 5mg/ml NTG. One ampule is added to normal saline and made a total of 500 ml solution. Calculate the rate of infusion, if NTG is required at the rate of 10 mcg/min (1 microdrip= 60 drops/ml)

Ans

Dose required = 10mcg/ml= $\frac{10}{100}$ mg/min
1 Ampule contains 25mg
25 mg is present in 500ml
1mg is present in $\frac{500}{25}$ x $\frac{10}{1000}$ =0.2ml
1ml = 60 drops
0.2 ml = 60x0.2 = 12 drops/ml

Q10. 5 IU oxytocin is added to 500ml normal saline. The patient's weight is 50kg. Calculate the rate of infusion at the dose of 5 mU /min (1ml = 16 drops).

Ans

5mU/min is dose required = $\frac{5}{1000}$ U
5IU added to 500ml NS
1IU added to $\frac{500}{5}$ ml = $\frac{500}{5}$ x $\frac{500}{1000}$ = 0.5, ml
1ml = 16 drops
0.5ml = 16 x 0.5 = 8 drops/min

Q11. You have to give 180 mg of Ceftriaxone to a patient in 2ml syringe that has 10 divisions per ml. The concentration of this drug in the vial is 500mg/5ml. How many divisions should be filled in 2ml of the syringe to give 180mg?

Ans

We need to give 180mg
500mg present in 5ml
1mg present in $\frac{5}{500}$ x180 = 1.8ml
10 division present per 1ml
1ml = 10 divisions
1.8 ml = 10x1.8 = 18 divisions

Q12. 1000mg of a drug was administered to a patient. 200mg was cleared in 60 minutes. How much of the drug would be left in the body after 3 hours, if the excretion of the drug follows zero-order kinetics?

Ans

Drug follows zero order kinetics, so constant amount is excreted
So amount excreted in 1hr = 200mg
So amount excreted in 3hr = 600mg
Remaining drug = 1000-600 = 400mg

Q13. 200 mg drug was administered to a patient. 75mg of that is excreted in 90min. The given drug follows 1st order Kinetics. How much drug will remain after 6 hours?

Ans

Dose given = 200mg
Drug follows .1st order kinetics, so constant percentage is excreted.
75mg is excreted in 1½ hrs, which is % $\frac{75}{200}$
Remaining = 1- $\frac{75}{200}$ = $\frac{125}{200}$ = $\frac{5}{8}$
So, Drug remaining after 1½ hr = 200 x $\frac{5}{8}$
So, Drug remaining after 3 hr = 200 x $\frac{5}{8}$ x $\frac{5}{8}$
So, Drug remaining after 4½ hr = 200 x $\frac{5}{8}$ x $\frac{5}{8}$ x $\frac{5}{8}$
So, Drug remaining after 6 hr = 200x $\frac{5}{8}$ x $\frac{5}{8}$ x $\frac{5}{8}$ x $\frac{5}{8}$
= 30.5mg

Q14. Calculate the half life of a drug 'x' if it has V_d = 60L and Clearance of 2.1 L/min.

Ans

$t\frac{1}{2} = \frac{0.7 \times Vd}{CL}$
$= \frac{0.7 \times 60}{21}$ = 20min

Q15. Calculate the hepatic clearance of a drug with hepatic blood flow of 1500ml/min and hepatic extraction ratio of 0.6?

Ans

Clearance= Blood flow x Extraction ratio
= 1500 x 0.6
= 900 ml/min

Q16. A female patient weighing 50kg is having P.vivax malaria to whom tablet chloroquine is given. The Target plasma concentration is 20mg/L. The volume of distribution of chloroquine is 0.6L/kg. What will be the loading dose of chloroquine in this patient assuming 100 per-oral bioavailability?

Ans

Loading dose = Vd x target PC
Vd = 0.6x50 = 30L
LD = 30x20 mg/L
= 600 mg

Q17. Calculate the maintenance for a drug with 100% oral bioavailability which needs a target concentration of 5mg/Land clearance of 10L/hr and dosed four times a day?

Ans

Maintenance Dose = Clearance x Target Plasma Conc.
= 5mg/L x 10L/hr

$= 50$ mg/hr

$= 50 \times 6 = 300$ mg QID

Q18. You have started a drug infusion at a rate of 60mg/h. The drug has Vd of 50 liters and Clearance of 50ml/min. How much will be the drug concentration at a steady state?

Ans

Maintenance dose = Clearance x Target PC

$$\therefore \text{Target PC} = \frac{\text{Maintenance dose}}{\text{Clearance}}$$

$$= \frac{60 \text{ mg/hr}}{50 \times 60} = \frac{60}{3000} = \frac{1}{50} \text{ mg/ml}$$

$$= \frac{1}{50} \times 1000 = 20 \text{ mcg/ml}$$

12 ADR AND PHARMACOVIGILANCE

Adverse Drug Reaction

- Anything which is unwanted and problematic, that occurs after taking a drug at a therapeutic dose
- They can be of various types
  - Type A -Augmented: Dose-related toxic adverse effects
  - Type B -Bizarre: Allergic reactions
  - Type C -Chronic: Occur on long term use
  - Type D -Delayed: Teratogenicity
  - Type E -End of dose: Rebound HTN
  - Type F -Failure of therapy: Considered only by FDA, not by WHO

Pharmacovigilance: Study of adverse effects 00:08:40

- Pharma-co-vigilance
  ↓ ↓
  Drug Keep an eye
- It consists of 4 things
  - **D** - **D**etection
  - **A** - **A**ssessment
  - **U** - **U**nderstanding
  - **P** - **P**revention

} of adverse effects

How to remember

- DAUP

Adverse Event v/s Adverse Drug Reaction (ADR)

Adverse Event (A/E)	Adverse Drug Reaction (ADR)
• Anything that happens to the person while he is taking the drug	• The adverse event that is likely caused by the drug itself

Causality Assessment

- We assess the cause, whether the adverse event is caused by the drug or not.
- It is assessed by using a questionnaire known as the Naranjo scale.
- Done by Rechallenge – Dechallenge method
  - When the adverse event occurs, we stop the drug to see if the adverse event subsides. This is called Dechallenge.
  - After a few days, we start the drug again. This is called Rechallenge
  - If the adverse effect appears again, this confirms the causality

National Pharmacovigilance Program of Indian (NPvPI) 00:14:50

- Almost all the medical colleges and major private hospitals in India have set-up ADR monitoring centers (AMCs).
- Any adverse effect which is reported from that institution will be monitored by that AMC
- AMCs have a computer that uses the software Vigiflow
- All the AMCs report to National Coordinating Center (NCC) which was previously in AIIMS but now at Indian Pharmacopoeia Commission (IPC) present at Ghaziabad
- The coordinating centers from all the countries report to the Uppsala monitoring center present in Sweden
- This Uppsala monitoring centre is in close coordination with FDA. FDA can take several actions according to the seriousness of the event.
- If the adverse effect is very serious, FDA can issue a black-box warning to the manufacturer of the drug which consists of – Adding a black slip with adverse effect warning written on it, in the box of the drug for the consumer
- But if the adverse effect is extremely serious, FDA can withdraw the drug

Materio-vigilance 00:19:16

- It is the monitoring of pharmaceutical materials like catheters, stents, pacemakers etc.
- Any adverse event occurring due to these pharmaceutical materials is monitored.

13 DRUGS IN PREGNANCY AND LACTATION

- Many drugs are teratogenic and can cause malformations in the baby, so they should be avoided during pregnancy
- Almost all drugs can cross the placenta but not each of these drugs causes teratogenicity
- Only 2 drugs cannot cross the placenta at all, these are: Insulin and Heparin
  i. So only those drugs should be avoided in pregnancy which is harmful to the body
  ii. The risk of teratogenicity is highest in 1st trimester
  iii. The risk of teratogenicity is dose dependent and duration dependent

Drugs in pregnancy according to organ system

00:02:08

1. Cardiovascular system

a. Antihypertensive drugs
- ACE inhibitors and ARBs are C/I in pregnancy.
- The ones which are safe are
  - Better →Beta-blockers (Labetalol)
  - Mother →Methyldopa
  - Care →Clonidine
  - During →Dipines (Amlodipine, Nicardipine)
  - Hypertensive →Hydralazine
  - Pregnancy →Prazosin (α blockers)

How to remember

- Better Mother Care During Hypertensive Pregnancy

1. CNS

a. Epilepsy – All anti-epileptic drugs are teratogenic
  i. Valproate – Most teratogenic anti-epileptic drug
  ii. Levetiracetam and Lamotrigine – Least teratogenic anti-epileptic drug
- If a female is already taking an anti-epileptic drug, thenthe same therapy should be continued in pregnancy. If we changed the drug, the therapeutic effect of the new drug is different. So,the mother can develop seizures

b. Bipolar disorder
  i. Lithium – Adverse effect: Ebstein anomaly. So, DOC for bipolar disorder in pregnancy is Antipsychotic drugs
- Alcohol should also be avoided in pregnancy because it is teratogenic

2. Endocrine system

  i. Diabetes: DOC for Diabetes in pregnancy is Insulin
  ii. Hyperthyroidism
- Propylthiouracil → DOC for 1st trimester
- Carbimazole and Methimazole → Used in 2nd and 3rd Trimester
- DES → Causes Vaginal Carcinoma in Female baby

Important Information

- If Ques says "DOC for hyperthyroidism in pregnancy" without mentioning the trimester. then mark the answer as PTU.

1. Anti-microbials
- Most of the anti-microbials should be avoided in pregnancy
  i. Tetracyclines →cause damage to Bone and Teeth
     Aminoglycosides →cause Hearing loss
     Fluoroquinolones →cause Cartilage and Tendon damage
  ii. Anti-microbials that are safe in pregnancy are
     P – **P**enicillins (β-lactams)
     C – **C**lindamycin
     M – **M**acrolides

How to remember

- PCM is safe

  iii. Anti-malarial drugs
    - ACT is the treatment of choice for malaria

- But Artemisinin's are C/I in 1st trimester
- So, in the first Trimester of malaria, we prefer Chloroquine
- But in Plasmodium falciparum malaria in 1st trimester, we give Quinine
- ACT can be given in the 2nd and 3rd trimesterof malaria

1. Hematology

- Warfarin is teratogenic. It causesFetal Warfarin syndrome
- Avoid it in 1st trimester and instead give heparin in 1st trimester
- Stop warfarin at <32 weeks and shift to heparin

2. Lactation

- Very few drugs are secreted in breast milk. So, most of the drugs can be continued during lactation
- Timing of Breast feeding is very important
- Feed the baby just before taking the drug
- Then take the drug after feeding the baby

14 TYPES OF ENZYME INHIBITORS

00:04:20

Enzyme inhibitors are broadly of three types

i. Competitive → Binds to free enzyme only
ii. Non-competitive → Binds to both free enzymes as well as enzyme-substrate complex
iii. Uncompetitive → Binds to enzymes - substrate complex only

- **Km**
  - Michaelis menten constant
  - It is the substrate required to produce half of the maximum reaction velocity
  - It is opposite to the affinity of the substrate for the enzyme
- **Vmax**
  - It is the maximum reaction velocity
  - It means how many more products can be produced

	Km	Vmax
Competitive Inhibition	↑	-
Non-competitive inhibition	-	↓
Un-competitive inhibition	↓	↓

- **Examples**
  - Non-competitive → Cyanide inhibits cytochrome oxidase enzyme
  - Un-competitive → Lithium inhibits enzymes in treatment of mania

15 TYPES OF DRUG ANTAGONISM

- Drug antagonism is of 2 types
  - Physiological →Occurs through different receptors
  - Pharmacological → Occurs through same receptors
- Histamine causes Bronchoconstriction by stimulation of H_1 receptors in the bronchus
  It also causes Vasodilation by stimulation of H_1 receptors in the blood vessels
- Adrenaline causes Bronchodilation by stimulation of β_2 receptors in bronchus
  It also causes Vasoconstriction by stimulation of α_1 receptors in blood vessels
- Histamine and Adrenaline produce opposite effects by acting on different receptors. So, they are physiological antagonists
- Histamine produces Vasodilation by acting on H_1 receptors. Promethazine produces vasoconstriction by acting on H_1 receptors. So, they are pharmacological antagonists
- Adrenaline produces Bronchodilation by acting on β_2 receptors. Timolol produces bronchoconstriction by acting on β_2 receptors. They are examples of pharmacological antagonists

16 COMBINED EFFECT OF DRUGS

Synergism

- It means if we give 2 drugs separately, they produce their actions individually. But if we combine them, the action is more than any of their individual effects.
- For example:
  - Cotrimoxazole – It is a combination of Trimethoprim with sulfamethoxazole
  - Trimethoprim – Bacteriostatic only
  - Sulfamethoxazole – Bacteriostatic only
  - But the combination is Bactericidal

Potentiation 00:03:04

- It means one drug is active and 2nd drug is inactive, but the inactive drug has increased the effect of the active drug. This is called potentiation

- For examp[s]
i. Amoxicillin + Clavulanic acid
  - Amoxicillin is an antibiotic but can be broken down by β-lactamase enzymes. So, cannot be given alone
  - Clavulanic acid is β-lactamase inhibitor. So, it prevents the breakdown of Amoxicillin. It doesn't have an effect of its own

ii. Levodopa + Carbidopa
  - In parkinsonism, Levodopa is given because there is deficient dopamine. But it can form dopamine outside the brain also. This dopamine cannot enter the brain. This is because of enzyme Dopa decarboxylase
  - Carbidopa can inhibit the enzyme Dopa decarboxylase. So there is no formation of dopamine in the periphery. All levodopa is available to the brain now and its action increases

Antagonism 00:05:55

- It is commonly seen in antibiotics
- If we give a bactericidal antibiotic with a bacteriostatic antibiotic, the bacterial multiplication stops because of the '-static' drug and the bacteria is not active anymore. So, the bactericidal drug is ineffective because it acts on rapidly multiplying bacteria only
- For e.g.: Amoxycillin + Tetracycline

17 PRACTICALS IN GENERAL PHARMACOLOGY

The practicals in pharmacology are
- Label
- Drug promotional literature

Drug label 00:01:10

- The drug label consists of the following details

i. Name
   - Generic name
   - Brand name
   - Chemical name
   - For example
     a. Generic name – Aspirin
     b. Brand name – Ecosprin
     c. Chemical name – Acetylsalicylic acid

ii. Abbreviations
   - For e.g.: Aspirin IP → This IP is the abbreviation
   - Commonly used abbreviations are:
     a. IP → Indian pharmacopoeia
     b. BP → British Pharmacopoeia
     c. USP → US Pharmacopoeia
     d. BNF → British National Formulary
   - These pharmacopoeias and formularies are large books that contain details about the drugs.

iii. OTC or Schedule - H
   - OTC → Over the counter drug
     → These can be given without prescription
   - Schedule H → Prescription only drug
     → It is represented by a red line on the drug label

iv. Storage Temperature
   - Keep frozen → -20°C
     → [illegible]zer section of refrigerator
   - Keep cold → 2-8°C
     → Stored in refrigerator but outside the freezer section
   - Keep cool → <25°C in India
     → Keep outside the refrigerator at room temperature

v. Expiry date
   - Expiry date tells about the last date until when the drug can be used
   - Expiry date simply means that 'till this specific date the drug will act just like the pharma company is advertising it to be'
   - It does not mean that the drug will become toxic or ineffective after that date

- Shelf life
   - It means 'for how much time, the pharmacist can store the drug'
   - It represents the total life period of the drug
   - It is given by
     Shelf life = Expiry date – Manufacturing date

Promotional Drug Literature 00:10:07

- Aka Drug Advertisement
- It consists of

i. Name
   - Generic name
   - Brand name
     → According to guidelines, the brand name should not be more than 3 times in size than the generic name

ii. Details of drug
   - Dose, Frequency, Route etc

iii. Cost of therapy
   - Total cost of the drug for the full duration of administration

iv. Adverse effects
   - Rare but serious
   - Common but non-serious
   - Serious and common

v. Claims by company
   - Reference must be given for the claim

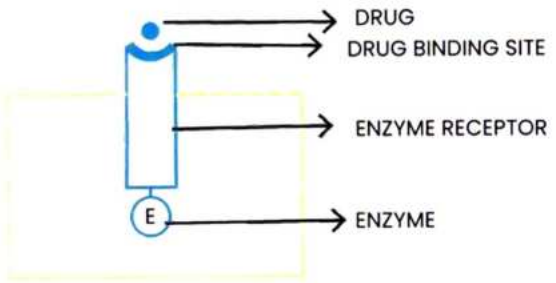
vi. Address of manufacturer
   - The manufacturing address of the drug

- Expiry date is not written on drug advertisement leaflet

18 DETAILS OF ENZYMATIC RECEPTORS

Enzymatic Receptors

- Enzymatic receptors have 2 ends
  - Extracellular end – Drug binds here
  - Intracellular end - Enzyme is present here
- So drug binds outside and enzyme is activated inside and action is produced
- Aka TYROSINE KINASE RECEPTORS because mostly associated enzyme is Tyrosine Kinase



Enzymatic receptors can be of 3 types

1. Intrinsic tyrosine Kinase activity

- Whenever drug binds outside
- Tyrosine Kinase enzyme gets activated inside
- E.g. Insulin receptor

2. No intrinsic tyrosine kinase activity

- Receptor will work through tyrosine kinase, but itself does not possess this activity
- Some proteins present on enzyme, which recruit tyrosine kinase from the cytoplasm & activate the tyrosine activity
- Receptor itself does not possess enzyme activity
- E.g.

i. JAK-STAT (JAK recruit STAT, that will result in enzymatic activity)

ii. Prolactin, Growth hormone

iii. Cytokines

3. Guanylate Cyclase

- Whenever drug binds outside, guanylate cyclase gets activated inside and generates cGMP.
- Substances which act through Guanylate cyclase are ANP, BNP, CNP (natriuretic peptides)

19 SPARE RECEPTORS

Spare Receptors

- At a particular number of receptor stimulation, the response becomes maximum & those receptors which are present in body beyond that are k/a Spare receptors

20 RECEPTOR REGULATION

- When a receptor in the body is constantly being stimulated, it gets saturated. Whereas when a receptor is not getting stimulated over a long time, its level will increase
- So constant presence of agonist will decrease the number of receptors and constant presence of antagonist increases the number of receptors

1. Constant stimulation (Agonist +++) ⏱ 00:01:30

- The mechanisms involved are

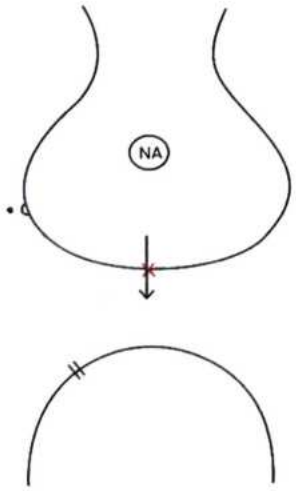
i. Masking – The receptors present on surface of membrane quickly go below and the number of receptors decreases. So, action decreases.

ii. Down – regulation – It is the actual decrease in number of receptors. It occurs via:
   - Less synthesis of new receptors
   - More degradation of existing receptors

iii. Uncoupling – There is uncoupling of signal transduction response
   - For e.g.: When β-receptors are stimulated constantly, it activates an enzyme called β-adrenergic receptor kinase (BARK). Kinase attacks the phosphate group. This targets the G-protein coupled receptor. This leads to binding of a protein called Arrest in to the phosphate group. So GPCR cannot produce its action

2. Constant Non-stimulation ⏱ 00:05:50

- For example: Clonidine inhibits release of Nor-adrenaline



   - So nor-adrenaline is decreased and there is decreased stimulation of α and β receptors
   - As these receptors are not stimulated for a long period, their number is decreased
   - Now when we stop giving clonidine from outside, NA gets released. This NA gets plenty of α and β receptors which were lying free. This leads to substantial increase in response
   - This results in Rebound HTN

- The mechanisms involved in Constant Non-stimulation are

i. Un-masking
   - All receptors come to the surface and get stimulated

ii. Up-regulation
   - Actual increase in number of receptors. It occurs via
     → Increase in synthesis of receptors
     → Decrease in metabolism or degradation of receptors

iii. Increase in coupling

21 DRUGS WITH PECULIAR NAMES

These include

I. Orphan Drugs
II. Essential Drugs
III. Me-too drugs
IV. Spurious drugs
V. Misbranded drugs
VI. Contaminated drugs

Orphan drugs

- These are drugs for which the expenditure done for the development of the drug is unlikely to be recovered from sale of the drug
- Includes drugs which are used for rare diseases
- Also includes drugs for relatively common diseases in third world countries with less paying capacity.

Essential drugs

- These are drugs that cater to priority health care needs of a population
- These drugs should be
  - Always available
  - In adequate quantity
  - With assured quality
- Mostly available as single compound

Me- too drugs

- Include drugs that has similar mechanism of action (similar pharmacodynamics) & minor pharmacokinetic differences
- Examples
  - Enalapril
  - Ramipril
  - Captopril
  - Lisinopril

Spurious drugs

- Include drugs that are manufactured, concealing the true identity of the product and made to resemble another drug (especially some popular bond)

Misbranded drugs

- Includes drugs that have false or misleading information on the drug label

Contaminated drugs

- Includes drugs that contain unhygienic or filthy matter

CLINICAL QUESTIONS

PHARMACOKINETICS – ABSORPTION

Q. A patient, Rajesh with a history of wheezing, coughing and shortness of breath is being evaluated in the asthma clinic. Several drug treatments with different routes are under consideration. Which of the following statements about routes of administration is most correct?

A. Administration of a bronchodilator drug by inhaled aerosol is usually associated with more adverse effects than administration of the same drug orally
B. The first pass effect is the result of metabolism of a drug after administration and before it enters systemic circulation.
C. Bioavailability of most drugs is greater with rectal administration than with sublingual administration
D. Administration of a drug by transdermal patch is often faster but is associated with more first pass metabolism than oral administration

Answer: B

Solution

- *Inhalational route* provides *localized* delivery to respiratory system and thus is associated with *lesser* adverse effectsthan the systemic routes like oral. Option (a) is thus false
- The **first pass effect** is the result of metabolism of a drug after administration and **before it enters systemic circulation.**
- When given by *sublingual* route, the *drug bypasses the portal circulation* and is thus protected from hepatic first-pass metabolism.
- Drugs given by oral and rectal route undergoes first pass metabolism in liver. All the drug absorbed from oral route is available for first pass metabolism whereas approximately 50% of the drug that is absorbed from the rectum will bypass the liver, thereby reducing hepatic first-pass metabolism. However, *rectal absorption can be irregular and incomplete.*
- The micropore membrane of a transdermal patch is such that rate of drug delivery to skin surface is less than the *slowest rate of absorption* from the skin. Thus, the drug is delivered at a constant and predictable rate. *First pass metabolism is avoided*

Q. A 33 year old male was brought to the emergency department by his family member, who happens to be a psychiatrist. History taken from the relative revealed that the patient suffered a loss in the stock market and attempted suicide with a prescription medication. If the doctor advises/ suggests to immediately initiate alkaline diuresis for treating this condition, which of the following drugs can it be?

A. Morphine
B. Amphetamine
C. Phenobarbitone
D. Atropine

Answer: C

Solution

- Phenobarbitone - is a derivative of barbituric acid **(weakly acidic drug)** and its excretion can be enhanced by **making the urine alkaline.**
- Absorption and reabsorption of a drug depends on its lipid solubility.
- When a drug is in a similar medium (acidic drug in acidic medium or a basic drug in basic medium), it easily crosses membrane in its non-ionized form and gets **absorbed/ reabsorbed.**
- Thus, in acidic drug poisoning (salicylate, barbiturates etc.) urine should be **alkalinized with sodium bicarbonate** because **weak acids are in ionized form in alkaline urine and thus are easily excreted**.
- Similarly, for basic drug poisoning (e.g. morphine, amphetamine etc.), urine should be acidified using ammonium chloride

PHARMACOKINETICS – DISTRIBUTION

Q. A 33 year old male, came in with complaint of constant right upper back pain. On examination, you find that the pain was 2/5 in visual analogue scale for pain and decide to give medication for the same. If you prefer to give an oral medication, which of the following drugs do you think has maximum chances of absorption from gastric mucosa?

A. Morphine sulfate
B. Diclofenac sodium
C. Hyoscine hydrobromide
D. Quinine dihydrochloride

Answer: B

Solution

- **Diclofenac sodium is a weak acid and is non-ionized in the acidic medium of stomach**.
- Drugs, when in similar medium are non-ionized and lipid-soluble. Therefore, Diclofenac sodium has the maximum chances of absorption from the stomach.
- Other drugs given in the options are weakly basic drugs that are ionized at gastric pH.

Note:

- **Most** of the **drugs ending with 'INE' are basic** in nature like morphine, quinidine, hyoscine, atropine, tubocurarine etc.
- Drugs forming salts with cations like sodium or potassium are **acidic** like diclofenac sodium, thiopentone sodium etc
- Drugs forming salts with anions like sulphate, phosphate etc. are basic like morphine sulphate, chloroquine phosphate etc

Q. You have joined residency in the department of Anaesthesiology recently. The chief resident during morning endorsement, mentions that the drug thiopentone is used for induction. You are asked as to why it is able to exert action at the CNS within 15 seconds, but is active only up to 15 minutes time on average. Which of the following would you mention as the reason?

A. Marked redistribution due to high lipid solubility
B. Marked redistribution as it contains weak electrolytes
C. Marked redistribution due tohigh plasma protein binding
D. Marked redistribution due tohigh water solubility

A. A only
B. A & B only
C. A, B & C only
D. D only

Answer: A

Solution

- Highly lipid- soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc.
- Later, less vascular but more bulky tissues (muscle, fat) take up the drug. Plasma concentration falls and the drug is withdrawn from the highly perfused sites.
- If the site of action of the drug was in one of the highly perfused organs, this redistribution results in termination of drug action. Anaesthetic action of thiopentone sod. injected IV is terminated in few minutes due to redistribution.
- **Greater the lipid solubility of the drug, faster is its redistribution**

PHARMACOKINETICS – METABOLISM

Q. Metabolism of a drug like diazepam has a different result when compared with the metabolism of a drug like levodopa. This is because metabolism is a process which primarily results in:-

A. Activation of the inactive drug
B. Conversion of prodrug to active metabolite
C. Conversion of lipid soluble drugs to water soluble metabolites
D. Conversion of water soluble drug to lipid soluble metabolites

Answer: C

Solution

- Major aim of metabolism **(Biotransformation)** is to convert lipid-soluble (non-polar) drugs to water soluble (polar) drugs.
- In the absence of metabolism, body will not be able to get rid of lipophilic substances, and they will become very long acting.

- Biotransformation of drugs may lead to any of the following
  1. Inactivation of an active drug
  2. Conversion of active drug to its active metabolite [Diazepam → Oxazepam]
  3. Activation of inactive drug (prodrug) [Levodopa → Dopamine]

Q. A 32yr old patient came to the Gyne. OPD with complains of bleeding per vaginum . Bleeding was for a prolonged period of time than her usual number of days in her regular menses. There was no significant finding on examination. On further examination, she told that she was on warfarin therapy for past 1 yr. And also told that she took some medication recently before the symptoms appear. Which of the following drug is not responsible for the condition ?

A. Clarithromycin

B. Sulphonamide

C. Ciprofloxacin

D. Carbamazepine

Answer: D

Solution

These are those drugs which inhibit cyt 450 and increase the half life of warfarin resulting in increased bleeding.sulphonamides don't allow degradation of warfarin : Increased bleeding, but carbamazepine is enzyme inducer and hence not responsible for the condition and decreases the half life of warfarin leading to decreased activity

LEARNING OBJECTIVES

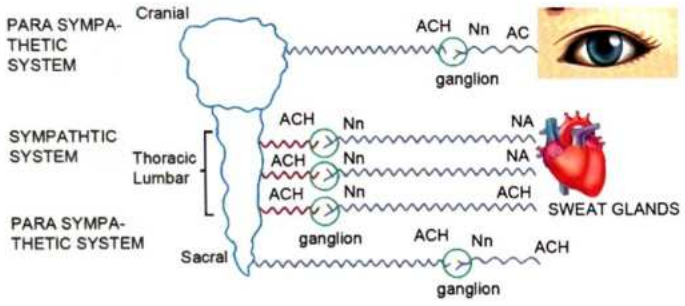
UNIT 2: AUTONOMIC NERVOUS SYSTEM

- Cholinergic drugs
  - Parasympathetic vs Sympathetic system
  - Parasympathomimetics
  - Ach esterase inhibitors
- Anticholinergic drugs
- Adrenergic drugs
  - NA receptors
  - Sympathomimetic drugs
  - Displacement
  - Catecholamines
  - Vasomotor reversal of Dale
- Anti-adrenergic drugs
  - Sympatholytic drugs
  - Cheese reaction
  - Clonidine withdrawal
  - Beta-blockers
- Tertiary and Quaternary Amines
- VMAT-2 inhibitors
- Active and Passive Mydriasis
- Rabbit experiments
  - Eye experiments
  - Ileum experiments
- Bladder pharmacology
  - Urinary incontinence
- Glaucoma

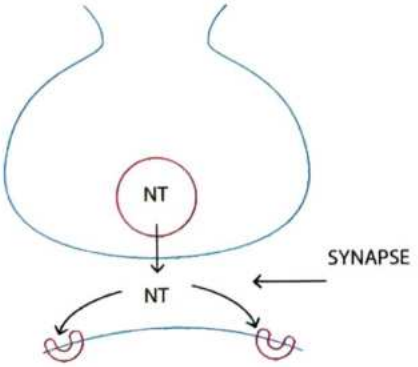
22 CHOLINERGIC DRUGS

Autonomic Nervous System (ANS) 00:00:15

- It is the part of the nervous system which controls involuntary functions.
- It consists of the efferent output from the central nervous system i.e., brain and spinal cord.
- ANS is divided into two parts, based on anatomy



Sympathetic system	Parasympathetic system
○ Nerve fibres which originate from the thoraco-lumbar portion of the spinal cord are called sympathetic nerve fibres.	○ Nerve fibres which originate from the Cervical or sacral portion of the spinal cord are called parasympathetic nerve fibres.
○ Consists of Thoraco-lumbar outflow	○ Cranio – sacral outflow
○ Pre-ganglionic fibres are small and post-ganglionic fibres are long	○ Pre-ganglionic fibres are long and Post-ganglionic fibres are small
○ Ganglion is near the spinal cord	○ Ganglion is away from the spinal cord



- All the pre-ganglionic fibres, whether they belong to the sympathetic system or parasympathetic system release the same neurotransmitter i.e., Acetylcholine.
- The receptor for this Ach is also the same i.e., N_N receptor, present at the post ganglionic fiber.
- The post-ganglionic fiber carries the information to the organ.
- This fiber releases a neurotransmitter which acts on the receptors present in the organ
- The neurotransmitter is different for different fibres
  - **i. Parasympathetic system:** Ach
    - ○ Since both pre-ganglionic and post-ganglionic fibers of the parasympathetic system release Ach, it is also called the Cholinergic system
  - **ii. Sympathetic system**: Nor-adrenaline
    - ○ The sympathetic system is also called the Adrenergic system
    - ○ **Exceptions**
      - a. Post ganglionic sympathetic fibres in sweat glands release Acetylcholine
      - b. At renal blood vessels, the neurotransmitter secreted is Dopamine

Actions of Sympathetic & Parasympathetic system 00:12:42

Organ / Sympathetic system	Parasympathetic system
i. **Heart:** +++ (+ve chronotropic, +ve dromotropic, +ve ionotropic)	-- (-ve chronotropic, -ve dromotropic)
• Apart from heart, at all other places the effect is opposite. Sympathetic will inhibit and Parasympathetic will stimulate	
ii. **Bronchus**: Broncho-dilation	Broncho-constriction
iii. **GIT**: Constipation	Diarrhoea
iv. **Bladder**: ↓ Urine outflow	↑ Urine outflow
v. **Glands**: ↓ Secretions (but sweat ↑)	↑ Secretions

vi.	**Eye**: Mydriasis (Dilation of the pupil)	Miosis (Contraction of the pupil)
vii.	**Sex**: Ejaculation	Erection

- In the case of the sexual system, both sympathetic and parasympathetic systems complement each other

Previous Year's Questions

Q. Which of the the following action is expected on stimulation of muscarinic receptors?
(AIIMS Jun 2020)

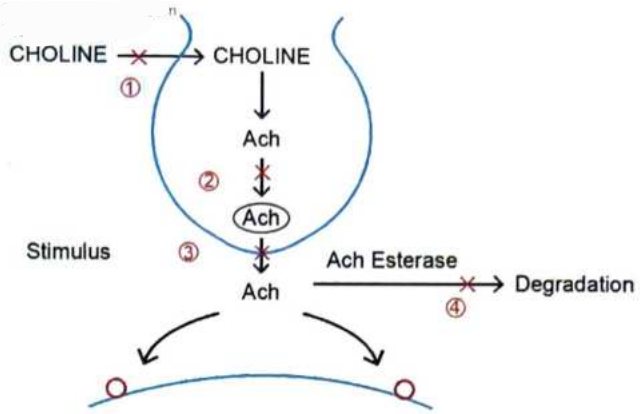
A. Erection
B. Ejaculation
C. Increased contraction of cardiac muscles
D. Bronchodilation

Understand with an example

- Point and Shoot: 'Point' means erection and 'P' for parasympathetic
- 'Shoot' means ejaculation and 'S' for sympathetic

Parasympathetic System 00:22:14

- It originates from cranio-sacral nerves
- **Cranial Nerves**
  - III, VII, IX, X are parasympathetic
  - Rest all are autonomic nerves
  - No cranial nerve is sympathetic
- **Sacral Nerves**: 2,3,4 are parasympathetic
- Also called a cholinergic system because both the pre-ganglionic and post-ganglionic fibres secrete Ach.
- **Acetylcholine synthesis**
  - The first step is the uptake of choline from outside the neuron
  - This choline forms Acetylcholine inside the neuron. This Ach is stored inside the vesicle where it remains safe
  - When the impulse arrives, this Ach is released into the synapse and starts stimulating the post-synaptic receptor.
  - To stop the action of Ach after stimulation of receptors is complete, the Ach is broken down by the enzyme Acetyl cholinesterase
  - Rate limiting step: Uptake of choline



- **Regulation of Ach level in the synapse**

i. **Inhibit choline uptake**
  - Hemicholinium: It inhibits the uptake of choline in the neuron so parasympathetic action decreases

ii. **Inhibit uptake of Acetylcholine**
  - Vesamicol: It inhibits the uptake of Acetylcholine in the vesicles

iii. **Inhibit release of Acetylcholine**
  - Botulinum toxin: It inhibits the release of Acetylcholine from the neuron into the synapse

iv. **Inhibit Ach breakdown**
  - Physostigmine: It increases the level of Ach by inhibiting its breakdown via Acetylcholine esterase (AchE)

- The 1st three drugs have actions opposite to the parasympathetic system
- The last drug physostigmine has a similar action as the parasympathetic system

Cholinergic Receptors 00:35:20

- The cholinergic receptor is of two types

Muscarinic (M)	Nicotinic (N)
M_1: Stomach -↑HCL secretion	N_N: Present at Ganglia (both SNS and PNS)
M_2: Heart - Bradycardia	N_M: Present at NMJ. It requires optimal stimulation
M_3: Present almost everywhere → Eye, Bronchus, GIT, Bladder, Glands	
M_4	
M_5	
All 5 Muscarinic receptors are present in the brain	

Drugs acting on these receptors 00:42:40

i. Parasympathomimetic drugs

- Their action is similar to the parasympathetic nervous system

ii. Parasympatholytic drugs

- These drugs block the action of parasympathetic system

PARASYMPATHOMIMETIC DRUGS (aka Cholinergic Drugs)

- These drugs mimic the actions of parasympathetic system
- They are also called cholinergic drugs
- These are of two types
  - **Directly acting**: These are the drugs that directly stimulate the Nicotinic and Muscarinic receptors
  - **Indirectly acting (AchE inhibitors)**: These drugs inhibit AchE, so Ach cannot be broken down and its level increases

i. Directly Acting drugs

- Ach
- Carbachol
- Bethanechol
- Methacholine
- Pilocarpine
  - AchE present in synapse: True AchE
  - AchE present in plasma: Pseudo AchE or Butryl ChE
  - If we give Ach clinically, as soon as it reaches the blood, it is broken down by the Pseudo ChE. Thus, Ach is very short-acting and not suitable to be used clinically
  - Bethanechol mainly works on the urinary bladder (M_3). It is used in the treatment of Atonic bladder
  - Methacholine acts on the myocardium (M_2). It is used in Tachyarrhythmia
  - Pilocarpine acts on the pupil (M_3). It is used for the treatment of glaucoma
  - These drugs act on muscarinic receptors. None of these 3 drugs acts on Nicotinic receptors
  - Carbachol is the only drug in the category which acts on both muscarinic as well as Nicotinic receptors
  - Cevimeline is a recent directly acting cholinergic drug, that acts on M_3 receptors. It stimulates the glands and increases secretions, so used in the treatment of Sjogren's syndrome

ii. Indirectly acting Cholinergic drugs (AchE inhibitors)

00:54:20

- These drugs are inhibitors of AchE. They may be of 2 types

Reversible AchE #	Irreversible AchE #
o These are commonly used clinically	o Permanently inhibits AchE, so there is permanent ↑ in Ach o So these drugs are not used clinically

a. Reversible AchE#

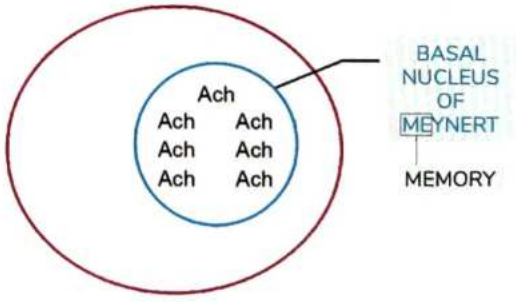
- These are of 2 types
  1) Lipid soluble: Physostigmine
  2) Water-soluble: Neostigmine

1. Lipid soluble drugs

- Lipid soluble drugs will cross the membranes and water-soluble drugs cannot cross the membranes
- So physostigmine can be used in GIT, Eye or CNS conditions and Neostigmine cannot be given as it won't get absorbed
- Physostigmine is lipid-soluble because it is a tertiary amine and tertiary amines are lipid-soluble
- Also, Neostigmine is water soluble because it is a quaternary amine and quaternary amines are water-soluble
- Physostigmine is used for the treatment of glaucoma. It leads to miosis in the eye.
- Physostigmine can cross the blood brain barrier, so can be used for the treatment of Atropine poisoning. Atropine is a muscarinic blocker, so in atropine poisoning muscarinic receptors are not working
- Atropine blocks the receptors both inside the brain and outside the brain because it is lipid soluble. Therefore, Physostigmine is DOC for Atropine poisoning

Basal Nucleus of Meynert 01:01:00

- Basal nucleus of Meynert is the area in the brain that contains plenty of Ach and is a major area of cholinergic supply.
- This area is involved in memory - it is responsible for acquiring and retaining the memory
- So Ach is required for memory



- If there is the death of neurons in the Basal area of Meynert, there is loss of memory, i.e. Dementia. This death of neurons occurs more in old age people, so this is called Senile Dementia or Alzheimer's dementia. It commonly occurs after 60 yrs of age
- If we give Physostigmine for Alzheimer's disease, it affects the muscarinic receptors outside the brain too. So it will improve the memory but also lead to various side effects

- Tacrine is also a lipid-soluble AchE# like Physostigmine. But unlike Physostigmine, Tacrine has >99% entry in the brain, so it will improve memory without causing significant side effects

- But problems with Tacrine are – it is short-acting and hepatotoxic. Also, it needs to be given 4 times a day and Alzheimer's patient cannot remember to take the drug 4 times a day, so Tacrine is not DOC anymore.

- **New drugs for Alzheimer's**
  - Donepezil
  - Rivastigmine
  - Galantamine

  } Lipid soluble AchE# with >99% entry in the brain, similar to Tacrine

- But unlike Tacrine, these drugs are long-acting and do not cause liver damage, so these have become the DOC for Alzheimer's disease

- **Other drugs used for Alzheimer's disease**
  a. **NMDA#**
  - Memantine: Blocks the receptors of Glutamate so it improves memory and can be used for Alzheimer's disease

  b. **Aducanumab**: It is a monoclonal antibody against A2 amyloid, which is causing destruction of neurons. So, it treats the underlying cause of Alzheimer's disease

Water soluble drugs 01:16:37

- Water soluble AchE# drugs are
  - Neostigmine
  - Pyridostigmine
  - Edrophonium

- These are preferred when we want action outside the brain. These are water-soluble so won't cross the blood-brain barrier
- Uses

i. Myasthenia gravis

- There is the formation of antibodies against N_M receptors, so less stimulation of N_M receptors occurs. This leads to muscle weakness
- Most commonly involved muscle is Levator Palpabrae Superioris (LPS), leading to Ptosis
- N_M receptors require optimal stimulation to work normally. If there is over-stimulation of these receptors it leads to a cholinergic crisis
- This is opposite to myasthenia gravis. The treatment is also opposite in both the conditions
- To differentiate between the 2 conditions, we give Edrophonium I.V. It inhibits AchE and leads to ↑ level of Ach. This Ach stimulates the N_M receptors. As a result, if the condition improves, the diagnosis is myasthenia gravis. But if the condition worsens, it is diagnosed as Cholinergic crisis
- Edrophonium is used because it is very short-acting. So if the condition worsens, it will not last beyond 10min. So, it is DOC for diagnosis of Myasthenia gravis. This test is known as the Edrophonium test or Tensilon test

Previous Year's Questions

Q. Agent used for eliciting diagnostic differentiation of myasthenia gravis from the cholinergic crisis is?
(NEET Jan 2019)

A. Echothiophate
B. Edrophonium
C. Neostigmine
D. Ambenonium

- For treatment of Myasthenia gravis, we need long-acting drugs like Neostigmine and Pyridostigmine
- Pyridostigmine is slightly longer acting than Neostigmine
- Apart from inhibiting AchE, these drugs also directly stimulate the N_M receptors.
- Neostigmine is given along with Atropine for the treatment of Myasthenia gravis. Atropine blocks the muscarinic side effect caused by neostigmine

ii. Cobra bite 01:30:50

- Cobra is a neurotoxic snake. Its venom goes to the NMJ and binds to the N_M receptors. This leads to muscle weakness
- The treatment of choice for any snake bite is Anti-Venom. But it is not available in every hospital, so we can treat the patient symptomatically by giving Neostigmine + Atropine

iii. Reversal of muscle relaxants 01:33:24

- Drugs which block the NM receptors like Atracurium, Pancuronium lead to muscle relaxation. These belong to the category of Non-Depolarizing Muscle Relaxants (NDMR)
- These drugs are used for surgery. Their action is long lasting, so we need to give a drug to reverse their action after the surgery is over
- We use Neostigmine + Atropine for reversal of muscle relaxants. Atropine is added to prevent the muscarinic side effects

Previous Year's Questions

Q. A person was given a muscle relaxant that competitively blocks nicotinic receptors. Which of the following drug is used for reversal of muscle relaxation after surgery? (NEET Jan 2020)

A. Neostigmine
B. Carbachol
C. Succinylcholine
D. Physostigmine

iv. Post operative paralytic ileus

- It is a muscarinic use of neostigmine
- After any abdominal surgery, we keep the patient NPO (Nil per oral) because the ileum is not working. We come to know that the ileum is working again, after the passage of the flatus
- In some people, flatus is not passed and the ileum does not start working again. This condition is called Paralytic ileus
- So we need to stimulate the ileus from outside. We give Ach to stimulate the M_3 receptors on the ileum. This is done by giving neostigmine which increases the level of Ach.
- We don't add Atropine with neostigmine in this case because Atropine will block the M_3 receptors
- Bethanechol can also be used

v. Post-op. urinary retention

- This is similar to post-operative paralytic ileus, so we give Neostigmine to stimulate the muscarinic receptors on the bladder
- Atropine is not used here
- Bethanechol can also be used for this condition

Previous Year's Questions

Q. A patient with diabetes developed post-operative urinary retention. Which of the following drugs can be used for short term treatment to relieve the symptoms of this person? (NEET Jan 2020)

A. Bethanechol
B. Methacholine
C. Terazosin
D. Tamsulosin

b. Irreversible AchE# 01:43:20

- Echothiophate is an example
- It can be used as eye drops for miosis
- These drugs can be divided into 2 types

Organophosphates	Carbonates
Malathion	Carbaryl
Parathion	Propoxur
Nerve gases	
→ Tabun	
→ Sarin	
→ DFP	

- Endrin is an organo-chlorine, not an organo-phosphate
- These drugs are not used clinically
- They are used commercially as insecticides, pesticides, etc. by farmers
- So, they can cause poisoning in farmers because they are highly lipid-soluble
- They permanently block the AchE and thus increase Ach. This leads to various muscarinic effects like:
  - M_1: ↑HCl
  - M_2: ↓HR, ↓BP
  - M_3: Pinpoint pupils
    Increased secretions
    Severe diarrhoea
    Urinary incontinence
    Broncho-constriction
- To treat these poisonings, we give Atropine. It is the DOC because it blocks the muscarinic receptors.
- Atropine is given by I.V. route because it is an emergency. The dose is repeated every 5 min because the amount of poison in the body is not known. So we repeat the dose till we see some signs. These signs are called Signs of Atropinization
- Signs of Atropinization are
  i. Mydriasis: When the pupil dilates, and we see reversal of atropinization
  ii. Decrease in secretions
  iii. HR >100: Tachycardia occurs.
  - MC sign is Mydriasis
  - Most reliable/specific sign is Decreased Secretions
- Atropine can reverse all the symptoms of OP poisoning except muscle weakness. In most cases, muscle weakness is seen after other symptoms have subsided.
- Other drugs given for poisoning are AchE Reactivators (aka Oximes)

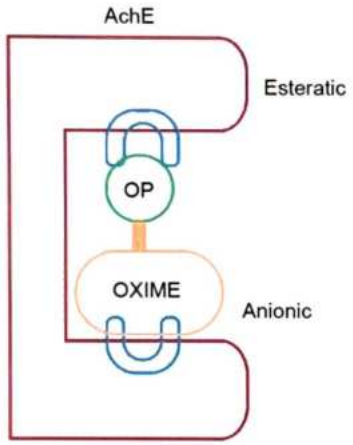
AchE Reactivators (Oximes) 02:05:08

i. Pralidoxime (PAM)
ii. Diacetyl monoxime (DAM)

AchE has 2 sites

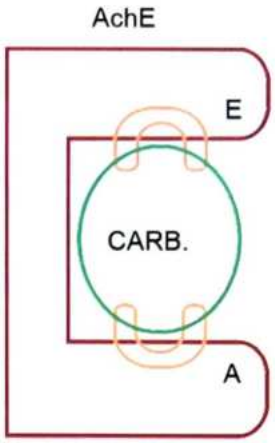
a. Esteratic site
b. Anionic site

- Ach binds to Esteratic site and it is broken down very fast. The breakdown is so fast that this site is considered always free



  - When Organophosphates bind to the esteratic site, they do not break down and do not leave, so when Ach comes it cannot bind and thus not broken down. So, Ach level increases.
  - We need to remove the OP from this site so that AchE is available again
  - We give Oximes which bind to the Anionic site. Then they form a bond with the OP on the esteratic site. This bond is very strong and breaks the bond between the OP and esteratic site. So esteratic site is now free

- In the case of Carbamates



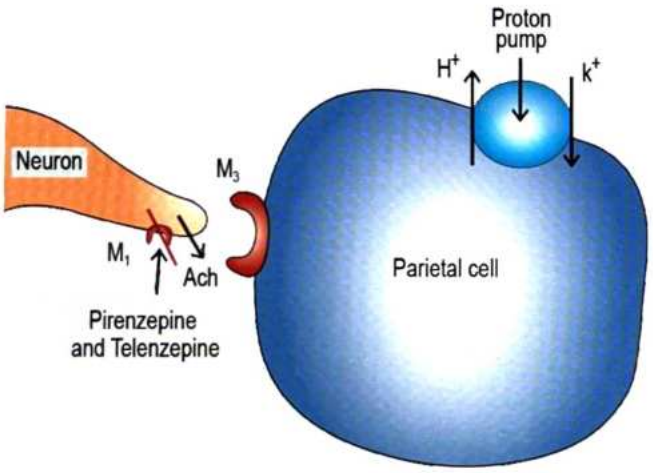
  - Carbamates are big molecules and occupy both esteratic and anionic sites
  - So, oximes cannot bind to the anionic site and thus cannot reverse the poisoning caused by carbamates
  - Oximes are C/I in carbamate poisoning
- Pralidoxime has peripheral action only whereas Diacetyl monoxime has dual action- brain as well as periphery
- If oximes are given early on in the poisoning, they work efficiently. But if we give them very late, they cannot work properly because the bond between OP and esteratic site has become too strong to break. This is called Ageing of Enzyme.

23 ANTI-CHOLINERGIC DRUGS

1. These drugs work on the muscarinic receptors present at various sites in the body.
2. The various anti-cholinergic drugs are

i. M_1 receptor blockers

- Selective M_1 blockers like Pirenzepine and Telenzepine.
- These drugs reduce the acid secretion in the stomach.
- So, they are used for the treatment of Peptic ulcer disease.
- Atropine is not used for Peptic ulcer disease because it also blocks the M_2 and M_3 receptors along with M_1 receptors. This leads to side effects.
- So, Atropine is contraindicated in Peptic ulcer disease.



ii. M_2 receptor blockers

- These drugs have the following effects
  a) Increased Rate → so used for Bradycardia
  b) Increased Conduction → so used for AV block
- Both these effects are caused by Atropine
- So Atropine is the DOC for Bradycardia and AV block.
- Pre-synaptic muscarinic receptors are more sensitive than post-synaptic muscarinic receptors.
- Pre – synaptic receptors act as a brake on the release of Ach into the synapse.
- Atropine blocks this pre-synaptic receptor, so the failure of break occurs. Thus, Ach level increases.
- This increased Ach stimulates more M_2 receptors and thus heart rate decreases. There is Transient bradycardia.
- But within a few seconds, the post-synaptic receptors are also blocked. This leads to Tachycardia.
- The final result is Tachycardia.

iii. M_3 receptor blockers.

a. Bronchus

- M_3 # cause Bronchodilation. So, they are used for Asthma and COPD.
- Drugs are Ipratropium and Tiotropium.
- They are given by inhalational route.
- Atropine is not used because it inhibits mucociliary clearance.
- Ipratropium inhalation causes Transient Bronchoconstriction initially (paradoxical) because of pre-synaptic receptors.
- This Transient Bronchoconstriction can also be caused by impurities in the nebulizer like Benzalkonium and EDTA. It can also be caused if the nebulizer solution is made in Hypertonic saline.

b. Urinary Bladder

- M_3 receptor blocker will inhibit the contraction of the urinary bladder and the person won't be able to urinate.
- This leads to urinary retention.
- So, Atropine like drugs should be avoided in patients with BHP.
- These are used for the treatment of Overactive Bladder or Urinary incontinence or Detrusor instability.
- These drugs include:
  - **S** - **S**olifenacin
  - **O** - **O**xybutynin
  - **F** - **F**lavoxate, Fesoterodine
  - **T** - **T**olterodine, Trospium
  - bla**D**der - **D**arifenacin

How to remember

- SOFT blaDder

- These drugs can cause side effects like Dry mouth and CNS side effects.
- Trospium does not cause CNS side effects and it is excreted by kidney instead of liver. So, it is avoided in renal failure.
- Fesoterodine is a prodrug.
- Solefenacin and Darifenacin are the most vesico-selective drugs.
- Oxybutynin and Flavoxate relax the urinary bladder directly also, apart from their anti-cholinergic action.

c. Glands

- M_3 # will decrease secretions from glands.
- This will lead to side effects like:
  - Dry skin
  - Dry mouth
  - Dry eyes
  - ↓ Sweating
- Giving these drugs in children will lead to fever because the child cannot regulate his body temp due to lack of sweating. This is called Atropine fever.
- If the drug is still not stopped, the temp will keep on increasing. This leads to Hyperthermia. This can be fatal to the child.
- So, Atropine is contra-indicated in children.

PRE-ANAESTHETIC MEDICATION ⏱ 00:24:02

- Atropine like drugs are also used for Pre-anaesthetic medication.
- When any inhalational anaesthic agent is given, it causes ciliary inhibition. So, the secretions keep accumulating in the respiratory pathway. As a result, air cannot pass to the alveoli. This leads to Atelectasis.
- To resolve this, we give anti-cholinergic medication. It will stop secretions. So, there is no buildup of secretions in the respiratory pathway.
- The drugs used are – Glycopyrrolate.
- Glycopyrrolate does not cross the Blood Brain Barrier

d. Smooth Muscles

- When a smooth muscle is irritated anywhere, it contracts. When there is an infection, the muscle contracts severely, so there is pain. After some time, the muscle relaxes, and the pain stops.
- But after some time, the muscle contracts again. So, the pain returns. This is again followed by relaxation. This leads to intermittent pain called Colic pain.
- Depending on the region, it is named accordingly. Like Biliary colic, ureteric colic, intestinal colic, etc.
- Renal colic is a misnomer. Stone in the kidney does not cause pain, when the stone comes to the ureter, it causes pain. So, it is actually ureteric colic.
- Anti-cholinergic drugs are used for the treatment of colic pain.

- These drugs include
  - Dicyclomine
  - Oxybutynin
  - Hyoscine
  - Propantheline

e. Eye

- M_3 # block the contraction of pupil. This leads to Mydriasis.
- Mydriasis is done when we need to examine the retina via Fundosocpy.
- Mydriasis cannot be done in patients with Angle Closure Glaucoma.
- M_3 # also lead to loss of accor[illegible]n. This occurs because M_3 # lead to paralysis of the ciliary muscle i.e. Cycloplegia occurs. This loss of accommodation leads to blurring of vision.
- Cycloplegia is required for refraction testing.
- The drugs used in the eye are:
  - Atropine
  - Homatropine
  - Cyclopentolate
  - Tropicamide
- Atropine is very long-acting (>7days). It is also a very strong cycloplegic.
- Atropine is the DOC for cycloplegia in children. But it is used as an ointment, not as eye drops.
- Tropicamide is the shortest acting mydriatic drug.

f. CNS

- Drugs used:
  - Hyoscine
  - Scopolamine
- These are CNS depressants.
- Hyoscine was used as a Truth serum earlier. Also known as Lie detector test or Narco-analysis.
- But during Narco-analysis, the dose of the drug required is very high. So, there is a risk of death also.
- So now-a-days instead of Narco-analysis, we use a test called Polygraph test.
- Hyoscine is also used for motion sickness. Motion sickness occurs when the CTZ is stimulated by too much motion at high altitude which leads to vomiting.
- Hyoscine is useful only to prevent the motion sickness. It is not useful for treatment once the motion sickness starts.
- Hyoscine can be given in 2 forms – Transdermal patch and Tablets.
- Patch takes 12-24 hrs to work whereas tablets produce action within 30 min only.

g. Basal Ganglia

- In basal ganglia, there are 2 types of neurons - Cholinergic neurons and Dopaminergic neurons.
- These neurons have opposite functions. So, their level must be maintained for the proper functioning of the basal ganglia.
- In Parkinsonism, there is an imbalance b/w the cholinergic and dopaminergic neurons in the basal ganglia. So, dopamine level decreases which lead to symptoms of Parkinsonism.

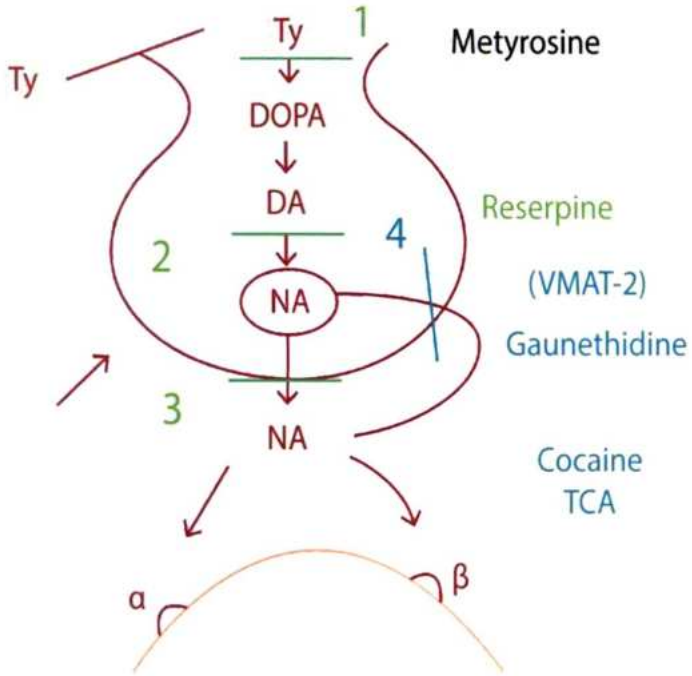
- Anti-cholinergic drugs are DOC for Drug Induced Parkinsonism. These include drugs like
  - Benzhexol (Trihexyphenidyl)
  - Benztropine
  - Procyclidine

h. Poisoning

- Atropine is DOC for
  - OP poisoning
  - Carbamate poisoning
  - Early Mushroom poisoning
- Early mushroom poisoning is caused by Inocybe.
- Late mushroom poisoning is caused by Amanita species. The symptoms are similar to Atropine poisoning. So, atropine is contraindicated in late mushroom poisoning.
- Belladonna is a plant from which we can get atropine. So, Belladonna poisoning means Atropine poisoning.
- Datura (Jameson weed) is also a source of Atropine
- So, DOC for Belladonna and Datura poisoning is Physostigmine.

24 ADRENERGIC DRUGS

- It is also known as the sympathetic system.
- It originates from the thoraco-lumbar outflow.
- Pre-ganglionic fibre is small and post-ganglionic fibre is long
- Sympathetic system will stimulate the heart and inhibit everything else.
- The major neurotransmitter is Nor-adrenaline (NA).
- The level of NA in the synapse can be manipulated and thus we can change the sympathetic activity.



- These drugs are
  1. Metyrosine: Inhibit Tyrosine hydroxylase enzyme
  2. Reserpine: Inhibit entry of Dopamine into the vesicle. This is done by inhibiting VMAT-2 transporter.
  3. Guanethidine: Inhibits the exocytosis of adrenaline into the synapse
  4. Cocaine, TCA: Inhibit reuptake of Nor-adrenaline
- The first 3 drugs lead to ↓ sympathetic action
- The fourth drug leads to ↑ sympathetic action.

Receptors of NA

- The adrenergic receptors are divided into and receptors.

- αReceptors are
  - α_1
  1. **Blood vessels**: Vasoconstriction
  2. **Eye:** Mydriasis
  3. **Prostatic urethra**: ↓ Urine outflow. α_1# can be used in patients with BPH.

  - α_2
  1. α_2 receptor is present on pre-synaptic membrane. When α_2 receptors are stimulated, they inhibit the release of NA into the synapse.
     → So $_2$ receptors act as a break
  2. Some α_2 receptors are present on post-synaptic membrane also. This post-synaptic α_2 behaves exactly like α_1.

- β receptors are
  - $\alpha_1\beta_1$
  1. **Heart** – Stimulates the heart
     It will increase the
     → Heart rate
     → Conduction
     → Contractility
  2. **JG cells of Kidney**: Renin secretion which activates the RAAS system.

  - β_2
  1. **Lungs**: Causes Bronchodilation. So α_2-agonists are used in the treatment of Bronchial Asthma
  2. **GIT**: Causes Constipation
  3. **Bladder**: Relaxes
  4. **Uterus**: Relaxes (Tocolytic effect). So used in the treatment of Pre-term Labour
  5. **Blood vessels**: Vasodilation
  6. **Skeletal muscles**: Tremors
  7. **Liver**

  - β_3
  1. Present on Adipose tissue
     → It causes Lipolysis
  2. β_3 is also present on the Urinary bladder. It causes relaxation of the bladder. So, it is used for the treatment of overactive bladder.
     Drugs include Mirabegron, Vibegron

Effects on Blood vessels

- α_1: Vasoconstriction
- β_2: Vasodilation
- The effect depends on the predominance of the type of receptors.
  - Heart & Muscles: $\beta_2 > \alpha_1$ = Vasodilation
  - Skin & Internal organs: $\alpha_1 > \beta_2$ = Vasoconstriction

Hypoglycemia

- There is sympathetic system activation in Hypoglycemia.
- There is stimulation of
  - β_1 - ↑HR, Palpitations
  - β_2 - Tremors
  - M - Sweating
- These are called Warning symptoms of hypoglycemia.
- Whenever these warning symptoms appear, the person should take some ready-made source of glucose like sugar.
- If the person does not take sugar, he won't go into a coma because the β_2 receptors in the liver will be stimulated. They try to increase blood glucose.
- β_2 will increase the blood glucose by
  I. (+) Glycogenolysis
  ii. (+) Gluconeogenesis
  iii. (-) Glycogenesis
- When we give -blockers, they block the receptors and the warning symptoms are not produced. So β-blockers mask the warning symptoms. This is also known as Hypoglycemia unawareness.
- So, there is a high risk as the person can go into coma. Even reversal of hypoglycemia is blocked because the β_2 receptors in the liver are blocked.
- So -blockers are contra-indicated in diabetic patients.
- The only reliable symptom of hypoglycemia in a person taking β-blockers is Sweating. This is because it occurs via Muscarinic receptors which are not blocked.

Drugs acting on Sympathetic system ⏱ 00:46:20

- The drugs acting on the sympathetic system can be of 2 types
  - Sympathomimetic drugs: Stimulate
  - Sympatholytic drugs: Inhibit

SYMPATHOMIMETIC DRUGS

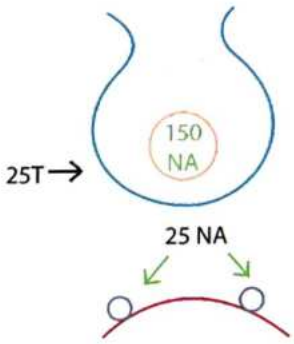
- These are also known as Adrenergic drugs
- These can be divided into
  I. Indirectly acting drugs
  II. Directly acting drugs

I. Indirectly acting sympathomimetic drugs

a. Reuptake inhibitors

- Cocaine
  - It is a local anaesthetic
  - All drugs ending with '- caine' result in vasodilation. This can lead to hypotension, except for cocaine.
  - Cocaine is the only local anaesthetic that causes Vasoconstriction. So, it results in Hypertension. This is because Cocaine is a sympathetic drug. It inhibits the reuptake of NA
  - Cocaine is an addictive drug. It can cause hallucinations. The person feels like insects crawling on the skin. This is called cocaine bugs
  - When cocaine is taken in large quantities repeatedly, it can lead to Palatine perforations. This occurs because cocaine is snorted through the nose and it causes cutaneous vasoconstriction with each use.

b. Drugs acting by Displacement ⏱ 00:52:02



- Tyramine: It acts by displacement of NA, indirectly only. Major source of Tyramine is cheese.
- Ephedrine, Pseudo ephedrine, Amphetamines } These drugs are Mixed acting sympathomimetics. They can act directly or indirectly
- All these drugs show Tachyphylaxis i.e. Rapid development of tolerance
- Ephedrine and pseudoephedrine are Nasal decongestants. These are given orally with cough syrups.
- Amphetamines can cross the blood-brain barrier.
- They have 2 effects
  - ↓Sleep
  - ↑Attention span
    → So, seem ideal for students. But the after effect is bad. The person becomes sleepy and over-confident the next day. These drugs are also addictive in nature.
    → MDMA – Methylene dioxy methamphetamine. It is used in rave parties.
    → Amphetamines are used in the treatment of Narcolepsy to reduce sleep attacks. The DOC for Narcolepsy is Modafinil.
- Narcolepsy: It includes the following:
  i. Excessive Daytime Sleepiness
    - Treatment includes

→ Modafinil
→ Armodafinil
→ Solriamfetol (new)

ii. Cataplexy
- Sudden muscle weakness
- Treatment includes Sodium oxybate or Na gamma-hydroxybutyrate (GHB)
- Pitolisant can also be given

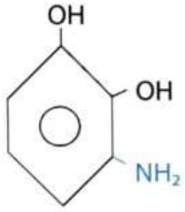
- Another use of drugs for Narcolepsy is ADHD.
- Attention Deficit Hyperactivity disorder (ADHD)
  - Amphetamines are given to increase the attention span of the child.
  - DOC for ADHD is Modafinil
  - Drugs used for ADHD can be

i. Stimulant drugs
→ Methylphenidate
→ Dex-methylphenidate
→ Serdex-methylphenidate

ii. Non-stimulant drugs
→ Atomoxetine
→ Guanfacine
→ Clonidine

II. Directly acting sympathomimetic drugs 01:11:01

A. Catecholamines



- Catecholamines are recognized by COMT enzyme in the GIT (Catechol Ortho Methyl Transferase)
- This enzyme binds to the catecholamines and makes them ineffective
- So catecholamines cannot be given orally.
- Catecholamines can be either Endogenous or Exogenous.

i. Endogenous Catecholamines
- Dopamine
- Noradrenaline
- Adrenaline

ii. Exogenous Catecholamines
- Dobutamine
- Fenoldopam
- Isoprenaline

Dopamine 01:14:38

- Dopamine affects three receptors depending upon the dose
  - D_1 - < 2 mg/kg/min
  - β_1 - 2 - 10 mg/kg/min
  - α_1 - > 10 mg/kg/min
- β_1 receptors are present on Heart
- α_1 receptors are present on Blood vessels.
- D_1 receptors are present on Blood vessels. The highest concentration is present in blood vessels of the Kidney.
- D_1 causes renal vasodilation.
- Dopamine is used in the treatment of Acute CHF via $_1$ receptor in the heart. The dose is 2-10 mg/kg/min.
- Dopamine is also used for the treatment of Shock via $_1$ receptor. The dose is > 10 mg/kg/min.
- So, for Shock with Oliguria, the DOC is Dopamine.

Dobutamine
- It does not work on D_1 receptors
- It is used in Acute CHF.

Fenoldopam
- It works only on D_1 receptors
- It causes vasodilation of blood vessels especially in the kidney
- It is used for the treatment of Hypertensive Emergencies. Not used for Routine HTN because it needs to be given I.V.

Adrenaline (Epinephrine) 01:24:15
- It stimulates all the sympathetic receptors - α_1; α_2; β_1; β_2

Isoprenaline (Isoproterenol)
- It stimulates only receptors i.e. $_1$ and $_2$. Does not stimulate receptors ($_1$ and $_2$).

Effect on Blood pressure and Heart rate

Refer Table 24.1

- Adrenaline increases the pulse pressure.
- NA decreases the pulse pressure
- Isoprenaline causes max. increase in pulse pressure
- Exogenous administration of NA decreases the HR.
- In a transplanted heart, the finer nerve supply is not developed. So, there is no indirect effect on HR. Only direct effect is seen.
- So, all the three drugs- Adrenaline, NA & Isoprenaline – produce the same effect on the heart, i.e., Tachycardia.
- Effect of NA on Atropinized Heart: it causes Tachycardia

Uses of these drugs 04:45:00

Refer Table 24.2

1. **DOC for Anaphylactic shock**
- Route preferred → I.M > S.C
- Concentration preferred → 1:1000 which means 1g Adrenaline in 1000 ml of solution, which means 1 mg/ml solution
- So, the dose is 0.5 ml
- If there is no response after 1st dose, we repeat within 10 min. with the same dose, same concentration, and same route.
- If the 2nd dose does not work, we do not repeat it again. We give I.V. adrenaline now. The concentration given is 1:10000

2. **Cardiac Arrest**
- We start the BLS protocol. It includes CAB → Compressions, Airway, Breathing.
- When the person is not responding after several minutes of CPR, we start giving drugs.
- DOC for cardiac arrest is Adrenaline
- It is given by I.V. route in a concentration of 1: 10000
- If I.V. access cannot be established, we prefer I.V. > Intra-osseous (Tibia) > E.T.
- Resume CPR immediately after giving Adrenaline.

3. **With Local Anesthetics**
- Adrenaline is added to make the local anaesthetic long-acting, due to vasoconstriction.

Previous Year's Questions

Q. Match the dilutions of adrenaline with its use?
(INI CET Nov 2020)

Dilution of adrenaline	Clinical use
A. 1: 1000	1. I.V. in cardiac arrest
B. 1: 10000	2. I.M. in anaphylaxis
C. 1: 100000	3. With lignocaine

Ans.
A → 2
B → 1
C → 3

VASOMOTOR REVERSAL OF DALE 01:57:09

- Adrenaline affects all 4 receptors - α_1 α_2 β_1 β_2
- α_1 leads to Vasoconstriction. It is a strong receptor
- β_2 leads to Vasodilation. It is a sensitive receptor.

i. When we give high dose I.V. Adrenaline
When Adrenaline is given I.V. at high doses,
- At first BP increases due to $\alpha_1 > \beta_2$ stimulation
- Then BP will decrease due to β_2 stimulation

ii. When Adrenaline is given I.V. at a high dose with α_1 blocker
- There is an exaggerated fall of BP because there is no α_1 stimulation.
- This is called Vasomotor reversal of Dale

iii. Now if we give β blocker, this is reversed. It is called Re-reversal.

- Clinical importance of Vasomotor reversal of Dale is seen in Pheochromocytoma
  - Pheochromocytoma is tumor of the Adrenal medulla. There can be 2 types of tumors Adrenaline producing & Non-adrenaline producing.
  - In both these Types, the BP will be high because of α_1 stimulation.
  - So, we need to block α_1. But in Adrenaline producing tumor if α_1 blocker is given alone, it will trigger a vasomotor reversal of Dale.
  - So α_1 blocker alone is contraindicated.
  - We cannot give -blocker alone also, it will cause re-reversal.
  - But α_1 blocker alone can be safely used in Non-adrenaline producing tumor.

B. Non – Catecholamine Drugs 02:09:00
- Their chemical structure does not contain the catechol nuclei, so they may be given orally.
- These drugs are divided according to the receptors on which they act

I. **α_1 receptors**
- Phenylephrine eye drops
  → It produces Mydriasis, but does not produce any cycloplegia along with it
  → It is given I.V.
  → Can be used for shock or hypotension

ii. **α_1 receptors in blood vessels**
- Methoxamine
- Mephentermine
- Midodrine
  → These drugs are used for shock without oliguria

iii. **α_1 receptors in nasal blood vessels**
- Xylometazoline
- Oxymetazoline
- Naphazoline
  → These are used as nasal decongestants in the form of nasal drops.
  → On prolonged usage, these drugs can lead to Rebound Congestion.
  → But on repeated usage, there is development of Atrophic rhinitis or Rhinitis medicamentosa.

iv. α_2 receptors

- Clonidine
- Methyldopa
  → These are used in treatment of HTN.

v. β_2 receptors

- Salbutamol, Terbutaline — Short acting
- Salmeterol, Formoterol — Long acting
  → These drugs stimulate the β_2 receptors.
  → Given by inhalational route.
  → These are used for Bronchial asthma.

vi. β_1 receptors

- There are no drugs in non-catecholamine category that stimulate β_2 receptors.

vii. Ritodrine
Isoxsuprine

- These drugs stimulate $_2$ receptors.
- These are used mainly for uterine relaxation (Tocolytic effect)
- So used in Pre-term labor

viii. β_3 receptors

- Mirabegron
- Vibegron
  → These are used for overactive bladder.

Table 24.1

	BP		HR		
	Systolic (β_1)	Diastolic (β_2)	Direct effect (β_1)	Indirect effect (opposite to Diastolic BP)	Net HR
Adrenaline (α_1 α_2 [illegible])	↑ (VC)	α_1 = VC β_2 = VD	↑	No effect	↑
NA (α_1 α_2 β_1)	↑(VC)	↑↑ (VC)	↑	↓↓	↓↓
Isoprenaline (β_1 β_2)	↑ (VC)	↓↓ (VD)	↑	↑↑	↑↑↑

Table 24.2

• NA (α_1 α_2 β_1)	Shock CHF
• Isoprenaline (β_1 β_2)	CHD Bronchial Asthma
• Adrenaline (α_1 α_2 β_1 β_2)	It is a highly arrhythmogenic drug. So, it has some specific indications only

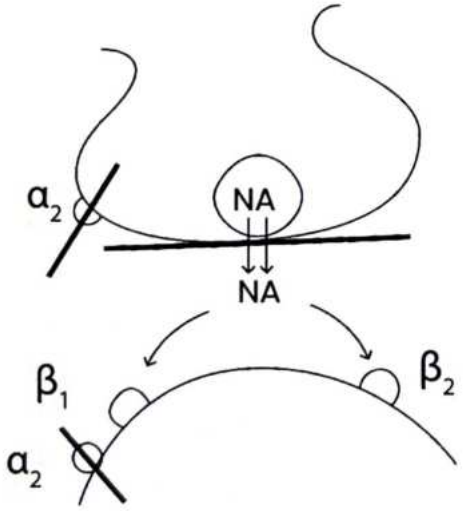
25 ANTI-ADRENERGIC DRUGS

- Anti-adrenergic drugs are a class of drugs that inhibit the sympathetic system.
- They are also called Sympatholytic drugs.
- They are of two types
  - α-Blockers
  - β-Blockers

α-BLOCKERS

00:01:05

- blockers are divided into three main categories depending on the receptors :
  i. ($\alpha_1 + \alpha_2$) # → Non-selective α blockers
  ii. α_1 # → Selective α_1 blocker
  iii. α2 # - Selective α_2 blocker
- Selective α_2 blockers are Yohimbine and Idazoxane. These are not approved for clinical use.
- So there are mainly two types of blockers that are used clinically i.e.
  - Non-selective α blockers
  - Selective α_1 blockers
- Both these types of drugs cause Vasodilation. So they can be used for the treatment of Hypertension
- Selective α_2 blocker acts like a break and blocks the α2



- If the post synaptic membrane has α_2 receptors, they will be blocked by the non-selective drug along with the $_1$ receptor. So the non-selective drugs cause severe vasodilation. As a result, the non-selective drugs are used for severe HTN
- But an adverse effect of non – selective blockers is that it can cause severe tachycardia
- Selective α_1 blockers are used for Mild to Moderate HTN. They don't cause any tachycardia.

i. Non – Selective (α_1+α_2) blockers:

00:06:14

- These can be of two types

Reversible	Irreversible

• Phentolamine
• Tolazoline
  ○ They are DOC for Cheese reaction and Clonidine withdrawal
	• Phenoxybenzamine
	  ○ It is used for Pheochromocytoma

Cheese reaction

- Tyramine is normally present in cheese. When we take cheese, Tyramine will displace Nor-adrenaline and result in sympathetic activity
- But this Tyramine is broken down by MAO in the blood and thus we can take cheese safely
- When a person is on MAO inhibitor therapy like Phenelzine and Isocarboxazide for the treatment of depression, these drugs block the MAO enzyme
- Now when this person will eat cheese, the Tyramine is not broken down and thus there is increase in blood pressure. This is called cheese reaction
- So we need strong and short acting drugs for cheese reaction i.e. Phentolamine and Tolazoline

Clonidine Withdrawal

- Clonidine is an α_2 agonist. It acts like a break and prevents NA release from the synapse. So BP is not increased
- As a result, there is increase in number of α and β receptors on the post-synaptic membrane as they are not being used.
- Now when this person stops taking clonidine suddenly,

there is release of NA and the post synaptic receptors are stimulated in large numbers. So there is sudden increase in BP.

- This results in Rebound HTN or Clonidine withdrawal
- So we give a strong drug which is reversible→ Phentolamine

ii. Selective α_1 blockers 00:14:42

- Prazosin
- Doxazosin
- Alfuzosin
- Terazosin
- These drugs are used for Mild to Moderate HTN
- They do not cause severe tachycardia
- We use α_1 blockers also for BPH
- So Prazosin like drugs are DOC for HTN with BPH
- Main side effect of these drugs in Postural HTN aka First Dose HTN or Orthostatic HTN
  - α_1 receptors are present in Blood vessels and Prostate also
  - By blocking in blood vessels, Vasodilation occurs and by blocking in prostate, there is increase in urine outflow
  - This vasodilation can result in Hypotension but this hypotension is mainly present at start of therapy
  - When the person stands up after sometime, the BP suddenly falls. So this person can fall and there can be fractures. This is a problem in elderly as fracture healing can be delayed in them.
  - So these drugs are always started at bed time, due to which the person doesn't have to stand up after taking the drug
- α_1 blockers can be of two types
  - α_{1A} blocker → Tamsulosin, Silodosin
  - $\alpha_{1B/1D}$ blocker
- α_{1A} is present on Prostate and $\alpha_{1B/1D}$ is present on blood vessels
- So for a patient with BPH without HTN, we need to give α_{1A} drugs, so that there is no postural HTN.

Important Information

- **DOC for BPH with HTN → Prazosin**
- **DOC for BPH without HTN → Tamsulosin, Silodosin**

- Other uses of Prazosin
  - Scorpion sting –DOC
  - HTN
  - BPH with HTN
  - Peripheral vascular disease like Raynaud's disease

Previous Year's Questions

Q. Hypertension and pulmonary edema associated with scorpion sting is managed by: (NEET Jan 2019)

A. Carvedilol
B. Prazosin
C. Spironolactone
D. Phentolamine

- Effect of α_1# on Eye
  - α_1 receptor causes Mydriasis in eye. So when we give α_1 blocker, it will result in Miosis
  - In patient of cataract, we remove the lens and for that we need to cause Mydriasis
  - But if the person is already on α_1 blocker, there is miosis
  - So the iris gets two different sets of instructions and tends to get confused
  - This is called Floppy Iris syndrome

β-BLOCKERS

- β-blockers are mainly of three types
  - Non –selective ($\beta_1 + \beta_2$) blocker
  - Selective β_1 blocker
  - Selective β_2 blocker
- Selective β_2 blocker : Butoxamine is not used clinically
- So effectively we have only two main types of β -blockers
  - Non-selective β blockers
  - Selective β_1 blockers
- Both these types of drugs block β_1 receptors present in heart. So both can be used for cardiac indications
- The main difference between these two drugs is that selective β_1 blocker does not block β_2 but non-selective -blocker blocks the β_2 receptors
- So selective β_1 blocker can be used for non-cardiac indications also.
- Non – selective β-blocker is avoided in three conditions
  - Peripheral vascular disease
  - Bronchial asthma
  - DM

Non selective β-blockers	Selective β_1 blockers (cardio selective)
• Cardiac + Extra cardiac uses • Contra indications are ○ Asthma ○ DM ○ PVD	• Cardiac uses only • Contra indications are less. So this drug is relatively safe

Previous Year's Questions

Q. Which of the following is a contraindication to the use of Beta Blockers. (NEET Jan 2019)

A. Glaucoma
B. Tachycardia
C. Bronchial asthma
D. Hypertension

Various properties of β-blockers are :

1. Cardio-selective β_1 blockers

- These drugs are 2nd generation β blockers
  - New - Nebivolol
  - Beta - Betaxolol
  - Blockers - Bisoprolol
  - Act - Acebutolol
  - Exclusively - Esmolol
  - At - Atenolol
  - Myo - Metoprolol
  - Cardium - Celiprolol

How to remember

- New Beta Blockers Act Exclusively At Myo Cardium

- These drugs are safe in Asthma, DM and PVD
- But they have only cardia uses. They cannot be used for non – cardiac indications

2. Intrinsic Sympathomimetic Activity (ISA):

- These drugs are partial agonist at $\beta_1$receptors. They neither completely block nor completely stimulate.

a. Normal phenomenon
   - 1 receptor stimulation leads to = 10 HR
   - 10 receptor stimulation leads to = 10x10 HR

b. In a normal person using β-blockers
   - β-Blocker blocks 20% of receptor, so HR=10x8

c. In a - blocker sensitive person
   - β-blocker blocks 80% of receptors, so HR =10x2
   - So there is severe bradycardia. Therefore, before giving β- blockers, sensitivity testing should be done via HR monitoring
   - Partial agonists are useful for these patients as they are safer but disadvantage is that they are also less efficacious

- The drugs included are
  - Contain - Celiprolol
  - Partial - Pindolol
  - Agonist - Alprenolol
  - Activity - Acebutolol

How to remember

- Contain Partial Agonistic Activity

3. Membrane Stabilizing Property (aka Na+ Channel Blocking Property or Local Anaesthetic Property)

- They are used to treat arrhythmias
- But local anaesthetic property is very harmful to the eyes
  - Cornea is supplied by large number of sensory fibres from the Trigeminal nerve. This sensitivity results in the protective mechanism of the eye called Corneal reflex
  - This corneal reflex is inhibited when we give β-blockers with membrane stabilizing property. So the cornea gets damaged as the eye is not able to close
  - As a result, these drugs are C/I in glaucoma
- The drugs included are :
  - Posses - Propranolol (max)
  - Membrane stabilizing - Metoprolol
  - or
  - Local - Labetalol
  - Anaesthetic - Acebutolol
  - Property - Pindolol

How to remember

- Possess Membrane stabilizing or Local Anaesthetic Property

- A β-blocker which possesses all the three properties i.e. cardioselective, intrinsic sympathomimetic activity and membrane stabilizing activity is Acebutolol.

4. Water solubility

- The β-blockers which are water soluble cannot cross membranes. So they cannot enter the brain. As a result, they cannot produce CNS adverse effects
- Water soluble β-blockers are excreted by kidney. So they cannot be excreted in the case of renal disease
- So they are C/I in renal failure
- The drugs included are :
  - A - Atenolol
  - N - Nadolol
  - S - Sotalol

How to remember

- ANS is water soluble

- Water soluble β–blockers are usually long–acting, whereas lipid soluble β-blockers are broken by the liver very quickly, so they are short acting

Important Information

- Longest acting β-blocker is Nadolol
- Shortest acting β-blocker is Esmolol (<5min)

5. Third Generation β-blockers :

- Any β-blocker which produces an additional property of Vasodilation is included in 3rd generation β-blockers
- (α+β) blocker is included in 3rd generation
- Various types are :

I. (α+β) blocker

- Labetalol
- Carvedilol

ii. Calcium channel blocker

- Carvedilol: Carvedilol also possesses Anti-Oxidant Property

iii. Potassium channel opener

- Tilisolol

iv. β_2 agonist

- Celiprolol
  - → It is a β_1 blocker but β_2 agonist
  - → It is relatively safe in Asthma, as compared to other β blocker
  - → It is the only β-blocker which causes increase in HDL

Indications of blockers 00:59:39

β_1# (Cardiac indications)	β_2# (Extra –cardiac indications)
• HTN • Angina → Classical • MI • CHF→ Chronic • Arrhythmia • HOCM → β- blockers are C/I in Variant angina and Acute CHF	• **Play**- Performance anxiety • **The**-Thyrotoxicosis • **G** - Glaucoma→Timolol • **A** - Akathisia (DOC) • **M**-Migraine→Propranolol • **E**- Essential Tremors → Propranolol

How to remember

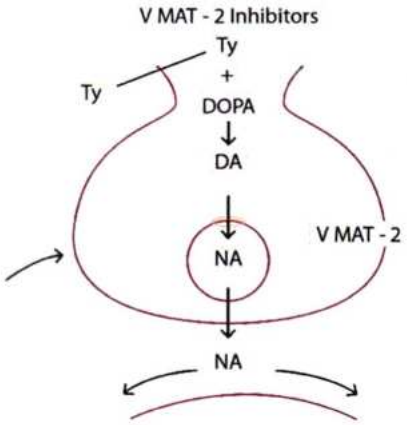
- Play the GAME

26 TERTIARY AND QUATERNARY AMINES

- NH3 is called Ammonia and NH4 is Ammonium ion
- So, if 3 groups are attached to Nitrogen, it is called Tertiary Amine
- Similarly, if 4 groups are attached to Nitrogen, it is called Quaternary Amine
- **Tertiary Amines** are non-polar or non-ionized like ammonia
- **Quaternary Amines** are ionized like ammonium ions
- So, Quaternary amines cannot cross the membranes and thus cannot cross the BBB. For example, Neostigmine.
- Tertiary amines can enter the brain. For example, Physostigmine.

27 VMAT 2 INHIBITORS

- VMAT stands for Vesicular Mono Amine Transporter.
- It is a transport protein that transfers Dopamine into the vesicles.



- But it is a monoamine transporter, which means that it is not limited to dopamine only. It also works for serotonin and other monoamines also.
- VMAT 2 inhibitors prevent the entry of dopamine and serotonin into the vesicles. So there is decreased production of adrenaline, noradrenaline, etc.
- The drugs include

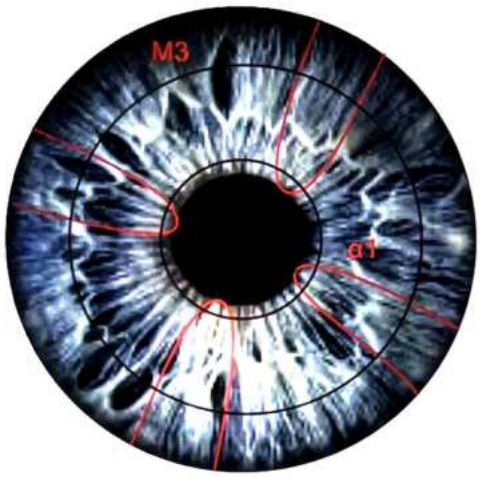
i. Reserpine
   - This drug was the earliest VMAT 2 inhibitor, and it inhibited the entry of dopamine into the vesicle.
   - It can be used for the treatment of psychosis.
   - Excessive decrease in dopamine can lead to symptoms of parkinsonism also.
   - When dopamine is not entering, noradrenaline is not produced. And when noradrenaline is not produced, that can be used to treat hypertension.
   - So primarily this drug was developed for the treatment of hypertension. But later it was found that because this drug is nonspecific, it also leads to a decrease in serotonin levels. This leads to depression and results in many cases of suicide.
   - So, this drug is not used now a days.

     i) Tetra-benazine
     ii) Deutetra-benazine
     iii) Val-benazine
     → These drugs are new VMAT 2 inhibitors.
     → They are called dopamine depletors.
     → Tetrabenazine and Deutetrabenazine are used in conditions with dopamine excess. So, used in the treatment of Huntington's chorea.
     → Valbenazine is used in the treatment of Tardive dyskinesia.
     → Tardive dyskinesia is an adverse effect of anti-psychotic drugs. In this condition, there is supersensitivity of dopaminergic receptors. So, by giving a dopamine depletor, we can manage this side effect.
     → Valbenazine is the only drug approved for Tardive dyskinesia.

28 ACTIVE & PASSIVE MYDRIASIS

- Pupil has 2 types of muscles
  i. Circular muscle (Sphincter pupillae)
  ii. Radial muscles (Dilator pupillae)

PUPIL



ACTIVE

M3↑ - Miosis

α1 + - Mydr.

PASSIVE

M3# - Mydr.

α1 # - Miosis

- On stimulation, circular muscle constricts the pupil and Radial muscle dilates the pupil
- Circular muscle contains M_3 receptors, so it is supplied by the parasympathetic system. Miosis occurs
- Radial muscle contains $_1$ receptor, so it is supplied by the sympathetic system. Mydriasis occurs
- Active miosis is when there is M_3 stimulation, which stimulates sphincter pupillae resulting in miosis
- Drugs causing active miosis
  - Pilocarpine
  - Physostigmine
- Active Mydriasis is when we stimulate $_1$ receptor which results in stimulation of Radial muscles
- Drugs causing active mydriasis → Phenylephrine
- Passive mydriasis means we block the M_3 receptors. So, sphincter pupillae won't work. This leads to Mydriasis
- Drugs causing passive mydriasis → Atropine
- Passive Miosis means we inhibit the action of Dilator pupillae
- It is caused by α_1 blocker

29 RABBIT EXPERIMENTS

- There are 2 rabbit experiments done in pharmacology
  - Eye experiments
  - Ileum experiments
- Scientific name of the rabbit is Oryctolagus cuniculus
- For experiments, the usual weight of rabbit should be 2-2.5kg

1. Rabbit Eye experiment ⏱ 00:01:08

- We put the drug in the eye and check for three parameters
  i. Size of pupil
  ii. Light reflex
  iii. Corneal reflex
  - Size of the pupil is measured by a pupillometer
  - Light reflex is seen by using a torch light. When we point a torch light on the pupil, it contracts. Light reflex is dependent on the intact parasympathetic pathway.
  - Corneal reflex is seen by touching a cotton piece on the cornea, if the rabbit blinks that means corneal reflex is present. Corneal reflex depends on the sensory system.

- **Drugs given**

	Pupil size	Light reflex	Corneal reflex
I. Cholinergic drugs (Pilocarpine)	Miosis (Active)	✓	✓
ii. Sympathetic drugs (Adrenaline)	Mydriasis (Active)	✓	✓
iii. Anti-Cholinergic drugs (Atropine)	Mydriasis (Passive)	Absent	✓
iv. Local anaesthetic (Lignocaine)	-	✓	Absent

- LR → Absent → Atropine
  ↓
  (+)
  ↓
  Corneal reflex → Absent → Lignocaine
  ↓
  (+)
  ↓
  Pupil { Mydriasis → Sympathetic
  Miosis → Parasympathetic

2. Rabbit Ileum experiment ⏱ 00:08:15

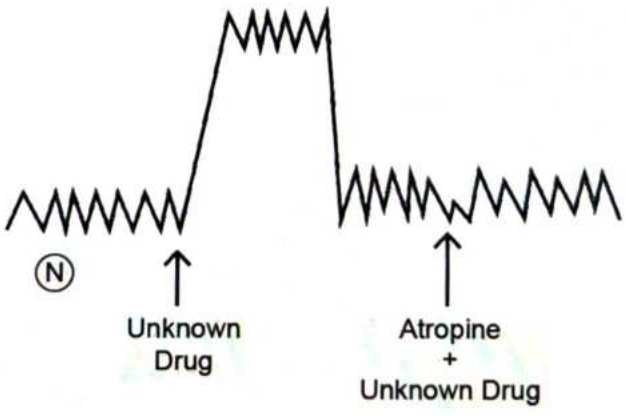
- Small piece of rabbit ileum is cut and attached to an organ bath.
- So ileum is attached on one end to the organ bath and on other end to the liver
- When the ileum contracts, the liver comes down but the other end goes up. So the graph goes high on ileum contraction. This means stimulant drug.
- When the ileum relaxes, the graph goes down. This means relaxant drug
- In normal ileal contraction, three things can be noted
  i. Height of contraction i.e. Amplitude
  ii. No. of contractions i.e. Frequency
  iii. Height from baseline i.e. Tone

- **Drugs given**

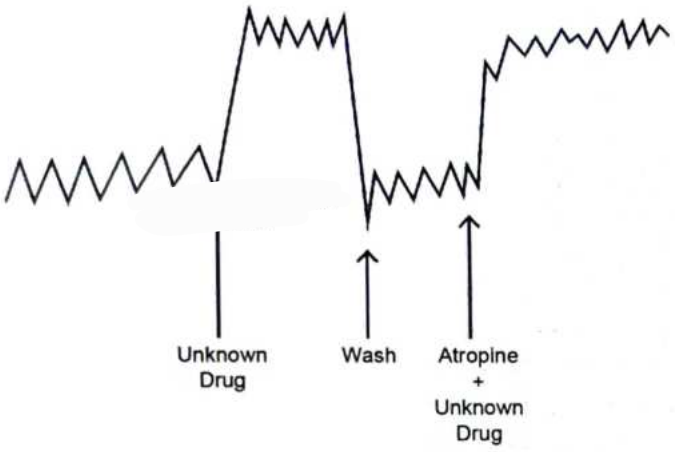
i. Stimulant Drugs	Directly acting $Cacl_2$ / $Bacl_2$ Indirectly acting → Ach
ii. Relaxant drugs	Directly acting → Papaverine Indirectly acting → Adrenaline

- **Scenarios**

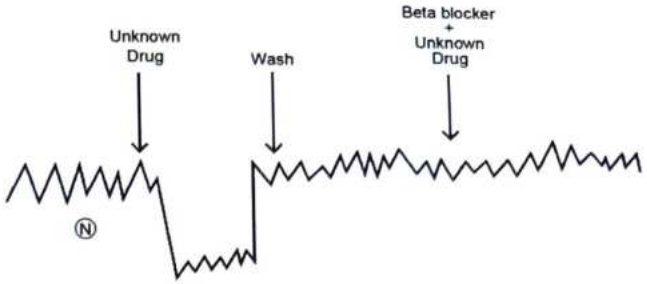
a. On giving the unknown drug if the graph goes up, this means a stimulant drug. We wash it and take baseline contractions again. Now we give Atropine which blocks the parasympathetic receptors and then we give the unknown drug again. If the graph does not rise, that means it is a cholinergic drug.



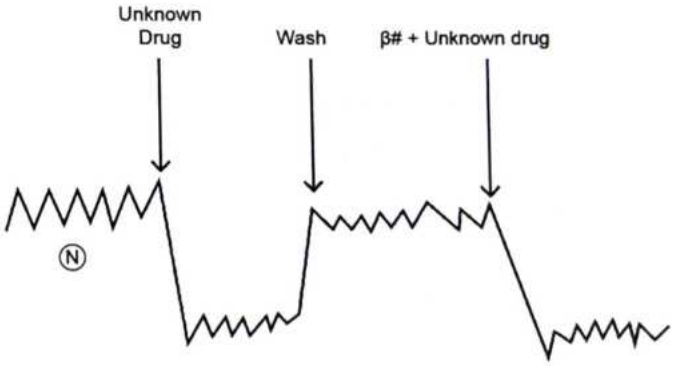
But if after giving atropine, the graph goes high, it is a directly acting drug like $Bacl_2$



b. When we add the unknown drug and the graph goes down, it means either sympathetic drug like Adrenaline or directly acting drug like papaverine. We wash it and take normal contractions. Now add -blockers and the unknown drug, if the graph does not change, it means Adrenaline

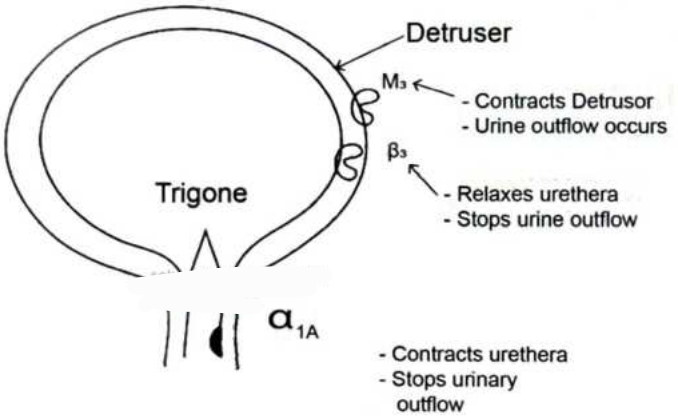


But if the graph goes down, it means papaverine



30 BLADDER PHARMACOLOGY

- Urinary bladder is bound on all sides by the detrusor muscle. It helps in the contraction of the bladder which leads to urine outflow



- Receptors present on detrusor are of two types
  i. β_3 receptor: Bladder relaxes
  ii. M_3 receptor: contracts bladder
- On the urethra there is present $_{1A}$ receptor, which when stimulated contracts the urethra and urine cannot be passed

Urinary Incontinence 00:02:00

- This means that urination is not under the control
- It can be of three major types
  i. Urge incontinence
  ii. Stress incontinence
  iii. Overflow incontinence

i. Urge incontinence

- It occurs due to an overactive bladder or Detrusor instability
- Detrusor contracts involuntarily, so there is a sudden urge to pass urine
- Drugs used

a. M_3 blockers

- **S** - **S**olifenacin
- **O** - **O**xybutynin
- **F** - **F**lavoxate, **F**esoterodine
- **T** - **T**rospium, **T**olterodine
- **Bladder** - **D**arifenacin

How to remember

- SOFT blaDder

b. β_3 agonists

- Mirabegron
- Vibegron

ii. Stress Incontinence 00:06:40

- This means that the person can normally control the passage of urine but when there is stress or intra-abdominal pressure on the bladder, the urine will suddenly pass
- One of the contributing factors is weak pelvic floor muscles
- Treatment includes
  a. Pelvic floor exercises
  b. Surgery
  c. Drug used: Duloxetine

iii. Overflow Incontinence 00:07:30

- There is no urge to urinate, so the bladder keeps on filling. When the bladder fills till the top, the sphincter opens due to pressure exerted by the urine and the urine overflows
- This is seen in two conditions
  - Atonic bladder
  - BPH
- For treatment, we need to stimulate the bladder.

The drugs used are

a. Atonic bladder $\rightarrow M_3$ (+) $\rightarrow$ Bethanechol
Neostigmine

b. BPH

- Dynamic outflow obstruction. So, we give α_1 blocker
- Prazosin
- Terazosin
- Doxazosin
- Alfuzosin

- But these drugs cause vasodilation ($\downarrow$ BP). So, these drugs are useful for the treatment of BPH with HTN
- These are always started at bedtime, to prevent the side effect of 1st dose hypotension

- So, we give α_{1A} blockers which treat BPH without causing postural hypotension. Drugs included are Tamsulosin, Silodosin
- 5-reductase inhibitors: They prevent the conversion of Testosterone to DHT. So, there is no ↑ in the size of the prostate. Drugs included are
  - Finasteride
  - Dutasteride

- 5-reductase inhibitors are used for the Static component of obstruction
- blockers are used for Dynamic components of obstruction
- Clinically, we start both drugs simultaneously i.e. Tamsulosin + Finasteride. Tamsulosin provides immediate relief. After some time, Finasteride also produces effect and ↓ size of the prostate.

31 GLAUCOMA

- Glaucoma is characterized by ↑ IOP. IOP is caused by Aqueous humor, so when there is more Aqueous humor, this will lead to ↑ IOP.

- Aqueous humor is produced after blood is filtered from the ciliary blood vessels. This aqueous humor comes via the pupil into the anterior chamber. It is drained through the angle in which there is presence of canal of schlemm. This outflow is called Trabecular outflow. It is the major drainage pathway.

- Some amount of aqueous humor, after formation, is drained via Uveo-scleral outflow. It is a minor drainage pathway.

- Glaucoma occurs when there is ↑ amount of aqueous humor in the eye. This can occur because of two main reasons
  - ↑ Production → k/a Open Angle Glaucoma
  - ↓ Drainage → k/a Closed Angle Glaucoma

- So, for the treatment of Glaucoma, we can either ↓ production or ↑ drainage of aqueous humor.

↓ Production 00:04:00

- Production can be reduced by causing vasoconstriction in the ciliary blood vessels. This can be done by
  - (+) α receptors
  - (-) β receptors
  - (-) carbonic anhydrase enzyme

I. α-agonists

- **Non – selective α agonists**
  - Adrenaline
  - Dipivefrine
    → These drugs majorly ↓ secretion but also affect the receptors to ↑ the outflow of aqueous humor

- **Selective α_2 agonists**
  - Apraclonidine
  - Brimonidine

ii. β_2 blockers

- Timolol
- Levobunolol
- Carteolol
  - But these drugs can cause Asthma also
  - So, we can give selective α blocker i.e. Betaxolol. But this is less efficacious
  - Levobunolol is the longest acting -blocker

iii. Carbonic anhydrase inhibitors

- Acetazolamide
- Brinzolamide
- Dorzolamide
  - Acetazolamide is given I.V. or oral. Not available as eye drops
  - Brinzolamide can be given as eye drops

Closed Angle glaucoma 00:08:30

- Angle is already narrow, so the best treatment is surgery. But till surgery is done, if there is sudden precipitation of glaucoma, the DOC is Mannitol.
- So DOC for Acute Congestive Glaucoma is Mannitol
- For long term management, we use CA inhibitors

↑ Outflow 00:09:35

- There are 2 types of outflow
  - Trabecular outflow
  - Uveo-scleral outflow

- To increase Trabecular outflow, we give
  - Miotic drugs
    → Pilocarpine
    → Physostigmine
    → Echothiophate
  - Rho-kinase inhibitors
    → Netarsudil
  - Main side effect of Miotic drugs is that they can cause cyclopsams, which results in Brow pain

  - Echothiophate can cause
    → Cataract
    → Stenosis of NLD

- To increase the uveo-scleral outflow, we give
  - $PGF_{2\alpha}$ agonists
    → Latanoprost
    → Bimatoprost
    → Travoprost
  - They are now DOC for Primary OA Glaucoma

Previous Year's Questions

Q. Anti-glaucoma drug that acts by increasing over scleral outflow is? (NEET Jan 2020)

A. Latanoprost
B. Timolol
C. Pilocarpine
D. Dorzolamide

Adverse effects of Anti-glaucoma drugs

I. Miotics

- Cataract
- Cyclopsams
- Stenosis of NLD

ii. β-blockers

- These have a lot of systemic S/E. So there are many C/I for β-blockers, which are
  - **A** - **A**sthma
  - **B** - **B**radycardia, AV#
  - **C** - **C**HF (acute)
  - **D** - **D**M

How to remember

- ABCD

iii. Clonidine

- Lid retraction

iv. Brimonidine

- Severe CNS depression which can result in Apnea, particularly in infants. So, it is C/I in children <2 years

v. Netarsudil

- Whorl-like corneal opacities or Cornea verticillata

vi. Adrenaline

- Metabolized to Adrenochrome which causes Black pigmentation of conjunctiva

vii. PGF2α

- Iris pigmentation or Heterochromia iritis
- Growth of eyelashes or Hypertrichosis
- Fluid in macula or Macular edema, particularly in DM patients
- They are avoided in inflammatory conditions like uveitis

CLINICAL QUESTIONS

CHOLINERGIC DRUGS

Q. A 49 year old male, came in to your clinic with complaints of diplopia, slurred speech, difficulty in breathing, drooping of eyelids and generalised fatigue by end of the day. The complaints worsened progressively through the day and patient comparatively felt better with rest. You suspect myasthenia gravis as the diagnosis and confirm the same with tests. For cases of MG, you would prefer to give neostigmine over physostigmine because of the fact that-

A. It is better absorbed orally
B. It has longer duration of action
C. It has additional direct agonistic action on nicotinic receptors at the muscle end plate
D. It penetrates blood brain barrier

Solution

Answer: C

- Neostigmine is a quaternary ammonium derivative and is water soluble.
- Its absorption from GIT and penetration in the brain and cornea is much less than physostigmine.
- **It produces additional action on NM receptors.**

Q. Lallu, a farmer comes to you in the emergency in comatose state. Platient had profuse sweating and lacrimation. Diarrhea and urination were apparent. On examination pupil was constricted and BP of the farmer was 80/60 mm Hg. You make a diagnosis of anticholinesterase inhibitor poisoning. You decide to administer him atropine. All of the following actions will be reversed by atropine EXCEPT:

A. Hypotension
B. Central excitation
C. Muscle paralysis
D. Bronchoconstriction

Answer: C

Solution

- Atropine is a non-selective antagonist at muscarinic receptors.
- It can penetrate blood brain barrier and reverse the muscarinic action in the CNS.
- It can also reverse hypotension and bronchoconstiction caused due to stimulation of muscarinic receptors.
- **However, muscle paralysis is due to Nicotinic (Nm) action on which it has no activity.**

ANTICHOLINERGIC DRUGS

Q. You join work in Australia as a full time consultant in paediatrics. When you return home tired from your duty, you park the car in the garage hastily and hang the keys on the wall. Suddenly a spider jumps on to your hand and bites on the dorsal surface. You push it away, wash hands immediately. After a few minutes, you develop redness, swelling and pain at the bite site and feel a bit nauseous. You rush back to the garage to see what bit you and take the car to the hospital, but you notice you are having tremors. Hence you call for the ambulance and inform what to keep ready, since the spider that bit you (as shown in image below), is known to produce a toxin that causes-

A. Excess release of Acetylcholine
B. Decrease release of Acetylcholine
C. Inhibits synthesis of Acetylcholine
D. Blocking Active transport of ACh into synaptic vesicle

Answer: A

Solution

- **Excess release of Acetylcholine**
  - **Black widow spider toxin**
  - Induces massive release and depletion of acetylcholine
- Decrease release of Acetylcholine
  - Botulinum toxin
- Inhibits synthesis of Acetylcholine
  - Hemicholinium (HC3) blocks choline uptake (the rate limiting step in Achsynthesis) and depletes Ach.
- Active transport of ACh into synaptic vesicle
  - Inhibited by vesamicol.

Q. A 28 yr old woman has been treated with several autonomic drugs for about a month. Which of the following signs would distinguish between an overdose of a muscarinic blocker and a ganglionic blocker?

A. Blurred vision
B. Dry mouth, constipation
C. Mydriasis
D. Postural hypotension

Answer: D

Solution

- **Postural hypotension** is due to **blockade of sympathetic system.**
- *Ganglion blockers inhibit the transmission through both sympathetic as well as parasympathetic ganglia whereas muscarinic blockers inhibit only parasympathetic activity.*

ADRENERGIC DRUGS

Q. A patient in shock comes to you in trauma ward. You examine him and decide not to give him vasoconstrictors. Which is the type of shock your patient is having?

A. Neurogenic shock
B. Haemorrhagic shock
C. Secondary shock
D. Hypotension due to spinal anaesthesia

Answer: C

Solution

- Sympathomimetic drugs are indicated in all types of shock except secondary shock.
- In this condition, there is *reflex vasoconstriction.* **Alpha blockers are useful** in this type of shock.

Q. A child, Ramu has swallowed the contents of 2 bottles of a nasal decongestant whose primary ingredient is α adrenoceptor agonist drug. The signs of α activation that may occur in this patient include:

A. Tachycardia
B. Dilatation of pupil
C. Vasodilation
D. All of the above

Answer: B

Solution

- α-receptors are present on the radial muscles of the iris, prostatic urethra and blood vessels.
- Stimulation of α-receptors cause contraction of the radial muscles and will cause **mydriasis.**
- It can also cause vasoconstriction (α1-receptor).
- Whereas, tachycardia and vasodilation, mentioned in the other options, are due to activation of β-adrenergic receptors.

ANTI-ADRENERGIC DRUGS

Q. You are in the eye OPD and wish to use a topical beta blocker in a patient. The chosen drug by you should have all the following properties EXCEPT:

A. Strong local anaesthetic activity
B. High lipophilicity
C. High ocular capture
D. Low systemic activity

Answer: A

Solution

- **Drugs possessing local anaesthetic property increases the risk of corneal ulcers.**
- Timolol and betaxolol are the preferred β-blockers for the treatment of glaucoma because they lack local anaesthetic activity.

Q. Beta blockers have a wide variety of actions in different locations of the body. Newer drugs have been created to target specific actions and reap the best from their use. Betaxolol is diff[illegible]ıolol in that, betaxolol:-

A. is a β1 selective blocker
B. is more efficacious in glaucoma
C. produces less ocular side effects
D. is shorter acting

Answer: A

Solution

- **Betaxolol** is **a cardioselective** Beta blocker (i.e Beta-1 blocker)
- **Timolol** is **a non-selective** Beta blocker (Beta 1 + Beta 2)
- Betaxolol - less bronchopulmonary and less cardiac, central and metabolic side effects.
- Betaxolol has protective effect on retinal neurons independent of i.o.t. lowering, by blocking some Ca^{2+}channels and reducing Na^{+}/Ca^{2+} influx. This action is more prominent in betaxolol than in timolol.
- **Betaxolol has a long serum half-life** and excellent oral bioavailability with little first-pass metabolism.
- **Betaxolol is less efficacious in lowering i.o.t. than timolol,** because ocular Beta receptors are predominantly of the Beta 2 subtype.

TERTIARY AND QUATERNARY AMINES

Q. You are being asked to give your expert opinion as a toxicologist regarding an effective antidote for belladonna poisoning. Which of the following agents would you suggest?

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

Answer: B

Solution

Atropine is obtained from atropa belladonna.

It is a non-selective muscarinic receptor antagonist

- **Physostigmine is the specific antidote for poisoning with belladonna.**
- It crosses blood-brain barrier and antagonises both central and peripheral actions.
- Physostigmine sometimes itself induces hypotension, arrhythmias and undesirable central effects. It is therefore employed only as a last resort.
- Neostigmine does not block the central effect, but is less risky.

LEARNING OBJECTIVES

UNIT 3: CVS

- CHF
  - Inotropics
  - Diuretics
- Ischaemic Heart Diseases
  - Angina
  - MI
  - Coronary steal phenomenon
- Hypertension
- Arrythmias
  - Resting membrane potential
  - Anti-arrhythmic drugs
- Dyslipidemia
- Pulmonary HTN
- Management of Shock

32 CONGESTIVE HEART FAILURE

- It means that the heart is not able to fulfill its work of providing the required amount of blood to the organs
- It can be of two types
  - High output heart failure
  - Low output heart failure

I. High output heart failure

00:01:40

- It is seen in conditions where the heart is pumping out a high volume of blood, but the blood requirement of the organ is even higher.
- For example
  - Thyrotoxicosis
  - Anemia
- The management includes treating the underlying condition.

II. Low output heart failure

00:03:52

- The cardiac output is low
- The basic underlying problem is that the heart is not pumping enough blood and as a result the blood pools back. This leads to congestion, hence the name congestive heart failure
- Drugs are given for treatment aim at
  - ↓ The fluid which has accumulated → Diuretics
  - ↑ Contractility of heart → Inotropics

1. Diuretics

Loop diuretics (Furosemide)	Thiazide diuretics (Hydrochlorothiazide)
• Strong diuretic	• Weak diuretic
• Short-acting	• Long-acting

- So, the preferred diuretic in CHF is Loop diuretics
- Side effects of diuretics
  - Common in Loop & Thiazide diuretics
    i. $\downarrow Na^+$
    ii. $\downarrow K^+$
    iii. $\downarrow Mg^{2+}$
    iv. $\downarrow H^+$
    v. ↑Blood sugar
    vi. ↑Lipids
    vii. ↑Uric acid
  - Loop diuretics → $\downarrow Ca^{2+}$
  - Thiazide diuretics → $\uparrow Ca^{2+}$

How to remember

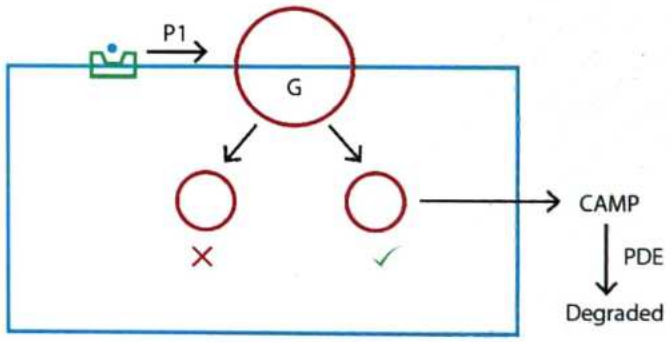
- Loop looses calcium

2. Inotropic Drugs

- They increase the contractility of the heart

a. β_1 agonist

- Dopamine - D, β, α
- Dobutamine - β_1
- Isoprenaline - β_1, β_2
- Noradrenaline - α1, α2
  - Dobutamine is the preferred drug
  - β_1 Agonist will ↑cAMP at places only where is present i.e., in the heart.



b. Phosphodiesterase inhibitors (PDE#)

- The drugs are
  - Amrinone
  - Milrinone
  - Vesnarinone
- PDE# will ↑ cAMP only at places where PDE is present i.e. Heart, Blood vessels, etc.
- In the blood vessels, they cause vasodilation. So PDE # can also be called Inodilators.
- For treatment of right-sided heart failure, usually inotropic drugs are not required. Vasodilators alone are sufficient.

ACUTE CHF

- Normally: Acute CHF
  ↓
  ↓C.O.
  ↓
  ↑Sympathetic action
  ↓
  ↑Adrenaline / NA
  ↓
  (+) α_1
  ↓
  ↑C.O.

- When the sympathetic system is activated, it will not only stimulate but α_1 receptor also.
- α_1 will cause Vasoconstriction. Vasoconstriction of
  - Veins will lead to ↑ Preload
  - Arteries will lead to ↑ Afterload
- This will increase the work of the heart
- Also, β_1 receptor will be stimulated in JG cells of the kidney, which will secrete Renin. This Renin will convert Angiotensinogen into Angiotensin I. Angiotensin I is converted into Angiotensin II by ACE enzyme. Angiotensin II stimulates AT_1 receptors.
- AT_1 receptors are present at many locations:
  - Blood vessels → Vasoconstriction
  - Adrenal medulla → Catecholamine release
  - Adrenal cortex → Aldosterone release
- Aldosterone causes retention of Na^+ and H_2O along with the release of K^+ and H^+
- So work of heart increases even more.
- When aldosterone is elevated for a long period of time, it results in LVH or cardiac remodeling. This leads to the death of the patient.

CHRONIC CHF

00:27:45

- It is aka Compensated CHF.
- Chronic CHF means when the compensatory mechanisms for CHF take place for a long period of time. This leads to problems
  - ↑ Work of heart
  - Fluid retention
  - LVH

- In this patient, the contractility of the heart is almost normal. So inotropic drugs are not the mainstay of treatment.

- So, the treatment of chronic CHF aims at
  i. ↓Fluid retention
  ii. ↓Work on heart
  iii. ↓LVH
  iv. ↑Contractility

I. ↓Fluid retention

- Loop diuretics

II. ↓Work on heart

- We give vasodilators
- Vasodilators acting on.
  a. Vein →↓Preload
     - Nitrates
  b. Artery →↓ Afterload
     - [illegible]
  c. Both Vein and Artery → ↓ Preload + ↓afterload
     - Sodium nitroprusside
     - ACE (-)
     - ARB

III. Reverse the LV hypertrophy

a. α-Blockers
b. ACE (-)
c. ARB
d. Aldosterone antagonists

- These four drugs are mortality reducing drugs

a. β-blockers

- They are given only in chronic CHF.
- They are C/I in Acute CHF, because they reduce contractility and in acute CHF it is already low.
- They should be started at a very low dose. The dose is then gradually increased.
- They reverse the LVH which leads to a decrease in mortality.
- α-Blockers which are approved for chronic CHF are
  - Carvedilol
  - Metoprolol
  - Bisoprolol
    → Carvedilol is MC used
    → It is 3rd generation β-blockers
    → It has Ca^{2+} channel # property also.
    → It also has antioxidant properties.

b. ACE (-)

- These are the drugs ending with "-pril"
  - Captopril
  - Lisinopril
  - Enalapril
  - Ramipril
  - Perindopril
  - Fosinopril
  - Moxipril
  - Trandolapril

- Special features of ACE (-)
  - **C** - **C**ough
  - **A** - **A**ngioedema

  } S/E which are seen in ACE (-) but absent in ARB

- P - Prodrugs (except captopril and Lisinopril)
- T - Taste disturbance (Dysgeusia)
- O - Orthostatic Hypotension (with diuretics)
- P - Pregnancy
- R - Renal artery stenosis (B/L) } C/I of ACE (-)
- I - Increase in K^+
- L - Lower the risk of diabetic nephropathy

How to remember

- CAPTOPRIL drugs

c. ARB (Angiotensin receptor blockers)

- They are selective AT_1 receptor blockers.
- Drugs ending with "-sartan":
  - Losartan
  - Valsartan
  - Telmisartan
  - Irbesartan
  - Eprosartan
  - Candesartan
  - Olmesartan
- Losartan causes a decrease in serum uric acid
- Telmisartan causes stimulation of a receptor called PPAR-, which leads to decreased insulin resistance.

d. Aldosterone antagonist

- This includes Spironolactone.
- It reverses the action of Aldosterone i.e. it removes the Na^+ and H_2O and leads to retention of K^+ and H^+
- They are potassium-sparing diuretics
- They increase H^+, so can cause metabolic acidosis
- Gynaecomastia can be seen as an adverse effect, because spironolactone blocks testosterone receptors also.
- Drugs causing Gynaecomastia are
  - D - } Digoxin
  - I - }
  - S - Spironolactone
  - C - Cimetidine
  - K - Ketoconazole
  - O - Oestrogens

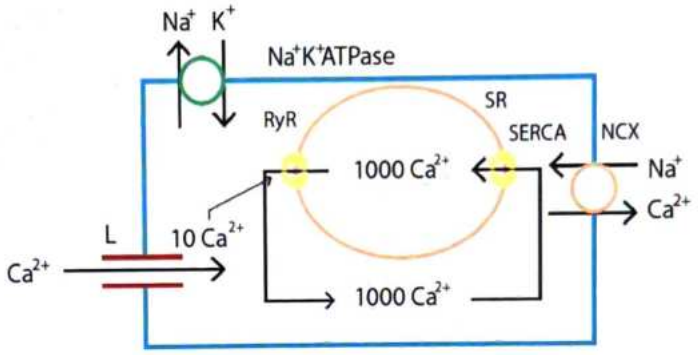
How to remember

- DISCKO drugs

- Drug which is selective on Aldosterone receptor and spares the testosterone receptors → Eplerenone, so it doesn't cause Gynaecomastia.

IV. ↑Contractility → Inotropic drugs 00:59:02

- They should be effective orally, because we want to give it for a long period of time
- They include cardiac glycosides. These are obtained from a plant called Foxglove. The common name is Digitalis purpura. So, these drugs are also called Digitalis group of drugs.
- They are used in Chronic CHF.



- Digitalis acts by inhibiting Na^+ - K^+ pump. So sodium can't go outside the cell. There is an increase in intracytoplasmic sodium.
- As a result, sodium won't be able to enter the cell and hence calcium won't go out.
- So indirectly Na^+ -Ca^{2+} exchanger is blocked
- Now the extra calcium in the cell is taken up by SERCA. So with the next impulse, more calcium is liberated. But this calcium also enters SERCA as NCX is blocked.
- As a result, there is a gradual build-up of calcium. So, there will be a sudden increase in contractility after some time.
- Therefore, digitalis is slow-acting and hence not suitable for Acute CHF
- Digitalis can cause Arrhythmias as an adverse effect.

- Digoxin also has a Vagomimetic effect
  - It works like a parasympathetic system.
  - So it will
    → ↓HR
    → ↓A-V conduction
- Digitalis is also used for Atrial fibrillation. The underlying mechanism is ↓A-V conduction. Because in Atrial fibrillation, our primary aim is to keep the ventricular rate in a lower range.
- Digitoxin is now withdrawn from the market. It was C/I in liver failure
- Digoxin is C/I in renal failure

- **Adverse effects of Digoxin**

a. Nausea, Vomiting → Earliest; MC S/E
b. Arrhythmias → MC cardiac S/E
   - MC arrhythmia → Ventricular bigeminy

- MC specific / characteristic arrhythmia → Non-paroxysmal Atrial Tachycardia with AV block.
- Not seen in this case are
  - → Mobitz type II heart block
  - → Atrial flutter

c. Xanthopsia (yellow vision)
d. Gynaecomastia

- **Factors which increase the risk of Digoxin toxicity**

a. Metabolic effects
- ↓K^+
- ↓Mg^{2+}
- ↑Ca^{2+}

b. Drugs
- Clonidine
- Verapamil
- Amiodarone

} ↑Plasma level of Digoxin

- Thiazides: They cause metabolic effects mentioned above.

c. Diseases
- Renal disease
  - → In liver disease, there is a high risk of Digitoxin toxicity

- DOC for Digitalis induced ventricular arrhythmia is Lignocaine. If it is not available, the alternate is Phenytoin

Previous Year's Questions

Q. Drug of choice for Digoxin induced Ventricular Tachycardia? (NEET Jan 2019)

A. Propranolol
B. Diltiazem
C. Verapamil
D. Lignocaine

- In the case of Severe Digoxin Toxicity, as the last option, we give DIGIBIND. It will bind to Digitalis and remove it. It acts like an antibody.

New drugs for CHF 01:28:50

a. Na^+ - K^+ pump # → Istaroxime
- It also stimulates SERCA, so lesser risk of arrhythmias

b. PDE # → Levosimendan
- It is also a calcium sensitizer

c. BNP (Brain Natriuretic Peptide)
- It has 2 actions
  - Removal of Na+ in urine
  - Vasodilation
- It is metabolized after some time by the enzyme Neprilysin (NEP)
- So we can give BNP from outside → Nesiritide
  - Nesiritide in a peptide, so not effective orally. It has to be given I.V.
  - It is quickly metabolized so it is short acting
  - So Nesiritide is used for Acute CHF only.

d. ACE (-) + NEP (-) → Vasopeptidase inhibitors (-patrilat)
- Drugs include
  - Omapatrilat
  - Sampatrilat
- They can cause cough, angioedema, hyperkalemia
- They are avoided in pregnancy

e. ARB + NEP (-) → ARNI drugs
- It includes a combination of Valsartan + Sacubitril

f. Vasopressin receptor antagonist (-vaptan)
- Vasopressin acts on V_1 receptors to cause Vasoconstriction. ADH acts on V_2 receptors to ↓urine.
- For patient of CHF, we need to block both V_1 and V_2
- Drugs are
  - Conivaptan
  - Tolvaptan
- Tolvaptan is also approved for APKD

g. Ivabradine
- It is a funny current blocker (I_f).
- These drugs act by producing Bradycardia
- Major S/E: ↓ Visual acuity.

h. SGC agonist (soluble Guanylate cyclase agonist)
- Normally NO stimulates the enzyme Guanylate cyclase. This enzyme increases the cyclic GMP (cGMP)
- In patients of CHF, there is less production of NO due to endothelial damage. So there is less production of cGMP.
- SGC agonist
  - Vericiguat
    - → It directly stimulates the Guanylate cyclase enzyme to produce cGMP.
  - Riociguat
    - → It is used in pulmonary HTN.

33 ISCHEMIC HEART DISEASE

- It can be
  - Angina pectoris
  - MI

ANGINA PECTORIS

- Angina means pain in the chest. This occurs due to decreased blood supply to the heart.
- It can be of two types
  - Stable angina
  - Unstable angina
- Unstable angina is managed just like MI.
- Stable angina is classified into:
  i. Classical angina or Exertional angina
  ii. Variant angina or Vasospastic angina or Prinzmetal's angina

i. Classical Angina ⏱ 00:01:30

- **Pathophysiology**
  - When there is atherosclerosis of small branches of the coronary artery, the vessels dilate. Due to which the effective diameter increases and so the blood supply becomes sufficient, so there is no pain at this site.
  - When the work of the heart increases due to any stress, the heart requires more blood. So, the blood vessels of the heart dilate to provide more blood.
  - But the atherosclerosed small vessel is already dilated from before, so it cannot dilate anymore. Now the pain will occur as blood supply will be inadequate.
- **Treatment**
  - The main mechanism of treatment of angina is to ↓work of heart

ii. Variant Angina

- **Pathophysiology**
  - It occurs due to vasospasm of blood vessels.
  - But the trigger of the vasospasm is not fixed. So, this pain can occur at anytime
  - So characteristic feature → Pain at rest
  - We cannot treat variant angina by ↓ work of heart
  - The only treatment possible is vasodilation of the coronary artery.

Drugs used in Angina ⏱ 00:07:16

1. Nitrates
2. Calcium channel #
3. β-blockers
4. K^+ channel openers

1. Nitrates

- They act by releasing nitric oxide (NO). It increases cGMP. This cGMP stimulates Protein Kinase – G (PKG). This PKG stimulates the Myosin Light Chain Phosphatase enzyme (MLCP). This enzyme removes the phosphate group which relaxes the muscles and leads to Vasodilation.

Previous Year's Questions

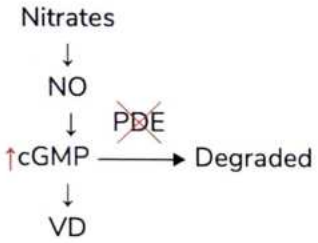
Q. A 50-year-old male presents with acute chest pain. A preliminary diagnosis of acute angina was made, and nitro-glycerine was given sublingually. The pain was relieved within 5 min. What is the likely mechanism of this drug? (FMGE Aug 2020)

A. Release of nitric oxide
B. Release of Endothelium
C. Calcium channel blockade
D. Be[illegible]ide

- Nitrates primarily dilate Veins >> Arteries.
- Vasodilation leads to ↓preload, so used in classical angina
- Nitrates can be used in variant angina also, due to dilation of the coronary artery.
- Nitrates are broken down by enzyme aldehyde dehydrogenase to form NO. This enzyme is present more in veins. So, NO is produced more in veins
- Drugs included are
  - Glyceryl trinitrate (GTN / NTG)
  - Isosorbide dinitrate (IDN)
  - Isosorbide mononitrate (IMN)
  - Pentaerythritol tetranitrate (PETN)
  - Amyl nitrite (AN)
- Nitrates have high first-pass metabolism, so we need to give a high dose if given by oral route.
- GTN and IDN are given by alternate route. They are given sub-lingually as DOC for Acute attack of angina
- IMN has minimum First Pass metabolism
- Longest acting nitrate → PETN

- Shortest acting → AN
- **Tolerance**
  - Nitrates should not be present in the blood for 24hrs a day otherwise tolerance develops.
  - We need to keep a 6-8 hrs nitrate-free period.
  - If the patient is using a transdermal patch, we instruct them to remove the patch before sleeping and reapply it in the morning.
  - Monday Disease: This is an example of Nitrate tolerance seen in Dynamite factory workers. The person is exposed to nitrate for the whole week so there is tolerance and hence no headache. But on weekend there is no exposure to nitrates, so when he returns to work on Monday there is a headache again.

- **Interaction of nitrates** 00:17:35



  - If a person who is on nitrate therapy takes sildenafil or Tadalafil, there is a risk of severe hypotension.
  - This is because Sildenafil & Tadalafil block the PDE enzyme and as a result, cGMP is not broken down. So, cGMP is increased considerably. This leads to severe hypotension due to vasodilation

- **Uses of Nitrates**
  - **A** - **A**ngina
  - **B** - **B**iliary colic
  - **C** - **C**yanide poisoning
  - **D** - MI (**D**il)
  - **E** - **E**sophageal spasm
  - **F** - **F**ailure (CHF)

How to remember

- A B C D E F

2. Cyanide poisoning

- Cyanide binds to an enzyme called cytochrome oxidase. Cytochrome oxidase is involved in energy generation.
- When cyanide binds to cytochrome oxidase, ATP generation stops. So, to treat cyanide poisoning, we need to remove the cyanide from the blood.
- We give Amyl nitrite in cyanide poisoning. It binds with hemoglobin to form Methemoglobin. This methemoglobin binds to the cyanide to form cyan-methemoglobin.
- This cyan-methemoglobin is also toxic and needs to be removed. It forms sodium thiocyanate with sodium thiosulphate, which is excreted by the kidney
- So Amyl nitrite is the antidote for cyanide poisoning. It is given by the inhalational route. But because it forms a toxic intermediate, it is not preferred.
- Hydroxocobalamin (Vit. B_{12}) given in cyanide poisoning will bind to cyanide to form Cyanocobalamin (Vit. B_{12}). So one form of Vit. B_{12} is converted into another form
- So Hydroxocobalamin is the antidote of choice for cyanide poisoning. It is given by the I.V. route.

Calcium channel blockers 00:25:30

- There are 2 types of calcium channels
  - L-type: Present in CVS
  - T-type: Present in CNS
- We use L- type calcium channel blockers here:

Refer Table 33.1

- All these CCB cause Vasodilation and ↓DBP
- Verapamil & Diltiazem cause ↓HR but only DHP cause Tachycardia
- So Dihydropyridines (DHP) can precipitate angina because they cause tachycardia
- Some "-dipines" are fast-acting like Nifedipine and Clevidipine. They can cause sudden VD. So, there is severe tachycardia as a result. Therefore, fast-acting drugs should be avoided in Angina.
- We prefer slow-acting drugs for angina like Amlodipine. These drugs cause slow vasodilation. So, they also produce tachycardia, but it is very less.
- CCB also decrease mortality in variant angina, so they are DOC in variant angina
- Nimodipine is Cerebro-selective CCB. It affects blood vessels of the brain causing vasodilation, so it is useful in Sub-arachnoid hemorrhage (SAH)
- Nimodipine is used after the hemorrhage has stopped, to prevent the over-compensatory vasoconstriction
- Clenidipine blocks not only L-type Ca^{2+} channels, but also N-type Ca^{2+} channels.

- **Adverse effects of CCB** 00:35:00
  - Headache
  - Constipation
  - Gum hypertrophy

Important Information

- Drugs causing Gum Hypertrophy
  - Cyclosporine
  - Phenytoin
  - CCB

3. β-Blockers 00:35:58

- Mechanism of action of -blockers in classical angina → ↓work of the heart by causing bradycardia.
- -Blockers are C/I in Variant angina because they may aggravate the spasms.

4. Potassium Channel openers 00:37:50

- Nicorandil is used in variant angina
- It is a K^+ channel opener as well as a NO releasers

New drugs in Angina 00:39:05

1. Funny current blocker (I,#): Ivabradine

- It blocks the hyperpolarization activated Na^+ channels
- Side effect: It ↓visual acuity
- It acts by causing bradycardia.
- Difference from -blockers is that Ivabradine only causes bradycardia. It does not cause a decrease in conduction or contractility.

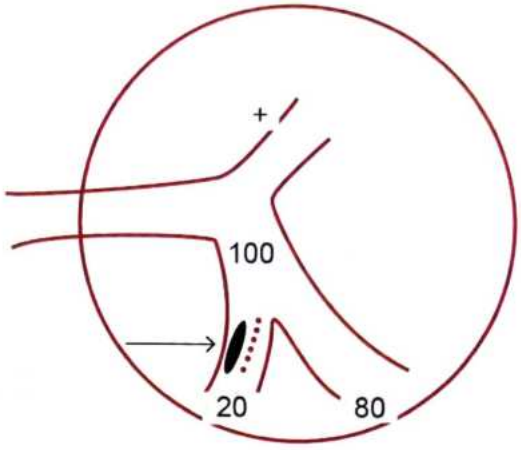
2. Rho-kinase inhibitors: Fasudil

- They cause vasodilation
- Netarsudil is also a Rho-Kinase inhibitor. It is used in Glaucoma

3. Fatty acid oxidation inhibitor (Metabolic modulators)

- Most of the body parts use glucose as a fuel to produce ATP
  - Glucose + O_2 → ATP
- Heart uses fatty acids as a fuel to produce ATP
  - F.A. + O_2 → ATP
- FAs are a poor fuel whereas glucose is a good fuel. F.A. requires more O_2 for the same energy production as compared to glucose.
- In angina, the blood supply is less and the oxygen supply is also less. So, there is less production of ATP.
- Metabolic modulation takes place → making the [illegible] utilize glucose as a fuel instead of FA. Because then even with less oxygen, it can produce more ATP.
- FA oxidation inhibitors will inhibit the enzymes involved in FA metabolism. So, the heart starts using glucose.
- Drugs included are
  - Trimetazidine
  - Ranolazine
    - → Ranolazine also acts on late Na^+ channels

Coronary steal phenomenon 00:45:20



- It is caused by drugs which dilate small vessels only.
- In angina, the small vessel with ischemia has already dilated.
- Drugs like Dipyridamole will dilate the vessels, but the ischemic vessel will remain the same, as it is already dilated. So only the normal vessels which are collaterals, will get dilated.
- Thus, the ischemic area supply becomes even less, and the blood goes towards collaterals more.
- This is called the coronary steal phenomenon.
- Because of this phenomenon, Dipyridamole increases the attacks of angina.
- Drugs included are
  - **H** - Hydralazine
  - **I** - Isoflurane
  - **D** - Dipyridamole
  - **E** - Enflurane

How to remember

- HIDE **drugs hide the blood**

- Coronary steal phenomenon is also called the Reverse Robinhood phenomenon
- -blockers take blood from the surplus area and give it to the needed area, so -blockers show the Robinhood phenomenon.

MYOCARDIAL INFARCTION (MI) 00:50:56

- Angina: Myocardial ischemia (reversible)
  MI: Myocardial infarction (irreversible)
- An important investigation to differentiate between Angina and MI → Cardiac enzymes
- MI can be of two types based on ECG findings:

Non-STEMI

- Treatment is the same as Unstable angina
  - M - Morphine
  - O - Oxygen
  - N - Nitrates
  - A - Aspirin (low dose)

STEMI (ST elevation MI)

- Treatment includes
  - S - Streptokinase
  - O - Oxygen
  - N - Nitrates
  - A - Aspirin
  - M - Morphine

How to remember

- NSTEMI: MONA
- STEMI : SONAM

Table 33.1

	BP	HR		
		Direct	Indirect	Net
Verapamil	VD ↓DBP	↓↓↓	↑	↓↓
Diltiazem	VD ↓DBP	↓↓	↑	↓
Nifedipine Amlodipine Nicardipine Clevidipine Nimodipine } DHP (-dipines)	VD ↓DBP	-	↑	↑

34 HYPERTENSION

- Hypertension is the increase in BP.
- BP is the pressure exerted by the moving column of blood on the vessel. If there is more volume of blood in the vessels, there is more pressure.
- So, the methods to reduce BP are
  - ↓ Volume of blood
  - ↓ Hardness of vessel wall (correlates with serum Na^+)
- **Drugs used for Hypertension include**
  1. Diuretics
  2. Vasodilators
  3. RAAS inhibitors
  4. Sympathetic blockers

1. Diuretics

⏱ 00:04:07

Loop diuretics	Thiazide diuretics
• Strong diuretic	• Weak diuretic
• Short-acting	• Long-acting

- We prefer Thiazide diuretics in HTN because they are long-acting and weak, so they don't cause dehydration.
- Thiazides are DOC for HTN unless they are C/I.
- Chlorthalidone is the preferred thiazide.
- Metolazone is effective even in the case of End-Stage Renal Disease (ESRD). Normally we use loop diuretics in renal disease.

Previous Year's Questions

Q. Which of the following antihypertensive drug is avoided in patients with higher serum uric acid level? (NEET Jan 2020)

A. Hydrochlorothiazide
B. Enalapril
C. Prazosin
D. Atenolol

2. Vasodilators

a. NO releasers

- Na nitroprusside
- Hydralazine
  - NO leads to an increase in cGMP. cGMP leads to vasodilation
  - Both these drugs are useful for HTN emergencies

- **Sodium nitroprusside**
  i. Sodium nitroprusside is given in a special infusion set called Micro drip set. It consists of 64 drops/min. If we give sodium nitroprusside quickly, it can lead to hypotension. So, we need a tight dose regulation.
  ii. Sensitive to light: Sodium nitroprusside is sensitive to light and needs to be covered by dark paper, otherwise it will become ineffective.
  iii. If Na nitroprusside drip is continued for >72hrs, it can lead to cyanide poisoning. Cyanide poisoning is treated with Hydroxocobalamin.

- **Hydralazine**
  i. It is metabolized by Acetylation. It is one of the SHIP drugs.
  ii. It can cause SLE, as all SHIP drugs can cause SLE as a side effect.
  iii. Hydralazine can act by opening K^+ channels also.

b. K^+ channel openers

- Drugs included are
  - **M** - Minoxidil
  - **D** - Diazoxide
  - **H** - Hydralazine

How to remember

- MDH masale

- Minoxidil ... hair growth. This can be either helpful or harmful.
  - It can be useful for the treatment of Alopecia
  - It can also cause Hirsutism in females, so it should be avoided in young females.
  - Minoxidil is a prodrug. Active metabolite is minoxidil sulphate which is formed by Phase I reaction.
- Diazoxide decreases Insulin
  - It can result in hyperglycemia, so avoided in diabetic patients.
  - It can be used in Insulinoma treatment.

c. Calcium channel blockers

- L-type CCB is used for hypertension.
- Drugs included are

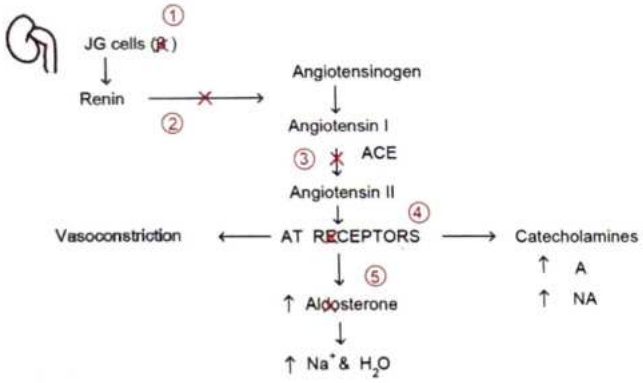
- Verapamil
- Diltiazem
- DHPs (-dipines)

- All three drugs cause vasodilation
- Verapamil and Diltiazem act directly on the heart. But DHPs act only on blood vessels, they don't act on the heart. They are peripheral CCB.
- DHPs used in HTN are
  - Amlodipine
  - Nicardipine

d. D_1 agonists

- Fenoldopam stimulates only D_1 receptors.
- It is a catecholamine and cannot be given orally
- Since it has to be given I.V., it is only useful for HTN emergencies.

3. RAAS # 00:15:45



a. β_1 blocker

- They inhibit Renin secretion

b. Renin inhibitors

- They inhibit the renin enzyme itself
- Drugs included are:
  - Aliskiren
  - Remikiren
  - Emalkiren

c. ACE (-)

- Drugs ending with '-pril'

d. ARB

- Drugs ending with '-sartan'

e. Aldosterone #

- Drugs included are
  - Spironolactone
  - Eplerenone

4. Sympathetic blockers

a. Ganglion blockers

b. Sympathetic neuron blockers

c. α_2 agonists

d. Sympathetic receptor blockers
   - α#
   - β#

a. Ganglion blockers

- These include N_N blockers.
- Drugs included are
  - Trimethaphan
  - Hexamethonium
- They have anti-cholinergic S/E
- They are used as an antidote for Nicotine poisoning

b. Sympathetic neuron blockers

- These include
  - Metyrosine
  - Reserpine
  - Guanethidine

c. α2 agonists

- These include
  - Clonidine
  - Methyldopa
- These cause side effects like
  - Dry mouth
  - Sedation
- Both drugs are safe in pregnancy
- Clonidine should not be suddenly stopped because it will lead to Rebound HTN.
- Methyldopa can cause hemolytic anemia also.

d. Receptor blockers

- These include
  - α Blockers
  - β Blockers

TREATMENT OF HTN (JNC-8 GUIDELINES)

00:28:30

I. HTN is defined as BP ≥ 140/90 mmHg.

II. Treatment includes
- Lifestyle changes
- Drugs for HTN

III. Target BP
- <140/90 for everyone
- In >60yrs patients without DM and without CKD: <150/90

IV. First line drugs
- **A** - **A**CE (-) / ARB
- **C** - **C**CB

- D - Diuretics (thiazides)

How to remember

- A C D

- In JNC -8, β-blockers have been removed from 1st line drugs.
- These are 1st line drugs when there is no compelling indicator i.e., the person has HTN only.
- DOC for (acc. To JNC-8)
  - HTN - Thiazides
  - Hypertensive emergencies - Na nitroprusside
  - HTN in pregnancy - Methyldopa
  - Hypertensive emergencies in pregnancy - Hydralazine

- DOC for (acc. To Harrison/ CMDT)
  - HTN - Thiazides
  - HTN emergencies - Nicardipine
  - HTN in preg - Labetalol
  - HTN emergency in pregnancy - Labetalol
- We always mark the answer according to Harrison, unless it is specifically asked in the question acc. to JNC-8.
- **American society of HTN (ASH) guidelines**
  - BP > 130/80 mmHg is considered HTN.
  - **Grade I**
    - → SBP: 130 - 139
    - → DBP: 80 - 89
  - **Grade II**
    - → SBP: ≥ 140
    - → DBP: ≥ 90
  - Acc. to ASH, till grade I HTN, drugs are not required
  - Drugs are only given from grade II onwards

Effects of Anti-HTN drugs on

I. Plasma Renin Level (PRL)
II. Plasma Renin Activity (PRA)

- By default, all anti-HTN drugs will increase the PRL and PRA, except those drugs which stop the sympathetic pathway themselves.
- These drugs are sympathetic blockers
  - Ganglion #
  - Sympathetic Neuron #
  - α_2 agonists
  - β #
- The only drug that increases Renin level, but decreases Renin activity → Renin inhibitors

Anti-HTN drugs which are safe in pregnancy

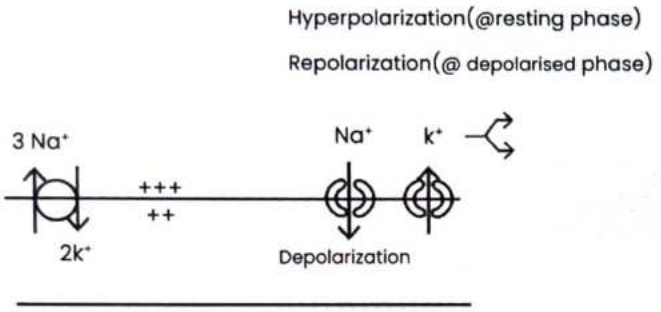
- These include
  - **Better** - β# (Labetalol)
  - **Mother** - Methyldopa
  - **Care** - Clonidine
  - **During** - DHP (-dipines)
  - **Hypertensive** - Hydralazine
  - **Pregnancy** - Prazosin (α#)

How to remember

- Better Mother Care During Hypertensive Pregnancy

- ACE (-) and ARB are absolutely C/I in pregnancy.

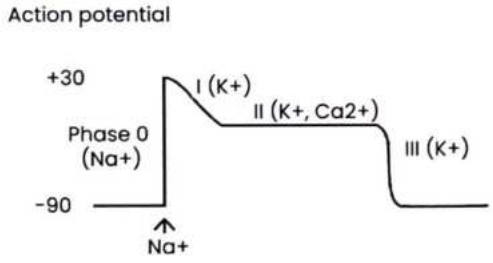
35 ARRHYTHMIAS



Resting Membrane Potential [-90mv]

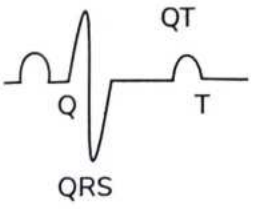
- Relative negative change inside the membrane d/t Na+ K+ ATPase
  - Depolarization: d/t Na+ entry through Na+ channel
  - Hyperpolarization: d/t K+ exist through K+ channel at resting state
  - Repolarization: d/t K+ exit through K+ channel at depolarization state

00:05:35



Effects of Drugs on AP and ECG 00:11:30

- **Na Channel Blockers**
  - Acts by ↓ Slope [dv/dt] of Phase 0
- **K+ channel blockers**
  - ↑Action potential duration [APD]
  - QT interval → Depolarization
  - Repolarization manifest as ↑ QT interval on ECG
  - Torsade's de Pointes [TDP] → Significant ↑ QT interval



- **K+ Channel Openers**
  - ↓Action Potential Duration [APD]

ANTI ARRHYTHMIC DRUGS

Vaughan Williams Classification 00:13:50

- Based on predominant mechanism of action
  - Class I: Na^+ Channel Blockers
  - Class II: β Blockers
  - Class III: K^+ Channel Blockers
  - Class IV: Ca^{2+} Channel Blockers
  - Class V: Others

1. Class I: Na+ Channel Blockers 00:15:42

- ↓Slope of phase 0
  - I_a - block K+ channel → Precipitates TDP
  - I_b - Open K+ channels
  - I_c - No effect on K+ channels

Class Ia drugs	Class Ib drugs	Class Ic drugs
• Quinidine • Procainamide	• Lignocaine • Phenytoin • Tocainide	• Encainide • Flecainide • Propafenone
• Causes QT Prolongation	• Used only for ventricular arrhythmia • Lignocaine is the DOC for most of the Arrhythmias	• Used for WPW syndrome • Treatment of choice for WPW syndrome is radio frequency ablation of aberrant pathway

2. Class II: β blockers 00:20:52

- Used in Tachyarrhythmias

3. Class III: K+ channel blockers 00:21:39

- **B** - **B**retylium
- **I** - **I**butilide
- **N**
- **D** - **D**ofetilide
- **A** - **A**miodarone

- S - Sotalol

How to remember

- BINDAS

- Sotalol has both Class III [major] & class II Actions

Amiodarone 00:24:55

- Longest acting [t1/2→>3wks] anti arrhythmic drug
- MOA
  1. Na+ channel blocker
  2. β Blocker
  3. K+ channel blocker [main action]
  4. Ca^{2+} channel blocker
- Indicated in all arrhythmias except TDP
- Adverse effect of amiodarone:
  - The: Thyroid (hypo / hyper) (40% iodine is present in amiodarone)
  - Periphery of: Peripheral neuropathy
  - My: Myocardial depression
  - Lung: Lung fibrosis
  - Liver and: Liver toxicity
  - Cornea is: Corneal deposits
  - Photosensitive: Photosensitivity Rash on exposure to sun (bluish: Blue man syndrome)

How to remember

The Periphery of My Lung Liver and Cornea is Photosensitive

- Dronedarone: Amiodarone without iodine but less effective and more Antiadrenergic property.

Important Information

Drugs Causing Pulmonary fibrosis

- Cyclophosphamide
- Busulfan
- Methotrexate
- Amiodarone
- Bleomycin

- Bretylium
  - Was used for ventricular fibrillation
  - Pharmacological defibrillator
- Ibutilide and Dofetilide
  - Used for atrial fibrillation
- Drugs like CCB, beta blockers and digoxin are also used for treatment of atrial fibrillation but these mainly control ventricular rate.
- Ibutilide and Dofetilide convert Atrial Fibrillation to normal sinus rhythm therefore it controls atrial rate also.

4. Class IV: L-type Ca2+ Channel blockers 00:31:42

- Verapamil
- Diltiazem
- DHPs (Not Used)
  - These drugs are used in tachyarrhythmias
  - Should not be combined with beta blockers [Risk of severe cardiac depression]

5. Class V: Others

- Digoxin: used for AF
- Atropine: DOC for Bradycardia & AV block
- Adenosine
  - Shortest acting antiarrhythmic drug (t1/2<10s)
  - DOC for PSVT
  - It is given as Rapid IV push in the Central veins
- Magnesium: DOC for long QT Syndrome / Torsade's De Pointes

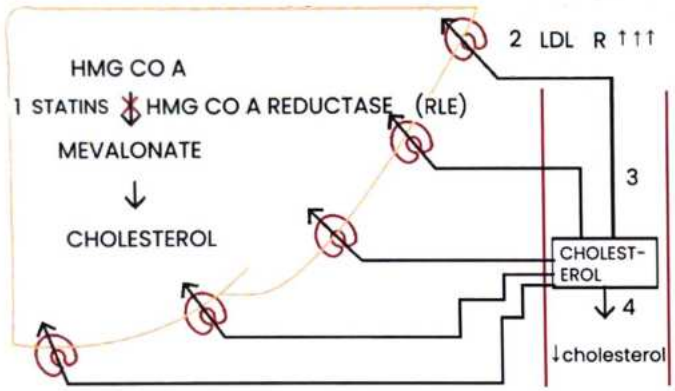
36 DYSLIPIDEMIA

ANTI-DYSLIPIDEMIC DRUGS

- The drugs included in this category are

1. Statins

00:00:50



- **MOA**
  - Statins act by inhibiting the enzyme HMG CoA reductase, so there is less formation of cholesterol by the liver
  - Now there is upregulation of LDL receptors on the surface of liver. They will take up cholesterol from the blood.
- Statins have maximum LDL cholesterol lowering potential
- Drugs included are (-vastatin)
  - Atorvastatin
  - Rosuvastatin
  - Pravastatin
  - Simvastatin
  - Fluvastatin
  - Cerivastatin
- Some drugs end in '-statin' but they are not HMG-CoA (-). These include
  i. **Cilastatin**: Given with Imipenem to inhibit its breakdown.
  ii. **Pentostatin**: It inhibits the enzyme adenosine deaminase (ADA)
  iii. **Somatostatin**: It is a hormone
- Special points of statins
  i. Food increases absorption of statins, so they are given just after meals. Exception → Pravastatin. It can be given irrespective of meals
  ii. HMG CoA enzyme is maximally active at night. So statins should be given late in evening or at night for maximum effect.
  Exception → Atorvastatin, Rosuvastatin. They are very long acting and can be given anytime of the day.
  iii. Statins are metabolized by CYP3A4, except pravastatin. So if we give them with enzyme inhibitors, it can lead to toxicity. For e.g. Ciprofloxacin, Erythromycin
  iv. Statin toxicity (features)
  - **M - M**yopathy (seen with Fibrates and CYP inhibitors)
  - **D - D**M
  - **H - H**epatotoxicity

  → So, whenever statins are started, we should check for Creatinine phosphokinase (CPK) levels for monitoring the muscle damage.

How to remember

- MDH

v. Pleiotropic effect

- Any other beneficial effects, apart from the anti-dyslipidemic effect, are called pleiotropic effects
- These include
  - P, L } Plaque stabilization
  - E - ↓Endothelial dysfunction
  - I - ↓Inflammation
  - O - ↓Oxidative stress
  - T, R } ↓ Thrombosis risk

  opic

How to remember

- PLEIOTRopic effects

- Atorvastatin & Rosuvastatin are longest acting statins
- **Pravastatin**
  - Minimum food interaction
  - Minimum drug interaction
  - Minimum CNS penetration
  - Minimize fibrinogen levels
- Simvastatin & Lovastatin are prodrugs. They have maximum CNS penetration

2. Intestinal Cholesterol Absorption Inhibitors

00:14:09

- They act by intubating a pump in the intestine called the Neimen pick-like 1C1 pump (NPL1C1). This pump helps in the absorption of cholesterol
- Ezetimibe drug inhibits this pump. So dietary cholesterol is not absorbed and level decreases in blood.

3. Fibrates 00:16:28

- Drugs included are
  - Clofibrates
  - Fenofibrates
  - Bezafibrates
  - Gemfibrozil
- Fibrates stimulate the PPAR γ receptors. These receptors ↑LPL concentration. This results in reduction of LDL, VLDL.
- Fibrates have maximum triglyceride lowering potential

Important Information

- **Statins: Max. LDL cholesterol lowering potential**
- **Fibrates: Max. TG lowering potential**

- Fibrates are commonly combined with statins. But this combination increases the risk of myopathy

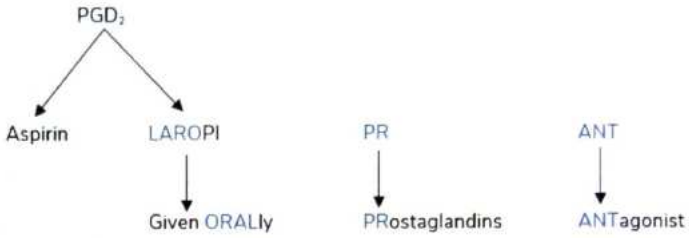
4. Niacin (Vitamin B_3) 00:18:33

- It is very inexpensive and easily available drug.
- It causes max. increase in HDL cholesterol.
- It causes max. decrease in Lipoprotein-A.
- It is not used commonly because it causes side effects like
  - Itching
  - Flushing

  } Compliance Limiting S/E occurring due to PGD_2

- To avoid these S/E, we can use Aspirin which a is COX (-). So, there is less production of PGD

- We can also use a drug called Laropiprant. It is an oral PGD_2 antagonist



- Niacin can cause other S/E like
  - ↑Uric acid
  - Insulin resistance
  - Hepatotoxicity

5. Bile acid binding agents (BABA) 00:21:02

- Drugs included are
  - Cholestyramine
  - Colestipol
  - Cholesevalam

- Enterohepatic cycling means that the same bile acid can be utilized repeatedly
- Bile acids act as carriers and carry cholesterol from GIT to blood.
- BABA drugs bind to bile acids in the GIT. Now cholesterol cannot bind to the bile acids. This BABA-bile acid complex cannot be absorbed. So it is removed, as a result there is decrease in bile acids in the GIT.
- Now liver will start forming bile acids. So there is decreased cholesterol in the liver. This will induce LDL receptor synthesis in the liver. Thus, it will take up cholesterol from the blood.
- BABA are DOC in children and in pregnancy.

New Hypolipidemic drugs 00:28:20

1. PCSK-9 inhibitors

- Pre-protein Convertin Subtilisin Kexin type 9 (PCSK-9) is a protein that binds to LDL receptor and takes it to lysosomes. This result in breakdown of LDL receptors.
- PCSK -9 inhibitors prevent the breakdown of LDL receptors. When more LDL receptors are present, they can take up more LDL cholesterol from blood.

- These drugs act by two methods:
  i. **↓Synthesis of PCSK-9**
  - Inclisiran: It is a small molecule inhibitor of RNA.

ii. **Monoclonal Ab against PCSK-9**
   - Alirocumab
   - Evolocumab
- These drugs are indicated in Homozygous hyper-cholesterolemia

2. Lomitapide
- It is microsomal triglyceride transport protein inhibitor (MTP inhibitor)
- Triglyceride is packed into VLDL & chylomicrons by MTP protein
- Lomitapide will inhibit the formation of VLDL etc, so LDL will not be formed.

3. Anacetrapib
- It is a Cholesterol Ester triglyceride Transport Protein inhibitor (CETP inhibitor)
- HDL normally takes up the cholesterol from the tissues and brings back to the liver (Reverse cholesterol transport)
- HDL exchanges its cholesterol & TG b/w LDL & VLDL with the help of CETP enzyme.
- When CETP is inhibited, HDL will not be able to exchange its cholesterol, so there is less degradation of HDL and the HDL level increases.

4. Mipomersen
- Drugs ending with '-rsen' are Antisense oligonucleotide against mRNA of Apo B_{100}
- It will decrease all the Apo B_{100} containing lipoproteins like LDL, VLDL, etc.

5. Evinacumab
- It is the only drug that acts independent of LDL receptors.
- It is a monoclonal Ab against Angiopoetin like 3 protein. This protein normally inhibits two enzymes: Lipoprotein lipase (LPL) & Endothelial lipase (EL)
- This drug results in↑action of LPL & EL, so this results in↓level of VLDL, LDL and chylomicrons. This also results in↓HDL levels.

37 PULMONARY HYPERTENSION

- There are two types of HTN
  - Systemic HTN
  - Pulmonary HTN
- For decreasing the pressure in the pulmonary circulation, we need to dilate the pulmonary arteries
- So, we give I.V. CCB to check whether the CCB can decrease the pulmonary HTN or not. This is called Intravenous Vasodilator testing.
- The test is negative in majority of the patients.
- If the test is positive, we start the patient on CCB. Amlodipine like drugs are DOC in this case
- If the test is negative, the DOC is Endothelin antagonists. They are DOC even if I.V. vasodilator testing is not mentioned.

i. **Endothelin antagonists are**
   - Bosentan
   - Ambresentan
   - Macitentan

ii. **PDE (-)**
   - If the endothelin antagonists do not work, we can give phosphodiesterase inhibitors.
   - These include
     → **Sildenafil**
     → **Tadalafil**: Longest acting
   - These drugs inhibit the breakdown of cGMP.
   - So there is ↑ level of cGMP which leads to vasodilation
   - Most effective drugs are
     → PGI_2: Iloprost
     → PGE_2: Treprostinil
   - But these drugs are not effective orally

iii. **Selexipag** is PGI_2 agonist. It is an oral drug

iv. **Riociguat**
   - It is a soluble Guanylate cyclase agonist (SGC (+))
   - It will stimulate guanylate cyclase. This stimulates cGMP which leads to vasodilation
   - So, it can be used in pulmonary hypertension.

38 MANAGEMENT OF SHOCK

- Shock means decreased tissue perfusion
- The type of shock can be determined by checking the extremities

Cold extremities	Warm extremities
↓	↓
Cardiogenic shock	Vasodilatory / Distributive shock
Hypovolemic shock	↓
	• Septic shock • Anaphylactic shock • Neurogenic shock • Hypoadrenal shock

Secondary Shock 00:02:45

- It is particularly seen in the brain. When there is hemorrhage in the brain, there is compensatory mechanisms. Sometimes the compensatory mechanisms are overpowered. This leads to intense vasoconstriction, which results in decreased tissue perfusion. This is called secondary shock.

Management of shock 00:03:40

- Shock is an emergency, so the 1st step will always be CAB.

i. CAB

- Circulation, Airway, Breathing

ii. Fluid replacement

- Fluid replacement is required for almost every type of shock
- It is more important than inotropic drugs
- Fluid requirement is judged by CVP → if CVP < 5 mmHg, we need to replace the fluids
- Mostly we give crystalloid fluids. These include → Ringer lactate and Normal saline
- If a lot of fluid has been lost, we can give blood transfusion also.

iii. Vasopressor drugs

- The drugs included are

a. Septic shock → Noradrenaline

- We check whether NA is working or not by checking the Mean Arterial Pressure (MAP)

b. If there is risk of arrhythmia, the drug given is Phenylephrine. Alternative is Dopamine

c. Cardiogenic shock → Noradrenaline > Dopamine

- Before giving vasopressors, adequate fluid replacement is required.

Specific treatment of shock 00:08:45

I. Hypovolemic shock	- Blood transfusion
II. Septic shock	- Broad spectrum antibiotics
III. Anaphylactic shock	- Adrenaline (I.M.) (1:1000)
IV. Hypoadrenal shock	- Steroids
V. Secondary shock	- βblocker (they cause vasodilation)

CLINICAL QUESTIONS

CHF

Q. Drugs that have been found to be useful in compensated heart failure include all of the following except:

A. Na+ K+ ATPase inhibitors
B. Aldosterone antagonists
C. BNP analogue
D. Beta receptor antagonists

Answer: C

Solution

BNP analogue (Nesiritide) are used in acute cardiac failure not used in chronic therapy.

Compensated heart failure (Chronic CHF):

Management:

- **Digitalis (Na+ - K+ ATPase inhibitor)** - Inhibit Na+/K+ ATPase--> positive inotropic action.
- It does not acts as chronotropic agent so no increase in workload on heart and useful in chronic conditions.
- **Aldosterone antagonist:** Decreases morbidity/mortality. Used to **prevent cardiac remodelling** along with **ACE inhibitors** and **ARBs**.
- **β blockers:** These drugs can precipitate acute decompensation of cardiac function but are used in chronic CHF as these decrease mortality by reversing LVH.

Q. Digitalis is one of the drugs studied extensively in medicine, especially due to its unique properties. For years, digoxin has been used in the treatment of acute CHF. It can still be used in long-term maintenance of CHF cases, if it is associated with:-

A. Hypertension
B. Hypertrophic obstructive cardiomyopathy
C. Atrial fibrillation
D. Mitral stenosis

Answer: C

Solution

- Digitalis helps controlling the VR (ventricular rate) in (AF +/- CHF).
- It can't cure/revert AF to sinus rhythm.
- It ↓ **VR** by ↓ **ing no. of impulses that pass down the A-V node**(AVN)+ bundle of His.
- ↑ ERP (Effective Refractory Period) of AVN by vagomimetic + antiadrenergic actions: ↑ min. interval b/w consecutive impulses that can traverse conducting tissue.

- Long ERP of AVN → many atrial impulses (~500/min) falling in the RRP get extinguished by decremental conduction (concealed impulses)

ISCHAEMIC HEART DISEASES

Q. You decide not to prescribe sildenafil in a patient because the patient told you that he is taking an antianginal drug. Which of the following can it be?

A. Calcium channel blockers
B. β adrenergic blockers
C. Organic nitrates
D. Angiotensin converting enzyme inhibitors

Answer: C

Solution

- **Nitrates** act by **increasing cGMP** and **sildenafil** inhibits the breakdown of this compound (by **inhibiting phosphodiesterase**).
- Marked **increase in cGMP** levels may result in the **profound hypotension** and reflex **tachycardia**.

Q. A patient of acute myocardial infarction being treated in intensive care unit developed left ventricular failure with raised central venous pressure. Doctor on duty decided to use nitroglycerine. Which route of administration would be most suitable?

A. Sublingual
B. Oral
C. Intravenous bolus injection
D. Slow intravenous infusion

Answer: D

Solution

- **Nitrates** can be used in acute LVF by **slow i.v. infusion** →→ affords rapid relief in **acute LVF**, particularly that due to myocardial ischaemia/infarction.
- It is indicated when the central venous pressure (CVP) is raised and in dilated cardiomyopathy.
- Vasodilators were first used I.V. to treat acute heart failure that occurs in advanced cases or following MI.
- Nitrates decreases Preload > After load.

HYPERTENSION

Q. Mr. Rushil has severe hypertension and is to receive minoxidil. Minoxidil is a powerful arteriolar vasodilator that does not act on autonomic receptors. When used in severe hypertension, its effects would probably include:

A. Tachycardia and increased cardiac contractility
B. Tachycardia and decreased cardiac output

C. Decreased mean arterial pressure and decreased cardiac contractility

D. Decreased mean arterial pressure and increased salt and water excretion by the kidney

Answer: A

Solution

- Minoxidil is a **powerful vasodilator** and leads to reflex **stimulation of sympathetic system**.
- Thus, it causes **tachycardia, increased contractility** and **retention of salt and water by the kidney**.

Q. All of the following antihypertensive drugs increase plasma renin activity except:

A. Clonidine

B. Hydralazine

C. Nifedipine

D. Captopril

Answer: A

Solution

- Plasma renin activity is increased by reflex increase in sympathetic discharge.
- **Clonidine decreases central sympathetic outflow** and thus will **decrease the plasma renin activity.**
- Vasodilators and ACE inhibitors result in reflex increase in plasma renin activity.

ARRYTHMIAS

Q. Which of the following antiarrhythmic drugs can decrease the slope of Phase 0 and prolong the action potential duration?

A. Lignocaine

B. Propanolol

C. Quinidine

D. Adenosine

Answer: C

Solution

- Na^+ channel blockers reduce the slope of phase 0 whereas K^+ channel blockers prolong the APD.
- Both of these properties are present in **class Ia antiarrhythmics** like **quinidine** and **procainamide**.

Q. A drug effect that is produced by therapeutic doses of both timolol and amiodarone is blockade of:

A. Cardiac Na+ channels

B. Cardiac K+ channels

C. Beta adrenoceptors

D. Alpha-adrenoceptors

Answer: C

Solution

Amiodarone has wide spectrum of **antiarrhythmic** actions. It acts by all the four mechanisms:

- blockade of Na^+ channels
- blockade of β receptors
- blockade of K^+ channels
- blockade of Ca^{2+} channels.

Timolol is a **β blocker**.

- Therefore, common action of these two drugs is inhibition of β-receptors.

DYSLIPIDAEMIA

Q. A 45 year old male patient walks in to your hospital for a master health checkup. The results come and you notice that the patient has an elevated cholesterol level and HDL about 31 mg/dL. Apart from diet and lifestyle modifications such an increasing physical activity/ exercises, which of the following vitamins can be given to help with this condition?

A. Thiamine
B. Biotin
C. Pyridoxine
D. Nicotinic acid

Answer: D

Solution

ANTI-DYSLIPIDEMIC AGENTS

Group	Mechanism	Drugs	Special points
Statins	HMG CoA reductase inhibition	Atorvastatin, Rosuvastatin	Max LDL lowering capacity
Fibrates	Stimulation of PPAR-alpha	Clofibrate Fenofibrate Gemfibrozil	Max TG lowering capacity
Bile acid sequestrants	Binds bile acids in GIT	Cholestyramine, Colestipol, Cholesevalam	Safe in pregnancy and children
Ezetimibe	Inhibit intestinal cholesterol absorption	Ezetimibe	Given with statins
Nicotinic acid	Inhibit lipase	Niacin	Max HDL increasing capacity

LEARNING OBJECTIVES

UNIT 4: KIDNEY

- Diuretics
  - Classification and uses
  - Diabetes insipidus

39 DIURETICS

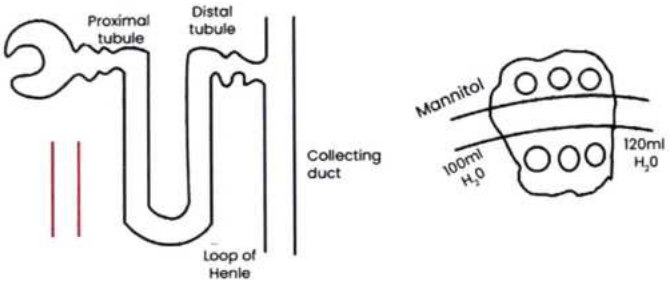
Diuretics 00:00:30

- Substances which cause loss of Na+ & H_2O in urine
- **Aquaretic**: causes loss of only H_2O

Classification is based on site of Action

1. OSMATIC DIURETICS 00:02:20

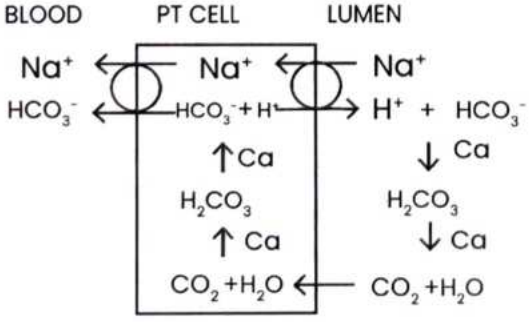
- Mannitol
- Properties:
  - Should be freely filterable
  - Should not be reabsorbed
  - Should not react chemically
  - Should exert osmotic effect



- Uses:
  - Angle Closure Glaucoma
  - Cerebral edema
  - Incipient renal failure : Because it increases renal blood flow
- Contra-indications:
  - Active Cerebral hemorrhage
  - Acute renal failure
  - Pulmonary edema

2. CARBONIC ANHYDRASE INHIBITORS

00:15:57

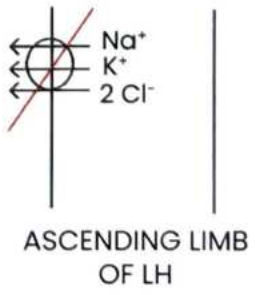


- Act on Proximal tubules
- They are non-competitive and reversible inhibitors of carbonic anhydrase enzyme
- Causes loss of Na^+ and HCO_3^- in urine
  - Na+ & H_2O: Diuretics
  - HCO_3: Urinary Alkalosis / Metabolic Acidosis
- Have self-limiting action
- Includes
  - Acetazolamide: Given by oral or injectable route
  - Brinzolamide, Dorzolamide } Given as eye drops
- Indications
  - Glaucoma (Angle closure glaucoma)
  - Alkalinization of urine
  - Mountain Sickness [DOC]
  - Epilepsy
- Adverse Effects
  - Metabolic acidosis
  - Hypokalemia [Maximum Hypokalemia among diuretics]
  - Paraesthesia
  - Renal stones
- Contra-indications
  - Liver disease

3. LOOP DIURETICS

- Act on thick ascending limb of loop of Henle
- Inhibits Na^+ K^+ 2Cl Symporter
- Includes
  - Furosemide
  - Torsemide
  - Bumetanide
- High ceiling diuretics [High efficacy Diuretics]
- 20-25% of Na+ is reabsorbed from ascending Limb of LH

Loop Diuretics

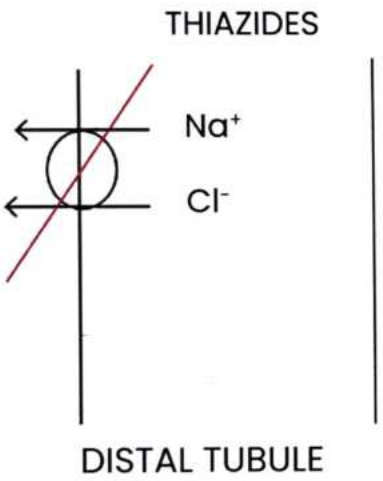


- Uses of Loop diuretics
  - Edema (CHF, Pulmonary edema, etc.)
  - Hypertensive emergency
  - Bromide and iodide poisoning
  - Hypercalcemia

4. THIAZIDES

00:32:55

- Act on Distal tubules
- Inhibits Na^+Cl^- symporter
- Includes
  - Hydrochlorothiazide
  - Chlorthiazide
  - Methiazide
  - Polythiazide
  - Indapamide } Thiazide like Diuretics
  - Xipamide }

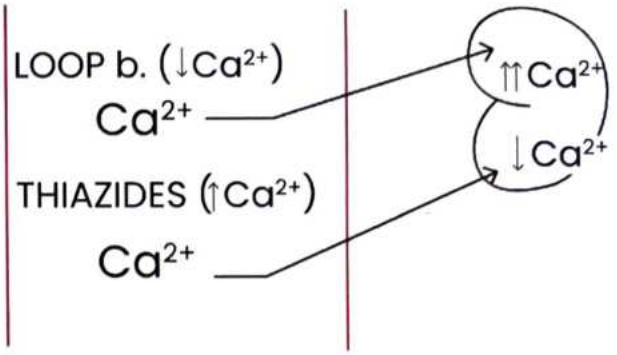


- **S/E** of both thiazides and loop diuretics:
  - $\downarrow Na^+$
  - $\downarrow K^+$
  - $\downarrow Mg_2^+$
  - $\downarrow H^+$
  - ↑ Glucose
  - ↑ Uric Acid
  - ↑ Lipids
- Loop diuretics decrease the serum calcium whereas Thiazide diuretics increase serum calcium

How to remember

- **Loop looses Calcium**

- Diuretic which is preferred in Recurrent Renal stones: Thiazide diuretic



  - Even through Thiazides ↑ Ca_2^+, but less Ca_2^+ reaches the kidney
- **Uses of Thiazides** 00:39:02
  - Hypertension (DOC)
  - Edema
  - Recurrent renal calcium stones
  - Bromide and iodide poisoning
  - Osteoporosis
  - Diabetics insipidus

Diabetes Insipidus 00:40:11

- ADH retains only water

Types	Etiology	Treatment
• Central DI	• ↓ADH	• Desmopressin (DOC) Thiazides
• Nephrogenic DI	• Renal cause	

- MOA of Thiazides in DI
  - ↑ Plasma osmolarity
  - Compensatory mechanisms for this are
  - i. ↑ ADH
  - ii. Thirst center stimulation
- Thiazides cause excretion of concentrated urine

↓Osmolarity
↓
↓Thirst
↓
↓Urine formation

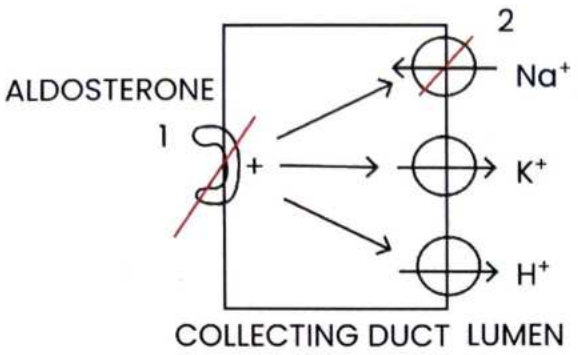
5. K+ SPARING DIURETICS

00:48:21

- Act on collecting ducts

i. Aldosterone Receptor #
  - Spironolactone
  - Epleronone

ii. Epithelial Na+ channel #
  - Amiloride
  - Triamterene



- These drugs cause
  - ↓Na+ & H_2O - Diuresis
  - K+ - Hyperkalemia
  - H+ - Metabolic Acidosis
- Drugs can be remembered by:
  - **P - P**otassium sparing Diuretics are

How to remember

- PASTE

- Uses
  - Conn's Syndrome (DOC)
  - Edema in Cirrhosis (DOC)
  - Prevent hypokalemia caused by other diuretics
  - CHF
  - Resistant hypertension (DOC)
- All diuretics work from Luminal side except Aldosterone antagonists. Aldosterone antagonists work from Basolateral side.

CLINICAL QUESTIONS

DIURETICS

Q. Intravenous furosemide is used for rapid control of symptoms in acute left ventricular failure. It provides quick relief of dyspnoea by:

A. Producing bronchodilation
B. Causing rapid diuresis and reducing circulating blood volume
C. Causing vasodilation
D. Stimulating left ventricular contractility

Answer: C

Solution

- Furosemide is a **high ceiling diuretic.**
- Its **major mode of benefit in acute pulmonary edema** is vasodilation. Due to its vasodilatory action, it shifts the fluid from pulmonary to systemic circulation. This **results in the rapid relief of symptoms**
- Diuretic action develops later.

Q. A 50-year-old man has a history of frequent episodes of renal colic with high calcium renal stones. The most useful diuretic in the treatment of recurrent calcium stones is:

A. Furosemide
B. Spironolactone
C. Hydrochlorothiazide
D. Acetazolamide

Answer: C

Solution

- **Thiazides** cause **hypercalcemia** by **decreasing the renal excretion of Ca^{2+}.**
- These are useful in a patient having hypercalciurea.
- In such a patient, **thiazides decrease the excretion of Ca^{2+}** in the kidney and thus **reduces the chances of stone formation.**

LEARNING OBJECTIVES

UNIT 5: RESPIRATORY SYSTEM

- Drugs for Cough and Bronchial Asthma
  - Expectorants vs Mucolytics
  - Bronchial asthma

40 DRUGS FOR COUGH AND BRONCHIAL ASTHMA

- Respiratory problems can be
  - Cough
  - Asthma

COUGH

- Cough can be
  - Dry cough
  - Productive cough
- Drugs for cough → Anti-tussives

i. Dry cough

- Codeine
- Pholcodeine
- Dextromethorphen
- Noscapine

ii. Productive cough → Mucokinetics

- Expectorants
- Mucolytics

a. Expectorants: They increase the secretion and dilute the existing mucus, so that it is easily passed.

- Guaifenesin
- Potassium iodide

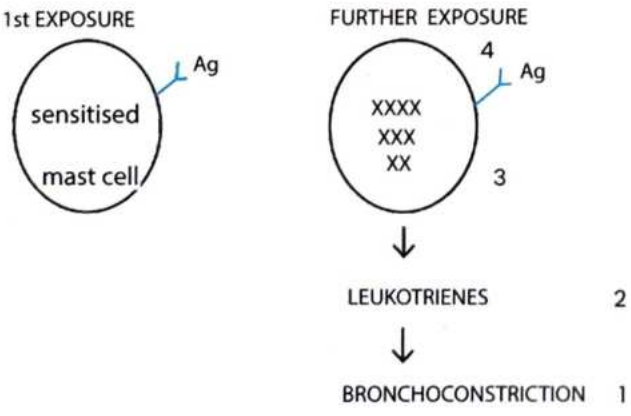
b. Mucolytics: They break the mucus so that it is easily removed.

- Ambroxol
- Bromhexine
- Acetyl cysteine
- Dornase alfa

BRONCHIAL ASTHMA

00:04:30

- It is a Type I HS reaction
- It is mediated by IgE antibody



1. Bronchodilators

a. Sympathomimetics

- These include β_2 agonists
- The drugs include:
  - Salbutamol, Terbutaline } Short acting
  - Salmeterol, Formoterol } Long acting
- They are given by inhalational route.
- Long acting drugs are used for prophylaxis of asthma.
- Short acting drugs are fast acting, so they are used for acute attack of asthma.
- Major adverse effects of β_2 agonists
  - Tachycardia
  - Tremors (MC)
  - Tolerance
  - T-wave changes

  } 4T'
- Tachycardia is mainly seen with high doses.
- Tolerance is seen when drug is given for a long period.
- T-wave changes seen because of hypokalemia.
- Those drugs may also cause hypoglycemia

b. Parasympatholytics

- These include M_3 blockers
  - Ipratropium
  - Tiotropium
- They are given by inhalational route.
- Ipratropium like drugs are DOC for acute attack of asthma when the person is already on β-blocker therapy.

c. PDE (-)

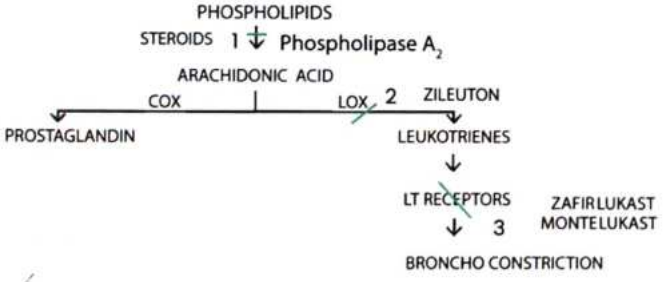
- PDE (-) inhibits the enzyme phosphodiesterase. This enzyme causes metabolism of cAMP which is a powerful bronchodilator.
- So these drugs cause increase in cAMP level. This leads to bronchodilation.
- Drug included → Theophylline
  - It is powerful bronchodilator
  - It is the only bronchodilator drug which cannot be given by inhalational route.
  - It is given by either oral or I.V. route
- Other mechanism of theophylline
  - Strong Adenosine A_1 receptor antagonist
  - Can restore the activity of Histone deacetylase (HDAC). This leads to anti-inflammatory action.

- **Adverse effects of Theophylline**

d/t PDE (-)	d/t Adenosine receptor #
• GIT S/E : Nausea, vomiting, diarrhea • Headache • Arrhythmias	• Diuresis • Seizures • Arrhythmias

- Theophylline follows Zero order Kinetics, so a constant amount is removed with time.
- Theophylline is metabolized by microsomal enzymes, so drug interactions are possible.
- **Enzyme inducers**
  - Smoking: The dose of theophylline to be given to a smoker should be higher than a non - smoker
- **Enzyme inhibitors**
  - Ciprofloxacin
  - Erythromycin
    - → These drugs inhibit the metabolism of Theophylline
    - → So this leads to toxicity which includes symptoms like
      - Seizures
      - Arrhythmias

2. Steroids 00:21:12



- Steroids are DOC for prophylaxis of bronchial asthma
- They can also be used in acute attack of asthma along with bronchodilators like Salbutamol.
- Steroids increase the bronchodilator effect of salbutamol like drugs.
- Inhalational corticosteroids include
  - Beclomethasone
  - Budesonide
  - Fluticasone
  - Flunisolide
  - Triamcinolone
  - Mometasone
  - Ciclesonide
    - → Only 5% of the inhalational corticosteroids reach the bronchus, rest of the 95% stick to the respiratory pathway. This leads to immunosuppression which results in increased risk of infections
    - → So, MC advers[illegible]oparyngeal candidiasis
    - → This adverse effect can be easily prevented by regular gargling with Topical Nystatin.
- Ciclesonide is known as Soft steroids. It is itself not a steroid, it is a prodrug and gets metabolized to form the active product. So the 95% of the drug, that is absorbed in the respiratory pathway is not activated. So it does not cause candidiasis, that's why it is called soft steroid.

3. Mast cell stabilizers 00:27:52

- The drugs included are
  - Sodium cromoglycate
  - Nedocromil
- They prevent the breakdown of mast cells.
- But if the mast cells are already broken down, then they are of no use.
- So they are only used for prophylaxis of bronchial asthma.

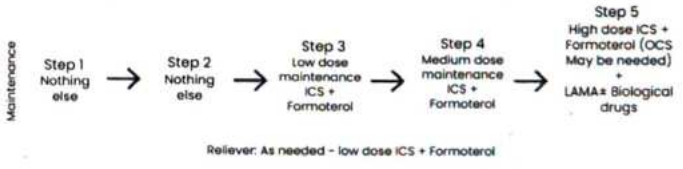
4. Omalizumab

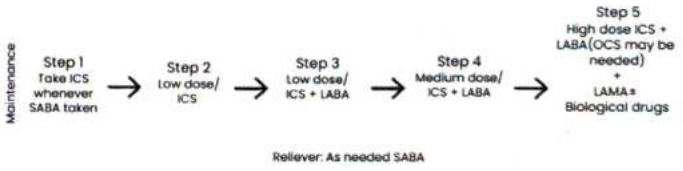
- It is a monoclonal antibody against IgE.
- It is used for prophylaxis of asthma
- It a mAb so cannot be given orally. It is given of Subcutaneous route.

GINA GUIDELINES – 2021 (GLOBAL INITIATIVE FOR TREATMENT OF ASTHMA)

00:30:06

- Acc to these guidelines, we have two types of medications
  - i. Reliever drugs →These are used to treat asthma and relieve the symptoms during an attack
  - ii. Maintenance drugs →These are given daily on a long-term basis, to prevent further attacks of asthma.





- Previously SABA were used as Reliever drugs. But now Low dose ICS + Formoterol combination is used as Reliever drug.

How to remember

- **The preferred reliever / treatment of choice for asthma is: Low dose ICS + Fromoterol**

CLINICAL QUESTIONS

DRUGS FOR COUGH AND BRONCHIAL ASTHMA

Q. Methylxanthines are derived from the purine base xanthine. They have long been used in the treatment of asthma and COPD and acts via all the following mechanism except?

A. PDE 4 Inhibition
B. Blockade of adenosine receptors
C. Interleukin-1 release
D. Activation of histone deacetylase

Answer: C

Solution

Mechanism of actions - Methylxanthines (Theophylline):

- **PDE Inhibition :** 3 & 4
- **Blockade of adenosine receptors**
- **Interleukin - 10 release**
  - Has a broad spectrum of anti-inflammatory effects, and there is evidence that its secretion is reduced in asthma. IL-10 release is increased by theophylline.
- Therapeutic range : 5-15 mg/L
- **Effects on gene transcription**
  - Inhibits transcription of inflammatory genes
- **Effects on apoptosis** (increased apoptosis of eosinophils and neutrophils)
- Activation **of Histone deacetylase**
  - Recruitment of histone deacetylase-2 (HDAC2) by glucocorticoid receptors switches off inflammatory genes
  - Therapeutic concentrations of theophylline activate HDAC, thereby enhancing the anti-inflammatory effects of corticosteroids.

Q. Inhaled corticosteroids have an important role in control and prevention of asthma exacerbations in general population. One of the most common side effects of inhaled beclomethasone dipropionate is:

A. Pneumonia
B. Oropharyngeal candidiasis
C. Atrophic rhinitis
D. Pituitary adrenal suppression

Answer: B

Solution

- Most common adverse effect of inhaled corticosteroids is **oropharyngal candidiasis.**
- Pituitary adrenal suppression is less likely with inhalational route of corticosteroids than with oral route.
- inhalational corticosteroids are associated with local effects more than systemic effects.

LEARNING OBJECTIVES

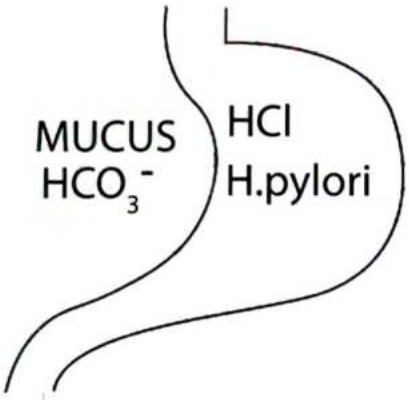
UNIT 6: GIT

- Drugs for Peptic ulcer
- Vomiting, Diarrhoea and IBD
  - Anti-emetic drugs
  - Anti-diarrheal drugs
  - Ulcerative colitis
  - Crohn's disease
- Laxative Purgatives

41 DRUGS FOR PEPTIC ULCER

Peptic Ulcer Disease 00:00:45

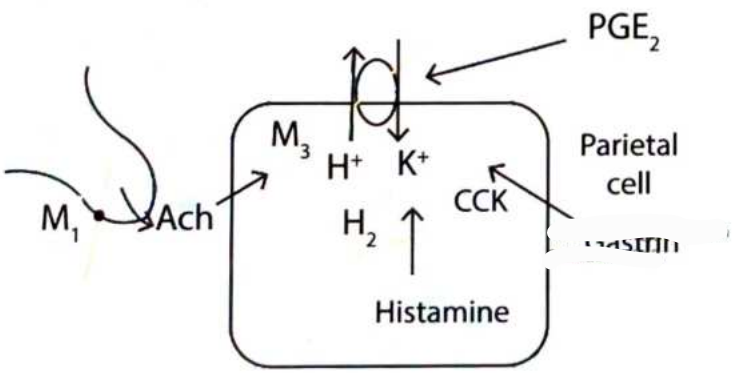
- It is d/t imbalance between Aggressive factors & protective factors of GIT
- Aggressive Factors: HCL, H. pylori
- Protective factors: Mucus & HCO_3



Treatment

1. ↓Acid secretion

- HCL is produced by Parietal cells of stomach
- Proton Pump (HK Pump)
  - helps in secretion of Acid
  - stimulated by
    - Ach (M)
    - Histamine [H]
    - Gastrin [CCK]



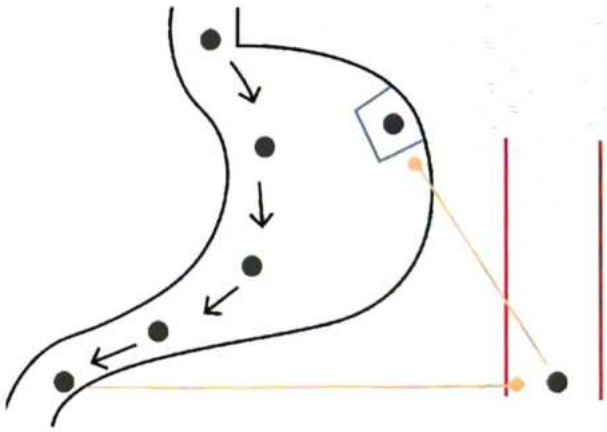
  - Inhabited by PGE_2
- These drugs can be divided into 4 types:

M1 blockers	H2 blockers	PGE2	PPI
•Pirenzepine	•Cimetidine	• Misoprostol	• Omeprazole
•Telenzepine	•Ranitidine		• Esomeprazole
	•Famotidine		• Pantoprazole
	•Loratadine		• Lansoprazole
			• Rabeprazole

- Most specific drug for NSAID induced Peptic ulcer → Misoprostol
- DOC for NSAID induced Peptic ulcer → PPI

PPIs [Proton Pump Inhibitors] 00:11:42

- Irreversible inhibitors
- Example of hit and run drugs
- Exerts systemic effect [does not work locally]

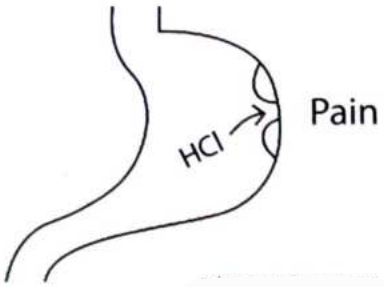


- Normally acid labile
- Given with acid resistant coating Enteric coating
- DOC for PUD d/t any reason
- DOC for GERD
- DOC for Zollinger Ellison Syndrome
- S/E [chronic use] :
  - ↓Ca^{2+} (Osteoporosis)
  - ↓Vit B12 (megaloblastic anemia)
  - ↑Infections
  - Carcinoid syndrome (not noted in humans)

2. Antacids

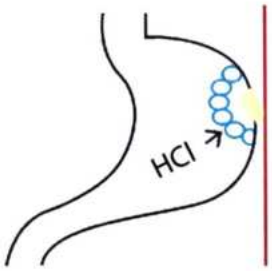
- Fastest pain relievers of PUD
- Includes

- Al [OH]; Cause constipation
- Mg[OH]; Cause Diarrhea



3. Ulcer Protective Drugs

- They form a protective covering over the ulcer, which helps the ulcer to heal
- Drugs include:
  - Sucralfate
  - Colloidal Bismuth sub-citrate (CBS)



- Sucralfate acts bypolymerization, requires acidic pH [<4]
  - Should not combined with antacids
- CBS can causeBISMUTH POISONING:
  - Bone: Osteodystrophy
  - Brain: Encephalopathy

4. H. Pylori Drugs

- Amoxycillin
- Metronidazole
- Clarithromycin

Treatment of Peptic ulcer disease:

- Triple Drug therapy: PPI + 2AMA
  - **C** - Clarithromycin
  - **A** - Amoxycillin
  - **P** - PPI

} Preferred

How to remember

- CAP therapy

42 VOMITING, DIARRHOEA AND INFLAMMATORY BOWEL DISEASE

ANTI EMETIC DRUGS

00:00:20

1. Anti-cholinergic drugs:
   - Hyoscine
2. H^1 blockers doxylamine [DOC for morning sickness]:
   - Doxylamine
3. $5HT_3$ blockers:
   - Ondansetron
   - Granisetron
   - Tropisetron
   - Palonoseton [most potent]

   } DOC for: Chemotherapy induced vomiting, Radiotherapy induced vomiting, Post op. vomiting
4. Neurokinin Antagonists [Substance-P Antagonists]:
   - Aprepitant
   - Neupitant
   - Rolapitant

   } DOC for Delayed vomiting by Cisplatin
5. D_2 Antagonists

Metoclopramide	Domperidone
• Cross BBB	• Do not cross BBB
• Can cause dystonia	• Do not cause dystonia
	• DOC for Levodopa induced vomiting
• 5 HT_3#	• No other action
• $5HT_4$ agonists	

ANTI-DIARRHEAL DRUGS

00:08:55

1. **ORS**
   - Contains
     - NaCl
     - KCl

     } Replenishes electrolytes
     - Trisodium citrate → prevent acidosis
     - Glucose → to help in Na^+ absorption
2. **Anti Microbials** (for infections)
   - Metronidazole for amoeba infection
   - Ciprofloxacin for bacterial infection

   } Combined usage is irrational
3. **Non infective diarrhea**
   - Loperamide
   - Diphenoxylate

   } ↓Intestinal motility
4. **Somatostatin derivative for Secretory diarrhea**
5. **Racecadotril**
   - It is an Enkephalinase inhibitor
   - Enkephelinase are one of the endogenous opioids
   - Enkephalins $\xrightarrow[\text{Enkiphalinase}]{}$ Degradation

INFLAMMATORY BOWEL DISEASE

00:12:15

I. **Ulcerative Colitis**
   - 5-ASA Derivatives
     i. Sulfasalazine → 5 ASA + Sulfapyridine
     ii. Olsalazine → 5 ASA + 5-ASA
     iii. Mesalamine
   - Steroids given if not responding with 5-ASA derivatives

II. **Crohn's disease**

i. Steroids → DOC

ii. TNF- blockers → if not responding with steroids
   - Adalimumab
   - Certolizumab
   - Etanercept
   - Infliximab

43 LAXATIVES AND PURGATIVES

Laxatives and Purgatives

- Laxative causes Semi Solid stools
- Purgative causes Watery stools

Uses

1. **Functional Constipation** [not for obstructive constipation]
- Constipation is preferably Rx by High fibre diet & regular exercise
2. **To prevent straining** in patients of:
- Hernia
- Piles
- Anal fissure
3. **X-rays of KUB**
4. **Along with Anti Helminthic Drugs** (Niclosamide)

The various types of purgatives include:

i. Bulk forming (should be given with plenty of water)
- Dietary fibre
- Psyllium
- Methyl cellulose
- C/I in megacolon

ii. Osmotic Purgatives
- Saline purgatives
  - $MgSO_4$ and $Mg(OH)_2$
  - C/I in chronic renal failure
- Lactulose
- Poly Ethylene Glycol (PEG)

iii. Stool Softeners
- Decrease the surface tension of fluids in GIT
- Docussate (Di Octyl Sodium Sulfosuccinate)

iv. Stimulant Purgatives
- Organic compounds: Bisacodyl, Na Picosulphate
- Side effect: Colonic atony (on long term usage)
- Anthraquinones: Senna, Cascara
- S/E: Melanosis coli
- Castor Oil
- Stimulation purgatives are C/I in Obstructive constipation

New drugs

1. Chloride channel activators
- They act by releasing chloride ions (Cl^-) in lumen of intestine. To maintain the electroneutrality, sodium (Na+) is also released in the lumen. Na^+ carries water with it. This makes the stool soft to treat the constipation.
- Two mechanisms of Chloride channel activators,

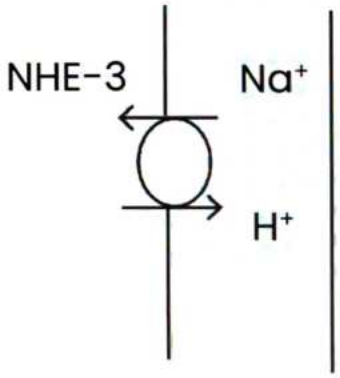
i. Direct Cl channel-2 activator
  - Lubipristone

ii. Guanylyl Cyclase activator

↓
↑cGMP
↓
CFTR is activated
↓
Opens Cl- channels

  - Guanylyl Cyclase activators include:
    → Plecanatide
    → Linaclotide
- Common side effect of both Direct chlorine channel activator and Guanylyl cyclase activator is: Dehydration.
- So these drugs are indicated only after 18 years of age and avoided in children

2. NHE_3 inhibitor



- Tenapanor (Sodium hydrogen exchange antagonist) is the drug that inhibits the exchange of sodium and hydrogen. It is administered via oral route and prevents the reabsorption of sodium in GIT. Water follows sodium which makes the stool soft.
- Tenapanor increases the tight junctions in intestine and by that mechanism it inhibits the phosphate reabsorption also.

3. Peripheral Opioid antagonists
- Alvimopan
- Methylnaltrexone
- Naloxegol
- Naldemedine
  - There are indicated for opioid induced constipation.

CLINICAL QUESTIONS

DRUGS FOR PEPTIC ULCER

Q. A 45 year old male, working as the CEO of a multi-million dollar Automobile company, comes to your clinic with complaints of burning sensation in epigastric region for the past 3 months, and claims to have taken on & off non-allopathic treatment, without much benefit. And since the patient claims to be a bit forgetful, which of the following medications would you prescribe, such that it provides round-the-clock protection, by inhibiting the acid secretion?

A. Omeprazole
B. Cimetidine
C. Pirenzepine
D. Misoprostol

Answer: A

Solution

- PPI like omeprazole are strongest acid inhibitors.
- PPI are drug of choice for peptic ulcer.

Q. A patient walks in to your clinic for the 10th time this year, with complaints of gastric irritation and diarrhoea. He was diagnosed to have peptic ulcer disease before and treated with different modalities, multiple times. You suspect something else being the primary cause, check for serum gastrin levels, which surprisingly turn out to be high and you lock on the diagnosis- Zollinger Ellison Syndrome. Which of the following medications would you prescribe for management of this?

A. Cimetidine
B. Omeprazole
C. Misoprostol
D. Aluminium hydroxide

Answer: B

Solution

- **Proton pump inhibitors** are the **drugs of choice** for **peptic ulcer disease (PUD)** due to any etiology (even NSAID induced).
- These are also the **agents of choice** for gastroesophageal reflux disease **(GERD)** and Zollinger Ellison Syndrome **(ZES)**.

Zollinger Ellison syndrome:

- It is a Pancreatic or duodenal gastrinoma which leads to secretion of large amounts of gastric acid causing severe ulcers and hyperchlorhydria. PPI are better than H2 blockers in this condition.

Q. The success of oral rehydration therapy of diarrhea depends upon which of the following processes in the intestinal mucosa?

A. Sodium pump mediated Na+ absorption
B. Glucose coupled Na+ absorption
C. Bicarbonate coupled Na+ absorption
D. Passive Na+ diffusion secondary to nutrient absorption

Answer: B

Solution

- **Glucose coupled Na+ absorption** from GIT remain patent even in presence of severe diarrhea whereas other mechanisms may fail.
- Thus, **glucose is added in the ORS**.

Q. A 20 year old foreigner, who had recently come to India for vacation, comes to the emergency with complaints of acute, multiple (6) episodes of loose bowel movement and informs that he is a diagnosed case of Ulcerative colitis. On probing, you hear that he had been symptom free for over 3 months, prompting him to go for a vacation he has longed for and on physical examination, you notice that he is tachycardia and mildly febrile. Which of the following medications would you prescribe for this patient?

A. Prednisolone
B. Sulfasalazine
C. Mesalazine
D. Vancomycin

Answer: A

Solution

- **Corticosteroids** are the mainstay of treatment of **acute exacerbation of ulcerative colitis**.
- so, among the given options **prednisolone** is best to be used in controlling acute exacerbation of ulcerative colitis

LAXATIVE PURGATIVES

Q. Laxatives are of multiple types, including bulk forming, stimulant and osmotic type. All of the following are examples of osmotic laxatives, except?

A. Sorbitol
B. Magnesium Hydroxide
C. Polyethylene glycol
D. Bisacodyl

Solution

Laxatives

Bulk forming	**Osmotic**	**Stimulant**
• Dietary fibre	• Sorbitol • Lactulose • Polyethylene glycol • Mg(OH)2 • MgSO4	• Senna • Cascara • Bisacody

Q. Colonoscopy performed on a 25 – year – old woman with eating disorder showed dark brown to black pigmentary deposit in the lining of the large intestine. Histopathology of biopsy revealed pigment laden macrophages within the lamina propria. The woman on probing revealed use of laxatives for the 9 months to lose weight. What could be the probable laxative agent that could have caused these findings?

A. Senna
B. Sorbitol
C. Castor oil
D. None of the above

Answer: A

Solution

Laxatives and purgatives causes **semi solid stools and watery stools** respectively.

Includes:

Bulk forming : Bran, Psyllium, Ispaghula

Osmotic purgatives: Saline, lactulose, polyethylene glycol, Sodium potassium tartrate

Stool softener: Docussate, Liquid Paraffin

Stimulant purgatives:

- **Organic** : Bisacodyl, sodium pico sulfate
- **Anthraquinones**: Senna and cascara. **S/E: Melanosis coli**.
- **Fixed oil** : Castor oil

As colonoscopy shows dark brown to black pigmentary deposit in the lining of large intestine, most likely drug she could be taking is Senna.

Bisacodyl is also implicated in causing **melanosis coli.**

LEARNING OBJECTIVES

UNIT 7: ENDOCRINE SYSTEM

- Pituitary Hypothalamic system
  - Pituitary gland
  - Anterior pituitary hormones
  - Posterior pituitary hormones
  - Diabetes insipidus
  - SIADH
- Thyroid
  - Thyroid hormones
  - Physiology
  - Hyperthyroidism
- Pancreas
  - Hormones
  - Glucagon
  - Insulin
  - New anti-diabetic drugs
- Adrenal gland
  - Medulla and cortex hormones
  - HPA axis suppression
- Osteoporosis
  - Calcium imbalance
  - Drugs for osteoporosis
- Sex hormones
  - Estrogens
  - Progesterones
  - Androgens
- Oral contraceptives
  - Drugs used
  - Adverse effects
  - Other benefits
- Bromocriptine in DM

44 PITUITARY HYPOTHALAMIC SYSTEM

PITUITARY GLAND

Pituitary gland is divided into

Anterior lobe	Posterior lobe
• GH • TSH • ACTH • Gonadotropins • Prolactin	• Oxytocin • Vasopressin

Pituitary Gland Hormones	Hypothalamus control
• Growth Hormone (GH)	• GHRH (GH Releasing Hormone)
•	• GHIH (GH Inhibiting Hormone)
• Thyroid stimulating Hormone (TSH)	• TRH (Thyrotropin Releasing Hormone)
• Adreno corticotropic Hormone (ACTH)	• CRH (Corticotropin Releasing Hormone)
• Gonadotropins	• GnRH (Gn Releasing Hormone)
• Prolactin	• PIH (Prolactin Inhibiting Hormone)

- All hormones of anterior lobe are under the control of hypothalamus, so hypothalamus will increase or decrease the level of anterior pituitary hormones
- If there is loss of connection / lesion between pituitary and hypothalamus , then the level of all anterior pituitary hormones will decrease and only prolactin level will increase
- Growth hormone Inhibiting hormone and prolactin are under inhibitory control (GHIH and PIH respectively)
- Prolactin is under only inhibitory control because there is no releasing hormone for prolactin

1. Growth Hormone Inhibiting Hormones (GHIH) / Somatostatin

00:04:24

Organs which secrete it	Action	Uses
• Hypothalamus • Pancreas ○ α Cells [Glucagon] ○ β cells [Insulin] ○ cells [Somatostatin] • GIT • Blood vessels	• ↓GH • ↑Blood sugar • ↓Blood sugar • ↓Glucagon ↓ Insulin • ↓Secretions • Vasoconstriction	• Acromegaly • Islet cell tumors • Secretory diarrhea • Esophageal varices

- **Somatostatin uses:**
  - **S** - Secretory diarrhea
  - **O** - Oesophageal varices
  - **M** - Malignancy [islet cell tumors]
  - **A** - Acromegaly

How to remember

- SOMA-tostatin

- Somatostatin: Short acting therefore not effective
  Octreotide: Long acting somatostatin derivative, therefore it is preferred
- Any drug ending with "-tide" is peptide
- Any endogenous substance ending with "-in" are peptides
- Eg:
  - Somatostatin
  - Vasopressin
  - Oxytocin
- Peptides can't be given orally
- Octreotide → Given by S/C route

2. Prolactin Inhibiting Hormone (PIH) or Dopamine [DA]

00:08:51

- Hypothalamus
  ↓
  Secrete PIH

↓

Stimulate dopamine receptors in anterior pituitary

↓

↓ Serum prolactin

- DA acts through D2 receptors
- Dopamine Agonists (Drugs stimulating Dopamine Receptors act like PIH i.e. drugs decreasing prolactin)
- Eg.
  - Bromocriptine
  - Cabergoline (Long acting)
- Uses of Dopamine Agonists:
  - **Dopamine**: Diabetes mellitus type 2 (Bromocriptine is approved for this because it decreases insulin resistance)
  - **Agonists**: Acromegaly (by decreasing GH)
  - **Suppress**: Suppression of lactation
  - **Plasma**: Parkinsonism (Bromocriptine can be used)
  - **Prolactin**: Hyperprolactinemia

How to remember

- Dopamine Agonists Suppress Plasma Prolactin

- **Acromegaly**
  - Drugs given are
    i. Decrease GH release - Octreotide and Cabergoline
    ii. GH receptor antagonist - Pegvisomant
- **Pegvisomant**
  - Somatotropin antagonist (not somatostatin antagonist)
  - Polyethylene glycol added to make it long acting
  - Visual problems is its main S/E
- Pegvisomant and Octreotide are injectable drugs
- Cabergoline and Bromocriptine are oral drugs. Cabergoline is longer acting than Bromocriptine
- Suppression of lactation
  - Prolactin is a milk secreting hormone
  - Decreasing the level of prolactin can suppress lactation. Cabergoline can be used

3. Gonadotropin Releasing Hormone (GnRH) 00:13:35

Pulsatile fashion	Continuous Fashion (non-pulsatile manner)
↓	↓
↑Gonadotropins	↓Gonadotropins
↓	↓
↑ Estrogen	↓Estrogen,
↑ Progesterone	↓Progesterone
↑ Testosterone	↓Testosterone

Indications of GnRH

i. **In pulsatile manner**

1. Anovulatory infertility
2. Hypogonadotropic hypogonadism
3. Delayed Puberty

ii. **In continuous Fashion**

1. Cancers
   - Prostate cancer
   - Breast cancer
2. Endometriosis
3. Precocious Puberty

- GnRH Agonists include:
  - Leuprolide
  - Nafarelin (nasal route)
  - Goserelin
  - Busurelin
  - Histarelin
- Not effective orally

(Mostly given by subcutaneous route)

- **Flare up reaction:** When these are given in continuous manner, during initial 2-3 days there is aggravation of disease. This is called Flare up reaction. To prevent this, we give GnRH antagonists.
- **GnRH Antagonists:**
  - Cetrorelix
  - Ganirelix
  - Abarelix
  - Degarelix
    → No flare up reaction
    → But they do not↑sex hormones (used only to↓sex hormones)
    → Not effective orally
- **Elagolix**
  - Recently approved oral GnRH antagonist
  - No other GnRH agonist or antagonist is effective orally
  - Approved for pain due to endometriosis

POSTERIOR PITUITARY

Secretes 2 main hormones

Oxytocin	Vasopressin / Antidiuretic hormone (ADH)

00:24:07

Oxytocin

Main function-contracts the uterus

- DOC for augmentation of labor
- DOC for postpartum hemorrhage

Other function – Ejection of milk

- DOC for breast engorgement

00:25:41

Vasopressin (Antidiuretic hormone) acts on

V1 receptors	V2 receptors
1. V1 receptor are present in blood vessels and cause vasoconstriction	1. V2 receptors are present in Kidney and cause decrease in urine 2. V2 receptors are also present in endothelium of blood vessels where vWF and Factor VIII are released

Vasopressin Receptor Agonists

V1 agonist	V2 agonist
Terlipressin ↓ DOC for Esophageal varices	Desmopressin ↓ • DOC for neurogenic (central) diabetes insipidus (given by nasal route) • DOC for nocturnal enuresis • Can be used for von Willebrand disease and Hemophilia

Diabetes insipidus

Central Diabetes insipidus / Neurogenic DI	Nephrogenic DI
• Due to deficiency of ADH • DOC for central / neurogenic diabetes insipidus- Desmopressin • Desmopressin is given by nasal route (Selective V2 receptor Agonist)	• Due to ADH being secreted normally in Pituitary but not able to work on Kidney. • DOC for Nephrogenic diabetes insipidus is– Thiazides

Vasopressin Receptor Antagonists:

- They cause Vasodilation (via V_1) and increase in urine (via V_2)
- Vasopressin Antagonists are '-vaptans'
- These include:
  - Conivaptan: Given via intravenous route
  - Tolvaptan: Given via oral route
- Uses of vaptans:
  - Congestive heart failure (due to property of diuresis and Vasodilation)
  - SIADH

SIADH (Syndrome of Inappropriate ADH Secretion):

- Function of ADH is to retain only water
- Excessive ADH causes increased water retention leading to Hyponatremia
- Stepwise management in cases of SIADH

1. Fluid restriction
2. 3% NaCl (Hypertonic saline)
3. If symptoms persist, then drugs are given. DOC- vaptans (Conivaptan / Tolvaptan)
4. Demeclocycline (inhibits the release of ADH from posterior pituitary)

45 THYROID

Thyroid gland secretes the following hormones:

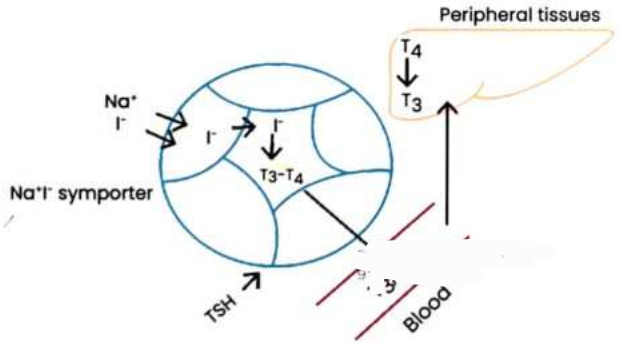
00:00:22

- T_3, T_4 } By follicular cells of thyroid gland
- **Calcitonin** – By parafollicular cells
  - TSH is secreted by Pituitary

00:01:12

T3	T4
• Short acting • More active	• Longer acting • Less active
• Liothyronine ○ Only indication: Myxedema coma (emergency hypothyroidism)	• L-Thyroxine ○ DOC for hypothyroidism (due to any reason) ○ DOC for myxedema coma

Physiology of Thyroid Hormone Production: 00:04:04



1. Iodide (I') enters into thyroid follicle by Na⁺ I symporter
2. From follicles, Iodide enters into colloid
3. In colloid, Iodide is converted into T_3 and T_4.

I⁻
↓ oxidation
I°
↓ organification tyrosine
MIT
DIT
↓ coupling
T_3
T_4

- All the 3 reactions i.e. Oxidation, Organification and Coupling are catalyzed by thyroid peroxidase
- T_3, T_4 are stored in colloid after formation

4. TSH stimulates the thyroid gland
5. T_3, T_4 are now released into circulation
6. Hormone reaches peripheral tissues/organs (Liver)

- In the blood, T_3 is active but less in quantity, T_4 is abundant but not much active

7. Peripheral conversion of T_4 into T_3 takes place in peripheral tissues/organs (Liver)

$$T_4 \xrightarrow[\text{metabolised}]{} T_3$$

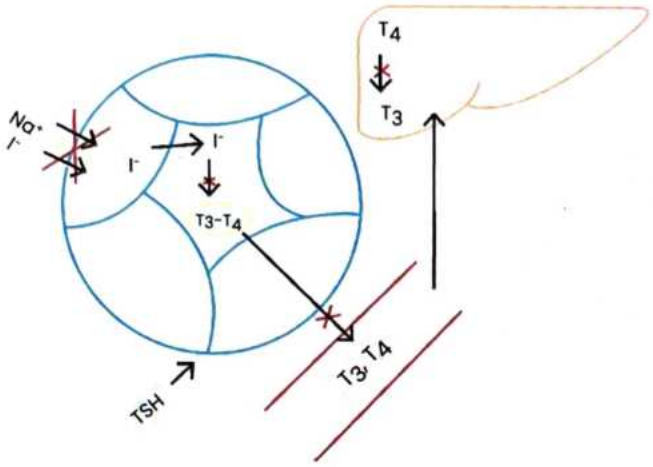
- Subscript 3, 4 in T_3 & T_4 represents → Numbers of Iodine atoms
  - T_3: 3, 5, 3'- Tri-Iodothyronine
  - T_4: 3,5,3',5'- Tetra-Iodothyronine
    - These are the positions where Iodine is attached in the chemical structure
- When iodine attaches to atoms without prime, it ↑ thyroid hormone activity
- When Iodine attaches to atoms with prime, it ↓ thyroid hormone activity → T_3 is quite active
  - In T_3 → 2 atoms ↑are without prime & 1 atom is with prime.
  - T_3 is quite active
  - In T_4 → 2 atoms ↑ 3, 3', 5'- Tri-Iodothyronine → Totally inactive
- When we want to convert T_4 to T_3 (Peripheral conversion)
  - T_4 (3,5,3',5 – Tetra-iodothyronine)
  - ↓5'-De-Iodinase: Helps in peripheral conversion of T_4 to T_3

HYPERTHYROIDISM

00:13:41

- Characteristic symptoms
  - Heat intolerance
  - Weight loss
  - Sympathetic features
- Drugs used
  I. NIS inhibitors
  II. Thyroid peroxidase inhibitors
  III. Secretion inhibitors

IV. Peripheral conversion inhibitors
V. Thyroid destroying drugs
VI. Adjuvant drugs



I. NIS Inhibitors

- Not used clinically (Toxic)
- Cabbage is a rich source of Thiocyanate → Goitrogen
- These include
  - Perchlorate
  - Pertechtenate
  - Thiocyanate

II. Thyroid Peroxidase Inhibitors

Thioamides

Carbimazole (inactive) Methimazole (active)	Propyl Thiouracil (PTU)
• More potent	• Less potent
• More plasma t ½	• Less plasma t ½
• Crosses placenta easily	• Less crossing of placenta • DOC in 1st trimester of pregnancy
• No action on peripheral conversion	• Decreases peripheral conversion

- All these 3 drugs can cause congenital malformation namely choanal atresia when used in pregnancy
- Doc for hyperthyroidism in pregnancy

1st trimester	2nd & 3rd trimester
• PTU	• Carbimazole • Methimazole

  - If trimester is not mentioned in the question, always mark PTU
- Slow acting drugs
- In normal person, stored T3, T4 suffice for 1-2 weeks
  - In hyperthyroidism, they suffice for 3-4 weeks
  - So dose increase of these drugs should be done after minimum 4 weeks
- Routinely for hyperthyroidism we prefer → Carbimazole, Methimazole

III. Secretion Inhibitors

1. NaI
2. KI
3. Lugol's Iodine

- Fastest acting anti-thyroid drugs
- Given preoperatively to make the gland small, firm and less vascular, reducing the blood loss during surgery.

IV. Peripheral Conversion Inhibitors

1. Propranolol
2. PTU
3. Prednisolone

V. Thyroid Destroying Drugs (I^{131})

- I^{131} (Radioactive Iodine) is used because:
  - NIS restricts I^{131} to thyroid gland
  - I^{131} is stored in centre of colloid, so emission of radioactive rays is confined
  - I^{131} mainly emits β-rays, which have less penetrating power
- C/I in pregnancy
- Can be given orally
- Radioactive drugs cause Irreversible hypothyroidism, so requires lifelong thyroid hormone therapy→so C/I in <35 yrs aged patients
- All other antithyroid drugs cause reversible hypothyroidism, discontinuation of the drug is sufficient
- I^{131} $t_{1/2}$: 8 days

I. Drugs Used for Controlling Symptoms (Adjuvant drugs)

- Mostly symptoms are sympathetic (like tachycardia, palpitations, tremor, hypertension etc.). So-β blockers can be used
- Most impβ#→Propranolol [along with treating the symptoms, it also peripheral conversion of $T_4 \rightarrow T_3$]
- It is the life – saving drug in Thyroid storm
- **Thyroid Strom** (Emergency hyperthyroidism):
  - DOC (overall) for thyroid storm: Propranolol
  - Antithyroid DOC: Propylthiouracil

46 PANCREAS

00:00:13

	Secretes	Action	Uses
αcells	Glucagon	↑Blood Sugar	Hypoglycemia
βcells	Insulin, Amylin	→↓Blood Sugar	DM
δcells	Somatostatin	↑insulin & glucagon	Islet cell tumor

GLUCAGON

00:01:31

Uses

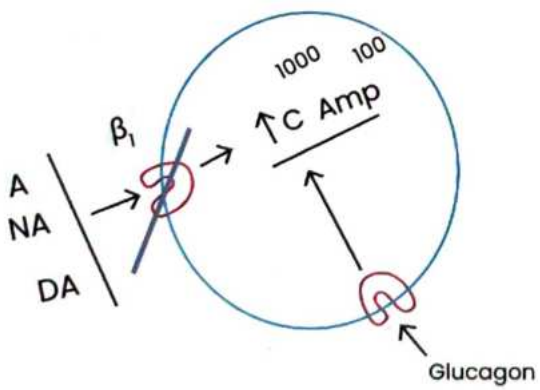
1. Hypoglycemia

- MOA – acts by Glycogenolysis
  - Not useful in hypoglycemia caused by
  - Starvation
  - Alcohol induced hypoglycemia

2. β-blocker poisoning [DOC]

- β1 → Stimulate the heart
- In β-blocker poisoning, these receptors are not working, resulting in depression of heart→Bradycardia and decrease in contractility
- As β receptors are not working, we should ↑ cAMP by other methods like stimulating glucagon receptors on heart
  - On heart, there are glucagon receptors:

Glucagon
↓Stimulates
Glucagon receptors on heart (GPCR)
↓cAMP
Heart is stimulated



  - Glucagon is antidote for β - blocker poisoning
  - Other drugs to treat β - blocker poisoning:

i. Anticholinergic drugs like Atropine. It will block M_2 receptors i.e reverse the bradycardia
ii. Ca^{+} directly stimulates the heart
iii. Phosphodiesterase inhibitors. They will inhibit metabolism of cAMP

INSULIN

00:06:59

Indications

1. Type 1 DM [IDDM] → All patients of type 1 DM require insulin (can be treated only with insulin)
2. Type 2 [NIDDM] → Uncontrolled patients (other patients can be treated without insulin)
3. Gestational DM (or any diabetes in pregnancy)→ DOC
4. Diabetic Ketoacidosis → DOC
5. Acute hyperkalemia → non-diabetic use (Hypokalemia is a side effect)

- Insulin
- Salbutamol

} Help in intracellular movement of blood K+ (i.e. movement of K+ from blood into cells) (Thus correcting acute hyperkalemia)

Routes of Administration

1. Sub – cutaneous route

- MC route (because self administration is possible with this route)
- All insulin preparations can be given by subcutaneous route
- Site of administration:
  i. Entire abdomen except area around umbilicus (thickness of skin is not uniform so insulin absorption is affected)
  ii. Anterior thigh
  iii. Lateral thigh
  iv. Arm

2. Intravenous route

- Only regular insulin can be given
- So, insulin of choice in diabetic Ketoacidosis→Regular insulin

3. Inhalational route:
- Exubera- withdrawn from market
- Afreeza- Short acting insulin – so, should be given before every meal
- It is not a stand–alone insulin (given with injectable insulin)

Preparations of Insulin

Short Acting	→Regular Semi-lente
Intermediate Acting	→NPH Lente
Long Acting	→ Ultra - lente

- Lente - Insulin with Zn combination
- Zn - Stabilizes the hexameric form of insulin
- More Zn - Longer acting
- Less Zn - Short acting

Insulin analogues

Insulin analogues

Rapid acting (ultra-short acting)	**Ultra long acting**
• LISPRO • ASPART • GLULISINE ↓ Fastest acting insulin. Given by s/c route	• GLARGINE • DETEMIR • DEGLUDEC ↓ Longest acting insulin ○ Also k/a peakless insulins (never attain a peak in the plasma) ○ Thus, have low risk of hypoglycemia

- Most insulin preparations are available at → Neutral pH (so can be mixed with other insulins) but Glargine is at acidic pH (<4) [No insulin should be mixed with it]
- All insulin can be given subcutaneously but regular insulin can be given IV also therefore regular is insulin of choice in Diabetic ketoacidosis

S/E of Insulin

1. Hypoglycemia
- MC & most dangerous
- S/E which can be easily prevented
- Advise to patients for prevention

1. Do not skip meals
2. Keep Glucose with them

2. Hypokalemia

3. Lipoatrophy
(Results from repeated injections at the same site)

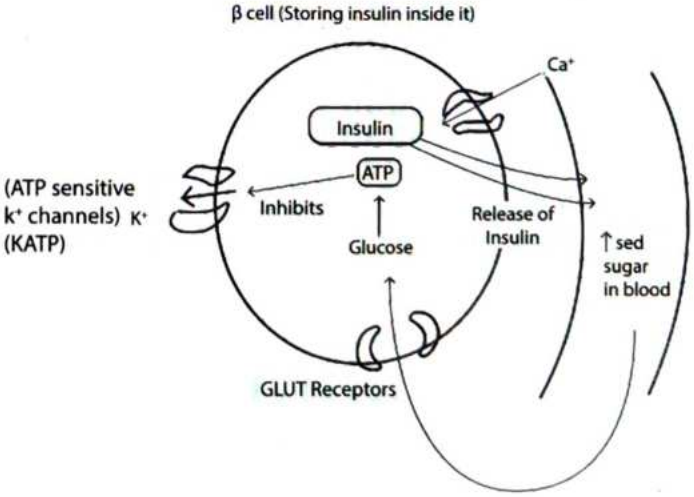
ORAL ANTIDIABETIC DRUGS

00:24:52

Acts by ↑**Insulin** (Insulin secretagogues)	Acts by **other mechanisms**
• S/E – hypoglycemia • > 30% functional β cells should be present	• No hypoglycemia • No such requirement

- **How beta cells secrete insulin**

Increase in blood glucose
↓
Entry of glucose in beta cells through GLUT receptors present on the cells
↓
Glucose is metabolized to form ATP
↓
ATP blocks KATP (ATP sensitive K+ channels) present on cells
↓
K^+ can't exit causing Increased K^+ inside cell leading to slight depolarization
↓
Slight depolarization leads to opening of calcium channel
↓
Influx of calcium leads to depolarization and release of insulin



- All the drugs which act by increasing inulin inhibits ATP sensitive K+ channel.

I. DRUGS WHICH ACT BY INCREASING INSULIN

00:27:29

Sulfonylureas

- 1st Generation
  - Chlorpropamide
  - Tolbutamide
- 2nd Generation
  - Glipizide
  - Gliclazide
  - Glibenclamide

Meglitinides

- Nateglinide
- Repaglinide

- Apart from Insulin, among antidiabetic drugs, drugs ending with "-ide" can cause hypoglycemia

Chlorpropamide

- It causes
  - Cholestatic Jaundice
  - Disulfiram like reaction
  - ↑ADH release [retains H20]
- Dilutional hyponatremia
- Also indicated for diabetes insipidus

Meglitinides

- Short acting [work for ~1hr]
- Indicated in post prandial hyperglycemia

II. DRUGS ACTING BY OTHER MECHANISMS

00:33:36

1. AMP Kinases or Biguanides

- Metformin
- Phenformin
  - Biguanides act by activating an enzyme AMP Kinase Phosphorylates
    ↓
    Rate limiting enzymes of many metabolic pathways resulting in
    ↓
    ↓Blood sugar { Some pathways → Activates; Some pathways → Inactivated }
- **Effects** of AMP Kinase
  i. Gluconeogenesis (-)
  ii. Glycogenolysis (-)
  iii. Glycogenesis (+)
  iv. Glycolysis (+)
- These drugs do not release insulin→so do not cause hypoglycemia
- **S/E** of biguanides
- Megaloblastic Anaemia→more a/w Metformin
- Lactic acidosis → more a/w Phenformin
- **Phenformin**→is more a/w Lactic Acidosis than Metformin so not used now
  - More a/w Megaloblastic anaemia
  - Contraindicated in
    → Liver diseases
    → Renal diseases
    → Lung diseases
- **Metformin**- DOC for Type 2 DM because:
  - No risk of hypoglycaemia
  - Max. reduction in HbA1c
  - Can cause weight loss (no weight gain)
  - **M** - **M**etformin preferred in
  - **O** - **O**bese patients
  - **S** - **S**uphonylureas preferred in
  - **T** - **T**hin patients

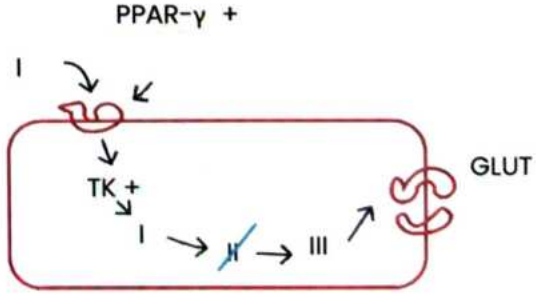
How to remember

- MOST

  - Metformin also indicated for PCOD [to reverse Insulin Resistance]

2. Glitazones (Thiazolidienediones)

- These include:
  - Troglitazone
  - Rosiglitazone
  - Pioglitazone
- Acts by stimulating PPAR-γ→Reversal of Insulin Resistance



- **S/E**

I. Hepatotoxic
   - Max. hepatoxicity→ Troglitazone [withdrawn]
   - Rosiglitazone & Pioglitazone requires LFT monitoring

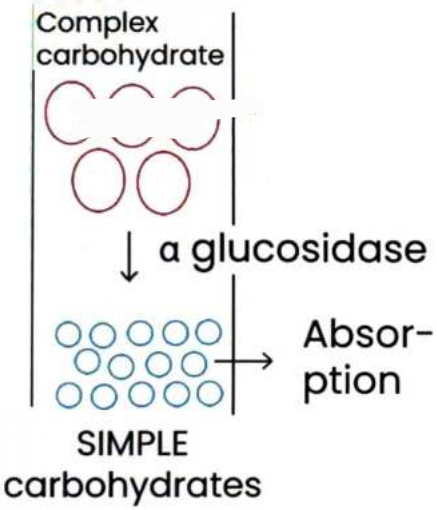
ii. Na^+ & Water retention → avoided in CHF & HTN

iii. ↑risk of MI by ROSIGLITAZONE

iv. ↑risk of urinary bladder carcinoma by Pioglitazone

3. α-glucosidase inhibitors

- Acts by inhibiting the intestinal absorption of carbohydrates (blood sugar decreases)
- These include
  - Acarbose
  - Miglitol
  - Voglibose



- MC side effect of this group: Flatulence (due to production of gases)
- C/I in Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease
- Bacteria will start metabolizing complex carbohydrates accumulated in GIT

↓

Fermentation of these complex carbohydrates

↓

Gas production

↓

Flatulence

- Hypoglycemia in presence of ∝-Glucosidase Inhibitors → treatment only by Glucose

NEW ANT DIABETIC DRUGS

00:53:34

1. Incretin – mimetics

- Normal physiological substances which are released in GIT after food intake and stimulates release of insulin which control blood sugar. (Prevent post prandial hyperglycemia)
- Most important endogenous incretin is GLP (Glucagon like peptide)
- **Functions** of GLP:-
  - Increase insulin release
  - Decrease gastric motility
  - Stimulate satiety centre of brain
  - Inhibit apoptosis of β-cells of pancreas
- GLP is metabolized by DPP – 4 and becomes inactive
- In diabetic patient, GLP is not enough secreted. So in diabetic patient we use:

a. **GLP analogues**

b. **DPP-4 inhibitors**

a. GLP analogues

- These include
  - Exenatide
  - Liraglutide
  - Albiglutide
  - Dulaglutide
  - Semaglutide

  } GLP-1 analogues

- Teduglutide
  - GLP-2 analogue
  - Given subcutaneously (cannot be given orally since these are peptides)
- **Semaglutide**
  - Only GLP analogue given Orally
  - Causes weight loss
- **Liraglutide**
  - Approved for obesity
  - Risk of hypoglycemia is very less (compared to other insulin releasing drugs)
- **Side effects of GLP analogues**
  - Acute pancreatitis (major side effect)
  - Nausea (most common)
  - Increased risk of Medullary carcinoma of Thyroid
- **GLP – 1**
  - Major function – insulin secretion

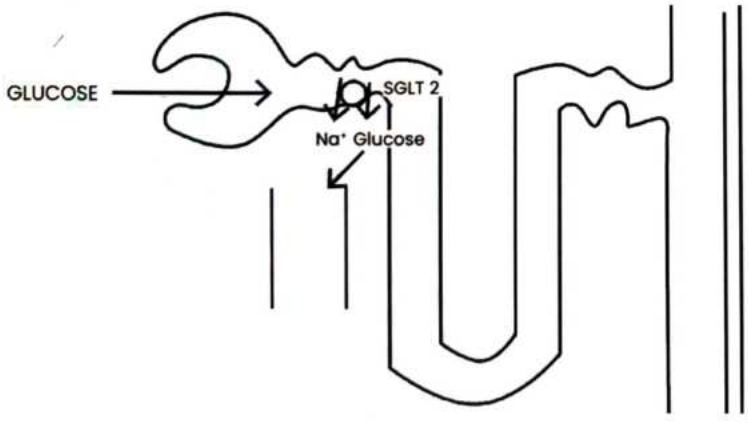
- Minor function – decrease in gastric emptying
- **GLP-2 (Teduglutide)**
  - Major function – decrease in gastric emptying
  - Minor function – insulin secretion
  - Teduglutide is indicated in Short Bowel Syndrome as it decreases gastric emptying.

b. DPP – 4 inhibitors

- These include:
  - Sitagliptin
  - Vildagliptin
  - Alogliptin
  - Linagliptin
  - Dapaliptin
  - Saxagliptin
- Gliptins are oral anti diabetic drugs. These can cause weight loss, but do not cause hypoglycemia
- **Side effects**
  - Nasopharyngitis (most common)
  - Pancreatitis
- **Contraindications:**
  - Gliptins are contraindicated in renal failure except Linagliptin which is safe in renal failure

2 SGLT – 2 Inhibitors

- Glucose is freely filtered by glomerulus but the clearance of glucose in urine is negligible
- Because the reabsorption takes place in proximal tubule by sodium glucose symporter (SGLT-2)



- SGLT – 2 inhibitors inhibit the sodium glucose transporter and hence glucose is not reabsorbed in proximal tubule and expelled in urine, which is also known as Glucosuria
- Drugs included are:
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Ertugliflozin
- Most common side effect of SFLT-2 Inhibitors is Urinary Tract Infections (Urosepsis) and genital Tract infections (Fournier's gangrene)
- If gliflozins are taken by type 1 diabetes patients, it controls blood sugar level and makes it normal and then if the patient stops taking insulin, it will result in Diabetic Ketoacidosis (as type 1 diabetes is characterized by complete deficiency of insulin)

3. Amylin Analogs

- Amylin is secreted from β-cells of pancreas
- Function of amylin is to ↓ blood sugar
- ↓ blood sugar by decreasing glucagon
- Pramlintide is an amylin analogue which is given by Subcutaneous route and it causes hypoglycemia as side effect.
- It is approved for both type 1 and 2 diabetes.
- Only 2 drugs are given in type 1 as well as type 2 diabetes which are Insulin and Pramlintide, rest all other drugs are indicated only in type 2 diabetes.

4. Bromocriptine

- Decreases insulin resistance
- It has been recently approved for type 2 diabetes
- Given in small dose and taken at early morning on awakening.
- Increases early morning dopaminergic activity and decreases sympathetic activity. This restores insulin sensitivity.

47 ADRENAL GLAND

Adrenal Medulla	Adrenal Cortex

• Secretes
  ○ Adrenaline
  ○ NA
  ○ DA
	• Secretes
	  ○ Glucocorticoids
	  ○ Mineralocorticoids

00:00:51

- **Aldosterone** → Major endogenous Mineralocorticoid
- **Hydrocortisone** → Major endogenous Hydrocortisone
- **Actions of Aldosterone:**

1 ↑Na^+, ↑H2O
2 ↓K^+, ↓H+

00:02:28

Hyperaldosteronism	Hypoaldosteronism
• Cushing syndrome • Conn's syndrome • Na+, H_2O retained ↓ HTN • K+ H+ removed ↓ Hypokalemia, alkalosis	Addison's disease • Na+ lost ↓ Hypotension • K+, H+ retained ↓ Hyperkalemia, Metabolic acidosis

- **Actions of Hydrocortisone:**

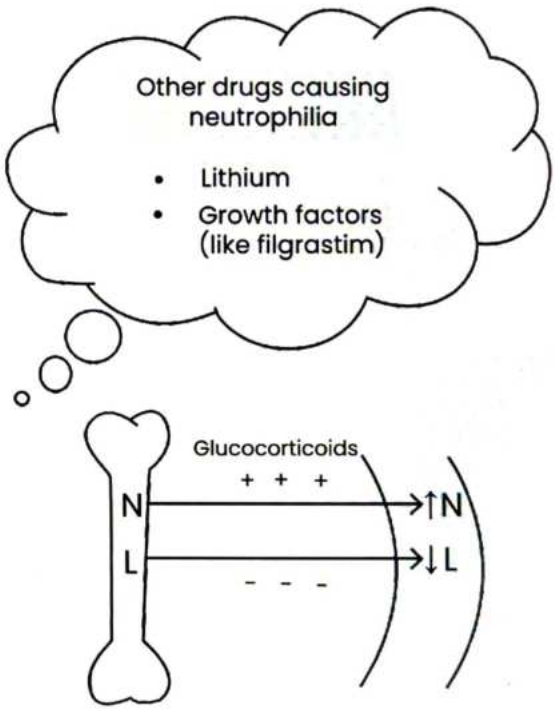
1. Catabolic Action
- Carbohydrate [CHO] breakdown to glucose→avoided in DM
- Protein breakdown myopathies can occur
- Fat breakdown [mainly from periphery] Cushing Syndrome
- Ca^{2+} metabolism causes Osteoporosis

2. Anti-inflammatory Action
- Mainly by inhibition of chemotaxis
- Used in inflammatory conditions (-itis)
- Cause delayed wound healing

3. Immune suppressant
- Indicated in Transplantation & Autoimmunity
- But predispose to infections

4. Anti-Cancer Action
- Indicated in
  - HL [Hodgkin Lymphoma]
  - NHL [Non Hodgkin lymphoma]
  - LL [Lymphocytic leukemia]
- C/I in Kaposi sarcoma

5. Effect on Blood:
- All the blood cells are produced in bone marrow and then sent to the blood.
- Glucocorticoids increase movement of neutrophils from bone marrow to blood which results in Neutrophilia, but glucocorticoids inhibit the movement of Lymphocytes from bone marrow to blood
- Hence the net effect of glucocorticoids in blood is,
  - Neutrophilia
  - Lymphopenia



00:08:20

Glucocorticoids (Anti Inflammatory)	Mineralocorticoids (Na^+, H_2O)
Short Action (<12 hrs) • Cortisone • Hydrocortisone	• Aldosterone • Fludrocortisone • DOCA
Intermediate Action (12-36 hrs) • Prednisone • Prednisolone • Triamcinolone	

Long Acting (>36 hrs)

- Dexamethasone
- Betamethasone
- Paramethasone

Max. glucocorticoid activity (Anti-inflammatory activity)

- **Dexamethasone**

Max. glucocorticoid potency

- **Betamethasone**

Glucocorticoid with max. mineralocorticoid activity

- **Hydrocortisone**

Max. mineralocorticoid activity (Salt + water retaining activity)

- **Aldosterone**

Mineralocorticoid with max glucocorticoid activity

- **Fludrocortisone**

Glucocorticoid with Zero Mineralocorticoid **activity**
(Selective glucocorticoid)
O Zero
M Mineralocorticoid activity

- Triamcinolone
- Dexamethasone
- Betamethasone
- Paramethasone

Mineralocorticoid with Zero Glucocorticoid **Activity**
(Selective mineralocorticoid)
O Zero
C Cortisone like activity

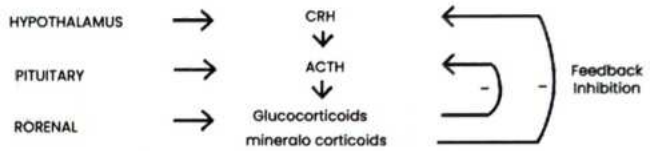
- DOCA

Uses of Corticosteroids 00:13:25

Antenatal Uses	Replacement Uses	Other Uses	Diagnostic Uses
Dexa/Betamethasone For fetal lung maturity (Glucocorticoids increase surfactant production)	Acute Adrenal insufficiency/ Addisonian crisis [by IV route] Chronic Adrenal Insufficiency/ Addison's disease [by oral route]	Inflammations Auto immune dis. Transplantations Anti-cancer therapy Asthma	Dexamethasone suppression test (used for diagnosis of Cushing syndrome)

Ante Natal Steriods dose	Total dose	Total duration
Betamethasone → I.M. 12 mg per 24 hrs x 2 Doses →	24 mg	48 hrs
Dexamethasone → I.M. 6 mg per 12 hrs x 4 Doses →	24 mg	48 hrs

HYPOTHALAMO – PITUITARY – ADRENAL Axis [HPA Axis]



Dexamethasone Suppression Test 00:19:02

- Excessive glucocorticoids in the blood may be a normal physiological process or due to Cushing syndrome
- Dexamethasone suppression test is used to confirm whether excessive steroids are due to Cushing syndrome or normal physiological process

1 mg dexamethasone at night 11 pm
↓
Measure the cortisol level at 8 am

Cortisol level <3 → No Cushing syndrome (proper suppression occurring) (Normal physiological process)

Cortisol level > 5 → Cushing syndrome present (improper suppression)

HPA AXIS SUPPRESSION

- Occurs when corticosteroids are given continuously for >2 wks.
- **Preventive Measures:**

1. Stop Unnecessary Use of Steroids
2. If indicated, prescribe them for <2wks
3. If indicated for long periods, prescribe them on Alternate day
   - Log acting steroids are avoided
4. If indicated daily & longer periods
   - Don't stop abruptly
   - Tapering should be done
5. A person taking steroids since 3 months but person develops infection (or stress induced under surgery)
   ↓
   Even then do not stop steroids
   ↓
   External supplementation of steroids must be given for preventing HPA axis suppression

Thus,
If HPA suppression is already present & person is in emergency

Give steroids from outside even if infection develops (Infection can be treated with antibiotics)

OTHER USES/ NON-REPLACEMENT USES

⏱ 00:29:00

1. Inflammations (anti-inflammatory action)
2. Auto immune Diseases & Transplantations (immunosuppression)
3. Anti-cancer therapy
   - HL [Hodgkin Lymphoma]
   - NHL [Non Hodgkin lymphoma]
   - LL [Lymphocytic leukemia]
   - MM [Multiple myeloma]
4. Asthma

ADVERSE EFFECTS & CONTRA INDICATIONS OF GLUCOCORTICOIDS

⏱ 00:31:09

- **G**-**G**laucoma [open angle glaucoma] [by long term topical steroids usage]
- **L** - **L**imb muscle atrophy
- **U** - **U**lcer [peptic ulcer]
- **C**-**C**ataract [mostly posterior subcapsular cataract] [long term oral steroids usage]
- **O**-**O**steoporosis (steroids serum Ca^{+2})
- **C**-**C**ushing syndrome
- **O**-**O**steonecrosis (Avascular necrosis of bone) [High dose of steroids]
- **R**-**R**enal Failure C/I
- **T**-**T**b [Ileo-cecal TB] → C/I
- **I**-**I**nfections } C/I
- **C**-**C**HF }
- **O**- **O**edema
- **I**-**I**mpair healing
- **D** - **D**M C/I
- **S**-**S**uppression of HPA axis [most dangerous complication]

How to remember

- GLUCOCORTICOIDS

48 OSTEOPOROSIS

Ca^2 balance 00:00:13

	Serum Ca^2	Serum PO^{3-}_4
Vitamin D	↑	↑
Calcitonin	↓	↓
PTH [Para thyroid Hormone]	↑	↑

- **Vitamin D increases serum calcium by:**
  ↑Absorption, ↓Excretion } ↑Ca^{2+} →Bone used in in Osteoporosis
- **PTH increases serum calcium by**
  - Resorption of Bone→↓Bone Ca^{2+} →causes osteoporosis
- **Calcitonin decreases serum calcium by**
  - Moving Ca^{2+} to bone →↓ Bone Ca^{2+} → used in osteoporosis

OSTEOPOROSIS 00:03:16

Drugs used

1. Ca^{2+}
2. Vitamin D
3. Calcitonin (Intranasal route)
4. Thiazides (retain Ca^{+2})
5. Bisphosphonates

- Alendronate
- Risedronate
- Zolendronate

Treatment of osteoporosis

- Drugs act by
  - Stimulate Osteoblast
  - Inhibit Osteoclast

Bisphosphonates

- Inhibit osteoclasts [Bone easters]
- DOC for Osteoporosis [Osteoporosis due to any reason]
- Highly toxic to esophagus
- Precautions when giving Bisphosphonates:

1. Given on empty stomach
2. Given with full glass of water
3. Should not lie down for a min of 30 min after taking

- Route of administration
  Alendronate, Risedronate } Given orally
  Zolendronate →Given IV once yearly (long acting)
- **Uses** of Bisphosphonates:
  1. D.O.C for osteoporosis (due to any reason)
  2. D.O.C for hypercalcemia of malignancy
     (Cancer cells→metastasis to Bone→Stimulates osteoclasts resorption of bone) → Hypercalcemia
  3. Used for early stage Paget's disease of bone

Paget's disease

Early stage	Late stage
↓	↓
Stimulation of osteoblast	Stimulation of osteoblast
↓	↓
Osteoporosis	Osteosclerosis

- **Side Effects** of Bisphosphonates:
  - Esophageal toxicity / esophageal ulcers
  - Osteonecrosis of mandible
  - Zolendronate →causes renal failure

Post-Menopausal Osteoporosis 00:12:30

Estrogen

- Decreased estrogen is responsible for post-menopausal osteoporosis (estrogen is a bone friendly)
- Actions of estrogen
  - Bone →↑ Formation
  - Blood →↑HDL/LDL Ratio
  - Breast →↑ Carcinoma
  - Endometrium →↑Carcinoma
  - Liver →↑Clotting factors → Thromboembolism
- Not preferred for Rx of PM Osteoporosis
- Earlier HRT [Estrogen + Progesterone] was given, but not now (Progesterone added because it decreases risk of endometrial cancer, but progesterone increases risk of breast cancer which is a major side effect.)

SERM [Selective Estrogen Receptor Modulator]

Raloxifene

- Used in PM osteoporosis
- Additional Benefits
  - Decreases HDL
  - ↓ Breast & Endometrial carcinoma risk
- Side effect- increases risk of Thromboembolism

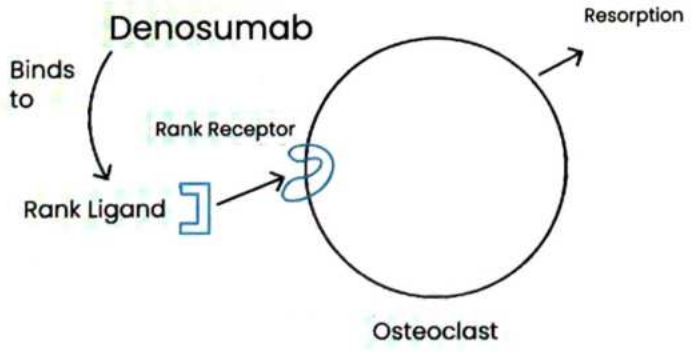
New Drugs ⏱ 00:18:34

1. PTH Analogues

- Each parathyroid molecule contains 84 amino acids (i.e. PTH1-84)
- Full molecule stimulates osteoclasts and induces osteoporosis by resorption of bone.
- A fraction of parathyroid (PTH 1 - 34) stimulates Osteoblast and it is isolated and used for osteoporosis treatment.
- Drugs (PTH1-34) are
  - Teriparatide
  - Abaloparatide (new drug)
- Mechanism of action: stimulation of osteoblasts
- Route of administration: Note effective orally. Given Subcutaneously
- Side effect: increase the risk of osteosarcoma

2. Denosumab

- On the surface of osteoclast cells, RANK receptors are present. When ligand binds to RANK receptors, it stimulates the resorption of bone.
- So, when the drug Denosumab binds to RANK ligand it inhibits the osteoclastic activity or resorption of bone.
- So Denosumab inhibits osteoclasts.



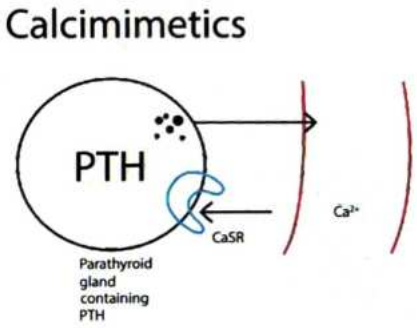
3. Strontium Ranelate

- It has Dual activity of stimulating osteoblasts and inhibiting osteoclasts
- Side effect
  - Thromboembolism

4. Romosozumab

- Sclerostin is a protein which has the function of inhibition of Osteoblast and stimulating Osteoclast (i.e. favours osteoporosis)
- Romosozumab is the drug which inhibits sclerostin activity
- Thus romosozumab also has dual mechanism.

5. Calcimimetics



- For osteoporosis occuring due to hyperparathyroidism
- Parathyroid gland has Calcium sensing receptors (CaSR). Whenever it senses and binds to calcium, it inhibits PTH release from Parathyroid gland.
- Hypocalcemia stimulates PTH release from Parathyroid gland.
- In Hyperparathyroidism patients, in spite of Hypercalcemia still PTH is more in the blood because the calcium is not able to stimulate CaSR.
- Calcimimetics are agonists of CaSR and when these stimulate CaSR, PTH is not released and bone resorption does not occur.
- Drugs are,
  - Cinacalcet
  - Etelcalcetide

Drugs	Stimulating osteoblasts	Inhibiting osteoclasts	Dual mechanism
	• PTH 1-34 analogues	• All other drugs	• Strontium ranelate • Romosozumab

49 SEX HORMONES

- Ovary in females secrete Estrogen and Progesterone
- Testes in males secrete Testosterone.

ESTROGENS

Natural Estrogens

- **E1** – Estrone – Predominant in Post-Menopausal Period
- **E2**- Estradiol- Predominant in Reproductive Age Group
- **E3**- Estriol – Predominant in Pregnancy

Drugs working on Estrogen Receptors

1. **SERM** (Selective Estrogen receptor modulators)
2. **SERD** (Selective estrogen receptor down regulators)
3. **STEAR** (Selective tissue estrogen activity regulators)
4. **Aromatase inhibitors**

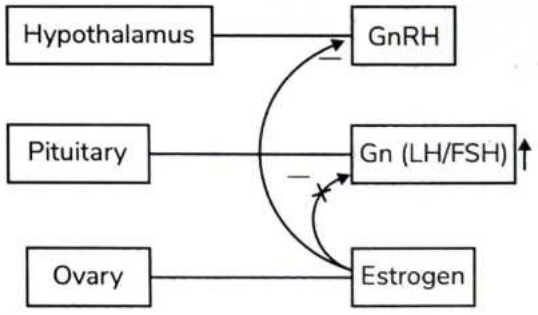
Estrogen works at

- Bone: inhibit osteoclast, so it increases bone formation
- Blood: increase HDL / LDL ratio
- Breast: increase the risk of cancer
- Endometrium: increase risk of cancer
- Liver: increase clotting factors and can lead to thromboembolism
  - In condition where there is absence of estrogen as in postmenopausal, there is vasomotor symptoms like hot flushes and vaginal atrophy.

1. Selective Estrogen Receptor Modulators (SERM)

00:03:55

- These act as agonist to estrogen receptor in some tissues and antagonist in some tissues.
- **Ideal SERM**
  - Increase bone formation
  - Increased HDL / LDL ratio
  - Decreased breast cancer risk
  - Decreased endometrial cancer risk
  - Decreased thromboembolism
  - Closest to ideal SERM is RALOXIFENE, however, it is agonist at liver. Therefore, the major side-effect is thromboembolism.
- **Newer SERMs** are
  - Tamoxifen
  - Doloxifen
  - Toremifen
  - Benefits:
    - Decreased breast cancer risk
    - Increase bone formation
    - Increase HDL / LDL ratio
  - S/E:
    - Increase risk of endometrial cancer
    - Increase risk of thromboembolism
- These new SERM are beneficial on three B'S:
  - Bone
  - Blood
  - Breast
- **Clomiphene**
  - SERM which are estrogen receptor antagonist in pituitary.
  - By inhibiting negative feedback of estrogen, it can increase LH / FSH and it can be used for treatment of anovulatory infertility.
  - Main side effect is Multiple pregnancy



- **Ospemifene**
  - Estrogen receptor agonist mainly in vagina.
  - Used for treatment of dyspareunia in post- menopausal women.
- **Ormeloxifene (Centchroman)**
  - Estrogen antagonist in endometrium
  - It is used for contraception
  - Brand name: SAHELI (developed by Central Drug

Research Institute in India, Lucknow)

2. Selective Estrogen Receptor Downregulator (SERD): 00:13:14

- Fulvestrant
- Used for Tamoxifen resistant breast cancer
  - More effective than Tamoxifen
  - Safer
  - Long acting

3. Selective Tissue Estrogen Activity Regulators (STEAR) 00:16:35

- Tibolone
  - Metabolized to different metabolites in different tissues. In some tissues, it forms agonist and in some it forms antagonist.
  - It is also known as Designer HRT
  - Forms agonist metabolite in:
    → Vagina (prevent vaginal atrophy)
    → Blood vessel (prevent vasomotor symptoms)
    → Bone (prevent osteoporosis)

4. Aromatase inhibitors 00:18:26

- These drugs are only indicated in Post – menopausal breast cancer, which is due to estrogen production outside ovary like adrenal gland.
- Not indicated in Pre-menopausal breast cancer
- Drugs
  - Letrozole
  - Anastrozole
  - Exemestane
- Androgen $\xrightarrow[\text{Aromatase}]{}$ estrogen

PROGESTERONES 00:20:43

	Also called	Potency	Androgenic Activity
1st Generation	Estranes	+	+++
2nd Generation	Gonanes	++	++
3rd Generation		+++	+
4th Generation		++++	Anti-androgenic

1st generation	2nd generation
• Nor-Ethindrone	• Norgestrel
• Nor-Ethinodrel	• Levonorgestrel (LNG)
3RD Generation	**4th generation**
• Desogestrel	• Nomegestrel
• Nor-Gestimate	• Drospirenone
• Gestedone	

- Drospirenone has anti-mineralocorticoid receptor activity also

Selective Progesterone Receptor Modulator (SPRM) 00:25:22

- Mifepristone
- Onapristone
- Ulipristal

Mifepristone

- Acts as antagonist of
  - Progesterone receptors in uterine endometrium
  - Glucocorticoid receptor
  - Androgen receptors
- **Major uses** of mifepristone:
  - **M** - Morning after pills (emergency contraception)
  - **I** - Induction of abortion
  - **F** - Fibroid
  - **E** - Endometriosis
  - **PR-PR**ogesterone Receptor positive cancer like Breast cancer and Meningioma
  - **I** - Increased } Cushing Syndrome
  - **S** - Steroids } Cushing Syndrome
  - **tone**

How to remember

- MIFEPRIStone

Onapristone

- Only progesterone antagonist (Does not block Glucocorticoid receptor)
- Indicated for abortion

Ulipristal

- Emergency contraceptive which can be given till 120

hours of unprotected sexual intercourse as a single dose of 30mg

TESTOSTERONE

00:29:07

- 5α-reductase converts testosterone into Dihydrotestosterone (DHT) which works on androgen receptors. Testosterone also can directly work on androgen receptors.
- **Functions** of Testosterone:
  - **F** - **F**eedback inhibition
  - **I** - **I**nternal genitalia development
  - **S** - **S**permatogenesis
  - **H** - **H**ematopoiesis

How to remember

- FISH

- **Functions** of Dihydrotestosterone:
  - **S** - **S**econdary sexual characters
  - **E**, **X** } External genitalia development
  - **U** - **U**rine (Prostate)
  - **A** - **A**lopecia (male pattern baldness)
  - **L** - **L**oss of hair

How to remember

- SEXUAL

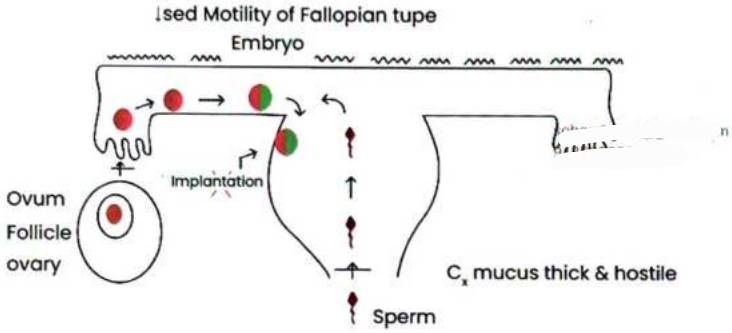
- **5α-reductase inhibitors:**
  - Finasteride
  - Dutasteride
- **Androgen receptor blockers:**
  - Flutamide
  - Nilutamide
  - Bicalutamide
  - Enzalutamide
  - Apalutamide
- Androgen receptor blockers are more potent than 5α-reductase inhibitors, as it directly blocks the receptors.
- In treatment of prostatic cancer, androgen receptor blockers are commonly used.
- In treatment of BPH and Androgenital alopecia (male pattern baldness), 5α-reductase inhibitors like Finasteride are used
- **Side effects** of both the class of drugs: Impotence

Anabolic Steroids

- Two main actions of testosterone are:
  - Androgenic
  - Anabolic
- Anabolic steroids have proportion of androgenic to anabolic action of 1:3 as compared to normal ratio of 1:1 in androgens
- **Examples** of anabolic steroids are
  - Nandrolone
  - Stanozolol
- **Side effects** of anabolic steroids
  - Hepatotoxicity
  - Impotence
- In dope test, which is done in competitive sports like Olympics, athletes are tested for intake of anabolic steroids.

50 ORAL CONTRACEPTIVES

- These are the drugs given orally to prevent contraception.



- The main mechanisms of oral contraceptives are:
  - Inhibition of ovulation
  - Inhibit FT movements
  - Thick and hostile cervical mucus
  - Inhibit implantation
- Oral contraceptives are of three types:
  1. Combined Oral Contraceptives (COC)-Inhibit ovulation
  2. Progesterone only pills (POP)-Make cervical mucus thick and hostile
  3. Emergency contraceptives – Inhibit implantation

COMBINED ORAL CONTRACEPTIVE PILLS

00:07:10

- **Estrogen**: Ethinyl Estradiol
  Progesterone: Levonorgestrel
- Dosage
  - 1 tablet daily for 21 days from 1st day of menstrual cycle
  - No tablet for next 7 days
  - To increase compliance:
    → 28 Tablets strip with 1st 21 tablets contain the drug
    → Next 7 tablets contain Fe
- If 1 tablet is missed → Take 2 tablets on next day
- If 2 tablets are missed → Discard remaining tablets & practice other method of contraception with it. Start fresh from the next cycle
- **Breakthrough Bleeding** (not normal)
  - Bleeding @ 1-21 days (because of sudden increase in progesterone)
  - Prevented by Phasic Pills
    → Gradual increase of progesterone from 1 to 21 days
    → Phasic pills are of 2 types:

Biphasic pills	1-10 (Less Progesterone)	11-21 (More Progesterone)	-
Triphasic pills	1-5 (Less Progesterone)	6-10 (More Progesterone)	11-21 (Full Progesterone)

Gradual increase of rogesterone to prevent breakthrough bleeding ⟶

- **Withdrawal bleeding** (normal)
  - Due to sudden progesterone withdrawal
- **Adverse Effects** of OCP

00:13:55

Mild (NORMAL)	**Moderate** (ABC)	**Severe** (4Cs)
N - **N**ausea **O** - **O**edema **R** - **R**ecurrent headache (so must be avoided in female with migraine) **M** - **M**astalgia **A** - **A**bnormal bleeding (Breakthrough bleeding) **L** - **L**oss of withdrawal bleeding	**A** - **A**cne **B** - **W**eight gain (**B**ulky) **C** - **C**hloasma	**C**VS [Thrombo Embolism] **C**NS [Depression] **C**holestasis **C**ancers: • Breast Ca • Cervical Ca

POP (MINIPILL)

00:18:56

- Used where Combined OCPs can't be used
- Contains LNG
- Indications
  1. Thromboembolism risk
  2. Lactation [oral contraceptive of choice]

EMERGENCY CONTRACEPTIVES ⏱ 00:19:56

- They are aka Post coital contraceptives / Morning after pills
- They include:

1. **COC**: 2 tablets at start + 2 tablets after 12 hrs
2. **POP [LNG]**: 1 tablet at start + tablet after 12 hrs

or

: 2 tablets at start

3. **Mifepristone**

- SPRM – Selective Progesterone Receptor Modulator
- Uses
  1. Emergency contraception
  2. Induction of abortion
- Above 3 drugs should be used with in <72 hrs of unprotected intercourse.

4. **Ulipristal**
   - Can be used within <120 hrs of unprotected intercourse
   - SPRM
   - 30mg

NON CONTRACEPTIVE BENEFITS OF OCPS

⏱ 00:22:29

- **Other** - ↓ **O**varian cyst [DOC For PCOD]
- **B** - ↓ **B**enign Breast Disease
- **E** - ↓ **E**ndometriosis
- **N** - ↓ **N**eoplasia (Endometrial & ovarian cancer)
- **E** - ↓ **E**ctopic pregnancy
- **F** - ↓ **F**ibroid
- **I** - ↓ **I**ron deficiency Anemia
- **T** - ↓ **P**remenstrual Tension syndrome
- **S** - ↓ **S**keletal Disease [Osteoporosis]

How to remember

- Other BENEFITS

Important Information

OCPs can:

↑ risk of	↓ risk of
• Cervical Ca	• Endometrial Ca
• Breast Ca	• Ovarian Ca

51 BROMOCRIPTINE IN DM

- **MOA** of Bromocriptine in **DM:**
  - Decreases insulin resistance
- It has been recently approved for Type 2 diabetes treatment.
- Given in small dose orally and taken at early morning on awakening.
- Bromocriptine resets the hypothalamus acc. to normal circadian rhythem
- Increases early morning dopaminergic activity and decreases sympathetic activity.
- This restores insulin sensitivity.
- Only S/E: Nausea

CLINICAL QUESTIONS

PITUITARY HYPOTHALAMIC SYSTEM

Q. A 34 year old female came in to your clinic with complaints of milky discharge from her nipples for the past 2 weeks. While taking the complete history, you would ask the patient if she is taking which of the following medications?

A. Omeprazole
B. Metoclopramide
C. Bromocriptine
D. Ranitidine

Answer: B

Solution

Galactorrhea (symptom described in the question) is caused by prolactin secretion.
Dopamine normally inhibits the secretion of prolactin.
Thus **dopamine antagonists** can cause hyperprolactinemia leading to galactorrhea.

The drugs include:

- Typical Antipsychotics like Haloperidol
- Antiemetics like **Metoclopramide**
- Dopamine depleter like Reserpine.

Drugs stimulating dopamine receptors like Bromocriptine and Cabergoline are used for treatment of Hyperprolactinemia.

Q. A 43 year old woman, came in to your clinic with complaints of excessive menstrual bleeding. After taking careful history, doing the physical examination and ordering tests, you confirm that the patient is suffering from endometriosis. While discussing treatment options, you mention about GnRH agonists as a possible treatment for this, though it will be given only for 6 months time, which may help patient prepare and schedule for a surgery, after. Which of the following will you not use for this patient?

A. Leuprolide
B. Nafarelin
C. Ganirelix
D. Busurelin

Answer: C

Solution

Option 3, since it is a GnRH antagonist.

GnRH Agonist Drugs

- **Leuprolide**
- **Nafarelin**
- Goserelin
- **Buserelin**
- They are all injectables.

They all have flare up reaction as adverse effect when given in continuous form

GnRH Antagonist Drugs

- Cetrorelix
- **Ganirelix**
- Abarelix
- Degarelix
- Given as injectables

They do not increase the sex hormone

THYROID

Q. All among the following factor(s) increase the binding of Thyroxine to Thyroxine-binding globulin except

A. Clofibrate
B. Glucocorticoids
C. 5 Flurouracil
D. Estrogens
E. Furosemide

Answer: B, E

Solution

Factor(s) affecting the binding of Thyroxine to Thyroxine-binding globulin	
Increased Binding	**Decreased Binding**
• Estrogen • Methadone • Clofibrate • 5-Fluorouracil • Heroin • Tamoxifen • SERMS • Liver disease • Porphyria • HIV	• Glucocorticoids • Androgens • L-Asparaginase • Salicylates • Mefenamic acid • Phenytoin • Carbamezapine • Furosemide • Acute ,Chronic illn

Q. In cases of hyperthyroidism, most of the effects mediated by the increased hormone levels is due to peripheral conversion of T4 to T3. Which of the following medications inhibit 5'- deiodinase?

A. Propylthiouracil
B. Methimazole
C. Lugol's iodine
D. Radioactive iodine

Answer: A

Solution

For the peripheral conversion of T4 to T3, the enzyme needed is 5'-deiodinase (deiodinase type 1 and 2). It is inhibited by peripheral conversion inhibitors

- Propanolol
- Propylthiouracil
- Prednisolone

Secretion inhibitors

- NAI
- KI
- Lugol Iodine

NIS Inhibitors

- Perchlorate
- Thiocyanate

Thyroid peroxidase inhibitor

- Carbimazole
- Propythiouracil

Thyroid destroying drugs

- Iodine 131

PANCREAS

Q. A 43 year old male came in to your OPD with complaints of excessive thirst. After collecting history, you notice that the patient has polyuria and polyphagia. You suspect it could be DM and order for FBS, PPBS & HbA1c. The HbA1c was about 12% and both the blood sugar values were over 240. You decide to start the patient on S/C Insulin therapy, and educate the patient regarding the same. What would you comment on its action, to the intern posted under you?

A. Stimulation of Ionotropic receptor
B. Stimulation of Enzymatic receptor
C. Stimulation of Metabotropic receptor
D. Stimulation of Nuclear receptor

Answer: B

Solution

- Insulin acts by stimulation of Tyrosine kinase receptor → enzymatic receptor.
- Full insulin receptor consists of two covalently linked heterodimers.
- containing α subunit, which is entirely extracellular and constitutes the recognition site,
- and a β subunit that spans the membrane.
- The β subunit contains tyrosine kinase.

Q. A 44 year old male visits your clinic situated in the outskirts of a town. He is a known diabetic who was having sugar on control, taking Metformin 500mg twice a day. The recent results make you consider adding another medication. Due to the financial crunch the patient is going through, you would prefer prescribing a sulfonylurea over the newer agents. Why would you pick glipizide over chlorpropamide?

A. It is more potent
B. It is longer acting
C. It does not lower blood sugar in nondiabetic subjects
D. It is less prone to cause hypoglycemic reaction

Answer: A

Solution

- Second generation sulfonylureas (like Glipizide) are more potent than first generation agents (like Chlorpropamide).
- Chlorpropamide is the longest acting sulfonylurea.
- Sulfonylureas can cause hypoglycemia (even in non-diabetics) due to release of insulin.

ADRENAL GLAND

Q. Aldosterone is known to cause sodium retention. Its Na^+ retaining action is exerted on which part of the nephron?

A. Proximal convoluted tubule
B. Ascending limb of loop of Henle
C. Collecting ducts
D. Early distal convoluted tubule

Answer: C

Solution

- **Aldosterone** is the principal mineralocorticoid.
- It stimulates the reabsorption of Na^+ and excretion of K^+ and H^+ by its action on **late distal tubules and collecting ducts.**

Q. During the Medicine outpatient posting, you see multiple cases of patients taking corticosteroids. If the Consultant asks you which of them have chances of getting the maximum adverse effects, which regime would you pick?

A. Prednisolone 20 mg/day oral for one year
B. Prednisolone 60 mg/day oral for 7 days
C. Dexamethasone 4 mg intravenous daily for 3 days
D. Methyl-prednisolone 1000 mg intravenous twice single dose

Answer: A

Solution

If **used for more than two weeks, corticosteroids** can lead to *HPA axis suppession.*

- If discontinued abruptly, precipitation of acute adrenal insufficiency can result.
- This is the most serious adverse effect seen with the use of corticosteroids that can cause death of the patient.

OSTEOPOROSIS

Q. A 62 year old female came in to your clinic with complaints of a swollen hand after she suffered from a fall. X-Ray revealed a fracture and you learn that it is due to osteoporosis. Which of the following is not given for cases like this, in post-menopausal women?

A. Alendronate
B. Teriparatide
C. Calcium
D. Thyroxine

Answer: D

Solution

Thyroid hormones and glucocorticoids increase the risk of osteoporosis whereas other drugs mentioned in the options are used to treat osteoporosis.

Q. A 62-year-old female, Phoolwati presents to the emergency with acute severe low back pain after sitting down quickly, onto a chair. She has a history of rheumatoid arthritis and bronchial asthma. She reports that she was on many medications for several years. X-ray shows a fracture of the fifth lumbar vertebra. Which of the following drugs are likely responsible for the patient's complaints?

A. Methotrexate
B. Prednisolone
C. Indomethacin
D. Salbutamol

Answer: B

Solution

- Osteoporosis is a common cause of pathological vertebral fractures.
- Chronic systemic use of **corticosteroids** like prednisolone promotes osteoporosis and therefore may cause such fractures.

LEARNING OBJECTIVES

UNIT 8: CNS

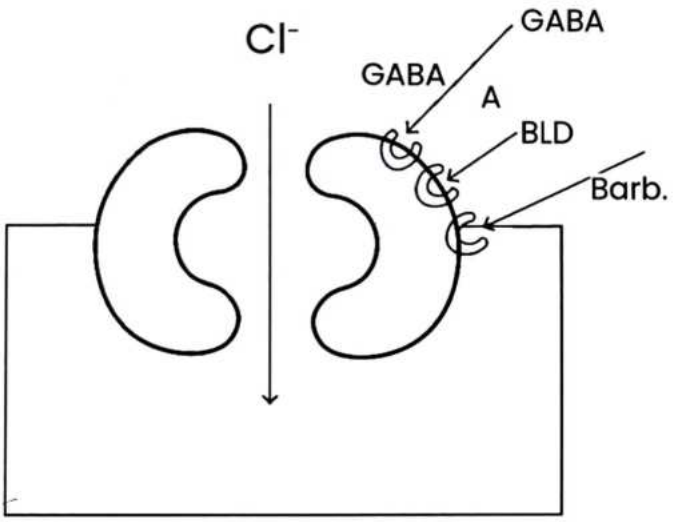
- Sedative hypnotics
  - Barbiturates
  - BZD
  - Z drugs
- Parkinsonism
  - Drugs used
  - On-Off phenomenon
- Epilepsy
  - Anti-epileptic drugs
  - Epilepsy in pregnancy
- Psychiatric illness
  - Schizophrenia
  - Mood disorders
  - Antipsychotics
  - Antidepressants
- Drug of abuse
  - Opioids
  - Alcohols
  - Dependence
  - Deaddiction

52 SEDATIVE HYPNOTICS

Sedative hypnotics

When given in low dose	When given in high dose
↓Induce Sedation	↓Induce Sleep / hypnosis

- Thus, sedatives hypnotics are CNS depressants
- **GABA** is the inhibitory neurotransmitter of Brain



- Neurons contain a channel for Cl^- entry
- $GABA_A$ receptors are present on this channel
- GABA stimulates these receptors, which leads to

↓

Cl channel opens and Cl^- enters inside the cells
Membrane potential inside the cell becomes negative
(Cl is negatively charged ion)

↓

Hyperpolarization of neuron

↓

Neurons can't be stimulated

↓

Brain is depressed

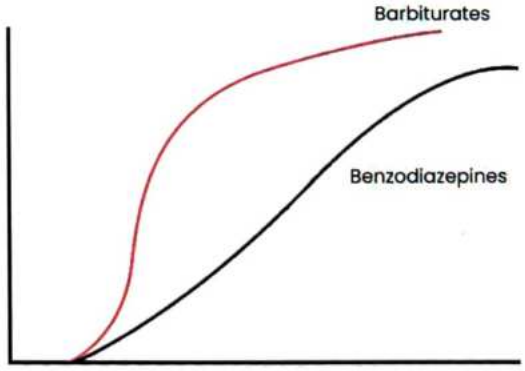
- Other receptors, namely receptors for benzodiazepines and barbiturates are also present on this channel:

	Barbiturates	Benzodiazepines
• GABA:	GABA-mimetics	GABA-facilitatory
• CL- channel opening:	↑Duration of channel opening	↑Frequency of channel opening
• DRC:	Steep (relatively unsafe)	Flat (safer)
• Enzyme inducers:	+++	xx
• Addiction:	++++	+
• Anterograde amnesia:	+++	+
• Antidote:	xx	Flumazenil

- **Benzodiazepine**

↓

Flumazenil
(Antidote)



- **Barbiturates**
  - Thiopentone
  - Phenobarbitone

  } The only 2 barbiturates currently used
  - Thiopentone is used for Anaesthesia
  - Phenobarbitone is used for Epilepsy

Benzodiazepines

- Drugs included are
  - Diazepam - Oxazepam is active metabolite

- Flurazepam
- Nitrazepam
- Flunitrazepam

- BZD are very long-acting d/t formation of **active metabolites**
- They cause Hangover
- C/I in elderly
- C/I in Liver failure
- BZD which do not form active metabolites are:

S - **S**hort Acting BZD are
T - **T**emazepam
O - **O**xazepam
L - **L**orazepam
E - **E**stazolam

- Short acting BZD:
  - No active metabolites
  - No hangover
  - Safe in elderly
  - Safe in liver failure

- Overall shortest acting benzodiazepine is Midazolam (but not used in insomnia)

How to remember

- STOLE drugs

SLEEP

- Good Quality sleep means that the Sleep architecture (phases of REM & Non-REM) is maintained
- **Barbiturates & BZD**
  - Distort the normal sleep architecture (Quality)
  - They increase the Quantity of sleep
  - But they decrease the Latency of sleep onset. So they decrease the Quality of sleep

Non-BZD Hypnotics (Z-drugs): 00:27:40

- These include:
  - Zolpidem
  - Zopiclone
  - Zaleplon
  - Eszopiclone
- They stimulate Omega1 or 1 subunit of Benzodiazepine receptor
- These drugs only decrease the latency
- Do not increase the duration of sleep
- Lack Antianxiety, Muscle relaxant, Anticonvulsant property (unlike benzodiazepines)
- Only hypnotic property (+)
- Antidote is Flumazenil
- No hangover
- No sleep quality compromised
- Non addictive
- DOC for insomnia

Melatonin Receptor Agonists

- Melatonin is secreted at night and produce sedative effect
- Maintain day-night cycle
- Uses:
  - Shift workers
  - Jet lag
- Example is **Ramelteon**:
  - Decreases latency of sleep onset
  - Non-addictive
  - Melatonin receptor agonist
  - Indicated for jet lag, shift workers and insomnia also
  - <2% oral bioavailability
  - Psychiatric adverse effects seen in overdose
  - Metabolized by microsomal enzymes, so prone to drug interactions

Orexin Receptor Antagonists

- Orexin receptor stimulation promotes wakefulness
- These include:
  - Suvorexant
  - Lemborexant
- These are used to induce sleep

53 PARKINSONISM

- Parkinsonism is a neurodegenerative disease (age related disease)
- In Parkinsonism, there is deficiency in dopaminergic activity in basal ganglia of brain
- Normally, there is balance b/w Dopaminergic (DA) & Cholinergic (Ach) neurons
- In Parkinsonism, this balance is lost (Relative cholinergic excess)

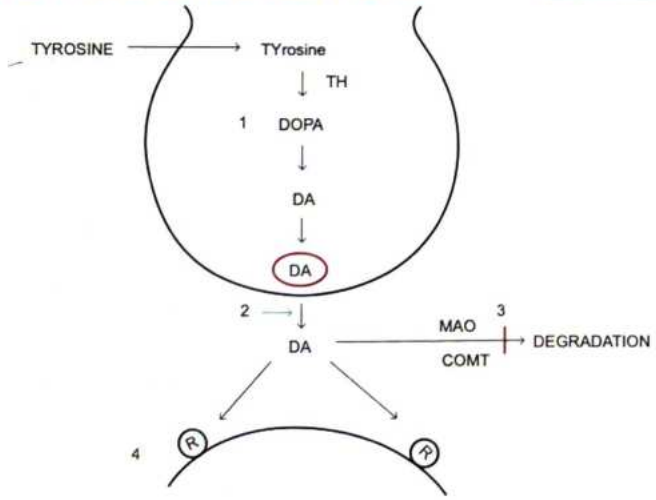
DA	⇌	Ach	DA	⇌	Ach
100		100	50		100
Normally			**Parkinsonism**		

- There are two ways to treat Parkinsonism:

1. Increase dopamine
2. Decrease Ach

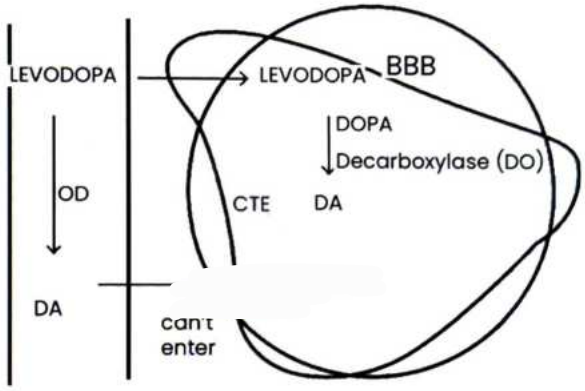
DOPAMINERGIC DRUGS

00:02:58



1. LEVODOPA

- It is less efficacious as Peripheral DOPA decarboxylase convert it to Dopamine
- DA produced outside the brain causes Peripheral Side Effects:
  - D1 stimulation - Hypotension
  - β1 stimulation - Arrhythmias
  - α1 stimulation - Hypertension
  - CTZ stimulation - Vomiting



- Carbidopa } Peripheral DOPA decarboxylase inhibitors
  Benserazide }
- These drugs will:
  - Increase Efficacy of Levodopa
  - Decrease Peripheral S/E of DA
- Central S/E cannot be reduced
- If vitamin B complex (containing pyridoxine) is given with levo-dopa, it will decrease its efficacy by increasing peripheral formation of dopamine
- Psychosis (d/t excessive DA in brain)
- All anti parkinsonism drugs can cause Psychosis

- This **Psychosis** can manifest as: 00:14:12
  - Dyskinesia
  - Abnormal behaviour

- **On-off phenomenon:** 00:16:58
  - In late parkinsonism, when we give levodopa, it controls symptoms for 20-200 hours. After that wearing off occurs leading to appearance of symptoms. This is called Wearing-off phenomenon.
  - In extreme cases, On-Off phenomenon occurs. During On-period, excess dopamine leads to psychosis.
  - During Off-period, lack of dopamine leads to appearance of Parkinsonism symptoms.

- So for On-Off phenomenon, we either give multiple small doses of Levodopa or we change the drug itself.

2. AMANTADINE

00:24:39

- Acts by releasing DA from the vesicles
- Also used as anti viral drug for Influenza-A virus
- **Side effects:**
  - Ankle edema (reversible)
  - Livedo reticularis (Pinkish pigmentation of skin in the form of meshwork)
  - Recently approved for treating Levo-dopa induced dyskinesia, as Amantadine acts as NMDA Antagonist
  - Only anti-parkinsonian drug to treat dyskinesia

3. COMT INHIBITORS & MAO INHIBITORS

a. MAO Inhibitors

00:27:57

MAO-A	MAO-B
• Present at all places • Metabolises all substances (both endogenous and exogenous substances)	• Present mainly in Brian • Metabolises DA mainly

- **Selective MAO-B Inhibitors**
  - These include:
    - → Selegiline
    - → Rasagiline
    - → Safinamide : approved for On-Off phenomenon of Levodopa
- May act as disease modifying agents for Parkinsonism (decreased neuronal degeneration)
- **MOA**

b. COMT Inhibitors

00:31:28

- It Includes:
  - Entacapone: Preferred drug
  - Tolcapone: Hepatotoxic (so not used)
  - Opicapone: Approved for on-off phenomenon

4. DOPAMINE AGONISTS

00:32:43

- Directly works on dopamine receptors

	Ergot Derivatives	Non-Ergot Derivatives
Drugs included:	• Bromocriptine • Pergolide	• Pramipexole • Ropinirole
Safety:		Safest Long Acting
Vasoconstriction →Gangrene:	✓	X
Fibrosis:	✓(On long term use)	X

- Pramipexole and Ropinirole are DOC for Parkinsonism
- Pramipexole and Ropinirole are DOC for Restless leg syndrome also
- These are associated with excessive day-time sleepiness and impulse control disorders like impulsive shopping, pathological gambling, etc.

DRUG INDUCED PARKINSONISM

00:39:13

- Anti Cholinergic drugs are DOC for Drug Induced Parkinsonism

1. Central Anti-cholinergic drugs:

- These include:
  - → Benzhexol (Trihexiphenydil)
  - → Benztropine
  - → Biperidine
  - → Procyclidine
- These are not available everywhere.

2. First Generation Anti-histaminic drugs

00:40:20

- If above drugs aren't available, then these can be used
- It includes Promethazine
- They can cross Blood Brain Barrier
- It has anticholinergic activity
- Promethazine-used as an alternative to Benzhexol in treating Drug induced Parkinsonism

Important Information

- DOC for Parkinsonism - Pramipexole/ Ropinirole
- Most Effective Drug for Parkinsonism - Levodopa + Carbidopa
- DOC for Drug Induced Parkinsonism - Benzhexol

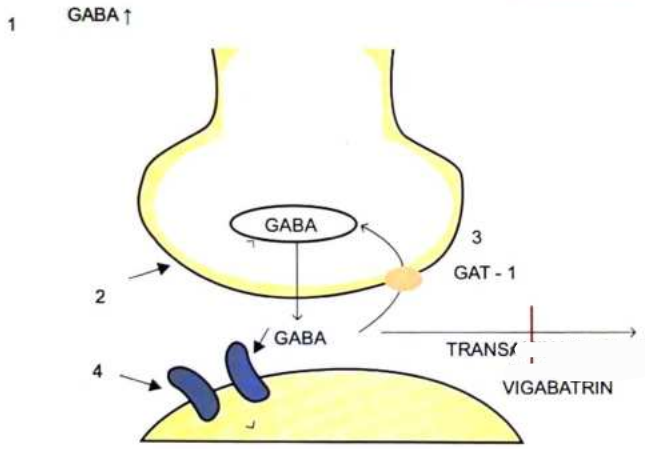
54 EPILEPSY

- Seizure is due to overstimulation of neurons. So to treat seizures, we need to depress the brain.
- **MOA of Anti-epileptic drugs**

1. GABA ↑
2. Glutamate ↓
3. Ca^{2+} #
4. Na^{+} #
5. K^{+} Channel Openers

DRUGS INCREASING GABA ACTIVITY

00:01:51



1. Pregabalin

Gabapentin

- Drugs act by releasing GABA
- DOC For Neuropathic pain due to:
  - Diabetic neuropathy
  - Post Herpetic neuralgia
- Recent update MOA mainly by Ca2+ channel inhibition

2. Vigabatrin

Visual Field Contraction[S/E]

Gaba Transaminase Inhibitors [MOA]

- Doc for infantile spasm – ACTH
- Doc for infantile spasm in a patient with Tuberous Sclerosis – Vigabatrin

3. Tiagabine

- It is transport inhibitor of GABA
- It inhibits GAT-1 transporter

4. Barbiturates and BZD

- BZD are:
  - Diazepam
  - Lorazepam
  - Clonazepam
  - Clobazam
- Barbiturate used: Phenobarbitone
- Phenobarbitone can cause Hyperkinesia in children
- DOC for Febrile Seizures - Diazepam
- DOC for Status epilepticus - Lorazepam
- Used for Absence seizures - Clonazepam
- Used in Lenox Gastaut Syndrome - Clobazam

DRUGS DECREASING GLUTAMATE ACTIVITY

00:10:52

NMDA #	AMPA #
Felbamate	Perampanel
• S/E: Bone Marrow Suppression	• Used in Focal Seizures

T-TYPE CA^{2+} CHANNEL BLOCKERS

- Ethosuximide
  - Used only for absence seizure
  - Not preferred for any other seizures

Na+ Channel blockers 00:13:37

- Phenytoin
- Carbamazepine
- Oxcarbazepine

} C/I in absence & myoclonic seizures; Useful in GTCS & focal seizures

- Topiramate, Zonisamide } Cause renal stones
- Lacosamide, Rufinamide } Used in Focal seizures
- **Topiramate** other uses:
  - ↓Craving of Alcohol
  - Obesity
  - Migraine prophylaxis
  - Bipolar disorder
- **Carbamazepine**
  - DOC for Focal seizures
  - DOC for Trigeminal neuralgia
  - Can be used for
    - → Diabetes insipidus [DOC for DI→ Desmopressin]
    - → Bipolar Disorder [DOC for BPD → Lithium]
  - **Adverse effects** (Remembered as **4A**):
    - → Auto induction: Increases metabolism of other drugs & itself. Initially started with lower dose and gradually dose has to be increased due to tolerance
    - → Aplastic Anemia: CBZ causes bone marrow suppression
    - → ADH release from post pituitary: Result in SIADH as a S/E
    - → ↑ADH = ↑water = Dilution of ions
      = ↓Na+
      = Dilutional hyponatremia
  - Therefore, CBZ is avoided in elderly patients
  - DOC for focal seizures in elderly is Lamotrigine
  - Ataxia, Nystagmus, Vertigo are mainly seen with overdose

- **Phenytoin**
  - Follow ZERO order Kinetics
  - Enzyme inducer
  - Used for anti-arrhythmic actions
  - Used for GTCS & Focal seizures
  - C/I in Absence & Myoclonic seizures
  - **Adverse Effects:**
    - → **H** - **H**irsutism, Hypertrophy of gums
    - → **O** – **O**steomalacia
    - → **T** - **T**eratogenicity [Fetal Hydantoin syndrome]
    - → **M** - **M**egaloblastic Anemia [↓Folate]
    - → **A** - **A**rrhythmia [only in overdose]
    - → **L** - **L**ymph node enlargement
    - → **I** - ↓**I**nsulin
    - → **K** - ↓Vitamin **K**
    - → **A** - **A**taxias, vertigo [cerebellar symptoms] (only at overdose)

How to remember

- HOT MALIKA

  - Phenytoin in pregnancy results in
    - → Congenital malformations
    - → High risk of hemorrhagic disease of newborn (vit K deficiency)
    - → So, after the delivery, newborn should be given Vitamin K supplementation.

K^+ CHANNEL OPENER

- **Retigabine [Ezogabine]**
  - Used for Focal seizures
  - Does not act on GABA

SODIUM VALPROATE

00:28:27

- **MOA**
  - Na^+ Channel Blocker
  - Ca^{2+} channel Blocker
  - ↑GABA
  - ↓ Glutamate
- It has all four mechanisms of action. So it is a broad spectrum anti-epileptic drug.
- **DOC** For:
  - GTCS
  - Absence Seizures
  - Myoclonic Seizures
  - Atonic seizures
  - Lennox Gastaut syndrome
- Also used For Bipolar disorder
- **Adverse Effects:**
  - **V** – **V**omiting
  - **A** – **A**lopecia / Curling of hair
  - **L** – **L**iver disease (hepatotoxicity in young has high incidence)
  - **P** – **P**ancreatitis, ↑ risk of PCOD (Gender specific S/E)
  - **R** – **R**ash, allergy
  - **O** – **O**besity
  - **A** – **A**taxia (in overdose)
  - **TE** - **TE**ratogenicity
    - Therefore, if administered in pregnancy, a high

dose of folic acid (400 g/day) should be supplemented to prevent neural tube defects.

How to remember

- VALPROATE

LAMOTRIGINE

- DOC for focal seizures in elderly
- Acts by:
  - Blocking Na channels
  - Increasing GABA
  - Decreasing glutamate activity
- Side effects:
  - Steven Johnson Syndrome (skin surface <30%)
  - Toxic Epidermal Necrolysis (Skin surface >30%)

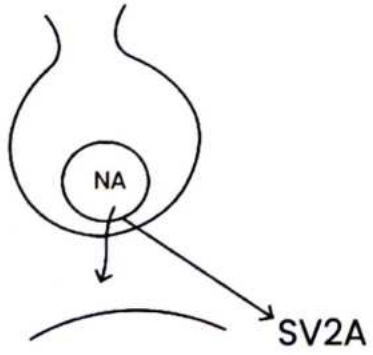
NEW ANTIEPILEPTIC DRUGS

00:34:24

1. Bind to SV2A: Levetiracetam
Brivaracetam

2. Cannabidiol:

- Stimulates Cb-1 receptors
- Approved for Dravet syndrome



3. Stiripentol

- Acts by:
  - Increasing GABA
  - Inhibiting LDH
- Also used approved for treatment of Dravet syndrome

EPILEPSY IN PREGNANCY

- Most teratogenic: Valproate
- Least teratogenic: Lamotrigine, Levetiracetam
- If patient is already controlled on antiepileptic medication: Don't change the medication even if it's valproate, add high dose folic acid i.e., 4000 microgram per day to prevent teratogenic effects.
- For first time treatment of epilepsy in pregnancy: Levetiracetam or Lamotrigine are preferred.
- For Eclampsia: $MgSO_4$ IV is DOC. It has neuroprotective properties

Epilepsy in pregnancy	Seizures in Eclampsia
• Seizures not occurring now, but want to prevent seizure • Therefore drug given throughout pregnancy to prevent seizures • Drug given should have least teratogenicity ○ Most-Valproate ○ Least-Lamotrigine/Levetiracetam	• Acute episode of seizures in pregnancy occurring now d/t high BP • DOC – $MgSO_4$

55 PSYCHIATRIC ILLNESS

Psychosis (no insight)	**Neurosis** (insight present)
1.Schizophrenia	1.Generalized Anxiety disorder
2.Mood Disorders:	2.Phobias
a. Mania	3.OCD
b. Depression	4.Bulimia
c. Manic-Depressive Psychosis / Bipolar Disorder	5.Post-Traumatic Stress Disorder

SCHIZOPHRENIA

Anti-Psychotic Drugs 00:02:55

- Typical Anti-Psychotic (D_2 #)
- Atypical Anti Psychotics ($5HT_2$ #)
  - Most drugs possess both properties
  - $\frac{D_2\#}{5HT_2\#} > 1 \rightarrow$ Typical Antipsychotics
  - $\frac{D_2\#}{5HT_2\#} < 1 \rightarrow$ Atypical Antipsychotics

I. Typical Antipsychotics 00:04:05

- **Strong D2#**
  - Haloperidol (Highest risk of EPS)
  - Droperidol
  - Fluphenazine
- **Weak D2#**
  - Chlorpromazine
  - Thioridazine (least risk of EPS among typical drugs)
- **Intermediate D2#**
  - Thiothixene
  - Chlorprothixene

- Side Effects: 00:06:35

a. Extra Pyramidal Symptoms (EPS)

i. Dystonia (Earliest)
ii. Akathisia (MC)
iii. Parkinsonism
iv. Tardive dyskinesia (Latest)

- MC a/w strong D2#
- Treatment:
  - **Benzhexol** used for:
    - → Dystonia (DOC)
    - → Parkinsonism (DOC)
    - → Akathisia
    - → Malignant neuroleptic syndrome
    - → C/I in Tardive dyskinesia
  - **Propranolol**: Akathisia (DOC)
  - **Dantrolene**: Malignant neuroleptic syndrome
  - **Valbenazine**: Tardive dyskinesia
- Pathogenesis of Tardive dyskinesia:
  - Different from all other EPS
  - Occurs with withdrawal of Anti-psychotic drugs
  - Chronic blockade of D2 receptors leads to Super-sensitivity
  - Therefore, dopamine depleters like Valbenazine (VMAT-2 inhibitor) are used for treatment

b. Hyperprolactinemia

- D_2 receptors: ↓Prolactin
- D_2#: ↑ Prolactin
- MC a/w strong D2

c. Ach #

- Dryness
- Blurring of vision
- Urinary retention

d. #:↓BP

e. H1#: Sedation

f. Seizures

- **Disadvantage of Typical Drugs:**
  1. S/E
  2. Not effective against negative symptoms

II. Atypical Anti-Psychotic Drugs

- **Advantages**
  1. Lesser S/E
  2. Effective against both positive & negative symptoms
- **Drugs**
  - Clozapine
  - Risperidone
  - Olanzapine
  - Paliperidone
  - Quetiapine
  - Iloperidone

- Asenapine
- Ziprasidone
- Zotepine
- Lurasidone
- Aripiprazole
- Pimavanserin

- **Side effects**
  - ↑Glucose, ↑Lipids } Lipodystrophy Syndrome (Highest risk with Clozapine & Olanzapine)
  - Weight gain
  - Insulin resistance
- **Clozapine**
  - DOC for Resistant Schizophrenia
  - Adverse effects are:
    - → Agranulocytosis (Dose independent)
    - → Seizures (Dose dependent)
    - → Myocarditis
    - → Sedation
    - → Sialorrhea (due to blockage of α_2 & stimulation of M_4 receptor)
- **Quetiapine**: It causes Cataract
- **Ziprasidone:** It causes Torsade's de Pointes (↑QT interval)
- **Risperidone**
  - Has Maximum D2 blocking property among the atypical drugs
  - Maximum risk for extrapyramidal symptoms and hyperprolactinemia among atypical drugs
- **Pimavanserin**
  - Atypical antipsychotic drug
  - Acts by blocking 5HT2 receptor
  - Specifically approved for treatment of Parkinsonism induced Mental Anomalies (Psychosis)
- **Uses of Antipsychotic Drugs:**
  - **Anti -Anti**emetic and Antimanic property
  - **Psy-Psy**chosis
  - **Cho**-Huntington's **CHO**rea (Tetrabenazine DOC)
  - **Tics-Tic** disorder (DOC is Tetrabenazine. Clonidine and Guanfacine are also used)

How to remember

- Anti-Psy-cho-tics

- Tics are sudden repetitive contractions of a group of muscles. Gille de La Tourette syndrome is a special type of syndrome with vocal tics.

MOOD DISORDERS

00:28:02

1. ACUTE MANIA

- Patient is aggressive and voilent
- Treatment of Acute Episode : Sedatives (Anti Psychotics / BZD) + Lithium
- Prophylaxis: Lithium (DOC)
- **Lithium:**
  - Pharmacokinetics:
    - → Almost 100% absorption
    - → Peak level reached in 2-4 hrs
    - → Half life: 24 hrs
    - → 95% excreted via kidney.
    - → 4% via sweat
    - → Less than 1 % via feaces
  - Actions of lithium:
    - → **L** - Leucocytes, → **I** - Increase } Leukocytosis
    - → **T** - **T**remors (MC)
    - → **H** - **H**ypothyroidism
    - → **I** - Increase, → **U** - Urine } Polyuria (Nephrogenic DI)
    - → **M** - Avoided in **M**others (Lithium in pregnancy → Ebstein anomaly)
    - → **A** - **A**cne
    - → **C** - **C**alcium increase
    - → **T** - **T** wave changes
    - → **I** - **I**ncoordination, Ataxia, Slurred speech
    - → **O** - **O**besity
    - → **N** - **N**ausea, Vomiting, Diarrhoea
    - → **S** - **S**eizures

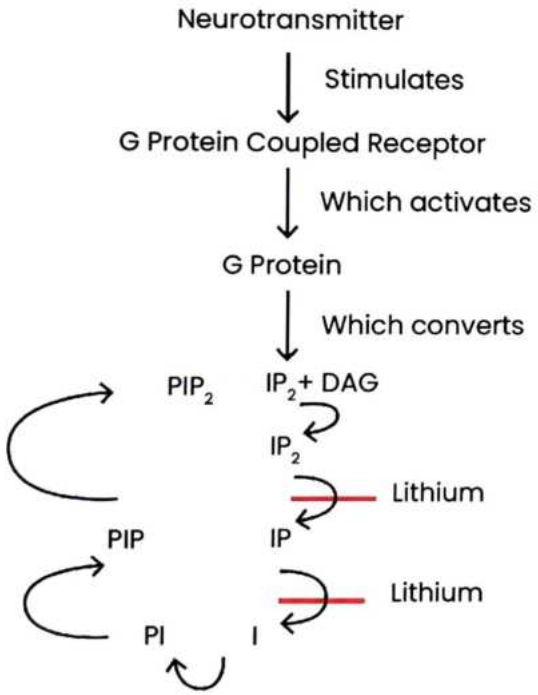
How to remember

- LITHIUM ACTIONS

  - If a person on Lithium therapy is sweating a lot, he is advised to drink water with sodium and not water alone
  - Drugs which increase the risk of Lithium toxicity are:
    - → Thiazides
    - → Lisinopril
    - → Indomethacin
  - Plasma concentration:

→ **Acute mania**: 0.8-1.2 mEq/L
→ **Prophylaxis**: 0.5-0.8 mEq/L
→ **Toxic**: >2 mEq/L

- Symptoms of **Lithium toxicity**:
  → Vomiting
  → Severe diarrhea
  → Ataxia
  → Incoordination
  → Tinnitus
- **Mechanism of Action**: Lithium controls
  → Mania
  → Depression
  → Mania occurs due to Overactivity of Neurotransmitters in brain particularly which acts through Calcium and the brain gets stimulated
  → In depression, there is deficiency of BDNF (Brain Derived Neurotrophic Factor) which is required for neuronal plasticity (connections between neurons). Neuronal plasticity is lost in depression.



- IP_3 (Inositol triphosphate) is required for increasing calcium. When calcium increases, it causes overactivity of brain.
- After activation of calcium, it is metabolized to IP_2 with help of phosphatase enzyme
- Further it is metabolized to form IP.
- IP is further metabolized to inositol by removing one more phosphate group.
- Inositol will attach with phosphatidyl group which results in formation of Phosphatidyl Inositol (PI)
- PI is then phosphorylated to PIP.
- PIP will then be converted again to PIP_2 (Phosphatidyl. Inositol bisphosphate) and this recycling process continues to produce more calcium leading to increased neuronal activity.
- In Mania, Lithium acts by inhibiting phosphatase enzymes, which then decreases calcium production and Mania is controlled.
- In Depression, BDNF is usually metabolized by Glycogen Synthase Kinas-3 beta (GSK-3β) enzyme, which is inhibited by Lithium, leading to decrease in BDNF breakdown, which leads to increase in Neuronal plasticity. Hence it reverses Depression

- **Uses** of Lithium:
  - Acute mania
  - Bipolar disorder (DOC)
  - Depression
  - Neutropenia

2. BIPOLAR DISORDER

00:50:02

Treatment of Bipolar disorder

Mania	Depression
• Lithium ○ DOC for prophylaxis • Anti-epileptic drugs ○ Carbamazepine ○ Valproate (DOC for Rapid cyclers) ○ Topiramate • Anti-Psychotics ○ DOC for Bipolar in pregnancy, as Lithium is contraindicated in pregnancy	• Lithium (DOC for prevention of suicide) ○ It is the only drug that decreases suicidal risk in bipolar patients. • Lamotrigine

- Overall DOC for Bipolar disorder is Lithium

3. DEPRESSION

00:53:16

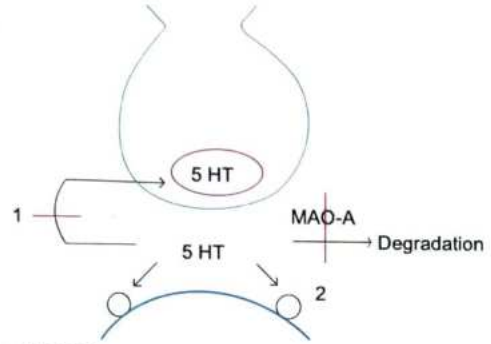
- Earlier it was believed that decrease in Monoamines (5HT>NA>>DA) causes depression.
- Later it was linked with decrease in BDNF i.e., when ↑ MA →↑ BDNF→↑ Neuro Plasticity →↓ Depression

Anti-Depressant drugs

- Typical anti-depressants: Act by ↑ 5HT

- Atypical anti-depressants: Act by other mechanisms

a. Typical Antidepressants



1. MAO-A inhibitors

- Moclebemide (aka RIMA)
  - **R** - **R**eversible
  - **I** - **I**nhibitor of
  - **M** - **M**AO
  - **A** – **A**

2. REUPTAKE INHIBITORS

Non-selective	Selective
• Inhibit reuptake of 5HT & NA • Avoided in cardiac patients • Indicated for severe depression	• Inhibit reuptake of 5HT only • Can be used in cardiac patients • Indicated for mild to moderate depression

I. Non-Selective Reuptake Inhibitors

- **TCA (Tricyclic antidepressants):**
  - It includes:
    - → Imipramine
    - → Desipramine
    - → Clomipramine
    - → Amitriptyline
    - → Nortriptyline
  - S/E:
    - → Ach#
    - → #
    - → H_1#
    - → Seizures
    - → Arrhythmias
    - → Metabolic acidosis
  - TCA are not preferred now because they are very toxic
- **SNRI (Serotonin Noradrenaline Reuptake Inhibitors)**
  - They inhibit the reuptake of 5HT and NA only
  - Less S/E
  - DOC for Severe depression
  - Drugs include:
    - → Venlafaxine
    - → Duloxetine
    - → Milnacipran
    - → Des-venlafaxine
    - → Levo-milnacipran

II. Selective Serotonin Reuptake Inhibitors (SSRI)

01:06:07

- They inhibit the reuptake of serotonin only
- So they are safe in cardiac tissues
- Drugs include:
  - Fluoxetine
  - Paroxetine
  - Fluvoxamine
  - Sertraline
  - Citalopram
  - Escitalopram
  - Dapoxetine: For premature ejaculation
  - DOC for mild to moderate depression or DOC for depression
  - DOC for all neurotic disorders

b. Atypical Anti-Depressants

- Drugs included are:
  - Bupropion : Anti – smoking drug
  - Amineptin, Tianeptin } ↑ reuptake of selective serotonin reuptake enhancer
  - Mirtazapine
  - Amoxapine: D_2# activity
  - Atomoxetine: used in ADHD
  - Mianserin
- **Mirtazapine**
  - It is a Noradrenergic and Specific Serotonergic Antidepressant (NSSA)
  - Acts by blocking α_2 & $5HT_{2,3,4}$ receptors
  - It increases both Noradrenaline & Serotonin in synapse. Noradrenaline can act on any receptor, but Serotonin can act on $5HT_1$ only ($5\text{-}HT_2$ /$5\text{-}HT_3$/$5\text{-}HT_4$ are blocked by Mirtazapine)
  - Advantage: It has less sexual side effects compared to other anti-depressants
- **Esketamine**
  - New recently approved drug
  - Acts by blocking NMDA receptor of Glutamate
  - Used as a nasal spray for depression
- **Brexanolone / Allopregnanolone**
  - Also a new drug
  - Approved for Post-partum depression

56 DRUGS OF ABUSE

OPIOIDS

00:00:40

- Obtained from Opium [Crude extract of Poppy plants]
- Opiates: drugs derived from opium
- Major opiate: Morphine
- Opioids: Opiate like substances

MORPHINE

00:01:51

- Acts on μ, K and δ receptors
- Stimulation of μ, K and receptors causes→ Analgesia

μ Receptor functions

- **S**: Sedation → Can cause coma
- **A**: Analgesia → used in severe pain
- **C**: Constipation → used in diarrhea
- **R**: Respiratory → avoid in asthma & COPD
- **U**: Euphoria → Addictive drugs
- **M**: Miosis
  - In Morphine poisoning, the patient usually presents in comatose state as μ receptor causes depression of brain.
  - Morphine is used to treat any pain like cancer pain, pain of Myocardial Infarction but it should not be used to treat Biliary colic.
  - Because in Biliary colic, stone in bile duct irritates it. When morphine is given in biliary colic, it causes spasm of sphincter of Oddi which increases the intra biliary pressure leading to rupture of bile duct.
  - Morphine can cause decreased GI motility which causes Constipation
  - Morphine is avoided in conditions like Asthma, COPD because it worsens the conditions as it may cause severe respiratory depression.
  - Morphine causes euphoria and it is highly addictive. Addictive drugs have 2 important properties:

Tolerance	Dependence
• Same dose of morphine, which was able to cause euphoria previously, is unable to cause it now • Due to tolerance, the person keeps on increasing the dose. • Tolerance can occur to all the actions of morphine except: **(3Cs)** ○ **C**: Constipation ○ **C**: Constriction of pupil ○ **C**: Convulsions	• Psychological dependance is characterized by craving • Physical dependance is characterized by withdrawal symptoms: ○ Withdrawal symptoms of any addictive drug are of 2 types: ○ **Sympathetic symptoms**: → Tachycardia, palpitations, tremors, Hypertension → Common to every addictive drug ○ **Opposite to normal action** of the drug: → Eg: Morphine → Causes sedation → Opposite action → Stimulation of brain

- Morphine causes constriction of pupil: Moisis. If overdose occurs it results in pinpoint pupils
- **Absolute C/I** of morphine: Head injury. This is because:

1. **It causes miosis**
   - Head injury patient: Mostly will be in a comatose state
   - Progress of patient after giving drugs is assessed by pupillary reaction
   - Morphine: Pupil remains in miosis assessment of progress cannot be done

   ↓

   Treatment is interrupted

2. **It causes respiratory depression**
   - Head injury R.R. is already depressed

   ↓

   Morphine aggravates it

3. **Morphine increases intracranial pressure**
   - Respiratory depression→CO_2 accumulates→ Vasodilation→ ↑ Intracranial pressure

DRUGS ACTING ON OPIOID RECEPTORS

00:11:31

- **Opioid Agonists**: Stimulate all 3 receptors [μ, K, δ]
- **Opioid Partial Agonists**: Partial agonist at μ receptors
- **Opioid Agonist Antagonists**: Agonist on one [K] and antagonist on other [μ]
- **Opioid Antagonists**: Blocks all 3 receptors

I. Opioid Agonists

- Drugs include
  - Morphine
  - Heroin -100 times more addictive than morphine
  - Methadone-very long acting, used in deaddiction of opioids
  - Pethidine
  - Codeine / Pholcodeine / Dextromethorphan / Noscapine
  - Loperamide / Diphenoxylate
  - Tramadol / Tapentadol
  - Fentanyl
  - Alfentanyl
  - Sufentanyl
  - Remifentanyl
- **Codeine** group of drugs are used as cough suppressants / Anti-tussives. Indicated for dry cough
- 99% of **Pethidine** undergoes degradation but 1% of it is converted to Nor-pethidine which is very long acting. If pethidine is given for a long period, nor-pethidine can accumulate in the body, leading to seizures.
- Pethidine is C/I along with MAO – Inhibitors
- **Loperamide / Diphenoxylate** are indicated for non-infective diarrhea. They are C/I in infective diarrhoea
- To prevent the drug abuse, the market preparation of loperamide and diphenoxylate are never given alone. They are always given in combination with Atropine **(Sub therapeutic dose)**
- **Tramadol / Tapentadol** stop pain not only through μ, k, δ receptors, but also by increasing 5HT and NA in spinal cord
- **Fentanyl, Alfentanyl, Sufentanyl and Remifentanyl** are Highly lipid soluble drugs and used in anaesthesia. Fentanyl causes Post op. muscle rigidity (but Post op. muscle pain is due to Succinylcholine)
- Sufentanyl is the most potent opioid
- Remifentanyl is the shortest acting opioid (d/t metabolism by Pseudo-choline esterase)

II. Partial Agonists

⏱ 00:25:14

- Buprenorphine
  - It is a partial agonist at μ receptor
  - It has a ceiling effect on respiratory depression. So, even if the dose increases, the respiratory depression will not increase.

III. Agonist Antagonist

⏱ 00:27:34

- Drugs include:
  - **P**- Pentazocine
  - **N**- Nalbuphine
  - **B**- Butorphanol
- These are agonist at K and antagonist at μ receptors
- S/E — Hallucinations

III. Opioid Antagonists

⏱ 00:28:43

- Drugs include:
  - Naloxone: Short acting, given I.V.
  - Naltrexone: Long acting, given orally
- DOC for Acute opioid poisoning – Naloxone
- DOC for Maintenance in opioid poisoning – Naltrexone

OPIOID DEADDICTION

⏱ 00:32:38

Short term addiction		Long term addiction
Stop opioids ↓ Withdrawal symptoms ↓		• Replace with methadone (Less addictive and long acting, causes less euphoria) ↓ Decrease dose gradually and stop • To prevent relapse, we give Naltrexone
Sympathetic symptoms • Rx by ○ β # ○ Clonidine	**Opposite action** • Rx by BZD	

ALCOHOLS

⏱ 00:39:30

Alcohol: ↓Alc. dehydrogenase	Ethyl Alcohol ↓	Methyl alcohol ↓
Aldehyde: ↓ Ald. dehydrogenase	Acetaldehyde ↓	Formaldehyde ↓
Acid:	Acetic acid	Formic acid

Ethyl alcohol

- Disulfiram:
  - inhibits Acetaldehyde dehydrogenase
  - Used as Alcohol Aversion Therapy
  - Instead of euphoria, Unpleasant symptoms occur on consuming alcohol d/t increased acetaldehyde
- **Disulfiram like reactions** shown by:
  - **C**- Cephalosporins, Chlorpropamide

- G - Griseofulvin
- M – Metronidazole
- P - Procarbazine

Methyl Alcohol

- Both Formaldehyde and Formic acid can cause retinal damage and blindness
- For inhibiting alcohol dehydrogenase, Ethanol has been used
- Ethanol (Ethyl alcohol) acts as a competitive inhibitor of methanol
- Ethanol:
  - Cannot be given Intravenously
  - Given by Intra-gastric route (through Ryle's tube)
  - Dependent on GIT absorption

↓

which is not reliable

↓

So, we cannot exactly titrate the effect with the dose

  - Further, it is an alcohol. So, it produces inebriant effect
- To avoid the above side effects, a new drug has been developed called Four Methyl Pyrazol or Fomepizol
  - It is a competitive inhibitor of alcohol dehydrogenase itself
  - Can be given by I.V route
  - It is not an inebriant
  - So, it is now DOC for methanol poisoning
- Folic acid–inhibits the metabolism of Formaldehyde / Formic acid

ETHYLENE GLYCOL

- It is used as Anti-Freeze / Lubricant in the industry
- Acts like alcohol i.e., metabolized to form aldehyde

Ethylene glycol

↓Alcohol dehydrogenase

Glycol aldehyde

↓converted to

Glycolic acid

↓ metabolized to form

Oxalic acid

- The patient comes with Metabolic acidosis and Oxalate crystals in urine
- **Treatment**: Fomepizole is DOC (Inhibits alcohol dehydrogenase)

ALCOHOL DEADDICTION

⏱ 00:50:40

- There are 3 methods
  I. Replacement method
  II. By decreasing craving of alcohol
  III. Aversion therapy

I. Replacement method:

- Replace the addictive drug with similar type of drugs which are long acting
- Alcohol → CNS Depressant
- So, replaced by long-acting C.N.S depressant i.e., Benzodiazepines Chlordiazepoxide / Diazepam

↓

Gradually dose is decreased

↓

Stop the drug

II. Drugs decreasing alcohol craving:

- **None**: Naltrexone – But it can't decrease opioid craving. It decreases the risk of relapse in opioids
- **Of**: Ondansetron
- **The**: Topiramate
- **Above**: Acamprosate

III. Alcohol Aversion Therapy:

Ethanol

↓alcohol dehydrogenase

Acetaldehyde

↓aldehyde dehydrogenase

Acid

- Major euphoric effect of alcohol is caused by ethanol
- After some time, metabolism occurs and it produces acid, which is inactive and produces no effects
- If acetaldehyde accumulates, it cause adverse effects:
  - Vomiting
  - Headache
  - Labile B.P
  - Blurring of Vision
- If aldehyde dehydrogenase doesn't work, aldehyde accumulates
- Drug inhibiting aldehyde dehydrogenase → Disulfiram. It is used for alcohol de-addiction
- It doesn't decrease craving
- The person will be afraid of taking alcohol because of the adverse effects that he experienced due to disulfiram

Psychological dependence

- Person has craving and he is psychologically dependent that he cannot live without alcohol
- But if person doesn't get alcohol, there are no physical symptoms

Physical dependence

- Person is physically dependent
- If the person doesn't get alcohol, he develops physical symptoms called withdrawal symptoms
- **Disulfiram** is indicated only in psychological dependent patients. It is C/I in physically dependent patients.

CLINICAL QUESTIONS

SEDATIVE HYPNOTICS

Q. Which of the following hypnotic drugs facilitates the inhibitory actions of GABA but lacks anticonvulsant or muscle relaxing properties and has minimal effect on sleep architecture?

A. Buspirone
B. Diazepam
C. Phenobarbital
D. Zaleplon

Answer: D

Solution

- Zolpidem, **zaleplon** and zopiclone are agonists at BZD receptors.
- These are **hypnotic drugs that lack muscle relaxant and anticonvulsant actions.**
- These have negligible effect on REM sleep and do not affect sleep architecture.

Q. A very potent and short acting benzodiazepine was given to a patient Kallu for the purpose of causing hypnosis but the drug caused psychiatric disturbances in him. Which of the following can be the hypnotic used?

A. Flurazepam
B. Nitrazepam
C. Temazepam
D. Triazolam

Answer: D

Solution

- **Triazolam** is a very potent BZD with ultra rapid elimination.
- Some cases of **paranoia and psychiatric disturbances have been noted with this drug.**

PARKINSONISM

Q. A 44 year old male came in with complaints of tremors in the hand. You notice he is unable to take proper stride while walking and on examination you see there is cogwheel rigidity in the arm. Which of the following antiparkinsonian drugs would you prescribe, that directly activates dopaminergic D2 receptors in the striatum?

A. Pramipexole
B. Entacapone
C. Benserazide
D. Selegiline

Answer: A

Solution

Directly acting D2 receptor agonists can be:

- Ergot derivatives e.g. bromocriptine and pergolide
- Non-ergot compounds e.g. **pramipexole** and ropinirole

Q. A patient of Parkinsonism, Mr. Ghai noticed that the therapeutic effect of levodopa decreased when he was given another drug by his physician but no interaction was seen when he switched over to levodopa-carbidopa combination. What drug is most likely prescribed by his physician?

A. Metoclopramide
B. Vitamin B complex
C. Chlorpromazine
D. Isoniazid

Answer: B

Solution

- **Pyridoxine is a component of vitamin B complex.**
- Pyridoxine is a **cofactor** for the enzyme, **dopa decarboxylase** and therefore, administration of vitamin B complex can stimulate the activity of this enzyme.
- **Dopa decarboxylase converts levo-dopa to dopamine.** Increased formation of dopamine in the periphery is undesirable because it cannot cross blood brain barrier. Therefore, stimulation of dopa decarboxylase decreases the therapeutic effect of l-dopa.
- If the enzyme, **dopa decarboxylase** is already inhibited with **carbidopa,** there will be **no interaction** with pyridoxine.

EPILEPSY

Q. A 11 year old child, known to have epilepsy from age of 9 months, has been taking a medication till date. He presents with fever, rash all over the body and noted lymphadenopathy. Which of the following medications do you think he might have consumed?

A. Valproate
B. lamotrigene
C. Phenytoin
D. Topiramate

Answer: C

Solution

Pseudolymphoma

- It is a hypersensitive reaction to drug
- Pseudolymphoma triad consists of
  - Fever, generalized rash and lymphadenopathy
- Anti epileptic drugs causing pseudolymphoma
  - Phenytoin> Phenobarbitone> Primidone
  - Carbamzepine

Q. The most common adverse effect particularly seen in young children because of the use of sodium valproate is:

A. Hepatitis
B. Loss of hair
C. Anorexia
D. Tremor

Answer: A

Solution

Sodium valproate is contra-indicated in children less than 3 years due to risk of **hepatitis.**

Other side effects of valproate-

- Vomting
- Alopecia
- Liver toxicity
- Pancreatitis, PCOD
- Rash
- Obesity
- Ataxia
- Teratogenic

PSYCHIATRIC ILLNESS

Q. Which of the following effects is unlikely to occur during treatment with imipramine?

A. Elevation of seizure threshold
B. Mydriasis
C. Sedation
D. Urinary retention

Answer: A

Solution

- Imipramine is a **tricyclic antidepressant.**
- MOA- **Imipramine is highly anticholinergic** and is relatively strong serotonin as well as norepinephrine reuptake inhibitor.
- Adverse effect- **Increased risk of seizures due to lowering of seizure threshold**, Anticholinergic side effects.

Q. A patient Ashwani has been brought to the hospital with non-stop talking, singing, uncontrollable behavior and apparent loss of contact with reality. You diagnose it to be a case of acute mania. Which of the following is the most suitable drug for rapid control of his symptoms?

A. Lithium carbonate
B. Phenobarbitone
C. Haloperidol
D. Valproic acid

Answer: C

Solution

- **Antipsychotic drugs like olanzapine and haloperidol** are agents of choice for **rapid control of symptoms in acute mania.**
- **Lithium is the drug of choice** for the treatment of **bipolar disorder (MDP) and prophylaxis of mania.**

DRUG OF ABUSE

Q. The combination of alcohol and disulfiram results in nausea and hypotension as a result of accumulation of:

A. Acetaldehyde
B. Acetate
C. Methanol
D. NADH

Answer: A

Solution

- Disulfiram is an **aldehyde dehydrogenase inhibitor** that can be used for **de-addiction of chronic alcoholics.**
- Due to **inhibition of aldehyde dehydrogenase,** there is accumulation of **acetaldehyde** that leads to **several distressing symptoms (which strengthens the resolution of a person to quit alcohol).**

Q. Naltrexone is:-

A. Mu receptor agonist
B. Delta receptor agonist
C. Kappa receptor agonist
D. Mu receptor antagonist

Answer: D

Solution

- **Naloxone, naltrexone** and **nalmefene** are potent mu receptor antagonists with significant blocking action at kappa and delta receptors also.
- **Naloxone** is given parenterally (**ineffective orally**) and is a **very short acting** drug.
- **Nalmefene** is also given **parenterally** but has a **longer half life**.
- **Naltrexone** is **long acting orally** effective opioid antagonist.
- **Naloxegol**-Naloxone conjugated to PEG polymer

LEARNING OBJECTIVES

UNIT 9: HEMATOLOGY

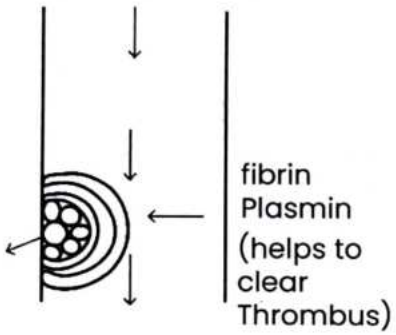
- Drugs affecting Blood Flow
  - Anti-platelet drugs
  - Anti-coagulant drugs
  - INR
- Drugs affecting Cells of blood
  - Haematinics
  - Growth factors
  - IDA
  - Megaloblastic anemia

57 DRUGS AFFECTING BLOOD FLOW

- Haematology: It is the study of blood
- In pharmacology, we study drugs related to problems in
  - Blood Flow
  - Blood Cells

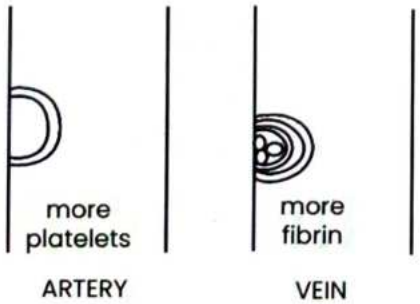
BLOOD FLOW

Haemostasis



Bleeding prevention

- When injury occurs to a blood vessel, bleeding starts. Within a few seconds this bleeding stops
- The first step in this process is that the platelets in the blood accumulate at the site of injury and form a temporary plug
- Then there is accumulation of fibrin over this platelet plug, making it a permanent plug
- After some time, the endothelium of the blood vessel heals. Now this plug is not required, so a factor called Plasmin is generated which removes this plug. Thus normal blood flow is re-established
- The difference in this process of haemostasis between an artery and a vein is:



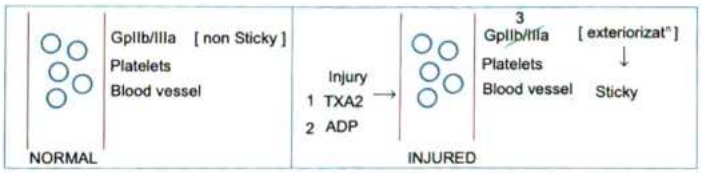
  - The basic process is the same, but in arterial thrombosis→Platelet plug is very large and the fibrin layer is very thin
  - In venous thrombosis→the platelet plug is very small and the fibrin layer is very thick
  - As a result, when thrombus is in an artery, the more effective drug will be an Anti-platelet drug. For eg- Aspirin for MI, stroke
  - When the thrombus is in a vein, the more effective drug will be an Anti-fibrin drug. For e.g Warfarin for DVT

Drugs used in thrombotic disorders 00:07:13

1. Anti-Platelet drugs
2. Anti-fibrin drugs
3. Thrombolytic drugs

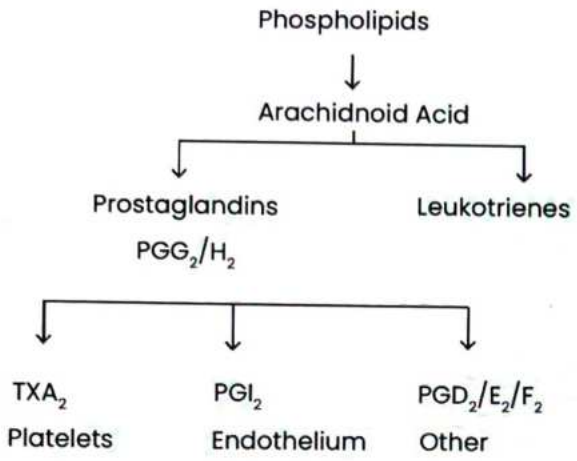
ANTI-PLATELET DRUGS

- The blood normally contains platelets but they do not aggregate randomly because they contain a receptor called glycoprotein (Gp) II_b/III_a. This receptor is normally present inside, so the platelet is not sticky
- Whenever injury occurs to blood vessels, there is release of some substances
  - Thromboxane A_2 (TXA_2)
  - Adenosine diphosphate (ADP)
  - Thrombin
- These substances lead to exteriorization of the Gp II_b/III_a receptors. Thus platelets become sticky and they aggregate



- Anti-platelet drugs can be
  i. Acting on TXA_2
  ii. Acting on ADP
  iii. Acting on Thrombin
  iv. Acting on Gp II_b/III_a

i. Drugs inhibiting TXA_2 00:11:50



- TXA_2 causes aggregation
- PGI_2 inhibits aggregation
- Aspirin inhibits the enzyme cyclo-oxygenase (COX). So it will decrease the production of both PGI_2 in the endothelium and TXA_2 in the platelets.
- Aspirin is an anti-platelet drug
- Endothelium cells contains nucleus, which produces new COX. Due to this COX, PGI_2 synthesis starts again. But platelets don't contain a nucleus, so TXA_2 level remains low
- Net result is that, PGI_2 level is normal whereas TXA_2 is reduced. So there is net anti-platelet action
- Low dose Aspirin (40-325 mg) is used as anti-platelet agent

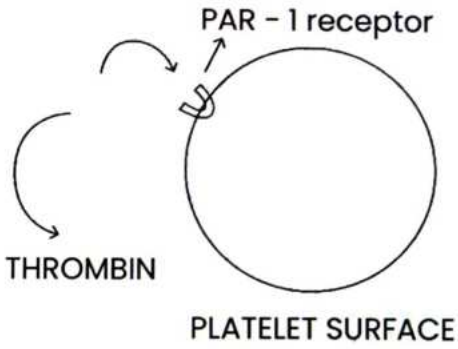
ii. Drugs acting on ADP receptors 00:17:55

- ADP receptors present on platelet are → P_2Y_{12}
- When ADP binds to this receptor, it will activate the platelet
- Drugs will block this receptor, which results in blockade of platelet aggregation
- Drugs include:

Irreversible antagonist	Reversible antagonist
• Clopidogrel	• Cangrelor
• Prasugrel	• Ticagrelor
• Ticlopidine	

- Clopidogrel and Ticlopidine are both prodrugs. They are activated by CYP2C19 enzyme.
- Omeprazole inhibits CYP2C19, so these drugs should not be combined with Omeprazole.
- Pantoprazole and Rabeprazole have least chance of inhibition of CYP2C19
- Ticlopidine has been removed from the market because of its side effect → Thrombocytopenia
- Prasugrel is faster acting than Clopidogrel. But it can cause side effect → Cerebral haemorrhage
- Irreversible drugs need to be stopped at least 7 days before surgery.
- Cangrelor is not available in market
- Ticagrelor is given orally

iii. Drugs acting on thrombin receptors 00:28:16



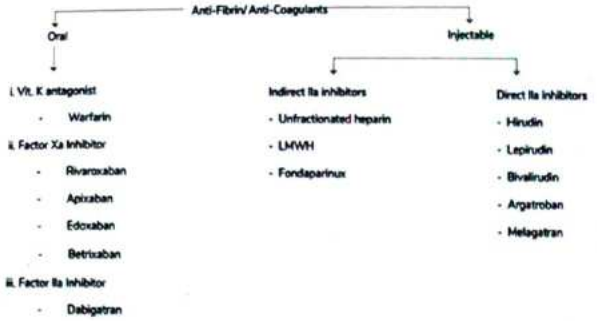
- Thrombin receptor on platelet is→PAR-1 (Protease Activated Receptor-1)
- When thrombin binds to this receptor, it will activate the platelets and lead to aggregation
- Drugs
  - Atopaxar
  - Vorapaxar
- Atopaxar is not used. Vorapaxar is used and it is given orally.

iv. Drugs actin on GP IIb / IIIa receptor 00:31:02

- These include
  - Abciximab
  - Tirofiban
  - Eptifibatide
- These are the strongest acting anti – platelet drugs
- These are injectable drugs and not effective orally.

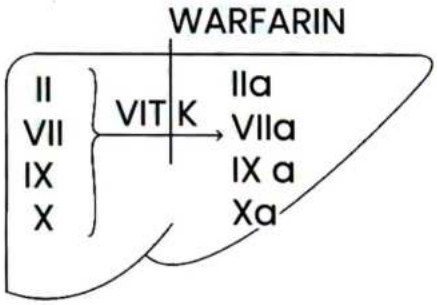
ANTI-FIBRIN DRUGS / ANTI COAGULANT DRUGS 00:33:11

Factor X → Factor Xa
↓
Factor II (Prothrombin) → Factor IIa (Thrombin)
↓
Factor I (Fibrinogen)→ Factor Ia (Fibrin)



I. Vit. K antagonist

00:37:48



- Liver can produce all clotting factors but there are 4 factors which require Vit K for activation. These are factor II, VII, IX, X
- Vit. K results in -carboxylation of glutamate residues of factor II, VII, IX, X to make them active.
- Vit. K itself becomes inactive after activating these factors. The inactive form is Vit K epoxide. To convert this inactive Vit K to active Vit K hydroquinone, we need Vit K epoxide reductase (VKOR)
- The drugs inhibit the already active factors. The already active factors can keep on working. Thus, the action of warfarin like drugs is delayed. It takes 4-5 days for the action to start.
- So warfarin like drugs cannot be used for treatment of acute thrombosis.
- They can only be given as maintenance drugs.
- Vit K can also activate some anti-clotting factors like protein C and protein S
- So if anti-clotting factors finish first, clotting will increase. This leads to Hypercoagulation which can result in Dermal vascular necrosis or Purple Toe Syndrome
- This is an early side effect, appearing in 1-2 days after giving Warfarin. It is not seen in normal people. Usually seen in people with genetic deficiency of protein C.

Important Information

- Warfarin like drugs
  - Given orally
  - MOA : Inhibit VKOR
  - Slow acting (4-5 days)
  - Early S/E : Hypercoagulation
  - Used mainly for maintenance
  - Teratogenic so avoided in pregnancy
  - Monitoring is required

- Osteocalcin also gets activated by -carboxylation. If we give warfarin during pregnancy, this is not activated. This leads to warfarin embryopathy or Fetal Warfarin Syndrome
- **Features of Fetal Warfarin Syndrome:**
  - Microcephaly
  - Hypoplasia of nasal bone
  - Microphthalmia
  - Telecanthus
- So warfarin is avoided in 1st Trimester. Also avoided in 3rd Trimester, because of risk of Vit. K deficiency in the new born
- **Monitoring**
  - Warfarin mainly affects the extrinsic pathway
  - It is monitored by Prothrombin time or INR (PT-INR)
  - Clotting pathway
    → Intrinsic pathway
    → Extrinsic pathway
  - Intrinsic pathway is measured by aPTT or activated partial thromboplastin time.
  - Extrinsic pathway is measured by PT or Prothrombin time
  - Warfarin affects the Extrinsic pathway. So it is monitored by Prothrombin time. This is given by mnemonic WEPT.

How to remember

- WEPT
  W - Warfar...
  E - Extrinsic pathway
  PT - Prothrombin Time

  - Similarly Heparin affects the Intrinsic pathway, so it is monitored by aPTT

How to remember

- HINT
  H - Heparin
  INT - Intrinsic pathway

  - Normal values
- aPTT : 26-32 sec (~30sec)
- PT : 12-16sec (~15sec)
  - But different labs give different control values for the same sample. To fix this, we measure both the samples in the same lab.
  - We can also use an alternative i.e. INR (International Normalised Ratio). INR value is the same in every lab.
  - INR value is calculated as :
    $INR = \left[\frac{PT_{test}}{PT_{control}}\right]^{ISI}$
    → Here ISI is International Sensitivity Index. This value is given by WHO.
- Warfarin overdose
  - There will be bleeding
  - Treatment of Bleeding d/t Warfarin:
    i. We give active factors which are deficient. These are factor IIa, VIIa, IXa, Xa. This is called Four Factor Complex or Prothrombin Factor Complex (PFC). This is the DOC.
    ii. If PFC is not available, we can give Fresh Frozen Plasma (FFP)
    iii. If FFP is not available, we can give Whole blood.
  - Treatment of Bleeding Tendency d/t warfarin: this means that the bleeding has not started yet. We have some time till the activation of actors. So we can give Vit K. Vit K is also antidote for warfarin overdose.
  - To check for bleeding tendency and risk of bleeding, we use INR:
    i. INR<5 → stop warfarin
    ii. 5-20 → stop warfarin
    +
    Give Vit. K
    iii. >20 → stop warfarin
    +
    Give four factor complex
- **Drug interactions**
  - Enzyme inducers:
    → Rifampicin, CBZ : They increase the metabolism of warfarin, so it becomes ineffective. INR value is lower. There is risk of thrombosis, so we need to increase the dose of warfarin.
  - Enzyme inhibitors:
    → Ciprofloxacin, Erythromycin: They inhibit the metabolism of warfarin, so INR increases. There is increased risk of bleeding, so we need to decrease the dose of warfarin.

II. Direct thrombin inhibitors 01:06:27

- Dabigatran: It is an oral thrombin inhibitor
- Unlike warfarin, the New Oral Anti-Coagulants (NOAC) do not require monitoring. They have consistant bioavailability. So they do not require monitoring
- Dabigatran overdose can be treated by a monoclonal antibody Idarucizumab.

III. Direct factor Xa inhibitors

- These also come in the category of NOAC
- Drugs are
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban

Important Information

- Rivar - Reversible
  O - Oral
  XA - Xa
  B - Blocker (or)
  AN - Antagonist

Previous Year's Questions

Q. Oral factor Xa inhibitor is : (NEET Jan 2019)
A. Dabigatran etexilate
B. Rivaroxaban
C. Fondaparinux
D. Bivalirudin

- Andexanet alfa is the antidote for factor Xa blocker overdose. But it is only approved for Rivaroxaban and Apixaban
- Another antidote: Ciraparantag. This drug has not yet been approved but it is a non – specific multiple anti-coagulant antidote. It can be used for :
  - Dabigatran
  - Factor Xa blockers
  - Heparins
- UFH

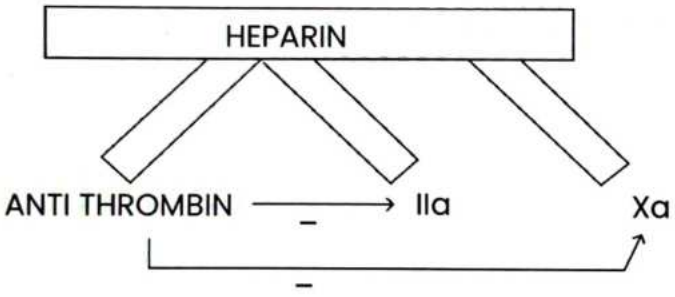
- LMWH
- Fondaparinux

Parenteral / injectable Anti – Coagulants 01:12:24

- The injectable anticoagulants are thrombin inhibitors. They start their action immediately.
- They may be
  - Indirect thrombin inhibitors
  - Direct thrombin inhibitors

i. Indirect thrombin inhibitors

- These are heparin group of drugs



I. **Unfractionated Heparin (UFH):** activates anti thrombin → inhibits both factor IIa and Xa equally.

ii. **LMWH**: activates antithrombin → inhibits factor Xa > IIa

iii. **Fondaparinux**: activates antithrombin→inhibits factor Xa only

- Examples of LMWH:
  - Enoxaparin
  - Dalteparin
  - Tinzaparin

Features of Heparin like drugs

i. Route of administration : S/C or I.V. ; never given by I.M. route

ii. MOA : They activate Antithrombin . May inhibit factor IIa and/or Xa

iii. Action starts immediately. So can be used for acute cases

iv. For acute cases, we give Warfarin + Heparin. Heparin acts immediately and warfarin starts acting by day five.

v. Heparins cannot cross the placenta. So they are anticoagulant of choice in pregnancy

vi. Monitoring : Done by aPTT (Activated partial Thromboplastin Time)

- UFH : Done by aPTT
- LMWH
- Fondaparinux

} No monitoring required, because they have consistent bioavailability

→ But in case of Renal failure, monitoring is required and done by Antifactor Xa Assay

vii. Heparin overdose antidote : Protamine

Previous Year's Questions

Q. Match the following drug with their antidote (INICET Nov 2020)

Drug	Antidote
a. Heparin	1. Calcium gluconate
b. Hydrofluoric acid	2. Protamine
c. Ethylene glycol	3. Carnitine
d. Valproate	4. Fomepizole

Ans.

a. → 2
b. → 1
c. → 4
d. → 3

viii. Interactions: Heparin is not metabolised by microsomal enzymes. So there are very few interactions

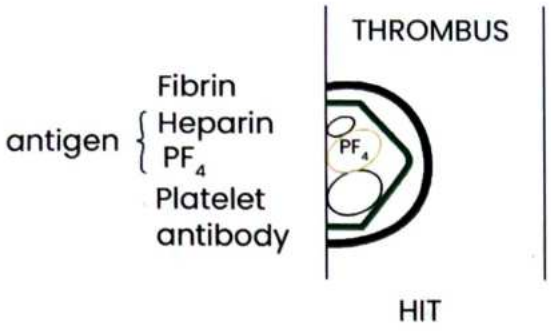
• In vivo usage	• In vitro usage
○ To be used in the body ○ Both warfarin & Heparin can be used in vivo, because all the drugs are meant to be used in body.	○ To be used in the lab. This can be either in blood bank or in blood sampling ○ Warfarin is not used in the lab, because it inhibits the activation of factors and not activated factors itself. Lab sample will contain active factors ○ So heparin is used in-vitro.

- **Adverse effects of Heparin**
  - **B - Bleeding**
  - **O - Osteoporosis**
  - **T-Thrombocytopenia→Heparin induced thrombocytopenia**
  - **H - Hyperkalaemia**
  - **A - Alopecia**

How to remember

- Johan BOTHA is a famous South African Cricketer

Heparin Induced Thrombocytopenia (HIT) 01:28:58



- Heparin is a Hapten i.e. incomplete antigen. When it combines with Platelet factor -4 (PF-4), it becomes complete and now can lead to formation of antibodies
- PF4 is normally present on the platelet surface
- Antibody combines to this Heparin-PF4 complex on the platelet surface
- Now fibrin will bind to this whole group and form a clot.
- If we check the platelet count now, it will be low because the platelets are deposited in the thrombus. So there is thrombocytopenia which is induced by Heparin
- It occurs 4-5 days after starting heparin
- It is characterised by clotting and not bleeding.
- Ischaemic symptoms can be seen like pallor.
- Warfarin like drugs cannot be used for treatment
- DOC is direct thrombin inhibitors. For Eg.
  - Hirudin
  - Lepirudin
  } Injectable
  - Bivalirudin
  - Argatroban
  - Melagatran
  - Ximelagatran
  - Dabigatran → Oral
- Out of these, Hirudin, Lepirudin and Ximelagatran are withdrawn. So the drugs which can be used effectively are:
  - Bivalirudin
  - Argatroban
  - Melagatran

THROMBOLYTIC DRUGS 01:38:00

- In acute conditions like Acute MI, Acute stroke, Acute PE, Acute DVT → the thrombus formation is complete. So our main aim of treatment is to resume blood flow at the earliest. For this, we break the thrombus by giving thrombolytic drugs.
- These drugs are aka Fibrinolytic drugs or Tissue Plasminogen Activators
- We cannot give Plasminogen as it is an inactive substance. Also we cannot give Plasmin, because there is Anti-plasmin already circulating in the blood.
- Drugs included are:
  - **S** - Streptokinase
  - **U** - Urokinase
  - **R** - Reteplase
  - **A** - Alteplase
  - **T** - Tenecteplase

How to remember

- SURAT

- Streptokinase is obtained from streptococcus, so it has some problems related to it:
  i. Some patients can be allergic to it because it is made from a foreign particle
  ii. It can act as an antigen and lead to antibody formation. This antibody will make the repeated doses of Streptokinase ineffective.
- Reteplase, Alteplase and Tenecteplase → These are purely human enzymes and made by recombinant DNA technology. So they don't have the problems which are associated with Streptokinase
- Streptokinase, Urokinase and Alteplase: They are short-acting drugs. So they are always given by I.V. infusion
- Reteplase and Tenecteplase: They are long acting so they are given by I.V. bolus
  - Tenecteplase is longest acting, so only Single bolus is required
  - Reteplase is comparatively less lon[illegible] doses are required k/a Double bolus
- Adverse effects of thrombolytics → Bleeding
- Antidote of thrombolytic / fibrinolytic drugs → Anti fibrinolytic drugs. These are
  - Epsilon Amino Caproic Acid (EACA)
  - Tranexamic Acid

Previous Year's Questions

Q. Which of the following drug can be used as an antidote for fibrinolytic overdose?
(AIIMS June 2020)

A. Ethamsylate
B. Alteplase
C. Andexanet alpha
D. Epsilon amino caproic acid

58 DRUGS AFFECTING CELLS OF BLOOD

- The drugs affecting blood cells are
  i. Haematinics
  ii. Growth factors

HAEMATINICS 00:00:41

- Haematinics are the nutritional substances that we take in the diet, which help in the formation of blood.
- The substances included are:
  1. Iron
  2. Folic acid
  3. Vit B_{12}

1. Iron 00:01:15

- Whenever there is deficiency of iron, it is called Iron deficiency Anemia (IDA)
- The causes of IDA are
  - Nutritional, Bleeding } Microcytic hypochromic anemia
  - Hookworm infestation
- The treatment for IDA is Iron therapy. It can be given by
  - Oral route (preferred)
  - Injectable route
- Preparations of oral iron are
  - Ferrous sulphate
  - Ferrous gluconate
  - Ferrous fumarate, etc.
- The factors which increase the absorption of iron are:
  i. Reducing substances: Ascorbic acid
  ii. HCl
- The factors which decrease the absorption are
  i. Phytates
  ii. Oxalates
  iii. Tannates: Tea, Coffee
- Once we start the iron therapy, the response can be seen by
  - Reticulocytosis: Earliest response
  - Hb level: If the Hb level rises by 0.5-1g/dL per week, we consider it adequate response.
- We continue the iron therapy even after Hb level becomes normal, for 2-3 months. This is done to replenish the iron stores in the body.
- Oral iron is available in the form of tablets. For children, drops are also available. But drops can cause permanent pigmentation if they come in contact with the skin. So, iron drops should be administered deep in the throat to prevent problems of pigmentation.

Indications for giving Injectable iron 00:08:10

i. When oral iron cannot be given, this can be due to
   - Side effects of iron – diarrhoea, vomiting
   - Malabsorption

ii. With Erythropoietin
   - When a person has deficiency of erythropoietin, we give erythropoietin from outside. It helps in formation of Hb. That will require iron in large quantity and quickly.

- Preparations of Injectable Iron are:
  - Iron sorbitol citrate
  - Iron dextran
- Iron sorbitol citrate can only be given by I.M. route never given by I.V. route, because it can quickly saturate the transferrin receptors. So, there is a lot of free iron which leads to toxicity.
- Iron dextran can be given by both I.M. and I.V. routes.

- **Dose of Injectable Iron:**
  - Dose = 4.3 x Body wt. (kg) x Hb deficit (g/dL)
  - This formula includes the dose for iron stores also. So no need to give separately for stores.

- Injectable iron is a liquid preparation, so can cause pr[illegible]ntation, when given by I.M. route especially
- To prevent this pigmentation, we give I.M. iron by Z-track technique.
- Iron overdose:
  - Antidote given is
    → Desferrioxamine
    → Deferiprone
  - Desferrioxamine is injectable and is the DOC for Acute Iron Poisoning
  - Deferiprone is oral and given for Chronic Iron overload.

2. Folic acid } Deficiency: Megaloblastic anemia

00:16:02

3. Vit B_{12}

- Normally these drugs are given orally.
- Pernicious Anemia: It is a special type of megaloblastic anemia. In this there is deficiency of Intrinsic factor in the stomach. It binds to Vit B_{12} and helps in absorption of Vit B_{12}. When there is deficiency of Vit B_{12} we cannot give oral Vit B_{12} ,as it won't be effective. We give I.M. Vit B_{12} for treatment of pernicious anemia.
- Folic acid is mainly involved in the formation of blood.
- Vit B12 has mainly two functions:
  - Blood formation
  - Myelin sheath formation
    - → When a person has Megaloblastic anemia due to vitamin B12 deficiency, there are symptoms of anemia initially. Deficiency of myelin sheath does not show symptoms in the initial period.
    - → So if we give Folic acid alone for treatment in this case, the blood picture will improve (RBC, Hb) and anaemic symptoms will improve initially. But the neurologic deficit continues.
    - → Further, the B_{12} stores in the body are used up for RBC formation. This will also worsen the symptoms. It results in a condition called Sub-Acute Combined Degeneration of spinal cord.
    - → The deficit of myelin sheath affects posterior column of the spinal cord first, so initially there are symptoms of
      - Loss of vibration sense
      - Loss of proprioception
    - → So the underlying message is → when a person has megaloblastic anemia:
      - Do not give folic acid alone, without diagnosing the cause (FA or B_{12})
      - If it is due to Folic acid deficiency, give FA.
      - If it is d/t B_{12} deficiency, give B_{12}
      - If it is not sure, give FA+ B_{12} both.

GROWTH FACTORS

00:21:16

Cells	Growth factors	Indication for use
RBCs	Erythropoietin	• Anemia d/t Chronic Kidney disease • Anemia d/t Bone Marrow Suppression (BMS)
WBCs	G-CSF GM-CSF	• Leucopoenia d/t BMS • Mobilization of peripheral blood stem cells
Platelets	IL-11 Thrombopoietin	• Thrombocytopenia d/t BMS

- Erythropoietin which is available as a drug is Darbopoietin
- Overdose of Darbopoietin results in Polycythaemia
- Drugs for
  i. G-CSF
  - Filgrastim
  - Pegfilgrastim

Previous Year's Questions

Q. A patient was receiving anticancer therapy. He presented with high grade fever and sore throat. Hemogram revealed that total leucocytes count of this patient was 200/mm^3. Which of the following drug is likely to be effective?

(FMGE Aug 2020)

A. Oprelvekin
B. Filgrastim
C. Erythropoietin
D. Romiplostim

  ii. GM-CSF
  - Sargramostin
  - Molgramostin
- Drug for IL-11: Oprelvekin
- All the drugs mentioned above are given by Sub-cutaneous route.
- Drug which stimulates thrombopoietin receptors → Romiplostim. It is used for Idiopathic thrombocytopenic purpura (ITP). It is used by S/C route.
- Other thrombopoietin receptor agonist is → Eltrombopag. It is the only oral drug. It is used for ITP.
- New drugs
  - Avatrombopag
  - Lusutrombopag
- These drugs are also oral thrombopoietin receptor agonists. But these drugs are mainly indicated to prevent thrombocytopenia in patients who have liver disease.

CLINICAL QUESTIONS

SEDATIVE HYPNOTICS

Q. Which of the following hypnotic drugs facilitates the inhibitory actions of GABA but lacks anticonvulsant or muscle relaxing properties and has minimal effect on sleep architecture?

A. Buspirone
B. Diazepam
C. Phenobarbital
D. Zaleplon

Answer: D

Solution

- Zolpidem, **zaleplon** and zopiclone are agonists at BZD receptors.
- These are **hypnotic drugs that lack muscle relaxant and anticonvulsant actions.**
- These have negligible effect on REM sleep and do not affect sleep architecture.

Q. A very potent and short acting benzodiazepine was given to a patient Kallu for the purpose of causing hypnosis but the drug caused psychiatric disturbances in him. Which of the following can be the hypnotic used?

A. Flurazepam
B. Nitrazepam
C. Temazepam
D. Triazolam

Answer: D

Solution

- **Triazolam** is a very potent BZD with ultra rapid elimination.
- Some cases of **paranoia and psychiatric disturbances have been noted with this drug.**

PARKINSONISM

Q. A 44 year old male came in with complaints of tremors in the hand. You notice he is unable to take proper stride while walking and on examination you see there is cogwheel rigidity in the arm. Which of the following antiparkinsonian drugs would you prescribe, that directly activates dopaminergic D2 receptors in the striatum?

A. Pramipexole
B. Entacapone
C. Benserazide
D. Selegiline

Answer: A

Solution

Directly acting D2 receptor agonists can be:

- Ergot derivatives e.g. bromocriptine and pergolide
- Non-ergot compounds e.g. **pramipexole** and ropinirole

Q. A patient of Parkinsonism, Mr. Ghai noticed that the therapeutic effect of levodopa decreased when he was given another drug by his physician but no interaction was seen when he switched over to levodopa-carbidopa combination. What drug is most likely prescribed by his physician?

A. Metoclopramide
B. Vitamin B complex
C. Chlorpromazine
D. Isoniazid

Answer: B

Solution

- **Pyridoxine is a component of vitamin B complex.**
- Pyridoxine is a **cofactor** for the enzyme, **dopa decarboxylase** and therefore, administration of vitamin B complex can stimulate the activity of this enzyme.
- **Dopa decarboxylase converts levo-dopa to dopamine.** Increased formation of dopamine in the periphery is undesirable because it cannot cross blood brain barrier. Therefore, stimulation of dopa decarboxylase decreases the therapeutic effect of l-dopa.
- If the enzyme, **dopa decarboxylase** is already inhibited with **carbidopa,** there will be **no interaction** with pyridoxine.

EPILEPSY

Q. A 11 year old child, known to have epilepsy from age of 9 months, has been taking a medication till date. He presents with fever, rash all over the body and noted lymphadenopathy. Which of the following medications do you think he might have consumed?

A. Valproate
B. lamotrigene
C. Phenytoin
D. Topiramate

Answer: C

Solution

Pseudolymphoma

- It is a hypersensitive reaction to drug
- Pseudolymphoma triad consists of
  - Fever, generalized rash and lymphadenopathy
- Anti epileptic drugs causing pseudolymphoma
  - Phenytoin> Phenobarbitone> Primidone
  - Carbamzepine

Q. The most common adverse effect particularly seen in young children because of the use of sodium valproate is:

A. Hepatitis
B. Loss of hair
C. Anorexia
D. Tremor

Answer: A

Solution

Sodium valproate is contra-indicated in children less than 3 years due to risk of **hepatitis**

Other side effects of valproate-

- Vomting
- Alopecia
- Liver toxicity
- Pancreatitis, PCOD
- Rash
- Obesity
- Ataxia
- Teratogenic

PSYCHIATRIC ILLNESS

Q. Which of the following effects is unlikely to occur during treatment with imipramine?

A. Elevation of seizure threshold
B. Mydriasis
C. Sedation
D. Urinary retention

Answer: A

Solution

- Imipramine is a **tricyclic antidepressant.**
- MOA- **Imipramine is highly anticholinergic** and is relatively strong serotonin as well as norepinephrine reuptake inhibitor.
- Adverse effect- **Increased risk of seizures due to lowering of seizure threshold**, Anticholinergic side effects.

Q. A patient Ashwani has been brought to the hospital with non-stop talking, singing, uncontrollable behavior and apparent loss of contact with reality. You diagnose it to be a case of acute mania. Which of the following is the most suitable drug for rapid control of his symptoms?

A. Lithium carbonate
B. Phenobarbitone
C. Haloperidol
D. Valproic acid

Answer: C

Solution

- **Antipsychotic drugs like olanzapine and haloperidol** are agents of choice for **rapid control of symptoms in acute mania.**
- **Lithium is the drug of choice** for the treatment of **bipolar disorder (MDP) and prophylaxis of mania.**

DRUG OF ABUSE

Q. The combination of alcohol and disulfiram results in nausea and hypotension as a result of accumulation of:

A. Acetaldehyde
B. Acetate
C. Methanol
D. NADH

Answer: A

Solution

- Disulfiram is an **aldehyde dehydrogenase inhibitor** that can be used for **de-addiction of chronic alcoholics.**
- Due to **inhibition of aldehyde dehydrogenase,** there is accumulation of **acetaldehyde** that leads to **several distressing symptoms (which strengthens the resolution of a person to quit alcohol).**

Q. Naltrexone is:-

A. Mu receptor agonist
B. Delta receptor agonist
C. Kappa receptor agonist
D. Mu receptor antagonist

Answer: D

Solution

- **Naloxone, naltrexone** and **nalmefene** are potent mu receptor antagonists with significant blocking action at kappa and delta receptors also.
- **Naloxone** is given parenterally (**ineffective orally**) and is a **very short acting** drug.
- **Nalmefene** is also given **parenterally** but has a **longer half life**.
- **Naltrexone** is **long acting orally** effective opioid antagonist.
- **Naloxegol**-Naloxone conjugated to PEG polymer

LEARNING OBJECTIVES

UNIT 10: ANTI-MICROBIAL DRUGS

- Cell wall synthesis inhibitors
  - Cidal drugs vs Static drugs
  - Beta lactams
  - Syphilis
  - Cephalosporins
  - Carbapenems
- Protein synthesis inhibitors
  - Classification
  - Tetracyclines
  - Chloramphenicol
  - Macrolides
  - Aminoglycosides
- Anti-metabolites and Quinolones
  - Sulfa drugs
  - DNA gyrase inhibitors
  - Quinolones
- Drugs not effective against particular bacteria
- Pseudomembranous colitis
- TDK, CDK and PAE
  - TDK, CDK
  - AUC-DK
  - Post antibiotic effect
- Antimicrobial resistance
  - Mechanism
  - Horizontal transmission
- Mycobacterial diseases
  - TB
  - RNTCP
  - Leprosy
  - MAC

- Anti-viral drugs
  - Virus multiplication
  - HIV
  - Influenza
  - Herpes
  - Hepatitis
  - COVID-19
- Anti-fungal drugs
  - Polyenes
  - Azoles
  - Allylamines
  - Other drugs
- Topical antifungal drugs
- Anti-parasitic drugs
  - Malaria
  - Amoebiasis
  - Leishmania
  - Trypanosomiasis

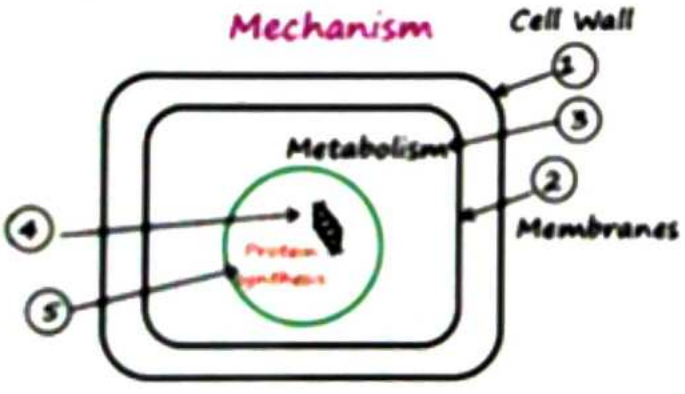
59 CELL WALL SYNTHESIS INHIBITORS

Classification of AMA is based on 00:00:13

1. **Cidal drugs (Kills)**
2. **Static drugs (inhibits growth)**

- Static and cidal drugs both can be used in normal immunocompetent persons
- In immuno-suppressed persons only cidal drugs are used, static drugs should not be used.
- Major cidal drugs are:
  - **BE**: Beta-lactams
  - **VA**: Vancomycin
  - **F**: Fluroquinolones
  - **A**: Aminoglycosides

3. **Types of Organism**
4. **Chemical Structure**
5. **Source**
   - Antibiotics (Obtained from microorganisms) & Non-antibiotics (obtained from plants or other sources)
   - All antibiotics are antimicrobials but all antimicrobials are not antibiotics
6. **Mechanism of action**
   a. Cell wall synthesis inhibitors
   b. Protein synthesis inhibitors
   c. Affecting Metabolism
   d. Affecting DNA
   e. Affecting Membranes

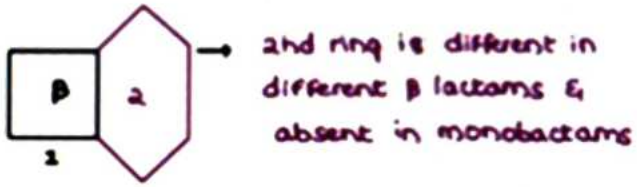


CELL WALL SYNTHESIS INHIBITORS

- Drugs include:
  - **Firmly**: Fosfomycin → used for UTI
  - **Bind to**: Beta-lactams
  - **Bacterial**: Bacitracin → Local use only
  - **Cell**: Cycloserine → Used in TB
  - **Vall**: Vancomycin

Beta-Lactams 00:08:03

- Beta-lactams contain a ring in their structure, except Monobactams
- These include
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams



PENICILLINS

Penicillin G/ Benzyl Penicillin

- **Limitations** of Penicillin G:
  1. Does not affect orally (Acid labile)
  2. Short acting (d/t rapid tubular secretion)
  3. Narrow spectrum
  4. Resistance
  5. Allergy
- To overcome these limitations, new drugs were developed. These include:

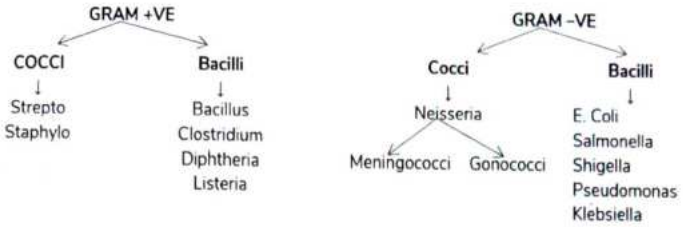
a. **Acid Resistant / Oral Penicillins:**
   - **V**: Penicillin V
   - **O**: Oxacillin
   - **D**: Dicloxacillin
   - **C**: Cloxacillin
   - **A**: Ampicillin, Amoxycillin

b. **Increased duration of action of Penicillin G:**
   - Probenecid completes with Penicillin at tubular pumps, which increases the duration of action of Penicillin
   - **Depot Preparations**:
     → Benzathine Penicillin G: Longest acting Penicillin

→ Procaine Penicillin G

→ Depot preparations are given by IM route only

c. Spectrum of Penicillin:



- **Extended / Wide Spectrum Penicillins** are:
  - **A**: Ampicillin, Amoxycillin
  - **Ci**: Carbenicillin
  - **Ty**: Ticarcillin
  - **M**: Mezlocillin
  - } Anti-Pseudomonal Drugs
  - **A**: Azlocillin
  - **P**: Piperacillin
- Vancomycin is not effective against Pseudomonas

d. Resistance:

- **β-lactamase Inhibitors**
  - They will inhibit the beta lactamase enzyme
  - These include:
    - → Clavulanic Acid + Amoxicillin
    - → Sulbactam + Ampicillin
    - → Tazobactam + Piperacillin
    - → Avibactam
- **Penicillinase Resistant Penicillins:**
  - **C**: Cloxacillin
  - **O**: Oxacillin
  - **N**: Nafcillin
  - **Do**: Dicloxacillin
  - **M**: Methicillin (most resistant)
- MRSA (Methicillin Resistant Staph. aureus):
  - Resistance is d/t altered Penicillin Binding Proteins
  - β-Lactams are ineffective except 5th gen. cephalosporins

e. Allergy

- Skin testing is done by intradermal injection of drug
- **Cross Allergy**: It means if a person is allergic to one penicillin, all β lactams can cause allergy, except Monobactam

Penicillin G Indications ⏱ 00:31:57

- They are First Line drugs in:
  - **L**: Listeria
  - **A**: Actinomycosis
  - **S**: Syphilis
  - **T**: Tetanus
  - **M**: Meningococcus
  - **AN**: Anthrax
  - **GO**: Gonococcus
- **Listeria:** DOC for listeria is Ampicillin
- **Actinomycosis:** DOC is Penicillin G
- **Syphilis:**

Syphilis types	Treatment
• **Primary** syphilis • **Secondary** syphilis	Single injection of Benzathine Penicillin G
• **Latent** – **Early**	IM route, dose of 2.4 MU
• **Latent** – **Late**	3 injections (1 injections a week) of Benzathine Penicillin G, IM with 2.4MU
• **Tertiary** syphilis (except neuro)	
• **Neurosyphilis**	Penicillin G (Aqueous / Crystalline) is the DOC for Neurosyphilis, several times a day for 10-14 days.

- **Tetanus:** DOC for tetanus is Penicillin G >> Metronidazole
- **Meningococcus:**

Refer Table 59.1

- **Anthrax:**
  - DOC for Gonococcal Urethritis: Ceftriaxone
  - DOC for Non- Gonococcal Urethritis: Azithromycin
  - DOC for Mixed Gonococcal and Non-gonococcal urethritis: Azithromycin

CEPHALOSPORINS ⏱ 00:43:09

Refer Table 59.2

1. Bile secreted Cephalosporins

- They are safe in renal failure
- Includes:
  - Cefoperazone
  - Ceftriaxone: S/E is Biliary sludge syndrome
- **Bile secreted** anti-microbial agents:
  - **Cef (safe) in**: Cefoperazone, Ceftriaxone
  - **The**: Tigecycline
  - **R**: Rifampicin

- **E**: Erythromycin
- **N**: Nafcillin
- **A**: Ampicillin
- **L**: Lincosamides (Clindamycin)
- **Disease**: Doxycycline

2. Anti-pseudomonal Cephalosporins

- Vancomycin is not effective
- Includes:
  - Cefepime
  - Cefpirome
  - Cefoperazone
  - Ceftazidime (most effective anti-pseudomonas cephalosporin)

3. Disulfiram like Reaction

- Not to be given with alcohol
- Includes:
  - Cefoperazone
  - Moxalactam
  - Cefotetan
  - Cefoxitin

4. Hypoprothrombinemia

- Includes:
  - Cefoperazone
  - Moxalactam
  - Cefotetan
  - Cefoxitin

CARBAPENEMS

00:58:33

Imipenem

- Effective against Gram (+), Gram (-) and Anaerobes
- Always given with Cilastatin, because if given alone it is broken down by Dehydropeptidase enzyme in the Kidney
- Imipenem is a broad spectrum antibiotic, it is also effective against Pseudomonas
- **Side effect** of Imipenem is Seizures
- **Contra-indicated** in Epileptic patients

Other Carbapenems:

- Meropenem
- Ertapenem
- Doripenem
- Faropenem

} Cilastatin is not required; Lesser risk of seizures

- All carbapenems are injectable, except Faropenem which can be given orally
- Any bacteria (mostly Klebsiella) which has Extended Spectrum Beta Lactamase (ESBL) enzyme is resistant to most of the antibiotics (except carbapenems)
- **Limitations of ESBL:**
  - Cannot break carbapenems and hence carbapenems are the DOC for ESBL producing bacteria.
  - Can be inhibited by beta lactamase inhibitors like Piperacillin + Tazobactam combination

New Delhi Metallo-beta lactamase (NDM)

- Can break even Carbapenems
- It cannot be inhibited by beta-lactamase inhibitor
- This infection is also known as Superbug
- Colistin can kill the bacteria that produces NDM beta lactamase
- Colistin is the DOC for NDM producing bacterial infections

MONOBACTAMS

01:07:41

Aztreonam

- Does not show cross allergy
- Effective only against Gm-ve bacteria including pseudomonas

VANCOMYCIN

- It is a glycopeptide
- Not effective orally (as it is not absorbed)
- Given by IV → releases Histamine → causes Red Man syndrome
- **S/E:**
  - Nephrotoxic
  - Ototoxic
  - Not effective against pseudomonas
- **Uses:**
  - MRSA (DOC). But the DOC for prophylaxis of MRSA is Mupirocin / Bacitracin
  - Pseudo-membranous colitis (oral route)
- **Other glycopeptide drugs**
  - Teicoplanin
  - Oritavancin
  - Telavancin
  - Dalbavancin

} They do not cause Red Man syndrome

Table 59.1

Meningococci

Treatment

Empirical → Ceftriaxone

Definitive → Penicillin-G

Prophylaxis

1. Rifampicin (not reliable now a days, due to resistance)
2. Ceftriaxone
3. Ciprofloxacin

↓

Ceftriaxone

- More effective than ciprofloxacin
- Injectable drug so cannot be used for masses
- Safe in pregnancy and children

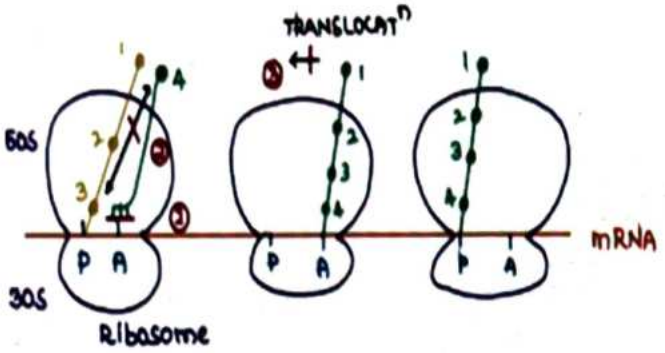
Ciprofloxacin

- Less effective
- C/I in pregnancy and children
- Can be given orally.
- DOC for Mass chemo prophylaxis of Meningococcal meningitis

Table 59.2

1st Generation	2nd Gen	3rd Gen	4th Gen	5th Gen
• Cefazolin	• Cefuroxime	• Cefixime	• Cefepime	• Ceftibiprole
• Cephalexin	• Cefoxitin	• Cefoperazone	• Cefpirome	• Ceftaroline
• Cefalothin	• Cefmetazole	• Ceftriaxone		
• Cefaloridine	• Cefamandole	• Cefotaxime		
• Cefadroxil	• Cefaclor	• Ceftazidime		
		• Cefpodoxime		
		• Ceftibu[illegible]		

60 PROTEIN SYNTHESIS INHIBITORS



- Proteins are synthesized according to the information present on mRNA.
- Ribosomes attach to this mRNA. Ribosomes have 50s and 30s subunits. Two sites are created: P site (Peptidyl site) and A site (Acceptor site)
- The already present amino acid chain is attached to the tRNA at the A site.
- Now there is formation of peptide bond between the amino acid chain and the new amino acid. This is formed by peptidyl transferase enzyme
- This amino acid chain now shifts from A site to P site. The new exposed site is now called the A site. This is called Translocation
- The drugs which stop these steps of protein synthesis are called protein synthesis inhibitors
- These drugs are
  i. Tetracyclines: Inhibit attachment of tRNA to A site
  ii. Chloramphenicol: Inhibit peptide bond formation
  iii. M: Macrolides
  C: Clindamycin
  Q: Quinpristin (+ Dalfopristin)
  } Inhibit Translocation
  iv. Aminoglycosides: Cause misreading of mRNA code
  - These are bactericidal drugs
  - All other protein synthesis inhibitors are bacteriostatic drugs

  v. Linezolide
  vi. Tedizolide
  } Inhibit initiation of protein synthesis
- Drugs which bind at 30s ribosomes
  - A: Aminoglycoside
  - T: Tetracycline

How to remember

- Bind AT 30s ribosome

- Rest all the drugs bind at 50s ribosome.

I. Tetracyclines 00:17:00

- Tetracyclines contain 4 rings in their chemical structure
- The drugs included are
  - Tetracycline
  - Oxytetracycline
  - Chlortetracycline
  - Demeclocycline
  - Minocycline
  - Doxycycline
- Tetracyclines are bacteriostatic drugs
- They bind at 30s ribosome.
- They inhibit the attachment of aminoacyl tRNA to A site
- Adverse effects of tetracyclines
  - **K** - **K**idney failure (C/I): exception - Doxycycline
  - **A** - **A**nti anabolic effect
  - **P** - **P**hototoxic effect: Demeclocycline (max)
  - **I** - **I**nsipidus (Diabetes): Demeclocycline(max)
  - **L** - **L**iver failure (C/I)
  - **D** - **D**entition & Bone problems: So C/I in pregnancy and children <8yrs
  - **E** - **E**xpiry date should not be crossed: Risk of Fanconi Syndrome
  - **V** - **V**estibular dysfunction: Minocycline (max)

How to remember

- KAPIL DEV

- Antibiotics which are safe in pregnancy
  - **P** - **P**enicillin (all β-lactams)
  - **C** - **C**lindamycin
  - **M** - **M**acrolides

How to remember

- PCM is safe in pregnancy

- **Uses of tetracyclines**
  - **S - S**IADH: Demeclocycline is preferred
  - **R - R**ickettsial infection: Doxycycline preferred
  - **I - I**nguinale (Granuloma): 1st line drugs with Macrolides
  - **L - L**GV: 1st line drugs
  - **A**, **N** } Atypical pneumonia: DOC is macrolides
  - **K** - Cholera: DOC: Doxycycline is preferred
  - **A - A**moebiasis (only in lumen of GIT)

How to remember

- SRI LANKA

- **Resistance**
  - Resistance to tetracyclines is due to the development of Efflux pumps in bacteria.
  - The group of drugs which are resistant to these efflux pumps are called Glycyl cyclins. The drug included is Tigecycline
    - → Tigecycline is similar to Tetracyclines in every aspect, except that it is resistant to efflux pumps
    - → Tigecycline has a wide spectrum of activity. But does not affect Pseudomonas
    - → Tigecycline is secreted in bile, so it is safe in renal disease

II. Macrolides 00:36:10

- The drugs included are
  - Erythromycin
  - Clarithromycin
  - Roxithromycin
  - Azithromycin
  - Fidaxomicin
  - Spiramycin
  - Tacrolimus
- Some features of macrolides are:
  - Macrolides bind to 50s subunit.
  - They are bacteriostatic
  - They inhibit translocation
- **Fidaxomicin**
  - It is used for pseudomembranous colitis
  - It has maximum relapse prevention activity
- **Spiramycin**
  - It is DOC for Toxoplasmosis in pregnancy
- **Tacrolimus**
  - It has very less antibacterial activity and major immunomodulator activity
- Uses of Erythromycin-like drugs are:
  i. Used as a 2nd line drug to penicillin
  ii. DOC for
  - **C - C**hancroid
  - **L - L**egionella
  - **A - A**typical pneumonia
  - **P - P**ertussis (Whooping cough)

How to remember

- CLAP

- **Adverse effects of macrolides**
  - M - Motilin receptor agonist in GIT: Diarrhoea
  - A - Allergy
  - C - Cholestasis (Erythromycin estolate)
  - R -, O - } Reversible ototoxicity
- Macrolides stimulate motilin receptors in GIT. This can be beneficial and the drugs can be used for
  - Paralytic ileus
  - Diabetic gastroparesis
- But erythromycin is associated with causation of Pyloric stenosis in the baby.
- The risk of cholestatic jaundice by using erythromycin estolate is greatly increased in pregnancy. So Erythromycin estolate is C/I in pregnancy. Rest of the macrolides are not C/I in pregnancy
- Azithromycin is different from other three "-thromycin" drugs
  - Azithromycin is long acting. All the other three are short acting
  - Azithromycin is not a microsomal enzyme inhibitor, while the other three are.

III. Lincosamide :- Clindamycin 00:48:00

- Some features of clindamycin are
  - They are static drugs
  - They bind to 50s subunit
  - They inhibit translocation
- They are rarely used now-a-days because they have a high risk of causing pseudomembranous colitis.
- **Uses for**
  - C - Cocci (gram+)
  - A - Anaerobic bacteria
  - P - Parasites (Pneumocystis, Malaria, Toxoplasma)
- Clindamycin is secreted in bile. So it is safe in renal disease

IV. Quinpristin 00:52:00

- It is given in combination with Dalfopristin
- Common points are:
  - It binds to 50s subunit
  - It is bacteriostatic
  - It inhibits translocation
- It is used for treatment of VRSA

V. Chloramphenicol 00:52:00

- Common features are:
  - It binds to 50s subunit
  - It is bacteriostatic
  - It inhibits peptide bond formation
- It is not commonly used because

i. It leads to toxicity symptoms like
  - Bone marrow suppression
  - Grey baby syndrome

ii. Many bacteria have developed resistance to chloramphenicol, so it is ineffective

- **Uses**
  - Meningitis
  - Endophthalmitis
  - Enteric fever

VI. Linezolide, Tedizolide 00:57:40

- Common points are
  - They bind to 50s subunit
  - They are bacteriostatic
  - They inhibit initiation of protein synthesis
- They are effective against VRSA and Mycobacterium TB.

VII. Aminoglycosides 00:59:30

- The drugs included are
  - Streptomycin
  - Gentamicin
  - Tobramycin
  - Netilmycin
  - Neomycin
  - Capreomycin
  - Kanamycin
  - Amikacin
- Common points are
  - They bind to 30s subunit
  - They are bactericidal drugs
  - They cause misreading of mRNA
- Aminoglycosides are not effective orally. They have big polar molecules, so not absorbed if given orally. They are given by I.M. or I.V. injection
- These drugs are mainly effective for Gram -ve bacteria. They are also effective against pseudomonas
- But not effective against Salmonella
- These drugs are not effective against Anaerobes
- Aminoglycosides + cell wall synthesis inhibitors is a synergistic combination. This is known as Empirical therapy
- One of the commonly used empirical therapy is: Penicillins + Aminoglycosides
- Adverse effects of Aminoglycosides are:
  - Common
    - → Nephrotoxicity → Neomycin (max)
    - → Ototoxicity
    - ular junction # → Neomycin (max)
  - Ototoxicity
    - → Auditory: Amikacin (max)
    - → Vestibular: Streptomycin (max)
- Streptomycin is used for
  - **T - TB**
  - **T - T**ularemia - 1st line drug for treatment
  - **P - P**lague

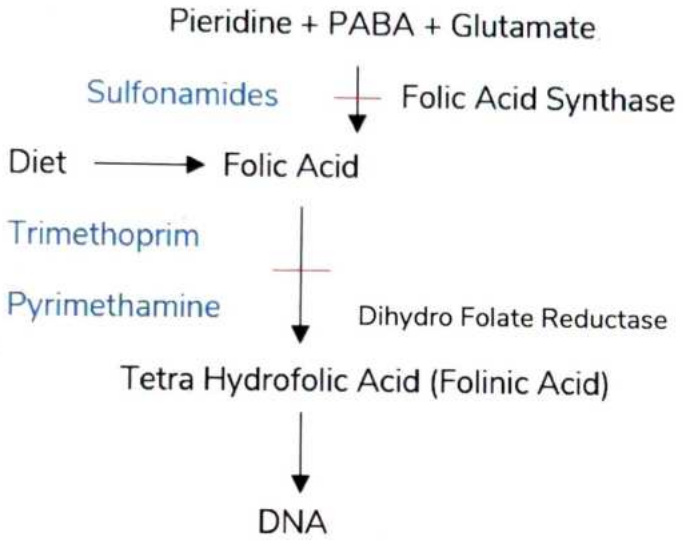
How to remember

- TTP

- DOC for prevention of plague: Doxycycline
- Capreomycin, Kanamycin, Amikacin are 2nd line drugs for TB
- Capreomycin is not an aminoglycoside, because its chemical structure is different from other aminoglycosides
- Neomycin is very toxic drug. We do not use it systemically now a-days. But it is used in Hepatic Coma
  - Hepatic coma: Normally liver converts ammonic to urea. But when liver is not working, this ammonia gets accumulated and goes to brain, which results in coma
  - This ammonia comes from GI infections mainly
  - This GI infection is caused by Urease positive bacteria
  - Neomycin is used for gut sterilization in patients with Hepatic coma.

61 ANTI-METABOLITES & QUINOLONES

METABOLISM INHIBITOR DRUGS



Sulfonamides / sulfa drugs

00:05:39

Drugs	Adverse effects
• Sulfadoxine • Sulfacytine • Sulfasoxazole • Sulfamethoxazole • Sulfasalazine • Sulfadiazine • Dapsone	• **A** - **A**plastic anemia • **B** - **B**ilirubin displacement: Kernicterus in newborn • **C** - **C**rystalluria of • **R** - **R**ash: Steven Johnson Syndrome • **A** - **A**cetylation • **S** - **S**LE • **H** - **H**emolysis in G6PD deficiency

- Sulfonamides are competitive inhibitors of FA synthase enzyme. They are structural analogues of PABA, which is essential for synthesis of folic acid.
- If we use them alone, they are bacteriostatic drugs.
- All these drugs can cause allergy
- Sulfadoxine is the longest acting sulfonamide
- Sulfacytine is the shortest acting sulfonamide
- Sulfasalazine is a prodrug. It is used for
  - Ulcerative colitis (DOC)
  - Rheumatoid arthritis
- Silver salt of sulfadiazine (SSD) is used for Burn dressings.
- Dapsone is used for treatment of leprosy. It is also DOC for Dermatitis herpetiformis
- In any infection with large amounts of pus, which usually contains PABA in large amount, sulfonamides are unlikely to be effective.

Combinations of sulfonamides

00:15:35

1. Cotrimoxazole: Trimethoprim + Sulfamethoxazole

- It is a bactericidal combination
- Ratio for best bactericidal activity = 1:20
  Ratio in tablet to attain this ratio = 1:5 (T : S)
- DOC for
  - **P** - **P**neumocystis jiroveci
  - **N** - **N**ocardia
  - **B** - **B**urkholderia cepacia

How to remember

- PNB

2. Sulfadoxine + Pyrimethamine

- It is used for treatment of
  - Malaria
  - Toxoplasmosis

DNA GYRASE INHIBITORS

00:21:54

- DNA gyrase does 3 things: First it cuts the DNA. Then DNA gyrase introduces negative coils in the DNA. Negative coil means rotation in opposite direction to uncoil the DNA. Lastly it rejoins the DNA.
- Thus DNA gyrase helps in replication of DNA.
- DNA gyrase inhibitors
  - Inhibit replication
  - They are bactericidal drugs
- Chemically they are called quinolones
- Quinolones
  i. Nalidixic acid: Used in UTI

ii. Fluoroquinolones: "Floxacins"

- Fluoroquinolones
  - Norfloxacin
  - Ciprofloxacin
  - Ofloxacin
  - Levofloxacin
  - Pefloxacin
  - Moxifloxacin
  - Gatifloxacin
  - Trovafloxacin
  - Sparfloxacin
- Common points
  - Oral drugs
  - Bactericidal drugs
  - Broad spectrum (Grams +ve & -ve)
- They are C/I in pregnancy and children <18 years, because they cause damage to cartilage & tendon.
- FQ are phototoxic drugs. Sparfloxacin is most phototoxic. It is also the longest acting FQ.
- FDA has given a black box warning against FQ regarding their neurological side effects which include seizures and peripheral neuropathy.
- Risk of seizures is least with moxifloxacin. The risk of seizures increases when they are combined with NSAIDs
- FQ are C/I in renal failure. Some are safe in renal failure
  - **P** - **P**efloxacin
  - **M** - **M**oxifloxacin
  - **T** - **T**rovafloxacin

    → But they are not effective in UTI.

How to remember

- PMT

- Respiratory FQ
  - **O** - **O**floxacin
  - **M** - Moxifloxacin
  - **G** - Gatifloxacin
  - **Levo** - **Levo**floxacin

How to remember

- OMG Levo
  - Respiratory FQ can kill most of the bacteria that cause respiratory tract infections.
- Norfloxacin is mainly used for UTI. It has least oral bio-availability
- Levofloxacin has max. oral bioavailability
- Ciprofloxacin is now the DOC for meningococcal meningitis. It is also useful for enteric fever. It is the 1st line drug for Anthrax.
- Moxifloxacin is safe in renal failure but not effective in UTI. It is very long acting. It is also effective against anaerobic bacteria.
- Gatifloxacin causes dysglycemia, so it is withdrawn in India.

DRUGS ACTING ON MEMBRANES ⏱ 00:39:24

- These drugs cause depolarization of membranes, which causes death of bacteria.
- Drugs included are:
  - Daptomycin
  - Polymyxin B
  - Polymyxin E (Colistin)
- All these are bactericidal drugs
- Daptomycin is DOC for VRSA. But it is made ineffective by pulmonary surfactants, so not effective for pneumonia. For pneumonia we give Linezolide.
- Major S/E for Daptomycin: Myopathy
- Polymyxins are effective against pseudomonas
- Colistin is effective against superbug- NDM.

62 DRUGS NOT EFFECTIVE AGAINST PARTICULAR BACTERIA

Bacteria	Not effective	Effective
1. Mycoplasma	Cell wall synthesis inhibitors like • Penicillins • Cephalosporins • Vancomycin, etc.	• Azithromycin (DOC)
2. Pseudomonas	Vancomycin	• Aminoglycosides + β lactams like Ceftazidime
3. MRSA	β lactams except 5th gen cephalosporins	• Vancomycin (DOC) • Topical mupirocin/ bacitracin for Nasal carriers
4. Enteric fever	Aminoglycosides	• Ceftriaxone (DOC)
5. Anaerobes	Aminoglycosides	• Metronidazole (DOC) • Clindamycin

63 PSEUDO-MEMBRANOUS COLITIS

- The GI tract contains large amounts of friendly bacteria called commensals. They prevent the growth of pathogenic bacteria, as they don't give any nutrition to the pathogenic bacteria. So the pathogenic bacteria starves to death.
- Commensals also secrete Bacteriocin: A substance that kills the pathogenic bacteria
- Broad spectrum antibiotics kill the commensals, so pathogenic bacteria can cause infections. This is called superinfection.
- As a result, WBCs activate and cover these bacteria. This forms a pseudo-membrane. Thus, it is called pseudomembranous colitis.

Important Information

i. Clostridium difficile is the most important pathogen causing pseudomembranous colitis

ii. 3rd generation cephalosporins are the most common cause
- 3rd Gen cephalosporins > Clindamycin > Aminopenicillins > Fluoroquinolones

iii. Treatment of Pseudomembranous colitis
- Vancomycin (oral): DOC
- Fidaxomicin: Max. relapse prevention
- Metronidazole: Not DOC anymore
- Bezlotoxumab
  - Last resort, used for severe cases
  - MAb against clostridium toxin
  - Does not kill the pathogen

64 TDK, CDK AND PAE

- Special pharmacokinetics of Anti-microbial agents

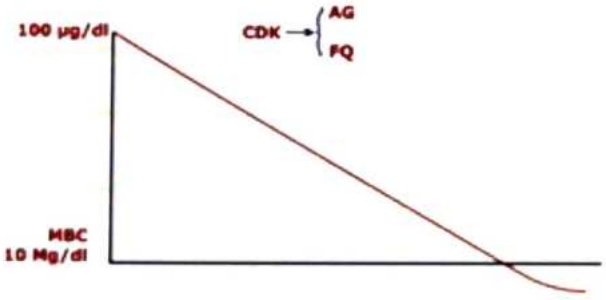
i. **Bactericidal drugs**
   - B, E } β-Lactams
   - V, A } Vancomycin
   - F: Fluoroquinolones
   - A: Aminoglycosides

- They show 3 types of pharmacokinetics

a. Concentration dependent killing (CDK)
b. Time dependent killing (TDK)
c. Area under curve dependent killing (ADK)

a. Concentration dependent killing (CDK) 00:02:00

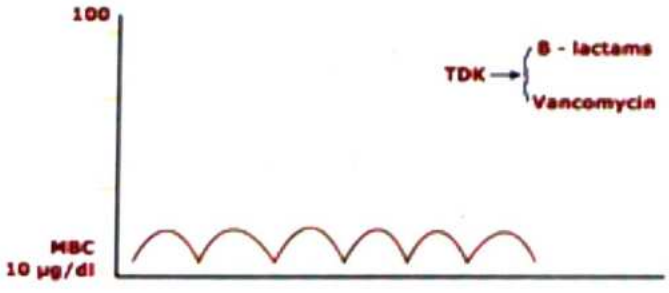
- It means higher the drug concentration, more bacteria will be killed



- These drugs are given in high doses but less frequently, so that a high concentration is attained
- This is followed by AG and FQ.

b. Time dependent killing (TDK)

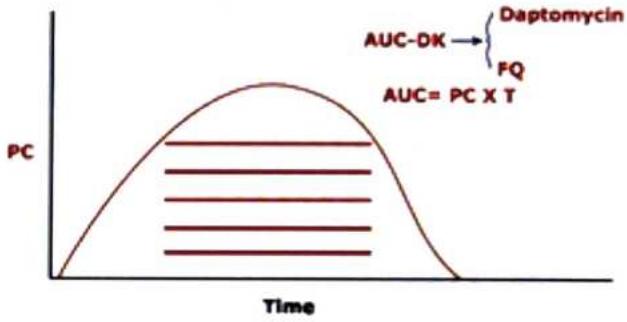
- It is concentration independent killing



- Killing activity depends on the time for which concentration of drugs remains above MBC (Min. Bactericidal conc)
- We don't want to attain very high conc as it will lead to side effects, so we give small but frequent doses.
- Followed by β-lactams and Vancomycin

c. AUC dependent killing

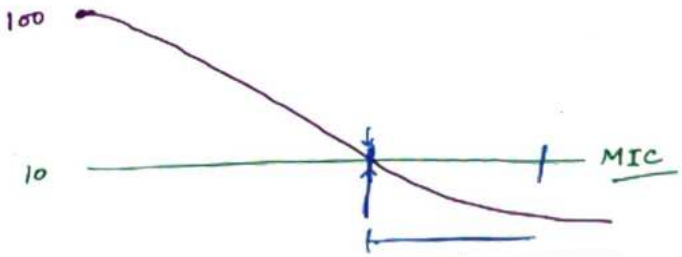
- Killing dependents on product of conc. and time



- Followed by Daptomycin

POST ANTIBIOTIC EFFECT 00:07:15

- This effect is seen for both cidal and static drugs



- When the antibiotic conc. is above MIC, the bacteria does not grow. But it is seen that when the conc. becomes less than MIC, still for some time, the bacteria does not grow. This time period is called Post antibiotic effect.
- Thus PAE is described as Persistent suppression of bacterial growth, even when the antibiotic conc is less than required.
- If PAE

- <90 min: Short PAE
- >90 min: Long PAE

- Most antibiotics have long PAE against Gram +ve
- Most Gram –ve bacteria have short PAE but some have long PAE
  - **Long PAE**

i. DNA (-): Fluoroquinolones
ii. Protein synthesis (-)
   → AG
   → Tetracyclines
   → Clindamycin
   → Macrolides
iii. Carbapenems (only βlactams)
  - **Short PAE**

I. All other β-lactams except carbapenems
ii. Vancomycin

65 ANTIMICROBIAL RESISTANCE

- Anti-microbial drug resistance can be either
  - Acquired
  - Natural: Candida krusei resistance to Fluconazole

Acquired resistance 00:01:40

- It means earlier the bacteria was affected by the drug but later becomes resistant

Mechanism of drug resistance

i. Enzymes
- Development of inactivating enzymes leads to resistance
- Seen in following drugs
  - Aminoglycosides
  - β-Lactams
  - Chloramphenicol

ii. Altered drug target
- Bacteria changes the target on which the drug acts
- Seen in
  - MRSA
  - VRSA
  - Fluoroquinolones

iii. Efflux pumps
- When drug enters the bacteria, these pumps push out the drug
- Seen in:
  - Tetracyclines
  - Tigecyclines

iv. Altered metabolism
- Seen in sulfonamides

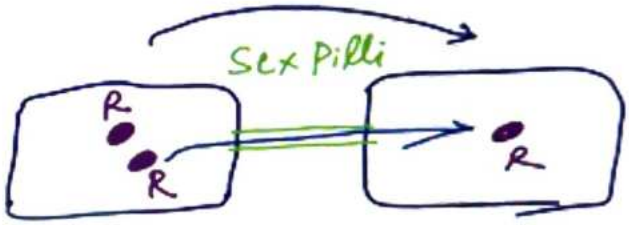
v. Decrease in permeability
- Seen in Aminoglycosides

Transfer of Drug resistance 00:06:30

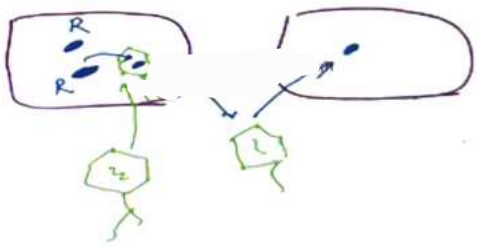
- It can be divided into:
  a. Vertical transmission
  b. Horizontal transmission

a. Vertical transmission
- It is the transfer of resistance from one generation to the next generation
- This occurs by mutation

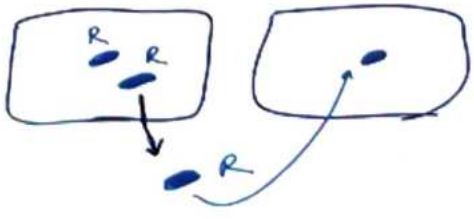
b. Horizontal transmission
- It is the transfer of resistance from one bacteria to other, in the same generation.
- It occurs by
  - Conjugation
  - Transduction
  - Transformation
- **Conjugation**
  - In conjugation, one bacteria transfers the resistance to other bacteria through a physical contact called sex pilli
  - This is the most common method of horizontal transfer.



- **Transduction**
  - Transfer of resistance from one bacteria to other by the help of a virus called bacteriophage



- **Transformation**
  - Transfer of resistance by free environmental DNA is called transformation



  - This is the least common method

66 MYCOBACTERIAL DISEASE (TB, LEPROSY AND MAC)

- **Mycobacterium species causes 3 important human infections**
  i. M. tuberculosis: TB
  ii. M. leprae: Leprosy
  iii. Atypical mycobacteria (MAC)

TUBERCULOSIS

- Anti-tubercular drugs are divided into
  I. First line drugs
  II. Second line drugs

I. First line drugs

- H – Isoniazid
- R – Rifampicin
- Z – Pyrazinamide
- E - Ethambutol
- S – Streptomycin

	Activity	Bacteria	Hepatotoxic	Pregnancy
H	Cidal	Both	✓	Safe
R	Cidal	Both	✓	Safe
Z	Cidal	I/c	✓✓✓	Avoided
E	Static	Both	X	Safe
S	Cidal	e/c	X	c/i

Mycobacteria	Location	Most effective drug
Fast growing	Wall of cavity	H
Intermediate Growing	Spurters (Casseous necrosis)	R
Slow Growing	Intra cellular	Z

- Pyrazinamide has the best activity against slow growing bacteria. So we say it has the best sterilizing activity.

1. Isoniazid (INH) 00:06:27

- It causes deficiency of pyridoxine (Vit B6) which results in peripheral neuropathy. So pyridoxine is supplemented when using isoniazid
- Isoniazid is hepatotoxic also
- It is one of the SHIP drugs so metabolized by acetylation. It can cause SLE as an adverse effect.
  - INH is metabolized by N–acetyl transferase and metabolized to Acetyl hydrazine.
  - Accumulation of INH causes Peripheral neuropathy
  - Accumulation of Acetyl hydrazine causes hepatotoxicity
  - So, in slow acetylators:- There is less amount of N – acetyl transferase leading to slow metabolism. Thus leading to isoniazid accumulation causing peripheral neuropathy
- In fast acetylators, there is more amount of N–acetyl transferase, leading to acetyl hydrazine accumulation causing hepatotoxicity

How to remember

SHIP Drugs
- S – Sulfonamides
- H – Hydralazine
- I – Isoniazid

P – Procainamide

2. Rifampicin 00:10:50

- Should be given empty stomach
- Secreted in bile so safe in renal failure
- Powerful enzyme inducer
- Interactions:
  - Warfarin: Replace with Heparin
  - OCP: Replace with other methods
  - Anti-HIV Drugs: Replace with Rifabutin
- Rifabutin v/s Rifampicin:

	Rifabutin	Rifampicin
Enzyme inducer	+	++++
Duration of action	Longer acting	Long acting

Effective on	Atypical mycobacteria	Mycobacterium TB
S/E	• Not hepatotoxic • Pseudo jaundice • Uveitis	• Hepatotoxic

- **Discoloration of Secretions**
  i. Urine: Orange
  ii. Tears: Orange staining of contact lenses

- **Other uses of Rifampicin**
  - Leprosy
  - Was used for prophylaxis of meningococcal meningitis
  - DOC for Brucella
  - Gram positive bacteria (including MRSA)
  - Gram negative bacteria (including Pseudomonas)

3. Pyrazinamide
- Effective only against intracellular bacteria
- Most hepatotoxic
- Causes hyperuricemia
- Possesses the best sterilizing activity (can kill slow growing bacteria)

4. Ethambutol
- Affects eye
- Causes Red Green color blindness (optic neuritis)
- Initially reversible, later irreversible. So avoided in < 6 yrs old children

5. Streptomycin
- Not effective orally, given by I.M. route
- It is nephrotoxic, ototoxic and causes neuro-muscular blockade
- It was initially considered as 1st line drug, it was shifted to supplementary category as it needs to be given as injections. Now – a – days, it is not even considered as 1st line drug

II. 2nd line drugs

00:22:18

1. Fluoroquinolones
- Ofloxacin
- Moxifloxacin
- Gatifloxacin
- Levofloxacin

2. Injectables
- Capreomycin
- Kanamycin
- Amikacin

3. Linezolid: Also used for VRSA
Clofazimine: Also used for multi bacillary leprosy

4. Cycloserine: Causes neuropsychiatric S/E
Ethionamide: Hepatotoxic, Hypothyroidism
PAS: Hypothyroidism

5. Thioacetazone
- Never given in HIV patients

6. Drugs with uncertain efficacy
- Amoxy-clav
- Imipenem

7. New Drugs
- Bedaquiline: Acts by inhibiting ATP synthase enzyme. Can result in QT prolongation
- Delamanid: Acts by inhibiting mycolic acid. Can cause QT prolongation
- Pretomanid: Acts by inhibiting mycolic acid. It is hepatotoxic
  - These drugs are used for MDR/XDR TB

New regimen for MDR/XDR TB – BPaL regimen
- **B** – **B**edaquiline
- **Pa** – **P**retomanid
- **L** – **L**inezolid

TREATMENT OF TB

00:30:08

- Previously RNTCP was used, but not used now.
- Now we follow National TB Elimination Program (NTEP)

i. Drug Sensitive TB

Intensive Phase (IP)	Continuation Phase (CP)
↓	↓
2 HRZE	4 HRE

ii. Drug Resistance TB
- H resistant :- 6 RZE + Levofloxacin

- R Resistant or MDR TB (Both H & R)

I. Shorter All oral MDR regimen
- Criteria
  a. Sensitive to FQ
  b. Exposed to 2nd line drugs
  c. Not for extrapulmonary disease
  d. Not extensive TB
  e. Not for pregnancy
  f. Not for less than 6 yrs old

- This regimen includes

IP	+	CP
(4-6 months)		(5 months)

- Bedaquiline →6 months
- HZE + Levofloxacin + Clofazimine + Ethionamide → 4 months
- Injectables not included

II. Longer MDR regimen

- If criteria for shorter regimen is not met, we give longer regimen
- This includes

IP	+	CP
(6 months)		(12 months)

- IP + CP

↓

Min. 4 drugs Min. 3 drugs

- The drugs are divided into 3 groups:
  - → Group A
    - Levofloxacin (or Moxifloxacin)
    - Bedaquiline
    - Linezolid
  - → Group B
    - Clofazimine
    - Cycloserine (or Terizidone)
  - → Group C
    - Ethambutol
    - Pyrazinamide
    - Delamanid
    - Imipenem-cilastin (or Meropenem)
    - Amikacin (or Streptomycin)
    - Ethionamide (or Protionamide)
    - PAS

III. BPaL Regimen

- Criteria
  a. FQ Resistance
  b. No exposure to Bedaquiline or linezolid
- It includes 6–9 months regimen
- Drugs
  - Pretomanid
  - Bedaquiline
  - Linezolid

PREVENTION OF TB

00:43:40

i. Drug Sensitive TB

- Isoniazid for 6 months (6H)
  - Safe in HIV
  - Hepatotoxicity
- 3 HR (Rifapentine)

ii. Drug Resistant TB

- 6 H
- 4 R
- 6 Levofloxacin

LEPROSY

00:46:28

- It is divided into Multibacillary & Paucibacillary
- Treatment:

i. MB

- Rifampicin 600 mg once a month } Supervised
- Clofazimine 300 mg once a month } Supervised
- Clofazimine 50 mg } Once daily x 28 days at home
- Dapsone 100 mg } Once daily x 28 days at home
- This Continues for 12 months

ii. PB

- The treatment is same as MB. But in PB, it is given for 6 months

Resistance

- We use
  - Ofloxacin
  - Minocycline
  - Clarithromycin

MAC (MYCOBACTERIUM AVIUM COMPLEX)

00:50:02

- These infections occur in immuno-compromised persons
- **Treatment**
  - Rifabutin + Ethambutol + Clarithromycin
- **Prophylaxis**
  - Azithromycin (weekly)
    or
  - Clarithromycin (daily)

67 ANTI VIRAL DRUGS

Virus multiplication

- Virus fuses with human cell and sends the genetic material inside human cell.
- Then uncoating occurs and genetic material is set free and then it multiplies
- Then replication occurs and inactive proteins are formed.
- These inactive proteins are activated and their assembly and maturation occurs
- At last they are released outside the cell

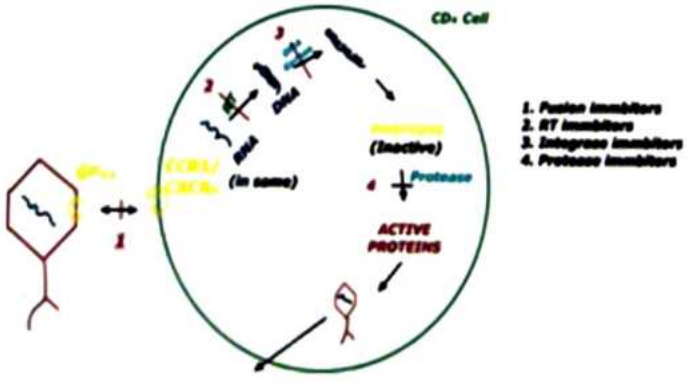
Drugs

1. Fusion inhibitors
   - Enfuvirtide: It inhibits the fusion of virus with the human cell
2. Uncoating inhibitors
   - Amantadine
3. Virus nucleic acid inhibitors
   - Acyclovir
4. Protease inhibitors
   - Inhibits activation of proteins
5. Virus maturation inhibitors
   - Tecovirimat
6. Virus release inhibitors
   - Oseltamivir

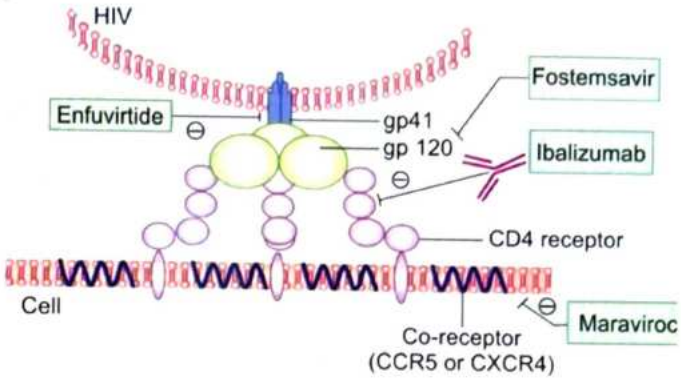
HIV

00:05:10

Anti – HIV drugs



1. Fusion inhibitors



Receptors	Drug binding to it	
• Gp 41	Enfuvirtide	○ Inhibits fusion of virus with T cell ○ Given by S/C route
• Gp 12	Fostemsavir	○ Oral prodrug of Temsavir ○ Inhibits fusion of virus with CD4 cell
• CD4	Ibalizumab	○ MAb against CD4 ○ Used for HIV ○ Given by I.V. route
• CCR-5	Maraviroc	○ Given orally ○ Can't bind with CD4 cells having CXCR4

2. Reverse transcriptase inhibitors

- They may be competitive or non – competitive
- They inhibit reverse transcriptase enzyme

Competitive
aka NRTI (Nucleotide or Nucleoside RT inhibitors)

- **Nucleoside RTI**
  - Zidovudine
  - Lamivudine
  - Stavudine
  - Didanosine
  - Zalcitabine
  - Emtricitabine
  - Abacavir
- **Nucleotide RTI**
  - Tenofovir

Non competitive
aka NNRTI (Non Nucleotide or Nucleoside RT inhibitors)

- **1st Gen**
  - Efavirenz
  - Nevirapine
  - Delavirdine
- **2nd Gen**
  - Etravirine
  - Rilpivirine
  - Doravirine

NRTIs

- Lamivudine: Safest NRTI

- Max. risk of peripheral neuropathy → Stavudine
- Max. risk of pancreatitis → Didanosine
- Bone marrow suppression caused by Zidovudine
- Myocardial infarction by –

NRTIs used for Hep B are:

- **L** - Lamivudine
- **E** - Emtricitabine
- **T** - Tenofovir

How to remember

- LET

NNRTIs 00:23:20

- These are never given alone as they are prone to resistance development
- Only effective against HIV-1
- These are metabolized by CYP enzymes, so prone to interactions especially with Rifampicin
- Drugs included

i. **1st gen**
   - Efavirenz
   - Nevirapine
   - Delavirdine

ii. **2nd gen**
   - Rilpivirine
   - Etravirine
   - Doravirine

- **Nevirapine**
  - Prevents vertical transmission from HIV infected mothers
  - Hepatotoxic so not included with other hepato-toxic drugs

3. Integrase inhibitors 00:26:20

- Drugs included are:
  - Raltegravir
  - Elvitegravir
  - Dolutegravir
- They can be given orally
- Acc. to latest guidelines, they are 1st line HAART therapy drugs.
- Elvitegravir combined with Cobicistat which is a CYP3A4 inhibitor, is used to boost the effect of elvitegravir.

4. Protease inhibitors (-navirs) 00:29:10

- Drugs included are
  - Ritonavir
  - Lopinavir
  - Amprenavir
  - Fosamprenavir
  - Atazanavir
  - Saquinavir
  - Nelfinavir
- They are metabolized by CYP3A4, so prone to interactions.
- They are themselves CYP3A4 inhibitors
  - Strongest inhibitors → Ritonavir
  - Ritonavir is used for this purpose only in low dose. This is called Ritonavir boosting.
- They cause Lipo Dystrophy Syndrome (LDS)
- It is characterized by:
  - Hyperglycemia
  - Hyperlipidemia
  - Insulin resistance
  - Weight gain
- It is also caused by atypical antipsychotic drugs.

i. **Ritonavir**
   - It is the strongest microsomal enzyme inhibitor.
   - It is used to boost other protease inhibitors

ii. **Nelfinavir**
   - Its effect is not boosted by Ritonavir because it is not metabolized by CYP3A4.

iii. **Indinavir**
   - It causes kidney stones and hyperbilirubinemia

iv. **Atazanavir**
   - It has minimum risk of LDS.
   - It can cause Hyperbilirubinemia

Treatment of HIV: HAART (Highly Active Anti-Retroviral Therapy) 00:35:02

1. When to start Rx→All patients irrespective of CD4 count
2. How long → life long
3. What drugs to be used min 3 drugs from min. 2 groups

- 2 NRTI +1 NNRTI / Integrase inhibitors
- Z+L+N
- T+L+E

Post exposure prophylaxis

- After the person has been exposed, to prevent HIV
- Used commonly in health care workers
- Should be given within 72 hrs
- Should be given for 28 days (4weeks)
- Given orally
- Drugs used T+L+PI / Integrase Inhibitors

Prevention of vertical transmission

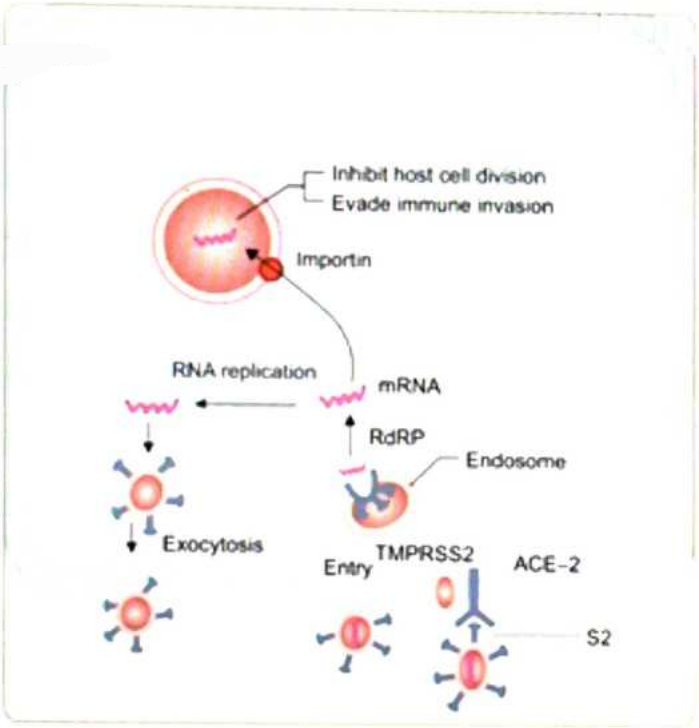
- Transfer of HIV from mother to baby through vertical

transmission
- Presented by giving
  - Full HAART therapy to mother
  - Nevirapine to the baby after delivery for 6 weeks.

COVID -19

00:41:01

- Caused by a corona virus called Novel corona virus
- It originated in Dec 2019 in Wuhan, China
- **Pathogenesis:**



- **Drugs used for COVID-19**
  i. Entry inhibitors : inhibit entry of virus in human cell
  ii. RdRP inhibitors
  iii. Importin inhibitors
  iv. Immunomodulatory effects

Entry inhibitors

00:47:23

a. Chloroquine & Hydroxy chloroquine

- They inhibit proteolysis of S2 protein
- Inhibit glycosylation of ACE-2
- Inhibit acidification of endosomes
- They are powerful immuno-suppressants also
- These drugs were widely used for treatment and prophylaxis of COVID-19 but later withdrawn because they were found to be not effective sufficiently.
- Adverse effects
  - Retinopathy
  - QT prolongation
  - Hypoglycemia

b. Umifenovir (Arbidol)

- It inhibits TMPRSS-2
- It was found to be ineffective so not used now.

c. Camostat / Nafamostat

- Not found effective so not used now

d. MAb against S2 protein

- Bamlanivimab + Etesevimab
- Casirivimab + Imdevimab
- Sotrovimab
  - They are given by I.V. route
  - Effective only if given early in disease and in OPD setup.
  - Given in high risk pts to prevent hospitalization.

RdRP inhibitors

00:52:01

a. Favipiravir

- Earlier widely used but later formed to be not effective so not used anymore

b. Remdesivir

- It is the only FDA approved drug for COVID-19
- Not WHO approved
- It is given I.V.
- Recommended in moderate to severe COVID -19 patient only. Not for OPD patients. Given for hospitalized pts who require oxygen. Should be given within 10 days of illness.
- Avoided in pt. with liver and kidney dis.

Importin Inhibitor

00:54:58

a. Ivermectin

- Used for scabies earlier
- Withdrawn for COVID now.

Immunity suppressants

a. Steroids

- They are the only mortality reducing drugs
- Should not be used in the first 7 days and not in mild cases.
- Drugs
  - Dexamethasone 6mg OD
  - Methyl Prednisolone 32 mg OD
  - Prednisolone 40mg OD
  - Hydrocortisone 50 mg TDS
- They increase the risk of opportunistic infections → MC is Mucormycosis
- They also cause hyperglycemia

b. Tocilizumab

- It is a MAb against Interleukin -6

- It can inhibit cytokine release syndrome
- Given by I.V. route
- Indicated for
  - Severe & life-threatening cases
  - Hospitalized pts
  - Require O_2 therapy even after steroids
  - CRP >75 mg/L
- Rule out all the infectious before starting drugs

c. Baricitinib

- It is a JAK inhibitor
- Oral drug
- Used for RA earlier
- Used with remdesivir as an alternative to steroids

INFLUENZA VIRUS

01:01:00

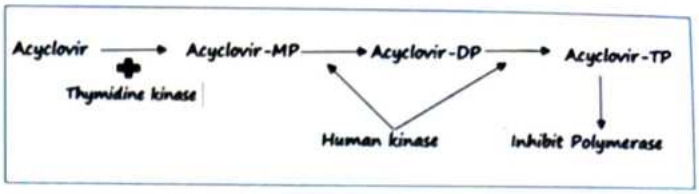
- Drugs are of 3 types

Uncoating inhibitors	Neuraminidase inhibitors	Polymerase inhibitors
Genetic material cannot become free As uncoating is Inhibited Drugs: AMANTADINE * Anti-Parkinson Drugs * used only for Influenza – A RIMANTADINE	• Virus after maturation ↓ Has to leave that cell & infect Other cells • Its connected with that cell Should be removed to infect Other cells ↓ Done by Neuraminidase 1. If this enzyme is inhibited, the virus remains clumped To that human cell only & its Infection is limited Drugs: • Oseltamivir – Oral • Zanamivir – • Inhalational • Peramivir – Parenteral • These are D.O.C for • Bird flu – H5N1 • Swine flu – H1N1	Baloxavir ↓ inhibit Multiplication of Influenza virus • It is single dose Treatment for influenza

Herpes virus (HHV)

01:05:34

- Various Herpes viruses are
  - HSV-1 : Mucocutaneous herpes & Herpes encephalitis
  - HSV-2 : Genital herpes
  - VZV : Chicken pox
- DOC for all these viruses is Acyclovir



- Problems with Acyclovir
  - Short acting
  - Nephrotoxic
- Other drugs belonging to Acyclovir group are
  - Valacyclovir
  - Penciclovir
  - Famciclovir
- Ganciclovir in DOC for CMV retinitis. It also causes BM suppression so it shouldn't be combined with Zidovudine

HEPATITIS VIRUS

01:11:08

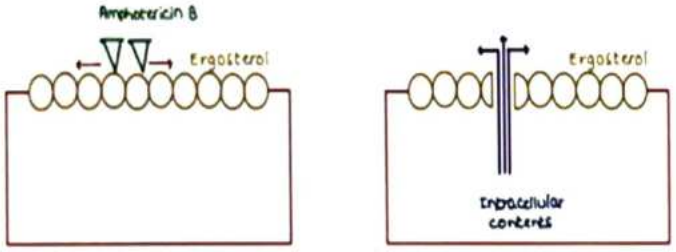
- Hep A and E are self-limiting, so no anti – viral drugs are required.
- Hep D : Causes infection only with Hep B, so no separate drugs required
- So anti-viral drugs are given for
  - Hep B
  - Hep C
- **Hep B**
  - DOC is Tenofovir / Entecavir
  - Alternate drugs which are oral and effective for HIV are
    → Lamivudine
    → Emtricitabine
    → Tenofovir
  - If oral drugs are not effective, then injection should be given → Interferon. It is non – specific & very toxic.
- **Hep C**
  - Previously treated with interferons
  - Now oral drugs are used
  - These include:

Protease inhibitors	NS5A inhibitors	NS5B inhibitors
-PREVIRS	-ASVIRS	-BUVIRS
Telaprevir	Elbasvir	Sofosbuvir
Simprevir	Ledipasvir	Dasabuvir
Boceprevir	Daclatasvir	Beclabuvir
Grazoprevir	Ombitasvir	
Paritaprevir	Pimbrentasvir	

68 ANTI FUNGAL DRUGS

1. POLYENES

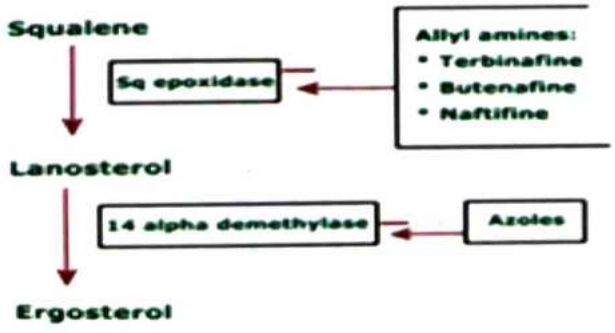
- Drugs include:
  - Amphotericin-B
  - Nystatin
  - Hamycin
- Mechanism of action of Polyenes:
  - They bind to Ergosterol and create pores. Through these pores, important molecules leak out, leading to death of fungus. This makes them fungicidal.



Amphotericin B 00:02:54

- Used for Serious fungal infections only (DOC for cryptococcal meningitis, mucor-mycosis)
- Given by IV route
- It is very toxic. Side effects include:
  - Infusion related reactions (MC side effect): chills, fever
  - Nephrotoxic (RTA with hypokalemia): MC dose dependent side effect.
  - Bone Marrow suppression
- **Liposomal amphotericin B:**
  - Less nephrotoxic as compared to conventional amphotericin B
  - But its cost is higher
  - DOC for Kala Azar

2. ALLYL – AMINES 00:13:35



- **Allyl-amines** inhibit Squalene epoxidase and lead to accumulation of squalene which is toxic to fungal cells (fungicidal drugs). Azoles inhibit 14-alpha demethylase and are fungistatic.
- Allyl- amines are fungicidal and are available in oral form as well as topical preparations.
- Drugs include:
  - Terbinafine
  - Butenafine
  - Naftifine
- After absorption, these drugs accumulate in Keratin rich areas like skin, hair and nails.
- Therefore, these drugs are used in fungal infection of skin, nail and hair, i.e. dermatophytosis (tinea infection)

3. AZOLES 00:12:52

- Azoles are fungistatic drugs
- Drugs include:
  - Ketoconazole
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
- **Ketoconazole** is not much in use these days due to:
  - Microsomal enzyme inhibition
  - Causes Gynecomastia
  - Causes Adrenal suppression
  - Hepatotoxic

Important Information

- Drugs causing Gynecomastia (DISCKO drugs)
  - DI - Digitalis
  - S - Spironolactone
  - C - Cimetidine
  - K - Ketoconazole
  - O - Oestrogen

- **Fluconazole**
  - Max Oral bioavailability
  - Max CNS penetration

- DOC for Candida and Cryptococcus (Maintenance phase)
- DOC for Cryptococcal meningitis is Amphotericin B (Acute phase)

- **Itraconazole** is DOC for:
  - Histoplasma
  - Sporothrix
  - Blastomyces
- **Voriconazole** is DOC for:
  - Aspergillosis
- **Posaconazole** can be used in
  - Mucor-mycosis (DOC is Amphotericin B)

4. HETEROCYCLIC BENZOFURAN

00:17:25

- Includes Griseofulvin
- Acts on mitotic spindle
- Oral and static drug
- Has high affinity for keratin
- Used for dermatophytosis
- Avoided in alcoholics, causes Disulfiram like reaction

5. 5- FLUCYTOSINE

- Inhibits DNA polymerase
- It is usually combined with Amphotericin B for Cryptococcal meningitis

6. ECHINOCANDINS

00:19:05

- Includes Caspofungin:
  - Used for Candida and Aspergillosis
  - Acts on beta 1, 3 – glycan of cell wall
- New drugs are:
  - Micafungin
  - Anidulafungin

MOA OF ANTIFUNGAL DRUGS

- Drugs acting on

a. Cell membrane
  - Amphotericin B
  - Terbinafine
  - Azoles

b. DNA
  - Griseofulvin
  - 5 Flucytosin

c. Cell wall
  - Echinocandins

69 TOPICAL ANTIFUNGAL DRUGS

Topical anti-fungal drugs are divided into 5 main classes:

- **C** - Ciclopirox
- **A** – Amorolofine, Azoles
- **T** – Terbinafine, Tavaborole

How to remember

- CAT drugs

1. CICLOPIROX

- Its salt is called Ciclopirox olamine
- It has high affinity for trivalent cations. After binding with them it can:
  - Inhibit cytochrome oxidase
  - Inhibit metal-based enzymes like those involved in oxidative stress
- It has additional activity against Gram -ve bacteria
- It is available as nail lacquer for fungal nail infections

2. AMOROLOFINE

- It acts by inhibiting Ergosterol synthesis
- It acts at a different place than the azoles. This leads to accumulation of Ignosterol
- Ignosterol is cidal for the fungus
- It is also available as nail lacquer, so can be used for onychomycosis

3. AZOLES

- Topical azoles include:
  - Econazole
  - Miconazole
  - Clotrimazole
  - Ketoconazole
- Newer azoles are:
  - **S** - Sertaconazole
  - **L** - Luliconazole
  - **E**: - Efinaconazole, Eberconazole
- Azoles act by inhibiting the enzyme Lanosterol-14-α-demethylase
- They have additional properties:
  - Strong anti-inflammatory activity
  - Anti-bacterial activity against Gram +ve cocci
- Azoles mainly inhibit chemotaxis
- **Sertaconazole** inhibits the release of several cytokines like IL-2 ,IL-4,TNF-α
  - It has additional anti-pruritic activity also. So can be used to stop itching
  - It also binds to cell wall of the fungus and increases permeability
- **Eberconazole** inhibits LOX and COX enzymes
- **Luliconazole** is very potent drug and long acting. So single daily dose is given.
- **Efinaconazole** is available as nail lacquer

4. TERBINAFINE

- It is a Squalene epoxidase inhibitor
- It is a long acting drug and given once a day
- It has activity against Gram +ve bacteria also

5. TAVABOROLE

- It forms a Boron based bond with Leucyl t-RNA synthetase
- This results in inhibition of protein synthesis
- Only antifungal drug which inhibits protein synthesis
- It is used topically
- It is also available as nail lacquer

Important Information

- **Antifungal drugs used for Onychomycosis: (CEAT)**
  - **C - Ciclopirox olamine**
  - **E - Efinaconazole**
  - **A - Amorolofine**
  - **T - Tavaborole, Terbinafine**

70 ANTI-PARASITIC DRUGS

Parasites

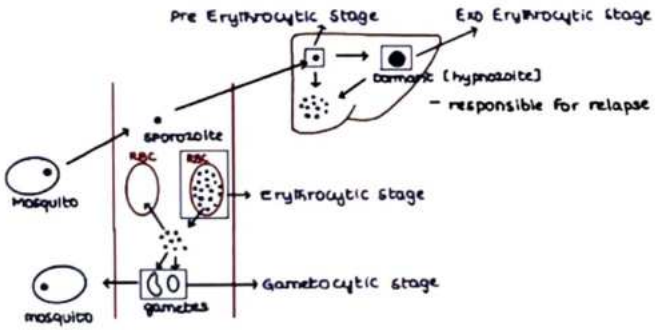
Protozoa		Helminths
Plasmodium	Others 1. Entamoeba 2. Leishmania 3. Trypanosome	• Platyhelminths • Nematodes

MALARIA

00:01:49

Anti-Malarial Drugs

- Malaria is caused by:
  - Plasmodium vivax
  - P. ovale
  - P. falciparum
  - P. malariae
  - P. knowlesi



- **Treatment modalities**

Cures

Clinical cure	Radical cure
Erythrocytic Stage	Exo-Erythrocytic Stage

Prophylaxis

Suppressive prophylaxis	Causal prophylaxis
↓	↓
Erythrocytic Stage	Pre-Erythrocytic Stage

Primaquine

00:12:08

- Acts on
  - Pre-Erythrocytic Stage- used for Causal prophylaxis
  - Exo-Erythrocytic Stage- used for Radical cure
  - Gametocytic Stage - used to Prevent Transmission
- Can't act on Erythrocytic Stage. So, not useful to treat or prevent malaria
- It can cause Hemolysis in G6PD Deficiency
- It is C/I in pregnancy & infants
- Can kill the gametes of all species of plasmodium (vivax, falciparum, ovale, malariae) in a single dose, whereas chloroquine and quinine can kill gametes of Plasmodium vivax only.
- Can kill the exo-erythrocytic stage (hypnozoites) when given for 14 days.
- In Plasmodium falciparum, there is no exoerythrocytic stage and hence there is no relapse in Plasmodium falciparum.
- So in,
  - Plasmodium falciparum, single dose of primaquine is given (to kill gametes).
  - Plasmodium vivax, it is given for 14 days to kill the hypnozoites.

Tafenoquine

- Can kill the hypnozoites in a single dose
- Like Primaquine, it can also cause hemolysis and hence it is also contraindicated in G6PD deficient patient. Also C/I in pregnancy and infants.

Drugs Acting on Erythrocytic Stage

00:15:21

- These can be of 2 types:

Fast acting	Slow acting
M - **M**efloquine	Proguanil
A - **A**tovaquone	Pyrimethamine
C - **C**hloroquine	Sulfadoxine
H - **H**alofantrine	Doxycycline
A - **A**rtemisinins	Clindamycin
R - **R**es – Q (Quinine)	

How to remember

- MACHAR is fast

- Fast acting drugs can be used alone for treatment of malaria.
- Slow acting drugs are never given alone because we want to treat malaria quickly. They are always combined with a fast-acting drug.

Mefloquine

- Long-acting drug.
- Given as single dose
- Neuropsychiatric side effects

Quinine

- It is effective against MDR parasites of malaria
- Safe in 1st trimester of pregnancy
- It is a derivative of cinchona plant
- Excess quinine will lead to development of Cinchonism:
  - Headache
  - Blurred vision
  - Tinnitus
  - Deafness
- It can lead to Arrhythmias and Hypoglycemia
- If only quinine has to be given, it is given for 7 days which is too long
- Therefore, we add doxycycline or clindamycin to quinine, so that we can decrease duration of treatment to 3 days.

Chloroquine

- It is safe in pregnancy
- It causes Bull's Eye Maculopathy (on prolonged usage for many years)
- **Other Uses:**
  - **R** - Rheumatoid Arthritis
  - **E** - Extra Intestinal Amoebiasis
  - **D** - DLE
  - **L** - Lepra reaction
  - **I** - Infectious mononucleosis
  - **P** - Photogenic reactions
  - Mahatma - Malaria
  - Gandhi - Giardiasis

How to remember

- RED LIPs of Mahatma Gandhi

Artemisinins

- Drugs include:
  - Artesunate
  - Artether
  - Artemether
  - Dihydroartemisinin
- They are fastest acting antimalarials
- Effective against MDR parasites
- Short acting drugs so cannot be used alone
- C/I in 1st trimester of pregnancy
- **Artemisinin based Combination Therapy [ACT]:** 00:27:30
  - Artemisinin + Long acting drug
  - DOC for chloroquine resistant malaria
  - Combinations used:

1. **Lumefantrine+Artemether:** DOC in Northeastern States
2. **Artesunate+Sulfadoxine Pyrimethamine**: DOC for rest of India

TREATMENT OF MALARIA UNDER NVBDCP

00:29:40

	DOC	1st Trimester
• P. vivax malaria	Chloroquine	Chloroquine
• P. falciparum malaria	ACT	Quinine
• Mixed infection	ACT	Quinine
• Complicated or Severe or Cerebral Malaria	I.V. Artesunate followed by ACT orally after 24hrs	I.V. Artesunate

Malaria Prophylaxis 00:32:40

- Given to travellers going from non-endemic area to endemic area.
- Drugs are given before the journey.
- Prophylaxis depends on duration of stay:

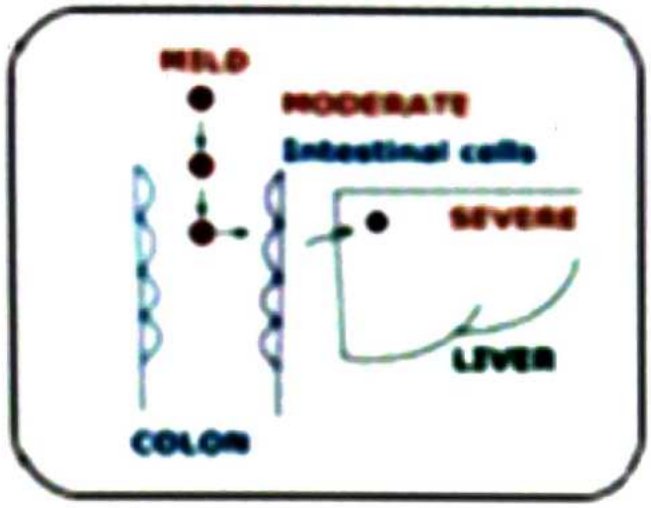
Short Term prophylaxis (<6 weeks)	Long Term prophylaxis(>6 weeks)
○ **Doxycycline**	○ **Mefloquine**
○ Given daily	○ Given weekly
○ Started 2 **days** before to 4 weeks after the journey	○ Started 2 **weeks** before to 4 weeks after the journey

OTHER PROTOZOAL DISEASES

1. AMOEBIASIS 00:35:46

- Entamoeba histolytica comes from faeco-oral route
- Through mouth it can penetrate cells of intestine reach liver

- **Luminal amoebiasis**-when it enters the lumen
- **Intestinal amoebiasis**-when it penetrates intestinal cells
- **Extra intestinal (Hepatic) amoebiasis**–when it penetrates the tissues



- **DOC** for various types:
  - Luminal amoebiasis and Carrier state-Diloxanide furoate (India) or Paromomycin (USA)
  - Intestinal & Hepatic amoebiasis–Nitroimidazole (-nidazoles). These include:
    → Metronidazole
    → Tinidazole
    → Secnidazole
    → Ornidazole
    → Satranidazole
  - Metronidazole like drugs:
    → Can cause disulfiram like reaction
    → So C/I in alcoholics (except satranidazole)
  - Other uses of Metronidazole:
    → **G - G**iardiasis, Gardnerella vaginalis
    → **U - U**lcer (Peptic ulcer)
    → **P - P**seudomembranous colitis
    → **T - T**richomoniasis
    → **A - A**moebiasis, Anaerobic bacterial infection

How to remember

- GUPTA

2. LEISHMANIA 00:41:51

Leishmaniasis

Visceral (aka Kala Azar)	**Mucocutaneous**	**Dermal** (aka PKDL)
• DOC is Liposomal Amphotericin B (L-AMB) (IV single dose) • Other drug – Antimony (Stibogluconate)	• L-AMB	• Miltefosine - only oral drug for Kala Azar

3. TRYPANOSOMA 00:46:01

- Trypanosoma causes 2 types of infections:
  - African Trypanosomiasis (aka Sleeping sickness)
  - South American Trypanosomiasis (aka Chaga's disease)
- **DOC** for:

a. African Trypanosomiasis in:
  - **Early** stage: Suramin
  - **Late** stage: Melarsoprol

b. South American Trypanosomiasis: Benznidazole

ANTI HELMINTHIC DRUGS 00:47:00

- There are 2 main types of helminths:

1. Platyhelminths
  - Tapeworms
  - Flukes

2. Nemathelminths / Nematodes
  - Roundworm
  - Pinworm
  - Hookworm, etc.

Tapeworms
- DOC Praziquantal
- Except for Echinococcus granulosus (Dog Tapeworm) – DOC is Albendazole

Flukes
- DOC Praziquantal
- Except for Liver fluke (Fasciola hepatica)-DOC is Triclabendazole

Nematodes
- DOC for all nematode including their larvae Albendazole
- Except for:

1. Filaria – DOC is DEC (Di ethyl carbamazine)
2. Strongyloides
3. Onchocerca } DOC is Ivermectin

- **Ivermectin** is the only oral drug approved for Scabies
- DOC for Scabies – Permethrin
- Treatment of **Neurocysticercosis**-Albendazole (DOC). Praziquantal can also be used.

CLINICAL QUESTIONS

CELL WALL SYNTHESIS INHIBITORS

Q. Which of the following is not an established antimicrobial drug synergism at clinical level?

A. Amphotericin B and flucytosine in cryptococcal meningitis
B. Carbenicillin and gentamicin in pseudomonal infections
C. Penicillin and tetracycline in bacterial meningitis
D. Trimethoprim and sulfamethoxazole in coliform infections

Answer: C

Solution

Combination of a bacteriostatic and a bactericidal drug in most cases is antagonistic.
Bactericidal drugs act on fast multiplying organisms whereas bacteriostatic drugs inhibit the growth.
Here, **penicillins** are bactericidal whereas **tetracyclines** are bacteriostatic.

Q. Which of the following statements about the biodisposition of penicillins and cephalosporins is NOT accurate?

A. Oral bioavailability is affected by lability to gastric acid
B. Procaine penicillin G is used via intramuscular injection
C. Renal tubular reabsorption of beta-lactams is inhibited by probenecid
D. Nafcillin and ceftriaxone are eliminated mainly via biliary secretion

Answer: C

Solution

- Probenecid inhibits renal tubular secretion of **penicillins** (not reabsorption)
- Beta lactams eliminated by biliary route are:
  - Ampicillin
  - Nafcillin
  - Ceftriaxone
  - Cefoperazone
- Penicillin G has to be given by i.m. route because it is broken down by gastric acid (decreases oral bioavailability).

PROTEIN SYNTHESIS INHIBITORS

Q. A 29-year-old male patient presented with dizziness, ataxia, nausea, and vomiting, the offending drug was stopped. He became symptom-free after 48 hours. Identify the drug?

A. Minocycline
B. Demeclocycline
C. Doxycycline
D. Tetracycline

Answer: A

Solution

Vestibular toxicity of **Minocycline** is exhibited as **Dizziness, ataxia, nausea, and vomiting.**

- Tetracycline causing maximum vestibular toxicity: **Minocycline**
- Tetracycline safe in renal failure: Doxycycline

Side effects of tetracycline

- **K** - **K**idney failure
- **A** - **A**ntianabolic
- **P** - **P**hototoxic
- **I** - **I**nsipidus diabetes
- **L** - **L**iver failure
- **D** - **D**entition
- **E** - **E**xpiry (Fanconi syndrome)
- **V** - **V**estibular dysfunction

Q. Antimicrobials effective against anaerobic bacteria include the following EXCEPT:

A. Tobramycin
B. Clindamycin
C. Chloramphenicol
D. Metronidazole

Answer: A

Solution

Aminoglycosides require **oxygen** for transport in the bacterial cell.
These are therefore **ineffective** against anaerobic organisms.

ANTI-METABOLITES AND QUINOLONES

Q. Which of the following statements about the fluoroquinolones is not FALSE?

A. Gonococcal resistance to fluoroquinolones may involve changes in DNA gyrase
B. Modification of fluoroquinolones dosage is required in patients if creatinine clearance is less than 50 mL/min
C. A fluoroquinolone is the drug of choice for the treatment of an uncomplicated urinary tract infection in a 7-year-old girl
D. Fluoroquinolones inhibit relaxation of positively supercoiled DNA

Answer: A, B, D

Solution

- **Fluoroquinolones** are contraindicated in children (due to risk of cartilage damage) and pregnant females.
- Most common mode of resistance to fluoroquinolones is due to a mutation in DNA gyrase.
- Dose of fluoroquinolones should be adjusted in renal failure (except moxifloxacin and trovafloxacin).
- These drugs act by inhibiting DNA gyrase.

Q. If a patient has a past history of these following conditions, use of ciprofloxacin is contraindicated

A. Epilepsy
B. Deep vein thrombosis
C. Gout
D. G-6 PD deficiency

Answer: A

Solution

- Ciprofloxacin is contraindicated with NSAIDs because this combination results in an increased risk of seizures.
- It is also contra-indicated with theophylline because it increases the risk of theophylline toxicity by inhibiting its metabolism.
- It is contraindicated in pregnancy because it increases the risk of cartilage damage in newborns.

DRUGS NOT EFFECTIVE AGAINST PARTICULAR BACTERIA

Q. Which of the following is not true for silver sulfadiazine?

A. The concentration used is 1%
B. It is used for preventing infections at burnt surfaces
C. It can used for treating established infections at burnt surfaces
D. It is active against Pseudomonas

Answer: C

Solution

SILVER SULFADIAZINE

- It is used topically as 1% cream.
- It is active against a large number of bacteria and fungi, even those resistant to other sulfonamides e.g. Pseudomonas
- It slowly releases silver ions, major active anti-microbial component

- It is **highly effective at preventing infections of burnt surfaces**
- It is **not good for** treatment of **established infections**

Q. A 73-year-old male presented to the emergency with pain in and behind the right ear. A preliminary diagnosis of otitis externa was made. He is a known case of diabetes mellitus. Gram staining of the exudates shows gram-negative rods and sample was sent for culture and sensitivity. What should be the best treatment of this patient pending result of culture?

A. Analgesics should be prescribed, but antibiotics should be withheld pending microbiological results
B. Oral cefaclor should be prescribed together with analgesics, and the patient should be sent home
C. The patient should be hospitalized and treatment started with imipenem-cilastatin
D. The Patient should be hospitalized and treatment started with gentamicin plus ticarcillin

Answer: D

Solution

- A diabetic patient with otitis externa is at high danger of spread of infection to the meninges and middle ear.
- Gram-negative rods may point towards **Pseudomonas infection.**
- Its early manifestations resemble diffuse otitis externa but there is excruciating pain and the appearance of granulations in the ear canal. Facial paralysis is common. Infection may spread to the skull base and jugular foramen causing multiple cranial nerve palsies.
- Anteriorly, the infection spreads to the temporomandibular fossa, posteriorly to the mastoid, and medially into the middle ear and petrous bone.
- **Diagnosis:** Severe otalgia in an elderly diabetic patient with granulation tissue in the external ear canal at its cartilaginous–bony junction should alert the physician of ***necrotizing otitis externa/ malignant otitis externa.***
- CT scan may show bony destruction but is often not helpful.
- Gallium-67 is more useful in the diagnosis and follow-up of the patient. It is taken up by monocytes and reticuloendothelial cells and is indicative of soft tissue infection. It can be repeated every 3 weeks to monitor the disease and response to treatment.
- Technetium 99 bone scan reveals bone infection but the test remains positive for a year or so and cannot be used to monitor the disease.
- ***Aminoglycoside* plus wider spectrum *penicillin* is appropriate and is used against many pseudomonas strains.**

LEARNING OBJECTIVES

UNIT 11: ANTICANCER DRUGS AND IMMUNOSUPPRESANTS

- Monoclonal antibodies
  - Production
  - Nomenclature
  - Changes in nomenclature
  - Uses of various MAb
- Cytotoxic anticancer drugs
  - Cell cycle
  - Anti-cancer drugs
  - Adverse effects of Important anticancer drugs
- Targeted anticancer drugs
  - Small molecules
  - Uses and adverse effects
  - Immunosuppressants

71 MONOCLONAL ANTIBODIES

PRODUCTION (SPLEEN CELLS+MYELOMA CELLS)

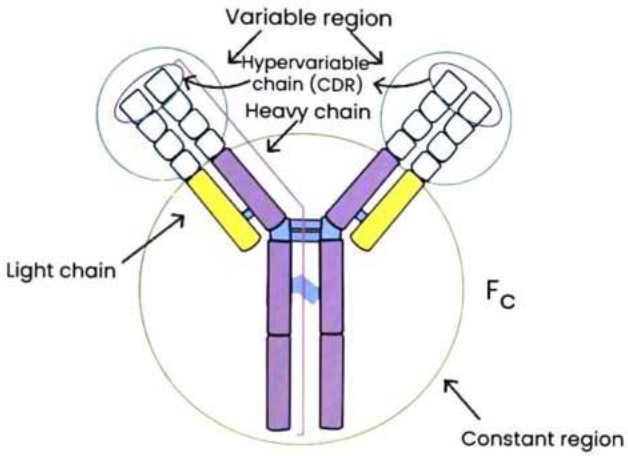
00:01:08

- The antibodies are produced by introducing an antigen to a mouse and then fusing polyclonal B cells from the mouse's spleen to myeloma cells
- The resulting hybridoma cells are cultured and continue to produce antibodies against the antigen.

NOMENCLATURE

00:02:30

Muromonab – Cd3



- It is the first monoclonal antibody which was produced in 1985
- This **MON**-oclonal **A**nti **B**ody (**MONAB**) is originated from mouse (**MUR**ine) and is effective against CD-3 antigen.
- It is approved for patients with organ transplants, as an immunosuppressant drug.
- The name of Monoclonal antibodies ends with either -MAB or -cept.
- The prefix letters of MAB are derived from the source of the drug, which can be:
  - Animal origin
  - Mixed origin: **Chimeric mixture**
  - Human origin (preferred)

  → Monoclonal antibodies of Animal origin are rarely used, as they can cause Allergic Reaction
- In case of **Chimeric** monoclonal antibodies, the constant region is of human origin and variable portion is of animal origin.
- In case of **Humanized** monoclonal antibodies, both the constant & variable portion is of human origin and only the hypervariable portion is of animal origin.
- In **Human** monoclonal antibodies, 100% component is of human origin.
- **Based on sources of MAB, nomenclature is as follows:**
  1. **Chimeric**: It ends with -ximab
  2. **Humanized**: It ends with -zumab
  3. **Human**: It ends with -umab
- The target of the Monoclonal antibodies is denoted at the start of the nomenclature. For eg:
  - Tumor (Target) - Tu
  - Lymphocytes - Lim

Changes in nomenclature (2009, 2017)

- Few changes have been made in the nomenclature of monoclonal antibodies to reduce the name size
- For eg. Adalimumab

↓

Adalumab

↓

Adalimab AQTD

- Source code has been removed from the nomenclature of monoclonal antibodies
- To differentiate the monoclonal antibodies originated from different manufacturing companies, FDA recommended the use of 4 alphabets after nomenclature.

TOX

00:15:13

- TOX' stand for toxins
  - **Bezlotoxumab**: Used against Clostridium difficile infections (Pseudomembranous colitis)
  - **Obiltoxaximab:** Used against Bacillus anthracis (Anthrax)

NE/N

00:17:08

- NE' stands for nervous system
  - Erenumab

- Eptinezumab
- Galcanezumab
- Fremanezumab

- All these 4 monoclonal antibodies are against Calcitonin Gene Related Peptide (CGRP) and approved for the prophylaxis of migraine.

BAC 00:18:39

- 'BAC' stands for bacteria
- **Raxibacumab** is approved for the use against anthrax

VI 00:19:17

- 'VI' stands for virus
- **Palivizumab is** useful against RSV (Respiratory Syncytial Virus)

CI/C

- 'CI' stands for circulatory system
- Drugs include

I. Abciximab	Inhibition of GP IIb/IIIa; used as Antiplatelet drug
ii. Bevacizumab	Inhibition of VEGF; useful against many cancers
iii. Caplacizumab	Inhibition of vWF; useful against TTP
iv. Emicizumab	Binding of factor IX and X; useful in hemophilia
v. Ramucirumab	Inhibition of VEGF; useful in NSC lung cancer and GEJ tumors
vi. Brolucizumab	Inhibition of VEGF; useful in ARMD (Age related Macular Degeneration)
vii. Idarucizumab	For treatment of Dabigatran toxicity
viii. Alirocumab	Inhibition of PCSK-9; useful in
ix. Evolocumab	Homozygous Hyper-Cholesterolemia

OS 00:29:24

- OS' stands for Osteo (bone)
- **Denosumab:** Causes inhibition of RANK-ligand. Useful in Osteoporosis
- **Romosozumab**
  - Causes inhibition of Sclerostin, which is Pro-Osteoporotic
  - It has dual action (inhibition of Osteoclast and stimulation of Osteoclast). Useful in Osteoporosis
- **Burosumab**
  - Causes inhibition of FGF-23, thus promotes PO_4^{3-} reabsorption in both kidneys & intestines
  - Useful in X-linked hypophosphatemia

KI/K 00:31:24

- 'KI' stands for Interleukin
  - **Ixekizumab**: against IL-17
  - **Secukinumab**: against IL-17
  - **Ustekinumab**: against IL-12, 23
  - **Risankizumab**: against IL-23
  - **Guselkumab**: against IL-23
  - **Tildrakizumab**: against IL-23
- These monoclonal antibodies act by inhibition of interleukins and are useful in Plaques and Psoriasis

ANIBI 00:36:33

- ANIBI' stands for Angiogenesis inhibitor
- **Ranibizumab** causes inhibition of VEGF. Useful in ARMD

LI/L 00:37:25

- Action in immune system (Lowering immunity)

1. TNF- inhibitors

- **A** - Adalimumab
- **C** - Certolizumab
- **E** - Etanercept
- **Inhibitors** - Infliximab
- **Goli** - Golimumab
- These monoclonal antibodies are useful in RA, Crohn's disease & Psoriasis

2. CD -25

- Daclizumab
- Basiliximab
- Useful in transplantations

3. B-LyS (B – lymphocyte stimulator)

- Belimumab
- Useful in SLE

4. C5

- Eculizumab
- Ravulizumab
- Useful in Paroxysmal Nocturnal Hemoglobinuria (PNH)

5. LFA - 1

- Efalizumab
- Useful in Psoriasis

6. LFA – 3

- Alefacept

7. CCR-4 (Chemokine receptor-4)

- Mogamulizumab
- Useful in Mycosis Fungoides & Sezary syndrome

8. Alpha-4 integrin

- Natalizumab
- Useful in MS, CD

9. Alpha-4/Beta-7integrin

- **For Asthma:**
  - Omalizumab
  - Reslizumab

  } Against IL-5

10. CD-20

- Ocrelizumab
- Useful in MS

11. IL-6R

- Sarilumab: Useful in RA
- Tocilizumab: Useful in RA: treatment of cytokine release syndrome
- Sactralizumab: Useful for treatment of Veno-occlusive disease in sickle cell anemia

12. P-Selection

- Crizanlizumab: Useful for treatment of Veno –occlusive in sickle cell anemia

13. CD-4

- Ibalizumab: Useful in HIV

14. IL-17RA

- Brodalumab: Useful in Psoriasis

15. IL-4R Alpha

- Dupliumab: Useful in atopic dermatitis

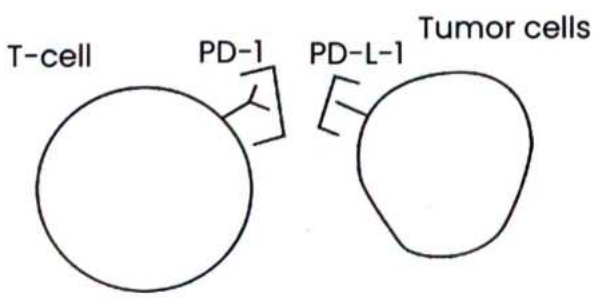
16. IFN - Gamma

- Emapalumab: Useful in Primary hemophagocytic lymphohistiocytosis

17. Kallikrein

- Kallikrein helps in the conveversion of high molecular weight Kininogens (HMWK) to bradykinin
- Lanadelumab: Useful in Hereditary Angioneurotic Edema (HAE)

18. Immune Check point Inhibitors



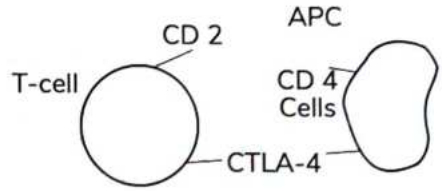
I. PD – 1

- Nivolumab: HL, NSCLC, MM
- Pembrolizumab: MM, NSCLC, Head and Neck cancers
- Cemiplimab: Squamous cell carcinoma of skin

ii. PD-L1

- Atezoli zumab: Urothelial & Breast cancers
- Avelumab: Merkel cell carcinoma
- Duruvalumab: Bladder carcinoma

iii. CTLA – 4



Ipilimumab : Malignant Melannoma

TU/TA

- TU stands for Tumors

1. Growth factor receptors

i. EGFR (HER-1)

- Cetuximab: Colorectal, Head & neck cancers
- Trastuzumab: Colorectal Cancers
- Necitumumab: NSCLC
- Nimotuzumab: Head & Neck cancers, Glioma

ii. HER – 2

- Trastuzumab: Useful in breast cancers
- Pertuzumab: HER-2 Inhibitors can cause cardiotoxic side effects

iii. PDGFR – Alpha

- Olaratumab: soft tissue sarcoma

2. CD markers

Marker	Drug	Use
CD-3,19	BLINATUMOMAB	Ph-ALL
CD-19	TAFASTIAMAB	DLBCL
CD-20	RITUXIMAB	NHL, CLL
CD-20	IBRITUMOMAB	BCL, CLL
CD-20	OFATUMUMAB	CLL
CD-20	TOSITUMOMAB	BCL
CD-20	OBINTUZUMAB	BCL, CLL
CD-22	INOTUZUMAB	ALL

Marker	Drug	Use
CD-30	BLINATUMOMAB	HL, TCL
CD-33	GEMTUZUMAB	AML
CD-38	DARATUMUMAB	MM
CD-38	ISATUXIMAB	MM
CD-52	ALEMTUZUMAB	CLL
CD-79B	POLATUZUMAB	DLBCL
CD-319 (SLAM-F7)	ELOTUZUMAB	MM

3. **IL -6**
   - Siltuximab: RCC, Castleman's disease
4. **TROP - 2**
   - Sacituzumab: Breast cancers
5. **IGF-1R**
   - Teprotumumab: Thyroid eye disease
6. **Nectin -4**
   - Enfortumab: Urotghelial cancer
7. **Glycolipid GD – 2**
   - Dinutuximab; Neuroblastoma
8. **BCMA**
   - Belantamab: Multipl

72 CYTOTOXIC ANTICANCER DRUGS

Anticancer drugs are of 2 types

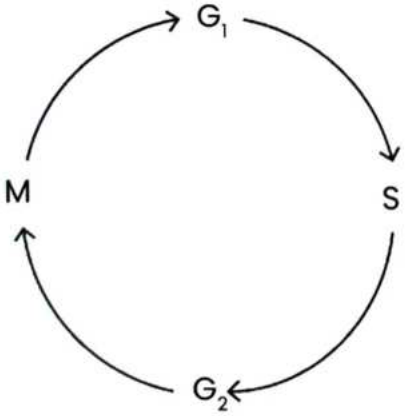
a. Cytotoxic
b. Targeted

Adverse Effects of anticancer drugs 00:02:27

1. BM Suppression
2. Alopecia
3. Mucositis → Diarrhea
4. Hyperuricemia
5. Secondary Leukemia
6. Sterility

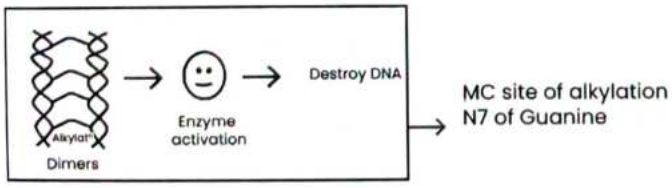
CELL CYCLE 00:04:38

- **Synthetic** Phase [S] - DNA Doubled
  Mitotic Phase [M] - DNA reduced to half
  Gap Phases [G_1 & G_2]
- Nonselective Drugs - bind to DNA
  Synthetic phase specific Drugs - inhibit DNA Synthesis
  M-phase specific Drugs - inhibit Mitosis

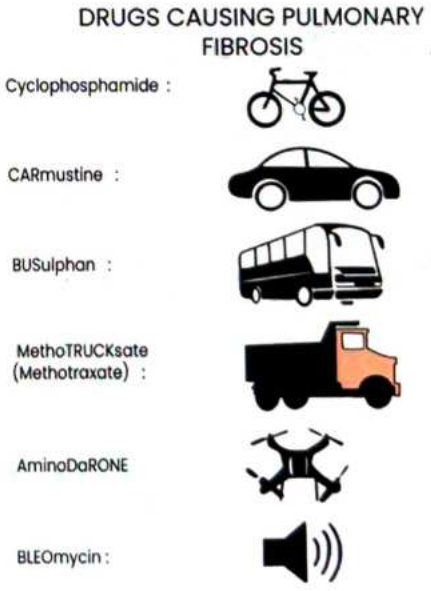


1. ALKYLATING AGENTS 00:07:09

- **MOA**



- **Drugs included**
  - **If** - Ifosfamide
  - **Bus** - Busulfan
  - **Not** - Nitrosoureas: Carmustine (BCNU), Lomustine (CCNU), Semustine (Methyl CCN
  - **Present** - Procarbazine
  - **Take** - Temozolomide
  - **My** - Melphalan, Mechlorethamine
  - **Cycle** - Cyclophosphamide
- **Ifosfamide** and **Cyclophosphamide**
  ↓metabolized to
  Acrolein
  ↓ causes
  Hemorrhagic cystitis (Ifosfamide > >Cyclophosphamide)
- Prevention of Hemorrhagic cystitis: MESNA (Mercapto Ethane Sulfonic Acid)
- Treatment of Hemorrhagic cystitis:
  - Steroids
- **Drugs causing Pulmonary Fibrosis:**
  - Cyclophosphamide
  - Busulfan
  - Methotrexate
  - Amiodarone
  - Bleomycin



- **Nitrosoureas**
  - Carmustine (BCNU)
  - Lomustine (CCNU)
  - Semustine (Methyl CCNU)
- **Uses** of Nitrosourea drugs:
  - As they can cross Blood Brain Barrier, they are used in Brain tumors.
- **Side effects**: Causes Delayed bone marrow suppression and Neutropenia
- **Procarbazine** causes Disulfiram like reaction i.e., intolerance to alcohol
- **Temozolomide** is DOC of Glioma
- **Melphalan** is used in Multiple Myeloma

2. PLATINUM COMPOUNDS

- Drugs included
  - Cisplatin
  - Carboplatin
  - Oxaliplatin: Used for Colorectal carcinoma
- **MOA**: Same as Alkylating Agents
- **S/E**: Same as Alkylating Agents
- **Cisplatin**
  - Most emetogenic anti-cancer drug (DOC → Ondansetron)
  - Nephrotoxic
  - Ototoxic
  - **S/E:** Vomiting
    - → **Early** vomiting (< 24 hours): DOC-Ondansetron, Granisetron
    - → **Delayed** vomiting (>24 hours): DOC – Neurokinin/ Substances P antagonists like Aprepitant
  - **Nephrotoxicity:**
    - → Reversible
    - → For prevention of nephrotoxicity
  - i. Slow intravenous infusion of cisplatin
  - ii. Saline loading can be done
  - iii. Amifostine → can also prevent radiation induced xerostomia.
  - **Ototoxicity** is Irreversible
- **Oxaliplatin** is used in colorectal carcinoma:
  - Colorectal Carcinoma Regimen

FOLFOX regimen		FOLFIRI regimen	
Folinic acid	+	Folinic acid	+
5 – FU	+	5 –FU	+
Oxaliplatin		Irinotecan	

3. ANTIMETABOLITES

- **S-phase specific**
  - a. Drugs affecting Purine Metabolism
  - b. Drugs affecting Pyrimidine Metabolism
  - c. Drugs affecting Folic Acid Metabolism

a. Drugs Affecting Purine Metabolism

- Drugs
  - 6 – Mercaptopurine } Hepatotoxic
  - 6 – Thioguanine }
  - Cladribine: DOC For Hairy cell Leukemia
  - Fludarabine: DOC For CLL
- **6 – Mercaptopurine:**

6 – MERCAPTOPURINE → Xanthine
↓xanthine oxidase ↓
Degradation → Uric acid

  - With Allopurinol combination, dose should be reduced
  - 6-MP is the active metabolite of Azathioprine

b. Drugs Affecting Pyrimidine Metabolism

- Drugs
  - 5-Fluorouracil [5-FU]: causes Hand & Foot syndrome
  - Capecitabine: cause Hand & Foot syndrome. Given orally. Metabolism to 5 – FU
  - Gemcitabine: DOC for Pancreatic carcinoma
  - Cytarabine: Causes cerebellar side effects
- MC S/E of 5-FU is Diarrhea:
  - Folic Acid Synthesis:

Pteridine + PABA + GLUTAMATE
↓
Diet Dihydro Folic Acid [FH2] [Folic Acid]
Methotrexate ↓DHF reductase
Tetra Hydro Folic Acid [FH4] [Folinic Acid]
↓
DNA

- **Methotrexate**
  - Methotrexate Poisoning is treated by Folinic Acid/ Leucovorin/ Citrovorum
  - Can cause megaloblastic anemia
  - Hepatotoxic
  - DOC for Chorio-carcinoma and Rheumatoid Arthritis
  - MC used DMARD
  - **Uses** of Methotrexate:

→ **C**: Choriocarcinoma (D.O.C)
→ **A**: Acute leukemias [ALL, AML]
→ **N**: Non- Hodgkin's lymphoma
→ **C**: Crohn's disease
→ **E**: Ectopic pregnancy
→ **R**: Rheumatoid arthritis (DOC)

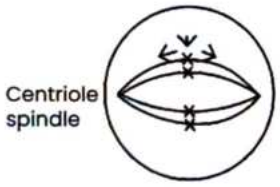
- **Adverse Effects** of Methotrexate:
  - → Bone marrow suppression, alopecia, diarrhea, hyperuricemia
  - → It inhibits folic acid metabolism-causes megaloblastic anemia
  - → It is hepatotoxic
  - → Methotrexate toxicity treatment-Folinic acid (Leucovorin or Citrovorum)

- **New DHFRase Inhibitors**
  - Pemetrexed – used in mesothelioma
  - Pralatrexate – used for peripheral T-cell lymphoma

  } both cause megaloblastic anemia

4. DRUGS ACTING ON MITOTIC SPINDLE

- Spindle formation:



Polymerization of Tubulin-> Spindle Formation

- Specific for M-Phase of cell cycle

Spindle formation inhibitors	Spindle breakdown inhibitors
Vincristine Vinblastine	Paclitaxel
S/E: Peripheral neuropathy, SIADH	**S/E**: Allergy

- **Vincristine** is Marrow Sparing anticancer drug
- **New drugs** which act on mitotic spindle:
  - Eribulin
  - Ixabepilone
  - Estramustine

  } M-phase specific
- **Eribulin** inhibits tubules

- **Eribulin**
- **Ixabepilone**

} Used in breast carcinoma

Estramustine is used for prostate cancer

5. TOPO-ISOMERASE INHIBITORS

- Topo-isomerase introduces negative coiling and aids in replication

Topoisomerase I inhibitors	Topoisomerase II inhibitors
Irinotecan • Used for colorectal carcinoma • S/E: cholinergic side effects like diarrhea, sweating	• Etoposide • Anthracyclines (cardiotoxic) ○ Doxorubicin ○ Daunorubicin

- **Etoposide**
  - Can cause 2° Leukemia [Early in onset]
  - Absence of myelodysplastic stage
- **Anthracyclines**
  - Cause Cardiotoxicity
  - Prevented by Dexrazoxane
- **Radiation Recall Syndrome**: If a person has head/neck cancer and is treated with radiotherapy and after 6 months, we plan for chemotherapy with anthracyclines, adverse effects (like redness, swelling etc.) can be seen in those areas where radiation was given.

6. MISCELLANEOUS DRUGS

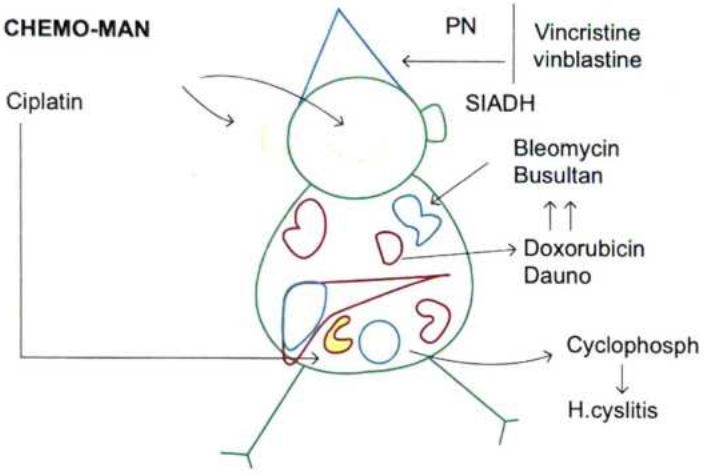
- **Bleomycin**
  - Marrow sparing
  - Causes pulmonary fibrosis
  - Bleomycin is metabolized by bleomycin hydrolase which is deficient at

Lungs → Pulmonary fibrosis
Skin → Flagellated pigmentation

- **L-Asparaginase**
  - Marrow sparing
  - Used for ALL
  - Causes Allergy
  - Causes Acute Pancreatitis
- **As_2O_3**
  - Used in Acute Promyelocytic leukemia [M3-AML] (All-Trans Retinoic Acid can also be used)
  - Acts as maturation agent
- **Thalidomide**

- Used for multiple myeloma (acts by inhibiting angiogenesis)
- C/I in pregnancy (Teratogenic as it causes phocomelia)
- Powerful immunosuppressant drug (inhibits TNF-)
- Causes peripheral neuropathy
- Causes constipation

ADVERSE EFFECTS OF IMPORTANT ANTI-CANCER DRUGS



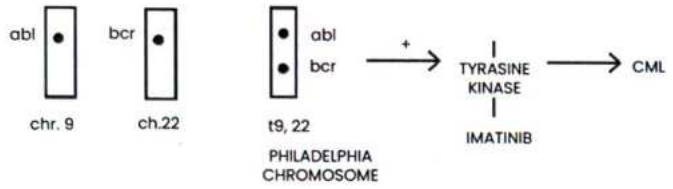
- **Vincristine** — Peripheral neuropathy
  Vinblastine — SIADH
- **Cisplatin**
  - Ototoxicity
  - Nephrotoxicity
  - Max vomiting
- **Bleomycin**, **Busulfan** } - Pulmonary fibrosis
- **Doxorubicin**, **Daunorubicin** } - (DIL) – Cardiotoxicity
- **6-MP**, **6-TG** } - Hepatotoxicity
- **[illegible]phamide** - Hemorrhagic cystitis

73 TARGETED ANTICANCER DRUGS

SMALL MOLECULES

1. Tyrosine Kinase Inhibitors

⏱ 00:01:30



- DOC For Chronic Myeloid Leukemia is Imatinib
- General properties:
  - All end with '-nib'
  - Orally effective
  - Metabolized by microsomal enzymes
- **Uses:**

a. CML
- **I** - Imatinib [DOC]
- **N** - Nilotinib
- **D** - Dasatinib

b. Lung Carcinoma
- **After** - Afatinib
- **E** - Erlotinib
- **C** - Ceritinib
- **G** - Geftinib

c. Renal Cell Carcinoma
- **P** - Pazopanib
- **A** - Axitinib
- **S** - Sorafenib
- **S** - Sunitinib

d. Hepatic Cellular Carcinoma Sorafenib

e. GIST [Gastrointestinal Stromal Tumors]
- **S** - Sunitinib
- **I** - Imatinib [DOC]
- **R** - Regorafenib also used for colorectal carcinoma

f. Malignant Melanoma
- **D** - Dabrafenib
- **V** - Vemurafenib
- **T** - Trametinib

g. Medullary CA of Thyroid Vandetanib

2. Proteasome Inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib
  - Used for Multiple Myeloma

3. PARP Inhibitors [Poly ADP Ribose Polymerase Inhibitors]
- Olaparib Used in Ovarian carcinoma
  - **O** - Ovarian carcinoma [Used]
  - **LA**
  - **P** - Poly
  - **A** - ADP
  - **RIB** - Ribose Polymerase

4. Cyclin Dependent Kinase Inhibitors [CDKI]
- Palbociclib-Oral drug For Breast carcinoma. Acts on CDK-4, CDK 6
  - **PAL**
  - **B** - Breast cancer [Used]
  - **O** - Oral
  - **CICLIB** - Cyclin dependent Kinase inhibitor

MONOCLONAL ANTIBODIES
- **Cetuximab** - Used for Colorectal CA
- **Panitumumab** - Used for Colorectal CA
- **Rituximab** - Used for NHL
- **Trastuzumab** - Used for Breast CA. S/E – cardiotoxicity
- **Pertuzumab** - Used for Breast CA
- **Daratumumab** - Used for Multiple myeloma
- **Olaratumab** - Used for Soft tissue Sarcoma

CLINICAL QUESTIONS

MONOCLONAL ANTIBODIES

Q. Mark the true statement regarding Bevacizumab among the options:

A. Humanized antibody directed against EGF
B. Acts on CD 33
C. First FDA-approved molecule that specifically targeted angiogenesis.
D. Used in Chronic lymphocytic leukemia

Answer: C

Solution

Bevacizumab

- Humanized antibody directed against VEGF-A
- First FDA-approved molecule that specifically targeted angiogenesis.
- As a single agent, it delays progression of renal-cell cancer
- Combination with cytotoxic chemotherapy effectively treats lung, colorectal, and breast cancers

Gemtuzumab

- Acts on CD 33
- Used in CD-33 positive AML

Obinutuzumab:

- Against CD20
- Used in Chronic lymphocytic leukemia

Ofatumumab

- Against CD20
- Used in Chronic lymphocytic leukemia

Q. Which of the following monoclonal antibodies is a humanized antibody?

A. Rituximab
B. Palivizumab
C. Infliximab
D. Basiliximab

Answer: B

Solution

Nomenclature of monoclonal antibodies:

- Their name ends with mab.
- Before mab the two letters tell the source:
- **XI** means **Chimeric**
- **ZU** means **humanized**
- **U** means **completely human**

CYTOTOXIC ANTICANCER DRUGS

Q. Match the following Anti Cancer drugs with the mechanism of action:

DRUGS	MOA
1. Cladribine	A. Proteasome inhibitor
2. Melphalan	B. Alkylating agent
3. Capecitabene	C. Purine inhibitors
4. Pralatrexate	D. Pyrimidine inhibitor
	E. FA inhibitor

A. 1-A 2-B 3-C 4-D
B. 1-C 2-B 3-D 4-E
C. 1-D 2-B 3-C 4-E
D. 1-C 2-B 3-D 4-A

Answer: B

Solution

- Cladribine is a synthetic purine nucleoside analogue (prodrug) which is approved for use in cases of hairy cell leukaemia.
- Melphalan is an anti-neoplastic agent that alters DNA nucleotide guanine through alkylation and causes linkages between strands of DNA. It is used in multiple myeloma.
- Capecitabine, whose active metabolite is fluorouracil, inhibits DNA synthesis by reducing thymidine production, is S-phase specific.
- Pralatrexate is a folate analogue that acts by competitively inhibiting DHFRase. It is structurally similar to methotrexate.

Q. All of following statements about 6-mercaptopurine are true except?

A. It is metabolized by xanthine oxidase
B. It does not cause hyperuricemia
C. Its dose should be reduced when allopurinol is given concurrently
D. It is an active metabolite of azathioprine

Answer: B

Solution

- **All anticancer drugs can result in hyperuricemia** by causing the destruction of excess cells.
- Azathioprine is an immunosuppressant drug that acts by generating 6-MP.
- 6-MP inhibits the formation of ribosyl-5-phosphate and it also inhibits the conversion of IMP to adenine and guanine nucleotides.
- When given **orally** the drug is subjected to **first pass metabolism by enzyme Xanthine Oxidase** which converts it into an inactive metabolite.
- So if **allopurinol is given along with 6-MP, the metabolism of 6-MP will be reduced and it will lead to toxicity.**
- Thus the dose of oral 6-MP is to be reduced by 75%.

TARGETED ANTICANCER DRUGS

Q. Which of the following immunosuppressants is not used for the treatment of cancers?

A. Cyclophosphamide
B. Cyclosporine
C. Methotrexate
D. 6- Mercaptopurine

Answer: B

Solution

- All **antimetabolites (including 6-MP and methotrexate)** can be used as anticancer drugs except azathioprine.
- **Cyclophosphamide** is alkylating agent used for anticancer purpose.
- **Cyclosporine** acts by inhibiting the transcription of IL-2 gene. **It has no anti-cancer property.** It is used to prevent organ rejection in patients who underwent kidney, liver or heart transplant.

Q. A widely used drug that suppresses cellular immunity, inhibits prostaglandin and leukotriene synthesis and increases the catabolism of IgG antibody is:

A. Cyclophosphamide
B. Prednisone
C. Cyclosporine
D. Infliximab

Answer: B

Solution

Glucocorticoids are powerful immunosuppressants. These **inhibit both cellular and humoral immunity** by:

- Decreasing the [illegible] of immune cells.
- Catabolism of immunoglobulins.
- Inhibiting the enzyme phospholipase A2 resulting in decreased production of PGs, LTs and TXs.

LEARNING OBJECTIVES

UNIT 12: AUTACOIDS

- Histamine and Serotonin
  - Histamine receptors
  - Drugs used
- Migraine
  - Acute attack
  - Prophylaxis
  - New drugs
- PGs, LTs and NSAIDs
  - Effects of PG
  - Side effects
  - NSAIDs classification
- Gout and RA
  - Acute gout
  - Chronic gout
  - RA
  - DMARDs

74 HISTAMINE AND SEROTONIN

- Autacoids are drugs having autacrine effects i.e. local effects
- They produce non – specific effects
- Divided acc. to chemical structure

a. Peptide autacoids
- Angiotensin
- Bradykinin

b. Amine autacoids
- Histamine
- Serotonin (5HT)

c. Lipid autacoids
- PG
- Leukotrienes
- Thromboxane

HISTAMINE

00:03:35

- It works through 4 main receptors:

	Locations	Action	Blockers
H_1		1. Allergy Inflammation 2. Stimulates RAS promote wakefulness	
H_2	Stomach	Secrete acid	
H_3	Pre synaptic	BRAKE	H3# or inverse Agonist Tiprolisant [Pitolsant] used for Narcolepsy
H_4	WBC	Chemotaxis	

H_1 blockers (H1 antihistaminics)

00:07:50

- These are divided into
  - 1st gen
  - 2nd gen

1st Generation	2nd Generation
Cross BBB, cause sedation	Do not cross BBB, no sedation
Ach #	No Ach #
• Anticholinergic S/E occur	

Useful for
- Motion sickness
- Drugs induced parkinsonism
- Muscular dystonia's
- Allergy

Useful only for allergy

Promethazine [max. Ach# action]
- Diphenhydramine
- Dimenhydrinate
- Pheniramine
- Chlorphenamine
- Cyclinizine
- Cinnarizine

Terfenadine → not used (TDP)
Fexofenadine → Terfenadine metabolite
Astemizole → not used (TDP)
Loratadine
Des-Loratidine
Cetirizine, Levocetirizine
Azelastine, Olopatadine → Topical

How to remember

- Possess: Parkinsonism
- Anti: Acute muscular dystonia / Akathisia
- Cholinergic: Common cold / allergy
- Property: Prophylaxis of motion sickness

- 3 drugs are withdrawn:
  - Cisapride
  - Astemizole
  - Terfenadine
    - → These are CAT drugs
    - → These drugs block potassium channels. This leads to QT prolongation which is known as Torsade's de pointes. This occurs only in overdose
    - → They are metabolized by CYP3A4. So metabolism is inhibited by – Ciprofloxacin, Ketoconazole and Erythromycin

How to remember

- CAT is cute (QT)

- **3rd gen anti-histaminics**
  - These are metabolites or isomers of 2nd gen
  - These include
    → Fexofenadine
    → Desloratadine
    → Levocetirizine
  - Their properties are same as 2nd gen drugs

SEROTONIN (5-HT)

00:25:10

- It has 7 receptors in the body: $5HT_1$ to $5HT_7$
- $5\text{-}HT_5$, $5\text{-}HT_6$, $5\text{-}HT_7$, are present in brain, but their exact function is not known.

	Location	Action	Agonist/antag.	Drug	Uses	S/e
5HT1						
IA			Agonist	BUSPIRONE	Anxiety	
IB/ID	BV of Brain	VC	Agonist	SMATRIPTAN NARATRIPTAN ELETRIPTAN RIZATRIPTAN	Acute severe Migraine [DOC]	
5HT 2S/2C			Blockers	CLOZAPINE OLANZAPINE	Atypical Antipsychotics	LDS
			5HT2c Agonist	LORCASERIN	Obesity	
5HT3	CT2	Emesis	Blockers	ONDANSETRON GRANISETRON TROPISETRON TROPISETRON PALONOSETRON	DOC For Chemotherapy/ Radiotherapy in Duced vomiting Post op vomiting	
5HT4	GIT	↑ Peri – Stali-SiS	Agonists | Prokinetics	CISAPRIDE MOSARPRIDE	GERD [DOC – PPIS]	

75 MIGRAINE

- Migraine is unilateral pulsatile headache. It can be with or without aura.
- Main reason is inflammation and dilatation of blood vessels in brain.
- Latest theory states that migraine is caused due to release of calcitonin gene related peptide (CGRP)

Treatment 00:01:51

i. Mild attack - Paracetamol (Acetaminophen)
ii. Moderate attack - NSAIDs
iii. Severe attack:

- DOC is Triptans (Sumatriptan)
- Alternate is Ergotamine

Mechanism of action

- Triptans act by stimulating $5HT_{1B}/_{1D}$ receptors
  - Vasoconstriction of blood vessels
  - Inhibit CGRP release that inhibits vasodilation and inflammation
- Drugs included are:
  - Sumatriptan
  - Naratriptan
  - Rizatriptan
  - Eletriptan
  - Zolmitriptan
  - Frovatriptan
- They have additional action:
  - Decrease vomiting associated with migraine
- Ergotamine increases this vomiting. So Triptans are preferred over ergotamine
- We never give triptans and ergotamine together
  - They both cause vasoconstriction which causes coronary artery spasm.
  - So they are also avoided in pts. with coronary artery disease

Prophylaxis of Migraine (ABC of Migraine) 00:07:02

A	B	C	of Migraine
ANTIDEPRESSANTS • Imipramine ANTIEPILEPTICS • Valproate • Topiramate	BETA BLOCKERS • Propranolol (DOC) BOTULINUM TOXIN	CCBs • Flunarizine CGRP # • Erenumab Fremanezumab • Galcanezumab	METHYSERGIDE • Ergot derivative • Risk of pulmonary Fibrosis (so, not Preferred)

New drugs for migraine

- These drugs act on CGRP

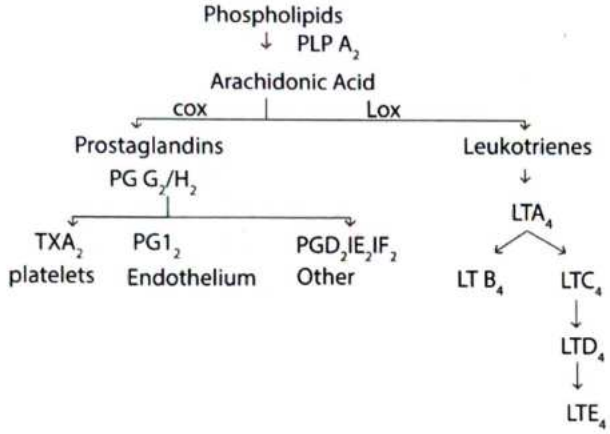
i. $5HT_{1F}$ agonist → Lasmiditan
  - Oral drug
  - Indicated for acute attack of migraine

ii. CGRP receptor blocker / antagonist
  - Olcegepant
  - Rimegepant
  - Ubrogepant
    → Given orally
    → Used for acute attack of migraine.

iii. MAb against CGRP receptors
  - Not given orally, given by injection
  - Used for prophylaxis
  - Drugs included are
    → Erenumab
    → Eptinezumab
    → Framanezumab
    → [illegible]nezumab

76 PGs, LTs AND NSAIDS

- **Production** of prostaglandins



- All the PG contain 2 double bonds whereas leukotrienes contain 4 double bonds.

Actions of PG 00:08:10

1. Fever, pain, inflammation

2. Platelets are also affected

- PGI_2 : inhibits platelet aggregation
- TXA_2 : causes platelet aggregation

> **Important Information**
>
> - Aspirin in irreversible COX inhibitor. So it reduces TXA_2. This results in antiplatelet affect.

3. CVS effects

I. Heart

- In embryonic stage, the ductus arteriosus is kept open by PGs. After delivery its production stops and DA closes physiologically.
- But in PDA, the DA does not close
- To treat this we give COX inhibitors
- These include
  - Ibuprofen (DOC)
  - Indomethacin
  - Aspirin
- In transposition of great vessels (TGV), we keep the DA patent by giving PGE_1 i.e., Alprostadil

ii. Blood vessels

- PGE_2 and PGI_2 cause vasodilation
  - This is useful in erectile dysfunction (Impotence)
  - We use PGE_1 (Alprostadil) for ED.
  - DOC is PDE#
    - → Sildenafil
    - → Vardenafil
    - → Udenafil
    - → Tadalafil (longest acting)
  - **Pulmonary HTN**
    - → PGI_2 (Iloprost)
    - → PGE_2

4. Uterus

- PGF_2 and PGE_2 cause contraction of upper part of uterus
- PGE_2 causes relaxation of lower part of uterus and cervix.
- But PGs cannot be used for labor because they are too strong and can cause strangulation. So we use oxytocin instead.
- In abortion, we can use PGE_1 which is Misoprostol
- Intra-vaginal Misoprostol can also be used in labor for relaxing the cervix.
- For treatment of PPH, we can give drugs like Misoprostol (PGE_1) and Carboprost (PGF_2) to stop the bleeding. But DOC is oxytocin
- Methergin is used to prevent PPH. It is given before delivery of anterior shoulder.

5. Stomach

- PGE_2 is gastroprotective because :
  - It inhibits proton pump. So less acid secretion
  - Increase mucus and HCO_3
  - Cause vasodilation
- NSAID long term use can cause peptic ulcers. This is called NSAID induced PUD. For treatment we use Misoprostol (PGE_1)
- We can also use PPI which is more effective and less toxic. So DOC is PPI

6. Eye

- $PGF_{2\alpha}$ stimulates Uveo-scleral outflow. So can be used for POAG. Drug used is Latanoprost (DOC). Not used in Uveitis

COX INHIBITORS

00:39:48

COX-1	COX-2

• Constitutive enzyme
• Little inflammation
• Present normally at all places
	• Inducible enzyme
	• Mainly cause inflammation
	• Normal sites are :
	  ○ Kidney
	  ○ Endothelium
	  ○ CNS

- COX inhibitors are of 2 main types

Non selective COX (-) (COX-1 and COX-2)	Selective COX 2(-)
• They lead to increased risk of PUD	• No risk

Non selective COX inhibitors

00:43:52

- Drugs included are
  - Aspirin
  - Acetaminophen (PCM)
  - Ibuprofen
  - Indomethacin
  - Ketorolac
  - Piroxicam
  - Nimesulide
- All COX inhibitors are
  - Used for pain, fever, inflammation
  - Increase risk of PUD
  - Can cause nephrotoxicity

1. Aspirin (Acetyl salicylic acid)

- Only irreversible COX inhibitors, so it has antiplatelet action
- Causes Hyperuricemia
- Can cause Reye's syndrome in child with viral illness

2. Acetaminophen (PCM)

- Does not have anti – inflammatory action
- Can be used for pain & fever
- This can be due to peroxide theory : PCM is active in presence of H_2O_2
- PCM inhibits COX-3 which is present in brain only, not peripheral so safe in kidney.
- Its metabolic acts on vanilloid receptor (TRPV) to reduce pain
- PCM is safe is children

3. Ibuprofen is the only anti – inflammatory drug which is approved in children

4. Indomethacin

- Causes sedation
- Can cause headache

5. Ketorolac can be given I.V.

6. Piroxicam is very long acting because of enterohepatic cycling

7. Nimesulide is withdrawn for use in children

Preferential COX-2 inhibitors

00:53:40

- They inhibit COX-2 more than COX-1
- Clinically they used exactly like non – selective dru-
- They include
  - **D - D**iclofenac, Aceclofenac
  - **M - M**eloxicam
  - **E - Et**odolac
  - **N - N**abumetone

How to remember

- DMEN

Selective COX-2 inhibitors

00:55:10

- They include :
  - Celecoxib
  - Rofecoxib, Valdecoxib } Withdrawn
  - Etoricoxib: Longest acting
  - Parecoxib: Only injectable drug
  - Lumirocoxib
- They do not inhibit COX-1, so don't cause PUD
- They can cause
  - MI
  - Stroke
- So these are only used in patient where we can cannot use non selective drugs

Toxicity

1. Aspirin toxicity

- It leads to stimulation of respiratory centre. This cause

hyperventilation. This leads to CO_2 washout and causes Respiratory alkalosis

- Symptoms
  - Vertigo
  - Headache
  - Tinnitus

  } Till this point, it is reversible poisoning called salicylism
  - Blurred vision
  - If aspirin is still not stopped, this respiratory alkalosis is converted into metabolic acidosis. This is irreversible
  - There is no antidote for aspirin
  - We give $NaHCO_3$
    → It corrects acidosis
    → It makes urine alkaline

2. PCM toxicity

- Most of PCM is metabolized to inactive product
- But 10% of PCM is converted to NAPQI. NAPQI has very high affinity for sulfhydryl group, which is provided by glutathione
- Poisoning can occur due to
  - Overdose (accidental)
  - Liver disease
  - Chronic alcoholism
- Antidote is N-acetyl cysteine

77 GOUT AND RA

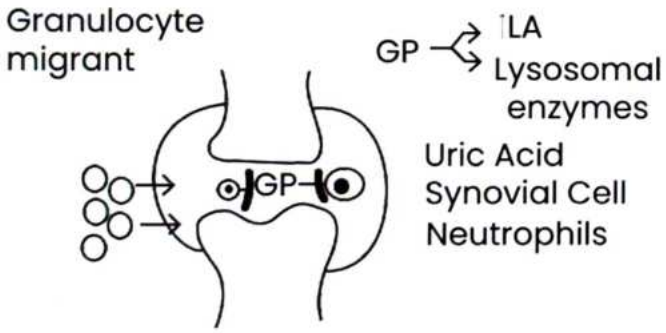
- Gout is characterized as Hyperuricemia
- It is divided into
  - Acute Gout
  - Chronic Gout

ACUTE GOUT

- It is characterized by Pain and inflammation of joints
- 1st joint involved : MTP joint
- Drugs used :
  - NSAIDs (except Aspirin & PCM)
  - Steroids (intra articular)
  - Colchicine

Colchicine

- It is the most effective drug
- It can cause S/E like
  - Severe diarrhea
  - Myopathy
- **Mechanism of action:**



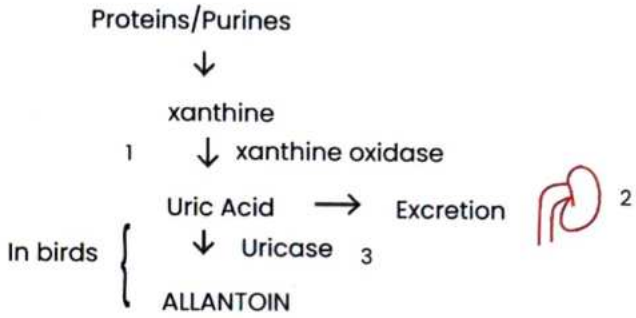
  - Inhibits granulocyte migration
  - Inhibits release of glycoprotein from neutrophils
- Use of Colchicine
  - **U** - Uric acid
  - **C** - Cirrhosis
  - **M** - Mediterranean fever (Acute)
  - **S** - Sarcoidosis

How to remember

- UCMS

CHRONIC GOUT

00:08:40



The main methods by which we can decrease uric acid are:

i. Decrease formation of uric acid

- Allopurinol
  - Inhibits xanthine oxidase
  - DOC for chronic gout
- Febuxostat
  - Inhibits xanthine oxidase

ii. Increase excretion of uric acid (Uricosuric drugs)

- Probenecid
- Sulfinpyrazone
- Benzbromarone
- Lesinurad
  - Plenty of fluids should be taken with these drugs
  - Not useful in renal failure

iii. Increase uric acid metabolism

- Rasburicase : Recombinant uricase
- Pegloticase : Long acting

RHEUMATOID ARTHRITIS

00:18:45

- Drugs used

NSAIDs or steroids	DMARDs or SAARDs
• Decrease pain & inflammation • No effect on disease progression • Fast acting	• Slows down the disease progression. So slows joint destruction • Slow acting

- DMARDs : Disease Modifying Anti Rheumatoid Drugs
- SAARDs : Slow Acting Anti Rheumatoid Drugs

DMARDs

DMARDS classification

Conventional DMARDS	Biological DMARDS
• Available since long time	• Formed by Biological methods like recombinant • DNA technology against some particular target

Conventional DMARDs:

Cute & - **C**hloroquine	DMARD of choice in pregnancy
P - **P**enicillamine	• Chelating agent • Used for CU poisoning/Wilson's disease
A - **A**zathioprine	
G - **G**old salts	
L - **L**eflunomide	Inhibit formation of pyrimidines by + Dihydroorotate dehydrogenase
I - **I**nhibitors of JAK	Tofacitinib Baricitinib
Malika - **M**ethotrexate	M.C used (D.O.C for RA)
Sherawat - **S**ulfasalazine	• Used in R.A. & U.C • Only DMART used as dis modifying agent in ankylosing spondylitis

How to remember

- Cute & PAGLI Malika Sherawat

Methotrexate 00:27:20

- It is used for RA and cancer

Cancer	RA
• High dose • - DHFRase (↓folic acid) • Cause megaloblastic anemia	• Low dose → 7.5 mg weekly • ↑ Extracellular adenosine ↓ • Anti – Inflammatory property

- Methotrexate can cause hepatotoxicity. So LFT should always be done.

Biological DMARDs"?" 00:29:39

- These include the drugs which
  - Inhibit TNF
  - Inhibit IL-1
  - Inhibit IL-6
  - Cause B-cell depletion
  - Co-stimulation inhibitors

I. Drugs which inhibit TNF

- These include MAb against TNF
- Drugs are
  - **A - A**dalimumab
  - **C - C**ertolizumab
  - **E - E**tanercept
  - **Inhibitor - Inf**liximab
  - **Goli : Goli**mumab
- All these drugs are given by Subcutaneous route, except Infliximab which is by I.V. route.

How to remember

- ACE inhibitor Ko Goli maro

- These drugs increase the risk of infections especially TB and Hep B. so they are C/I in patients of TB and Hep B.

ii. IL-1 receptor antagonists

- Drug is Anakinra

iii. IL-6 receptor antagonist

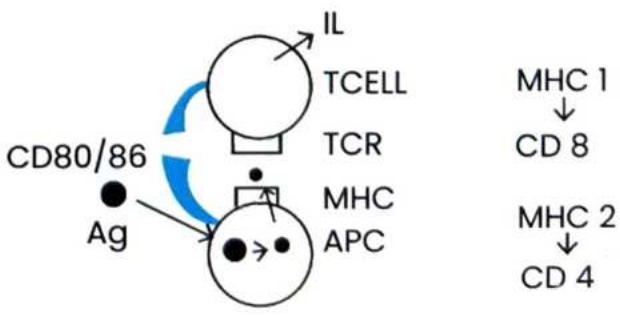
- Tocilizumab: Also approved for Cytokine Release Syndrome
- Sarilumab

iv. B-cell depletors

- Rituximab : Also used for Non-Hodgkin lymphoma and CLL

v. Co-stimulation inhibitors

- Abatacept
  - It inhibits the interaction of T-cell and Antigen presenting cell.



CLINICAL QUESTIONS

HISTAMINE AND SEROTONIN

Q. Which of the following drugs can cause hypotension by release of histamine from mast cells?

A. Aspirin
B. Procaine
C. Morphine
D. Sulfadiazine

Answer: C

Solution

Basic drugs like **morphine, d-TC(tubocurarine) and amphotericin B etc**. act as histamine liberators and can cause acute reaction leading to itching and hypotension.

Q. Selective 5-HT4 agonist useful in gastroesophageal reflux disease and lacking arrhythmogenic property is:

A. Buspirone
B. Sumatriptan
C. Cisapride
D. Tegaserod

Answer: D

Solution

- Both cisapride and tegaserod are selective 5HT4 agonists useful in the treatment of GERD.
- Cisapride possesses cardiac K+ channel blocking activity and can lead to torsades de pointes. **Tegaserod is devoid of this adverse effect.**
- However, **tegaserod has recently been withdrawn due to increased risk of MI and stroke.**

MIGRAINE

Q. After taking some drug for acute attack of migraine, a patient developed nausea and vomiting. He also developed tingling and numbness on the tip of the finger that also turned blue. Which of the following is the most likely drug implicated in causing the above findings?

A. Dihydroergotamine
B. Sumatriptan
C. Aspirin
D. Butorphanol

Answer: A

Solution

- This is a classical sign of ergot induced vasoconstriction.
- Dihydroergotamine can be used for acute attack of migraine and can result in these symptoms.
- **Due to their vasoconstricing potential, ergot alkaloids are contra-indicated in a patient with peripheral vascular disease. These may also lead to development of gangrene.**

Contraindications for ergotamine usage:

- Peripheral vascular disease
- Coronary artery disease
- Uncontrolled hypertension
- Fever and/or sepsis
- Pregnancy
- Within 24 hours of using triptans

Q. Drug of choice for acute severe migraine is:

A. Methysergide
B. Sumatriptan
C. Ergotamine
D. Propranolol

Answer: B

Solution

- Drug of choice for mild to moderate attacks of migraine is **NSAIDs like paracetamol and aspirin etc.**
- Drug of choice for acute severe migraine are **triptans like sumatriptan.**
- Drug of choice for prophylaxis of migraine is **propranolol.**

PGs, LTs AND NSAIDs

Q. All of the following effects are produced by inhibitors of prostaglandin synthesis EXCEPT:

A. Prolongation of bleeding time
B. Prolongation of prothrombin time
C. Prolongation of labour
D. Gastric mucosal damage

Answer: B

Solution

- **Prothrombin time is increased by the drugs interfering with the coagulation pathway (e.g. warfarin).**
- As COX has no role in coagulation, inhibitors of PG synthesis do not prolong PT.
- However, bleeding time (BT) is prolonged by the drugs interfering with platelet function.
- Aspirin increases BT by acting as an antiplatelet agent.

Q. Which of the following prostaglandin analogue is used for treatment of primary open angle glaucoma?

A. PGI_2
B. PGD_2
C. PGE_2
D. PGF_{2alpha}

Answer: D

Solution

- Prostaglandin analogues such as latanoprost (PGF_{2alpha}) is the drug of choice for primary open angle glaucoma. It acts by increasing the uveosacral outflow.
- Use of latanoprost can be associated with adverse effects like pigmentation of iris (heterochromia iritis) and growth of eye lashes (hypertrichosis).

GOUT AND RA

Q. A drug X is useful in the treatment of rheumatoid arthritis. It is available only in parenteral formulation and its mechanism of action is antagonism of tumor necrosis factor. Which of the following can be X?

A. Cyclosporine
B. Penicillamine
C. Phenylbutazone
D. Etanercept

Answer: D

Solution

- **Infliximab** and **Etanercept** are TNF-αantagonists useful for the treatment of rheumatoid arthritis.
- These are administered by parenteral route.
- TNF-α antagonists can **cause reactivation of latent tuberculosis.**

Phenylbutazone -can precipitate the acute attack of asthma

Q. Which of the below mentioned options is the most common dose limiting adverse effect of colchicine used in treatment of Gouty arthritis?

A. Sedation
B. Kidney damage
C. Diarrhea
D. Muscle paralysis

Answer: C

Solution

- **Colchicine** is the **most effective drug** for **acute attack of gout.**
- However, it is used for patients not responding to NSAIDs because of its adverse effects.
- **Diarrhea and myopathy** are **major adverse effects.**

LEARNING OBJECTIVES

UNIT 13: ANAESTHESIA

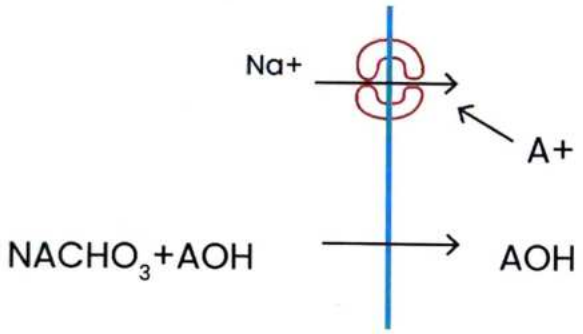
- Local anaesthesia
  - Infiltration anaesthesia
  - Esters and Amides
- General anaesthesia
  - Inducing agents
  - Inhalational agents
  - MAC
  - Boyle's machine
- Skeletal muscle relaxants
  - Central vs Peripheral
  - Hoffman elimination
  - Reversal agents

78 LOCAL ANESTHETICS

- In Anaesthesia, there are 3 main types of drugs:
  - Local anaesthesia
  - Skeletal muscle relaxants
  - General anaesthesia

LOCAL ANAESTHETC AGENTS

00:01:03



- Local anaesthetics cross the membrane in un-ionized [illegible] and they block the Na^+ channels in ionized form
- Local anaesthetics are mainly of 2 types:
  - Esters
  - Amides

Esters	Amides
• Cocaine	• Lignocaine
• Procaine	• Bupivacaine
• Chlorprocaine	• Prilocaine
• Tetracaine	• Etidocaine
• Benzocaine	• Ropivacaine
	• Dibucaine

- Only LA causing vasoconstriction → Cocaine
- MC used LA → Lignocaine
- Shortest acting LA → Chlorprocaine
- LA causing methemoglobinemia → Prilocaine
- Max. cardiotoxic → Bupivacaine

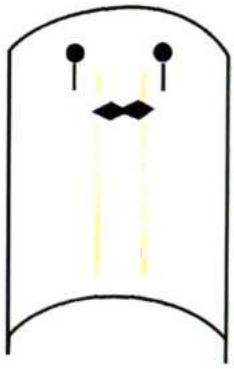
Infiltration Anesthesia

00:06:28

- Short acting
- Systemic adverse effects

} d/t entry into blood

- Adrenaline / Epinephrine are added for long action
- Adrenaline in conc. 1:100000-1:200000
- Adrenaline should not be added to local anesthetic in those area where end arteries are present
- End arteries are present in
  a. Pinna of ear
  b. Tip of nose
  c. Tip of finger
  d. Penis



- Vasoconstriction at end arteries will cause ischemia of distal portion of constricted part.

79 GENERAL ANAESTHETICS

- General anaesthetics are the drugs which are used to make the person unconscious. This is done by giving the drug by I.V. route mainly
- So, GA agents are mainly of 2 types:
  - **Inducing** agents: I.V. route
  - **Maintenance** agents: Inhalational route

INDUCING AGENTS 00:01:30

- Thiopentone
- Ketamine
- Propofol
- Etomidate

1. Thiopentone 00:02:00

- Highly lipid soluble
- It can very quickly cross the blood vessels and enter the neurons
- So it is has very fast action
- We start giving it and ask the patient to count to 10.
- But it very short acting due to Redistribution, which means that 1st it is distributed to the brain and then it is distributed to less vascular areas outside the brain. So its action stops.

2. Propofol 00:04:09

- DOC for day care surgery
- Propofol injection is painful
- **Other drugs** used in **Day care Surgery:**
  - **Dr**- **D**esflurane
  - **Manmohan** - **M**idazolam
  - **Singh** - **S**evoflurane
  - **Is** - **Is**oflurane
  - **A** - **A**lfentanil
  - **Prime** - **P**ropofol
  - **Minister** - **M**ivacurium

How to remember

- Dr Manmohan Singh Is A Prime Minister

3. Etomidate

- Agent of choice for CVS surgery
- Causes adrenal suppression

4. Ketamine 00:07:15

- **K** - Agent of Choice in Kids
- **E** - Emergence Reaction
- **T** -Thalamo-Cortical junction (site of action) (Dissociative Anaesthesia)
- **A** - Analgesic
- **M** - Meals (can be given full stomach)
- **I** - ↑BP / IOP/ICP (so Agent of Choice in Shock)
- **N** - NMDA # (so avoided in Glaucoma)
- **E** - Excellent bronchodilator

INHALATIONAL AGENTS 00:11:10

- These drugs include:
  - Ether
  - Chloroform
  - Cyclopropane
  - Trilene

  } Inflammable (so Cautery is C/I with these drugs)

  - N_2O
  - Halothane
  - Enflurane
  - Isoflurane
  - Sevoflurane
  - Desflurane
  - Methoxyflurane
  - Xenon

  } Non-inflammable

MAC (Minimum Alveolar concentration) 00:13:39

- Minimum concentration of the agent required in alveoli to produce anaesthesic effect
- MAC is inversely proportional to Potency
- If MAC is max → Potency is least. Seen in N_2O and Xenon
- If MAC is min → Potency is max. Seen in Methoxyflurane
- **N_2O** has MAC of 104%. So even if we give 100% of this agent, it will not produce anaesthetic effect. So N_2O is used as a supplemental agent. It is rather used as an analgesic and muscle relaxant.

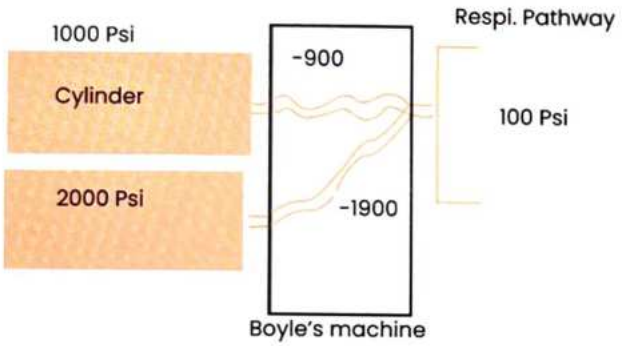
Blood Solubility 00:17:18

- Blood solubility of an agent is inversely proportional to the speed of anaesthesia
- Blood solubility $\alpha \frac{1}{\text{speed of action}}$
- More soluble drug will be slow acting and vice versa
- Blood solubility is measured by a parameter called Blood Gas Partition coefficient

BGPC

Highest (so slowest acting)	Lowest (so fastest acting)
↓	↓
Methoxyflurane	Xenon > Desflurane

BOYLE'S MACHINE 00:19:33



- Boyle's machine is useful to reduce the pressure of anaesthesic agents. This is because the anaesthetic agent is in a high pressure state inside the cylinder and this pressure can damage the respiratory pathway, leading to barotrauma.
- This machine contains many tubes which reduce the pressure by different amounts.
- Safety measures to prevent the wrong cylinder from connecting are:
  - Color coding
  - Pin Index safety system

1. Color Coding

- **N_2O**: Blue (NEELA)
- **Cyclopropane**: Orange (SANTRI)
- **O_2**: Black and white
- **Entonox**: Blue and White
  - (N_2O+ O_2)
  - 50% 50%

2. Pink Index system

- **Air**: 1,5
- **O_2**: 2,5
- **N_2O**: 3,5
- **CO_2** >7.5%: 1,6
- **CO_2** >7.5%: 2,6
- **Cyclopropane**: 3,6
- **Entonox**: 7

GENERAL PROPERTIES OF ANAESTHETIC AGENTS 00:28:18

- **N_2O** → MAC is 104%
- **Halothane**
  - Risk of hepatitis
  - Sensitizes the heart to Adrenaline
  - C/I in Pheochromocytoma Surgery
  - Tocolytic effect
- **Enflurane**: Max seizures seen with it. So it is C/I in epilepsy
- **Isoflurane**
- **Sevoflurane**

} Safe in CVS / CNS patients

- **Methoxyflurane**: Most potent agent but slowest acting. Also, it is Nephrotoxic
- **Desflurane**: Max irritation to respiratory pathway
- **Xenon**: Ideal anaesthetic agent. This is because of the following properties:
  1. Anaesthesic property
  2. Analgesic property
  3. Muscle relaxant action
  4. Fastest induction and recovery
  5. Smooth induction
  6. Safe drug
     - But one drawback is that Xenon is not easily available and has to be made in the laboratory. This makes it very costly.

80 SKELETAL MUSCLE RELAXANTS

- Skeletal muscle relaxants are of 2 main types
  - Centrally acting
  - Peripheral acting

CENTRAL MUSCLE RELAXANTS 00:01:12

- These act within the CNS
- They mainly depress the CNS
- Drugs included are:
  - **$GABA_A$ (+):** Diazepam
  - **$GABA_B$ (+):** Baclofen
  - **$_2$ (+):** Tizanidine
  - **Inhibit polysynaptic reflexes**
    - → Mephensin
    - → Chlorzoxazone
    - → Thiocholchicoside

PERIPHERAL MUSCLE RELAXANTS 00:03:26

1. Directly Acting on the muscle

- Dantrolene
  - It acts by blocking the Ryanodine receptors in the ER
  - Used for Malignant hyperthermia and Neuroleptic malignant syndrome
  - It is Hepatotoxic

2. Neuro Muscular Junction blocker (NMJ #) / Indirectly Acting

- These are of 2 main types:
  - Depolarizing muscle relaxants / Non – competitive MR
  - Non depolarizing muscle relaxants / Competitive MR

a. Depolarizing MR / Non-competitive MR:

- Succinyl choline
  - → It is the shortest acting MR (<5 min)
  - → C/I in nerve & muscle injuries (as it can cause severe hyperkalemia)
  - → Hyperthermia (can precipitate malignant hyperthermia)
  - → Fasciculations
  - → Responsible for post operative muscle pain (Post operative muscle rigidity is caused by Fentanyl group of drugs)

b. Non-Depolarizing / Competitive MR:

- D- Tubocurarine (Curare)
  - → Do not cause post op muscle pain
  - → But it causes release of Histamine
  - → It causes Severe bronchoconstriction and Hypotension due to histamine
  - → So, we developed new drugs with less or no histamine release:

Curium (release Less histamine)	Curonium (No histamine is released)
• Atracurium • Cis-atracurium • Mivacurium (Shortest acting among these)	• Pancuronium • Pipecuronium • Vecuronium • Recuronium • Rapacuronium

- **MR of choice** in a patient of **Bronchial Asthma** is Curonium drugs
- **Atracurium** and **Cis-atracurium** undergo Hoffman's elimination

HOFFMAN'S ELIMINATION 00:13:49

- Normally a drug is metabolized by liver to become inactive or excreted by kidney.
- But in these drugs, there is spontaneous, non-enzymatic inactivation which occurs by molecular rearrangement. This is called Hoffman's elimination
- Shown by Atracurium & Cis-atracurium
- **MR of choice** in Liver and Renal disease

Atracurium	Cis-Atracurium
• Releases Histamine • Some amount is metabolized by liver also, which generates a metabolite called Laudanosine • This metabolite can cause seizures	• Negligible release of Histamine • Undergoes 100% Hofmann elimination. So, no risk of seizures

Gantacurium

- Not yet approved by FDA
- Shortest and fastest acting (around 10 min) non-depolarizing muscle relaxant

REVERSAL AGENTS

⏱ 00:17:15

- They are used to reverse the action of NDMR after surgery
- These include:
  - Neostigmine
  - Suggamadex

Reversal Agents

Neostigmine	Suggamadex
• Stimulates ○ N_M Receptors: Reverse the action of NDMR ○ M_1, M_2, M_3 receptors: → Produces cholinergic S/E → Atropine stops these S/E	• Directly binds to muscle relaxant and removes them from N_M receptor. • Also called Selective Relaxant Binding Agent (SRBA) • Faster acting than neostigmine • Higher risk of allergy

CLINICAL QUESTIONS

LOCAL ANAESTHESIA

Q. A 33 year old male comes in to your clinic with a 4.5cm long superficial cut wound. You decide to suture it yourself, take consent and ask the nurse to bring a local anaesthetic. Which of the following, though has the longest action, would not be your primary choice as it is the most toxic local anaesthetic?

A. Procaine
B. Chlorprocaine
C. Lignocaine
D. Dibucaine

Answer: D

Solution

- Longest acting, **most potent and most toxic** LA is **dibucaine**.
- **Chlorprocaine** is the **shortest acting** LA.

Q. The eutectic mixture approved for use, lignocaine-prilocaine, has which of the following unique as unique property?

A. It causes motor blockade without sensory block
B. By surface application, it can anaesthetize unbroken skin
C. It is not absorbed after surface application
D. It has strong vasoconstrictor action

Answer: B

Solution

- Lignocaine or prilocaine cannot anaesthetize intact skin.
- **Eutectic mixture** is the combination of equal proportions of **lignocaine and prilocaine at 25 °C**.
- This mixture has a lower melting point than any of the two ingredients. It helps to make the preparation oily that **can be applied on the intact skin**.
- It has a concentration of 2.5% each with a contact period of 1 hour.
- Eutectic mixture can be used to anaesthetize intact skin.

Q. Ether is still used as a general anaesthetic in India, specially in peripheral hospitals because:

A. It is non-explosive
B. It is pleasant smelling and non irritating
C. It induces anaesthesia rapidly
D. It is cheap and can be administered without anaesthetic machine

Answer: D

Solution

- Ether is the only **complete anaesthetic agent**.
- It is **highly inflammable and explosive**.
- It has **good analgesic** and **muscle relaxant** action.
- It can be delivered by **open method**.
- It is a **pungent smelling** liquid.
- **Induction** of anaesthesia with ether **is quite slow**.

All the four stages can be seen.

Q. Of the different induction agents, ketamine is the preferred anaesthetic of choice for all of the below mentioned cases, except?

A. Emergency procedure on a 66 year old hypertensive
B. Trauma cases that have bled significantly
C. Dressing of burn wounds
D. Short operations on asthmatics

Answer: A

Solution

- **Ketamine** is **contra-indicated in hypertensives** because it increases the blood pressure.
- It is the **induction agent of choice** for:
  - Asthmatics
  - Shock
  - Children
  - Patients with full stomach
- It possesses very powerful analgesic action.
- It can be used as a sole agent for minor procedures.

Q. Of the neuromuscular blockers, the drug pancuronium differs from the drug d-tubocurarine in that:

A. It is a depolarizing blocker
B. Its action is not reversed by neostigmine
C. It can cause rise in BP on rapid I.V. injection
D. It causes marked histamine release

Answer: C

Solution

- **Pancuronium** possesses **vagolytic activity** and can cause **hypertension and tachycardia** on rapid i.v. injection.
- Pancuronium is a competitive NM blocker (Non-depolarizing NM blocker).
- Its actions can be reversed by anticholinesterases like neostigmine.
- Unlike d-TC, histamine release is not seen with pancuronium.

Q. The most rapidly acting nondepolarizing neuromuscular blocking agent which can be used as an alternative to succinylcholine for tracheal intubation is:

A. Rocuronium
B. Pancuronium
C. Doxacurium
D. Pipecuronium

Answer: A

Solution

- **Rocuronium** is the **fastest acting** Non-depolarizing muscle relaxant (**NDMR**). It can be used for the rapid sequence endotracheal intubation in patients having contra-indications to the use of SCh.
- **Mivacurium** is the **shortest acting NDMR**.
- **SCh** is the **shortest and fastest acting** skeletal muscle relaxant. It is a **depolarizing NM blocker**.

LEARNING OBJECTIVES

UNIT 14: MISCELLANEOUS

- Chelating agents
  - Heavy metal poisoning
  - Uses
- Hyperkalaemia

81 CHELATING AGENTS

- Chelating agents are used for treatment of heavy metal poisoning
- Various chelating agents are:

1. **BAL (British Anti Lewisite) / Dimercaprol** ⏱ 00:00:34

- **Uses** are:
  - **B** - Bismuth poisoning
  - **A** - Arsenic poisoning
  - **L**: - Lead poisoning
- **C/I** are:
  - Cadmium poisoning
  - Iron poisoning

2. **EDTA (Calcium Di-sodium EDTA)**

- **Uses**:
  - **M** - Manganese poisoning
  - **I** - Iron poisoning
  - **L** - Lead poisoning
  - **K** - Cadmium poisoning

3. **D-Penicillamine**

- **Uses**: Copper poisoning (Wilson disease)

4. **Iron chelating agents**

- Desferrioxamine
  - Injectable
  - Used for Acute Iron poisoning
- Deferipirone
  - Oral
  - Used for Chronic Iron overload

82 HYPERKALEMIA

Hyperkalemia treatment

Acute Hyperkalemia

1. Salbutamol
2. Glucose + Insulin (DOC)
3. Calcium gluconate: Only indicated when ECG changes are seen

Chronic Hyperkalemia

- Potassium binding Resins:
  a. Patiromer
  b. Polystyrene sulfonate: These are Na^{+}-Ca^{2+} exchangers

CLINICAL QUESTIONS

CHELATING AGENTS

Q. Which of the following chelating agent is not used in lead poisoning

A. EDTA
B. CUPRIMINE
C. DMSA
D. DESFERRIOXAMINE

Answer: D

Solution

Chelating agent used in lead poisoning

a. EDTA
b. CUPRIMINE
c. DMSA
d. BAL
e. DMPS

HYPERKALAEMIA

Q. A patient is brought in to the ED by his brother, who claims that the patient has had a high temperature since yesterday and has not passed urine in the past few hours. On evaluation, patient was noted to have a temperature of 40 C, RR of 22 cycles/min, BP 94/66 mmHg and HR 104 beats/min. Blood work up was done, revealing en elevated potassium levels. You suspect AKI secondary to septic shock. Which of the following cannot be used in emergency treatment of acute hyperkalemia?

A. Calcium gluconate
B. Salbutamol
C. Glucose-Insulin
D. Intravenous magnesium sulphate

Answer: D

Solution

Treatment of Hyperkalemia

- IV Ca gluconate

- Insulin drip
- Salbutamol (nebulization)
- IV Furosemide
- Hemodialysis

Q. Amiloride can cause hyperkalemia due to its action on:

A. Electrogenic K+ channels
B. Electrogenic Na+ channels
C. Non electrogenic Na+-Cl– symporter
D. H+-K+-ATPase

Answer: B

Solution

Amiloride and triamterene are **K^+ sparing diuretics** that **act by inhibiting epithelial Na^+ channels.**

- In the distal tubules and collecting ducts, three separate channels are present (one for Na^+, K^+ and H^+ each). Aldosterone acts on DCT and CD to cause reabsorption of Na^+.
- This generates a lumen negative potential difference across the membrane of this part of the nephron. To maintain the electric neutrality, K^+ and H^+ are secreted in the lumen.
- When amiloride and triamterene inhibits epithelial Na^+ channels, transepithelial potential difference is not generated and therefore K^+ and H^+ are not secreted in the lumen.
- Thus due to more retention of K^+, amiloride may result in hyperkalemia.

LEARNING OBJECTIVES

UNIT 15: CONTROVERSIAL QUESTIONS

83 CONTROVERSIAL QUESTIONS

MENINGOCOCCAL MENINGITIS

- **Treatment**
  1. Empirical treatment: DOC is Ceftriaxone
  2. Definitive Treatment: DOC is Penicillin G
- **Chemoprophylaxis**
  1. Ceftriaxone: most effective
  2. Ciprofloxacin: for masses. Cannot be given in pregnancy and children

NEUROSYPHILIS

- For all other syphilis except neurosyphilis is Benzathine Penicillin G
- For Neurosyphilis, we give
  - Penicillin G (crystalline)
  - Procaine Penicillin G

PLAGUE

- **Treatment:** DOC is Streptomycin / Gentamycin
- **Prophylaxis:** DOC is Doxycycline

CHOLERA

- DOC is Doxycycline
- But it cannot be given in pregnancy and children less than 8 years old. For them we give Azithromycin
- Prophylaxis: Doxycycline

PSEUDO-MEMBRANOUS COLITIS

- It is **caused by:**
  - 3rd gen Cephalosporins
  - Clindamycin
  - Aminopenicillins
  - FQ
- **Treatment**
  - DOC is Oral Vancomycin
  - Max relapse reduction caused by Fidaxomicin

CYANIDE POISONING

- Antidotes
  1. Amyl nitrite: Inhalational route
  2. Hydroxocobalamin: IV route
- Amyl nitrite produces an intermediate which is toxic. To detoxify this intermediate, we add Thiosulfate.

LITHIUM LEVELS

1. **For prophylaxis:** 0.5 – 0.8 mEq/L
2. **For treatment:** 0.8 – 1.2 mEq/L
3. **Toxic levels:**

- More than 2.0 mEq/L
- Dialysis required at More than 4.0 mEq/L

TOURETTE SYNDROME

- It is characterized by tics
- Drugs used:
  - Clonidine / Guanfacine (MC used)
  - Anti-psychotics: Haloperidol, Risperidone (for Severe Tics, not controlled by other drugs)
  - Tetrabenazine (DOC)

ABSENCE SEIZURES

- Drugs used: Ethosuximide and Valproate
- DOC is Valproate (acc to textbooks)

GTCS

- DOC is Valproate
- For FOCAL SEIZURES: DOC is Carbamazepine
- For Focal seizures in elderly: DOC is Lamotrigine

GLAUCOMA

- **Open** angle: DOC is Latanoprost
- **Closed** angle: DOC is Pilocarpine (local drug); Acetazolamide (oral drug)
- **Acute congestive**: DOC is Mannitol

LEISHMANIASIS

- **Visceral leishmaniasis (Kala azar):** DOC is L-AMB (IV)
- **Muco-cutaneous leishmaniasis:** DOC is L-AMB
- **Cutaneous leishmaniasis (Dermal/ PKDL):** DOC is Miltefosin (oral)

INFANTILE SPASMS

- DOC is ACTH
- But if it occurs along with Tuberous sclerosis, DOC is Vigabatrin

SENSITIVITY OF NERVE FIBRES TO LA

- **Peripheral nerves:** A > B > C
- **Spinal nerves:** B > C > A
- If not mentioned, whether peripheral or spinal, follow acc to peripheral.

VRSA

- DOC is Daptomycin (except for Pneumonia)
- For Pneumonia caused by VRSA: DOC is Linezolid

ACUTE MANIA

- Best treatment: Lithium + Antipsychotics
- But if both are given as separate options: DOC for acute mania is Antipsychotics

CARRIERS OF AMOEBIASIS

- 1st line drugs are: Diloxanide furoate (India) and Paromomycin (USA)

CYTOPLASMIC AND NUCLEAR RECEPTORS

- **Nuclear receptor superfamily:** Receptors which act through nucleus
- In cytoplasm, the receptors are
  - **C:** Corticosteroids
  - **D:** Vit D
- In nucleus, receptors are:
  - **S:** Sex hormones (E, P, T)
  - **A:** Vit A
  - **T:** Thyroid hormones
  - PPAR

ENTERIC FEVER

- DOC is Ceftriaxone
- It is safe in pregnancy
- It cannot be given orally
- Drugs used orally are: Cefixime and Ciprofloxacin

POST EXPOSURE PROPHYLAXIS OF HIV

- Three drugs are used for 28 days: T + L + PI

PHASE 1 CLINICAL TRIALS

- Major aim is to know the: Maximum tolerable dose > Dosing > PK > Safety

NEW TB GUIDELINES

- For both Category 1 and Category 2, treatment is same.
- It is: 2 HRZE + 4 HRE for 6 months

NEW LEPROSY GUIDELINES

- Treatment for both multi and pauci-bacillary leprosy
- The only difference is the duration.
- For multi-bacillary leprosy, the treatment is given for 12 months
- For pauci-bacillary leprosy, the treatment is given for 6 months

MISOPROSTOL

- Chemically it is PGE1
- It works exactly similar to endogenous PGE2

ANAPHYLACTIC SHOCK

- DOC is Adrenaline via I.M. route. Dose is 0.5 ml (1:1000)

TAMSULOSIN

- It is $\alpha_{1A/1D}$ blocker

NSAIDs INDUCED PEPTIC ULCER

- DOC is PPI
- Most specific drug is Misoprostol

DOPAMINE DOSES

- **Low dose:** D1 (< 2 microgram/kg/min)
- **Intermediate dose:** β1 (2-10 microgram/kg/min)
- **High dose:** α1 (> 10 microgram/kg/min)

HYPERTENSION

- DOC for:
  1. **HTN:** Thiazides
  2. **HTN in pregnancy:** Labetalol
  3. **Emergency:** Nicardipine
  4. **Emergency in pregnancy:** Labetalol

PULMONARY HTN

- DOC is Endothelin antagonists like Bosantan
- Most effective drug is PG like Iloprost
- MC used drug is Warfarin

ESOPHAGEAL VARICES

- Drugs used:
  - Octreotide
  - Terlipressin
- Terlipressin > Octreotide

HYPERTHYROIDISM IN PREGNANCY

- DOC in:

- 1st trimester: PTU
- 2nd / 3rd trimester: Carbimazole/ Methimazole

THYROID STORM

- DOC is Propranolol
- Antithyroid DOC is PTU

PARKINSONISM

- DOC is Pramipexol / Ropinirole
- Most effective drug is Levodopa + Carbidopa
- DOC for drug induced parkinsonism is Benzhexol / Promethazine

EPILEPSY IN PREGNANCY

- DOC for Eclampsia is $MgSO_4$
- **Epilepsy in pregnancy:**
  - Female already controlled on some drug therapy: Continue the same therapy, do not change
  - For starting drug treatment in pregnancy: DOC is Lamotrigine / Levetiracetam

MAINTENANCE IN OPIOIDS

- Maintenance in Addiction: DOC is Methadone
- Maintenance in Poisoning: DOC is Naltrexone

NALTREXONE AND CRAVING

- Naltrexone decreases Alcohol craving
- It does not decrease Opioid craving

WARFARIN INDUCED BLEEDING

- DOC is: Four Factor Complex / Prothrombin complex > Fresh frozen plasma > Whole blood
- For Bleeding Tendency, we give Vit K

MECHANISM OF LMWH

- **UFH:** Inhibits both factor 2a and 10a
- **LMWH:** only 10a
- **Fondaparinux:** only 10a

URETHRITIS

- **Gonococcal urethritis:** DOC is Ceftriaxone
- **Non-gonococcal urethritis:** DOC is Azithromycin
- For both **Gonococcal + NGU:** DOC is Azithromycin

LEARNING OBJECTIVES

UNIT 16: COVID-19

- COVID-19
- Drug updates for COVID-19

84 COVID-19

- Novel corona virus
- Likely originated from bats
- Family contains:
  - SARS CoV
  - MERS CoV
  - SARS CoV2

Pathogenesis

Refer Diagram 84.1

Drugs

I. Virus entry inhibitors

- Drugs include:
  - Chloroquine and hydroxychloroquine
  - Umifenovir
  - Camostat

Chloroquine / HCQ:

- Inhibit glycosylation of ACE-2
- Inhibit proteolytic processing of S2
- Decrease cytokine production
- Inhibit lysosomal activity
- Adverse effects:
  - QT prolongation
  - Hypoglycemia
  - Retinopathy
  - Hemolysis in G6PD def
- C/I in allergy and retinal defects

Umifenovir

- Inhibits endocytosis
- Approved for influenza
- Adverse effects:
  - GI upset
  - Increases transaminases

Camostat / Nafamostat:

- Inhibits TMPRSS-2
- Approved for pancreatitis
- Given by IV route

II. Change in Endosomal pH

- Drugs include **HCQ**
- Makes the pH alkaline and inhibits fusion

III. RdRP inhibitors

- Drugs include:
  - Remdesivir
  - Galidesivir
  - Favipiravir
  - Ribavirin

Remdesivir / Galidesivir:

- Adenosine analogue
- Prodrug
- Given by IV infusion
- Adverse effects:
  - Reversible increase in transaminases
  - Kidney injury

Favipiravir

- Purine analogue
- Dose adjustment required in liver disease
- Adverse effects:
  - Diarrhoea
  - Hyperuricemia
  - Increases transaminases
  - Neutropenia

Ribavirin:

- Guanine analogue
- Required in very high doses
- Adverse effects
  - Hemolytic anemia
  - Hepatotoxicity
  - Teratogenicity

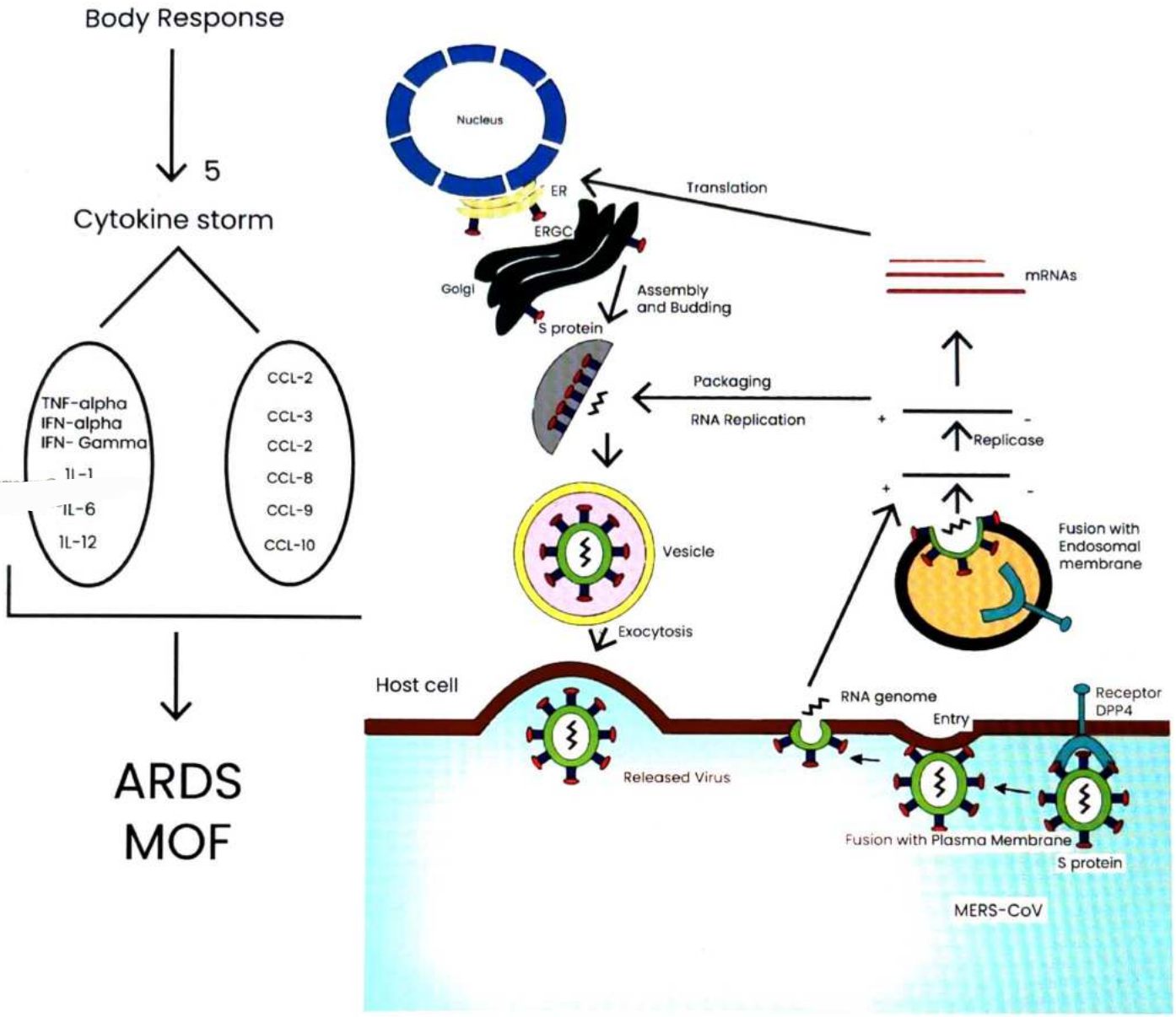
IV. Importin inhibitors

- Drugs include **Ivermectin**
- Used as anti-helminthic and also used for scabies
- Adverse effects:
  - CNS side effects like ataxia, drowsiness

V. Immunomodulators

- Corticosteroids are the only drugs with mortality benefits
- **IL-6 antagonists**: Sarilumab, Tocilizumab
- **Anti VEGF**: Bevacizum
- Convalescent plasma

Diagram 84.1


Body Response
5
Cytokine storm
TNF-alpha
IFN-alpha
IFN- Gamma
IL-1
IL-6
IL-12
CCL-2
CCL-3
CCL-2
CCL-8
CCL-9
CCL-10
ARDS
MOF
Nucleus
ER
ERGC
Golgi
Translation
mRNAs
Assembly
and Budding
S protein
Packaging
RNA Replication
Replicase
Vesicle
Exocytosis
Fusion with
Endosomal
membrane
Host cell
RNA genome
Entry
Receptor
DPP4
Released Virus
Fusion with Plasma Membrane
S protein
MERS-CoV

85 DRUG UPDATES FOR COVID-19

- Latest guidelines for treatment

Category	Mainstay Treatment
Asymptomatic	No Medication
Mild (No SOB, RR < 24, SpO2 > 94%)	Anti-pyretic Anti-tussive Inhalational budesonide (800 mcg BD for 5 days)
Moderate (SOB, RR 24-30, SpO2 90-93%)	Oxygen support (to maintain SpO2 above 92%) Steroids (if SpO_2 is less than 92%) Prophylactic anticoagulants Other therapies depending upon investigation
Severe (SOB, RR > 30, SpO2 < 90%)	Oxygen support (to maintain SpO2 above 90%) Steroids Prophylactic anticoagulants Other therapies depending upon investigations

STEROIDS

- Steroids are the only mortality reducing drug
- Harmful in asymptomatic and mild cases
- Recommended dose:
  - Dexamethasone 6mg OD
  - MPS 32mg OD
  - Prednisolone 40mg OD
  - Hydrocortisone 50mg TDS
- They decrease immunity and thus increase the risk of infections like Mucormycosis
- They cause Hyperglycemia, so monitoring blood sugar level is very important
- **Mucormycosis**:
  - Life threatening condition
  - DOC is L-AMB by IV route
  - Oral drugs: Posaconazole and Isuvaconazole
  - Solution of L-AMB is made in 5% dextrose

REMDESIVIR

- Not recommended for mild cases
- Only FDA approved drug for COVID-19
- Indications
  - Selected cases of moderate to severe COVID-19 patients
  - Hospitalized patients
  - On oxygen therapy
  - Should be used within 10 days of disease onset, after that it won't provide any benefits
- MOA
  - Inhibits RdRP
  - Monitoring of KFT, LFT and PT is required
  - Avoid if eGFR < 30 ml/min or ALT > 5 times
  - Can be combined with Baricitinib
- Adverse effects
  - Anaphylaxis
  - Infusion related reactions
  - Nausea

TOCILIZUMAB

- MAb against IL-6
- Used for Cytokine Release syndrome
- Indications:
  - Only in severe to critically ill patients
  - No improvement of oxygen requirement after 24-48 hrs of steroids
  - Raised CRP > 75 mg/L
  - No bacterial, fungal or TB infections present
- Dose: 8 mg/kg (max) by IV route
- Avoided in:
  - Immunosuppressive patients
  - Liver disease
  - High risk of GIT perforation
  - ANC < 500 cells/mcL
  - Platelet count < 50000 cells/mcL

MONOCLONAL ANTIBODIES

- Drugs included
  - Bamlanivimab
  - Bamlanivimab + Etesevimab
  - Casirivimab + Imdevimab
- These are MAb against Spike protein
- Given EUA by FDA
- Given IV for OPD patients
- Not given to hospitalized patients

BARICITINIB

- JAK inhibitor
- Dose adjustment is required in renal and hepatic diseases
- Increased risk of thromboembolism
- Used along with Remdesivir (when steroids cannot be used)

ANTICOAGULANTS

- Drugs include:
  - UFH
  - LMWH
  - Fondaparinux
- They act by activating antithrombin
- So inhibit factor 10a and 2a

2-DEOXY-D-GLUCOSE

- Approved by DCGI and developed by DRDO
- It is a glucose molecule in which the 2 hydroxyl groups have been replaced by hydrogen, so that it cannot undergo further glycolysis
- So it acts by inhibiting glycolysis at the 2nd step
- Given EUA by DCGI for moderate to severe cases, as an adjunct to reduce oxygen requirement

THERAPIES NOT RECOMMENDED NOW

- Chloroquine / HCQ
- Ivermectin
- Azithromycin
- Colchicine

CLINICAL QUESTIONS

COVID-19

Q. Which of the following is true about the novel antiviral drug Remdesivir?

A. Was developed during the MERS outbreak in 2012
B. An adenosine analog, interferes with the action of viral RNA-dependent RNA polymerase and causes decrease in viral RNA production
C. Drug of choice for the treatment of pneumonia caused by SARS-CoV-2
D. It is an FDA approved drug for COVID-19

Answer: B

Solution

Remdesivir

- Novel antiviral agent developed by Gilead Sciences
- First developed as an antiviral against Ebola virus during the 2014 outbreak in West Africa.
- Adenosine analog
- Interferes with the action of the **viral RNA dependent RNA polymerase**
- Evades proof reading by the viral exoribonuclease causing decrease in viral RNA production.
- Promising results in animal studies for MERS-CoV and SARS, suggesting it may have some effects in patients with COVID-19.
- Dose being studied is 200mg IV on day one followed by 100mg IV once daily for 4 to 9 days.

Currently Remdesivir has received investigational new drug (IND) status and several clinical trials are ongoing on patients with SARS-CoV-2 infection.

Q. WHO declared COVID- 19 as Global pandemic on:

A. 11th Feb 2020
B. 11th March 2020
C. 30th Jan 2020
D. 15th March 2020

Answer: B

Solution

Origin- Wuhan, China

- 1st Dec, 2019- 1st case was reported
- 1st Jan, 2020- Wuhan seafood market was closed
- 7th Jan, 2020- Chinese health authority identifies Novel Corona virus
- 30th Jan, 2020- 1st case reported in India (Kerala); WHO declared it as Health emergency of international concern
- 11th Feb, 2020- Name COVID-19 by WHO
- 11th March, 2020- WHO declared COVID- 19 as global pandemic

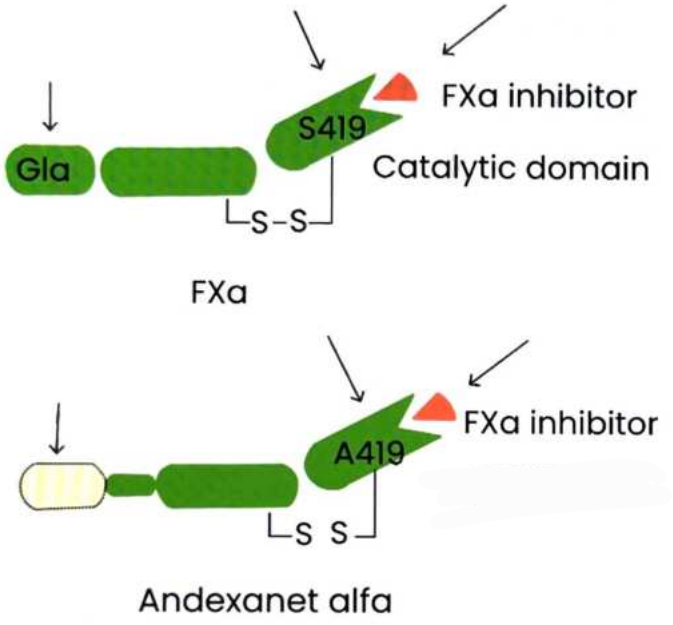
LEARNING OBJECTIVES

UNIT 17: DRUG UPDATES

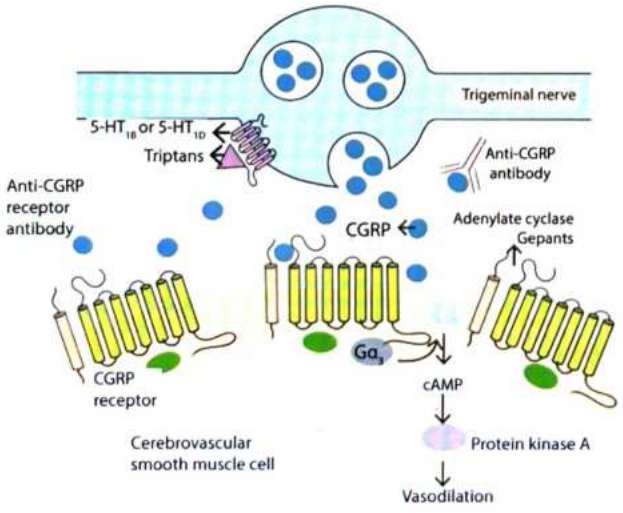
- New Drugs 2018-19 (Part 1)
- New Drugs 2018-19 (Part 2)

86 NEW DRUGS 2018-19 (PART-1)

1. **Andexanet alfa**
- Factor Xa inhibitors:
  - Rivaroxaban
  - Edoxaban
- Antidote for factor Xa inhibitors is Andexanet alfa



2. **Erenumab**: AOEE
Galcanezumab: GNLM
Fremanezumab: VFRM



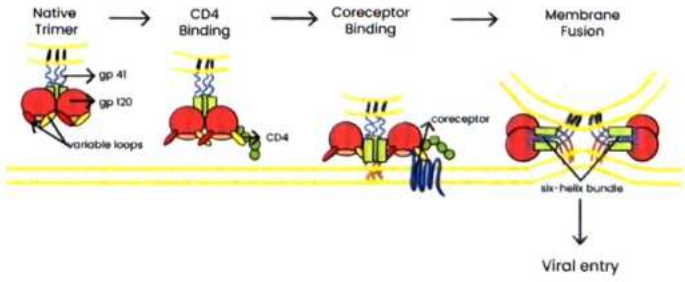
3. **Migalastat**
- For Fabry Disease:
  - Mutation of α-galactosidase on X-chromosome
  - Leads to its misfolding
  - Migalastat is a pharmacological chaperone. Improves misfolding

4. **Patisiran**
- Small interfering RNA based drug
- Gene silencing drug–Interferes with production of abnormal Transthyretin
- Approved for Polyneuropathy with hereditary transthyretin mediated amyloidosis

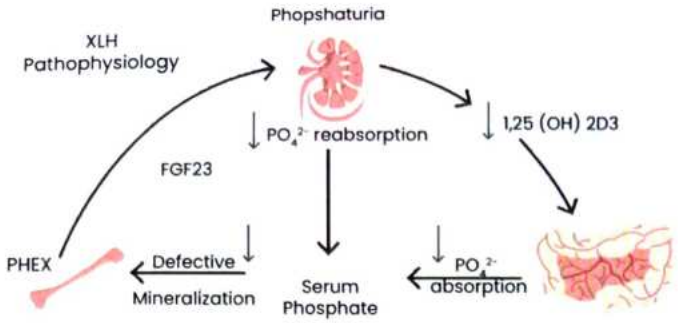
5. **Elagolix sodium**
- GnRH antagonist
- Given orally
- Approved for pain associated with endometritis
- Short acting drug

6. **Tafenaquine**
- Used for radical treatment of plasmodium vivax malaria
- Causes hemolysis in G6PD deficiency
- Single dose is given

7. **Ibalizumab**
- Monoclonal antibody against CD4 receptors
- Used in HIV



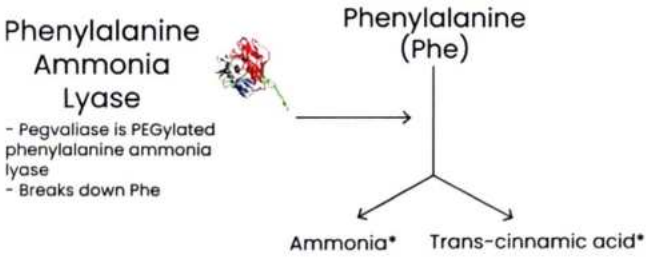
8. **Burosumab**
- Used for X-linked hypophosphatemia
- Overactivity of FGF-23



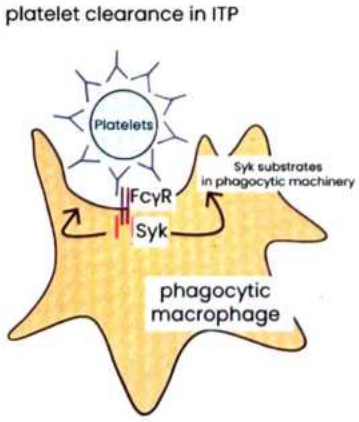
9. **Eltrombopag**: Approved for ITP
   Avatrombopag: Approved for Chronic liver dis with thrombocytopenia prior to surgery
   Lusutrombopag: Same as Avatrombopag

10. **Tildrakilumab**
- MAb against IL-23
- Approved for Psoriasis

11. **Pegvaliase**
- Recombinant form of phenylalanine ammonia lyase
- Used in phenylketonuria
- Long acting



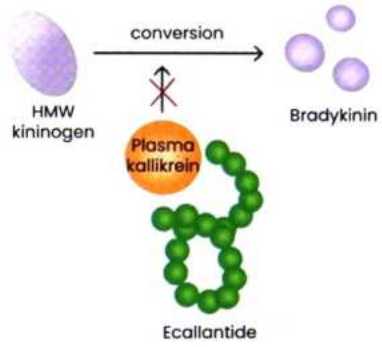
12. **Fostamatinib**
- Spleen tyrosine kinase inhibitor
- Used in ITP



13. **Sodium Zirconium Cyclosilicate**
- Potassium binder drug
- Used to treat Hyperkalemia

14. **Lanadelumab**
- Hereditary Angioneurotic Edema is due to excessive bradykinin
- Lanadelumab inhibits plasma Kallikrein
- Used for HAE

Icatibant
- Used for HAE
- Bradykinin antagonist

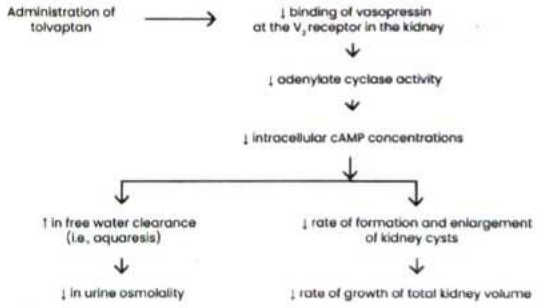


15. **Cenegermin**
- Recombinant human nerve growth factor
- Used for neurotrophic keratitis
- Available as eye drops

16. **Stiripentol**
- Approved for Dravet syndrome, along with Clobazam
- Increases GABAergic activity
- Inhibits LDH

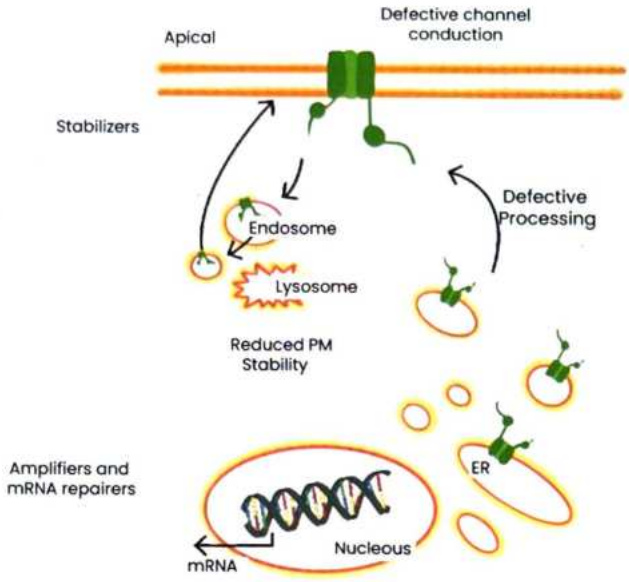
17. **Cannabidiol**
- Derived from marijuana
- Used for LGS and Dravet syndrome
- 1st FDA approved drug which is directly obtained from cannabis

18. **Tolvaptan**



- Used for ADPKD

19. **Tezacaftor / Ivacaftor**
- Used for Cystic fibrosis



20. **Apalutamide**
Flutamide
Nilutamide
Bicalutamide
Enzalutamide
- These are androgen receptor blockers
- Used for prostate cancer

21. **Lofexidine**
- Approved for Opioid addiction

22. **Lutetium dotatate**
- Approved for Pancreatic neuroendocrine tumor

23. **Bicetegravir / Emtricitabine / Tenofovir alafenamide**
- Used for HIV treatment

24. **Plazomicin**
- New aminoglycoside
- Given by IV route
- Used for complicated UTI including Pyelonephritis

25. **Omadacyclin**
- Used for CAP and acute skin infections

26. **Sarecycline**: Approved for acne vulgaris

27. **Eravacycline**: Used for complicated intra-abdominal infections

28. **Doravirine**
- It is NNRTI
- Used for HIV

29. **Moxidectin**
- New anti-helminthic drug for onchocerciasis
- Binds to GABA and Glutamate channels

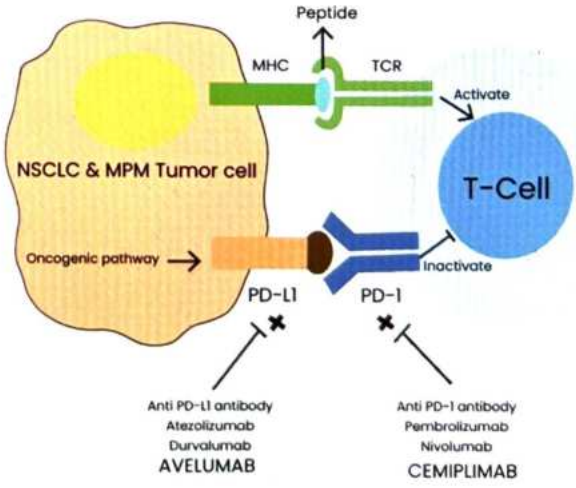
30. **Tecovirimat**
- Used for smallpox
- Oral drug
- Binds to envelop protein
- Inhibits transmission

31. **Segesterone acetate + Ethinyl estradiol**
- Used in Vaginal ring for contraception
- Used once yearly

32. **Baricitinib**
- JAK inhibitors for RA, similar to Tofacitinib
- Oral drug

33. **Moxetumomab pasudotox**
- Moxetumomab + Pseudomonas toxin
- Used for hairy cell leukemia

34. **Cemiplimab**



- Approved for Cutaneous Squamous Cell Carcinoma

35. Duvelisib

- Similar to Idelalisib, Copanlisib
- Phosphoinositide-3-kinase inhibitors
- Used for CLL, SLL, Follicular lymphoma

36. Ivosidenib

- Similar to Enasidenib
- Used for AML with IDH-1 mutation

37. Encorafenib

- Encorafenib + Binimetinib is used for malignant melanoma
- Oral drug
- BRAF kinase inhibitors

38. Mogamulizumab

- MAb against CCR4
- Used for Mycosis fungoides and Sezary disease

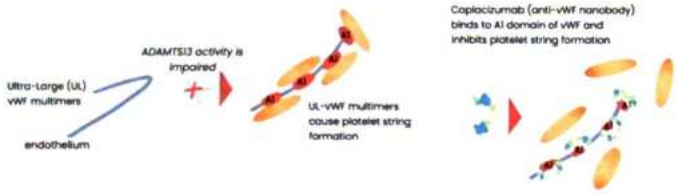
39. Dacomitinib

- Inhibits tyrosine kinase activated by EGFR
- Used for non-small cell lung carcinoma

87 NEW DRUGS 2018-19 (PART-2)

1. **Prabotulinum Toxin A**
- Ach release inhibitor
- To improve glabellar lines

2. **Caplacizumab**
- vWF directed antibody fragment
- Targets the A1 domain of vWF, and inhibits the interaction between vWF and platelets, thereby reducing both vWF mediated platelet adhesion and platelet consumption
- Used for aTTP



3. **Elapegdemase**
- Recombinant adenosine deaminase enzyme replacement therapy
- For ADA-SCID
- By IM injection
- Decrease in toxic adenosine and deoxyadenosine nucleotide levels
- Increase in lymphocyte number

4. **Inotersen**
- Transthyretin directed antisense oligonucleotide
- Causes degradation of mutant and wild type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues
- For polyneuropathy of hereditary transthyretin mediated amyloidosis
- By SC injection
- Can cause thrombocytopenia and glomerulonephritis

5. **Talazoparib**
- PARP inhibitor like Olaparib
- For breast cancer

6. **Baloxavir Marboxil**
- Prodrug: converted by hydrolysis to baloxavir
- Inhibits the endonuclease activity of polymerase acidic protein, an influenza virus specific enzyme in the viral RNA polymerase complex, required for viral gene transcription, resulting in inhibition of influenza virus replication
- Oral single dose treatment of acute uncomplicated influenza

7. **Revefenacin**
- Long acting muscarinic antagonist
- For maintenance of patients with chronic obstructive pulmonary disease
- By inhalational route

8. **Calaspargase pegol**
- L-asparaginase is an enzyme that catalyzes the conversion of amino acid L-asparagine into aspartic acid and ammonia
- It is an asparagine specific enzyme
- For ALL by IV route

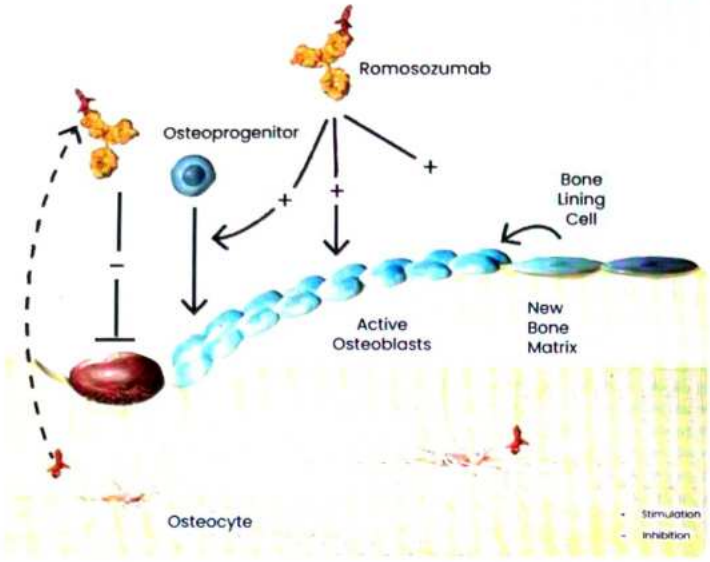
9. **Brexanolone**
- Allopregnanolone: a neuroprotective steroid
- GABA-A receptor positive modulator
- For post partum depression
- By IV route

10. **Solriamfetol**
- Dopamine and norepinephrine reuptake inhibitor
- To improve wakefulness in adult patients with excessive daytime sleepiness
- By oral route

11. **Esketamine**
- Non-competetive NMDA receptor antagonist
- For treatment-resistant depression
- Given as nasal spray
- Black box warning

12. **Siponimod**
- For the treatment of relapsing forms of multiple sclerosis
- By oral route

13. **Romosozumab**
- MAb against Sclerostin
- Sclerostin stimulates osteoclasts and inhibits osteoblasts



14.Edafitinib
- TK inhibitor

15.Risakizumab
- MAb against IL-23
- For plaque and psoriasis

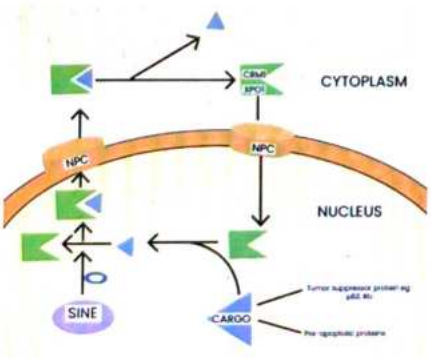
16.Tafamidis
- Used for preventing cardiomyopathy in TTR amyloidosis

17.Alpelisib
- PI-3 kinase inhibitor
- For breast cancer

18.Polatuzumab
- Antibody against CD79b component of B cell receptor
- For refractory or relapsed DLBCL

19.Bremelanotide
- For hypoactive sexual desire disorder in females
- By SC route
- Melanocortin receptor agonist

20.Selinexor
- Oral selective inhibitor of nuclear export compound
- For multiple myeloma and DLBCL



21.Relebactam
- Beta lactamase inhibitor
- Like sulbactam, tazobactam, avibactam

22.Darolutamide
- Androgen receptor blocker like flutamide

23.Pexidartinib
- Tyrosine kinase inhibitor of CSF-1 receptor

24.Pretomanid
- Inhibits mycolic acid synthesis
- For MDT TB

25.Pitolisant
- H3 inverse agonist
- For narcolepsy

26.Entrectinib
- Oral TK inhibitor

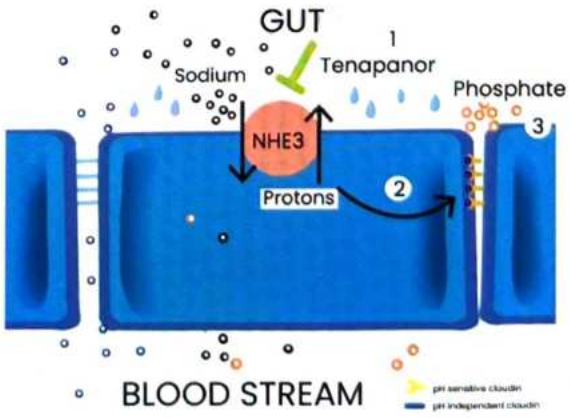
27.Fedratinib
- Oral JAK-2 inhibitor
- For Myelofibrosis

28.Upadacitinib
- Oral JAK inhibitor
- For RA

29.Lefamulin
- Protein synthesis inhibitor
- For CAP

30.Istradefyline
- Adenosine A2 receptor antagonist
- For On-off episodes of parkinsonism

31.Tenapanor
- NHE inhibitor
- Oral route
- For IBS with constipation



32.Trifarotene
- Retinoic acid receptor agonist
- Topical use
- For acne vulgaris

33.Brolucizumab
- VEGF inhibitor
- IV route

34.Afamelanotide
- Melanocortin-1 receptor agonist

35.Lasmiditan
- 5HT1F agonist
- For acute severe migraine

36.Elexacaftor / Ivacaftor
- CFTR correctors
- For cystic fibrosis

37.Luspatercept
- Recombinant fusion protein that binds several endogenous TGF-beta superfamily ligands
- For anemia in pts with beta thalassemia

38.Zanubrutinib
- Bruton tyrosine kinase inhibitor like Ibrutinib
- For mantle cell lymphoma

39.Cefiderocol
- It is a synthetic conjugate with cephalosporin moiety to inhibit cell wall synthesis and a siderophore moiety to gain entry into bacterial cells
- Used for UTI

40.Crizanlizumab
- Monoclonal antibody against P-selectin

41.Givosiran
- Small interfering RNA
- For acute hepatic porphyria

42.Cenobamate
- Voltage gated sodium channel blocker
- For focal seizures

43.Voxelotor
- A sickle hemoglobin polymerization inhibitor
- For oral treatment of sickle cell anemia

44.Golodirsen
- Induces exon 53 skipping in dystrophin gene
- For Duchene muscular dystrophy

45.Enfortumab vedotin
- Nectin-4 directed antibody and microtubule inhibitor conjugator
- For urothelial carcinoma

46.Lumateperone tosylate
- 2nd gen antipsychotic
- 5HT2A receptor antagonist

47.Lemborexant
- Orexin receptor antagonist like Suvorexant
- For treatment of insomnia

48.Fam-trastuzumab Deruxtecan
- Conjugation of MAb against HER-2 with topoisomerase inhibitor
- For breast cancer

49.Ubrogepant
- Oral CGRP antagonist
- For acute treatment of migraine

LEARNING OBJECTIVES

UNIT 18: FDA APPROVED NEW DRUGS

88 FDA APPROVED NEW DRUGS

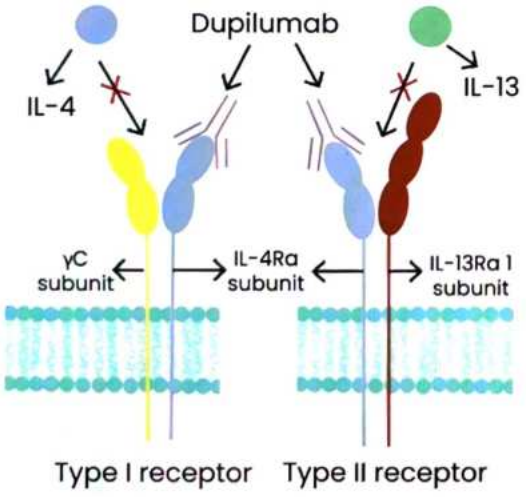
1. **Voretigene Niparvovec**
- For Leber's congenital amaurosis
- AAV2 vector containing human CDNA
- Subretinal injection

2. **Netarsudil**
- For glaucoma
- Rho kinase inhibitor
- Increases aqueous outflow

3. **Latanoprostene bunod**
- Metabolized by esterases to Latanoprost and Butanediol mononitrate
- Approved for glaucoma

4. **Betrixaban**
- Oral anti-coagulant drug

5. **Dupilumab**
- Approved for atopic dermatitis
- MAb against IL-4R alpha



6. **Semaglutide**
- Recombinant GLP analogue
- Only oral drug from its group
- Approved for type 2 DM

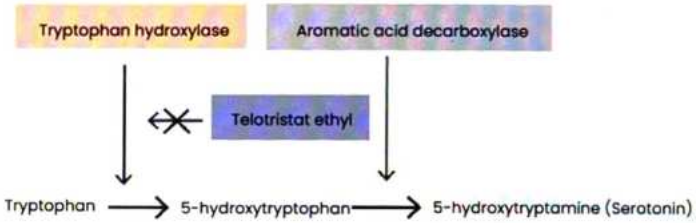
7. **Etecalcetide**
- Calcium sensing receptor agonist
- For hyper-parathyroidism

8. **Dapagliflozin**
- SGLT-2 inhibitor
- For type 2 DM

9. **Plecanatide**
- Stimulates GC-C
- For chronic idiopathic constipation

10. **Naldmedine**
- Opioid receptor blocker
- For Opioid induced constipation

11. **Telotristat ethyl**
- Inhibits tryptophan hydroxylase
- For diarrhoea due to carcinoid syndrome



12. **Cerliponase alpha**
- For infantile neuronal ceroid lipofuscinosis
- Recombinant TPP-1

13. **Vestronidase alpha**
- For MPS 7
- Recombinant beta glucuronidase

14. **Inotuzumab ozogamicin**
- MAb against CD-22 linked to calicheamicin
- Approved for ALL

15. **Emicizumab**
- Bispecific MAb
- For Hemophilia

16. **Glicaprevir / Pribrentasvir**
- Approved in hepatitis C
- Combination of protease inhibitor with NS5A inhibitor

17. **Sofosbuvir / Velpatasvir / Voxilaprevir**
- Approved for Hep C

18.Tocilizumab
- MAb against IL-6
- For RA and Cytokine release syndrome

19.Letermovir
- Drug for CMV
- Inhibits DNA terminase complex

20.Lesinurad
- Inhibits URAT-1
- Used for chronic gout

21.Sarilumab
- MAb against IL-6
- For RA

22.Abaloparatide
- Used for osteoporosis
- Injectable drug

23.Amantadine
- NMDA receptor blocker
- Used for levodopa induced dyskinesia

24.Edaravone
- Free radical scavenger
- For ALS

25.Safinamide
- MAO-B inhibitor
- Used for parkinsonism

26.Ribociclib
- CDK4 and 6 inhibitor
- Used for breast cancers

27.Niraparib
- Inhibits poly ADP ribose polymerase
- For ovarian cancers

28.Durvalumab
- MAb against PD ligand
- Used for bladder carcinoma and urothelial carcinoma

PREP NUGGETS

Prep Nuggets

1st order

- .....
- CL = constant
- T ½ = constant
- .....

Zero order

- .....
- .....
- .....
- .....

Prep Nuggets

	Km	**V max**
• Competitive	.....	.....
• Non- competitive	.....	.....
•	.....	.....