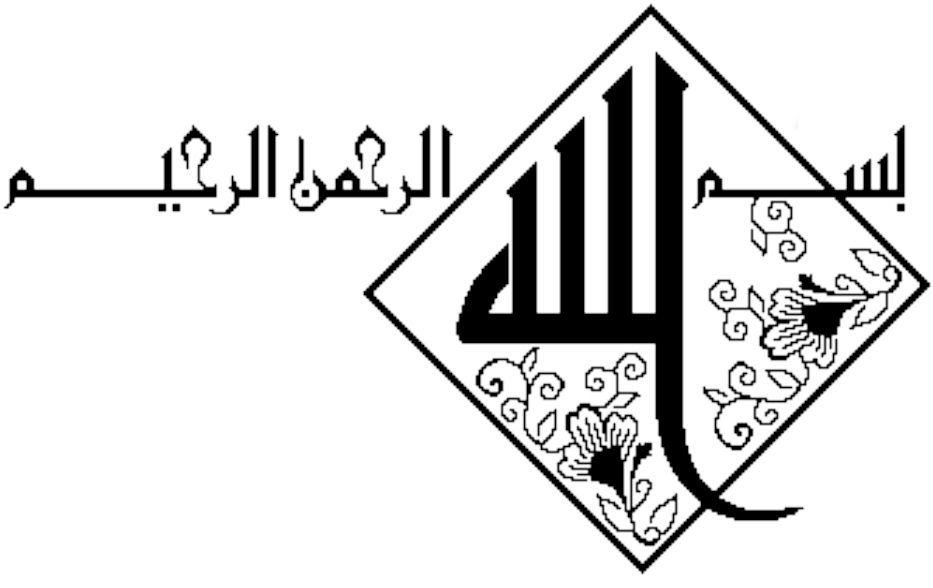
PHARMACOLOY SHORT NOTES& MNEMONICS

BY MUHAMMAD RAMZAN UL REHMAN

FIRST EDDITION



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This book is dedicated to Hazrat Muhammad s.a.w....

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Special thanks to my Parents who encouraged me to do this and especially. My father **Muhammad Boota** who always and always supported me in my works and motivated me. And My Friends and my Class fellows (Nishtar Medical College Batch N62) who encourage me to complete this work

(Muhammad Ramzan Ul Rehman)

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PREFACE

This book contains Mnemonics and short notes for pharmacology. Helpful for both students and teachers of Pharmacology for learning and teaching purposes. Pharmacology is one of the most boring and difficult subject considered in MBBS and is base of Clinical treatment.

In usual the stuff is present But you have to memorise that stuff by either way making concepts or by using Ratta. But still you have to remember the names of drugs, classifications, some special uses, side effects, contraindications and Bla Bla Bla.....

Another problem is if you remember them then there will be mixing because there are a lot of Drugs and each drug will have a lot of uses, side effects, contraindications etc. The student is left with three methods one is to make concepts and everything understandable (This is the Best method), second method is to remember them all by ratta and clear your exams (but this will result in mixture in your mind) third last method is using some mnemonics or your emotions or your thoughts and relate them to Drugs and this will result increased retention power and this book is all about third method

This book contain

- Short notes
- Mnemonics
- Pictures related to mnemonics
- Tables
- Tricks to remember

I tried my best to make these things more and more palatable for ordinary students

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For Suggestions, mistakes, spelling, mistakes, new mnemonics, additions, new ideas, and other things that can help to make this better are always welcomed

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Only Thing needed in Return is remember me in your Prayers If you find this Useful (This Book is FeSabeel ALLAH.)

Muhammad Ramzan UL Rehman
(Author)

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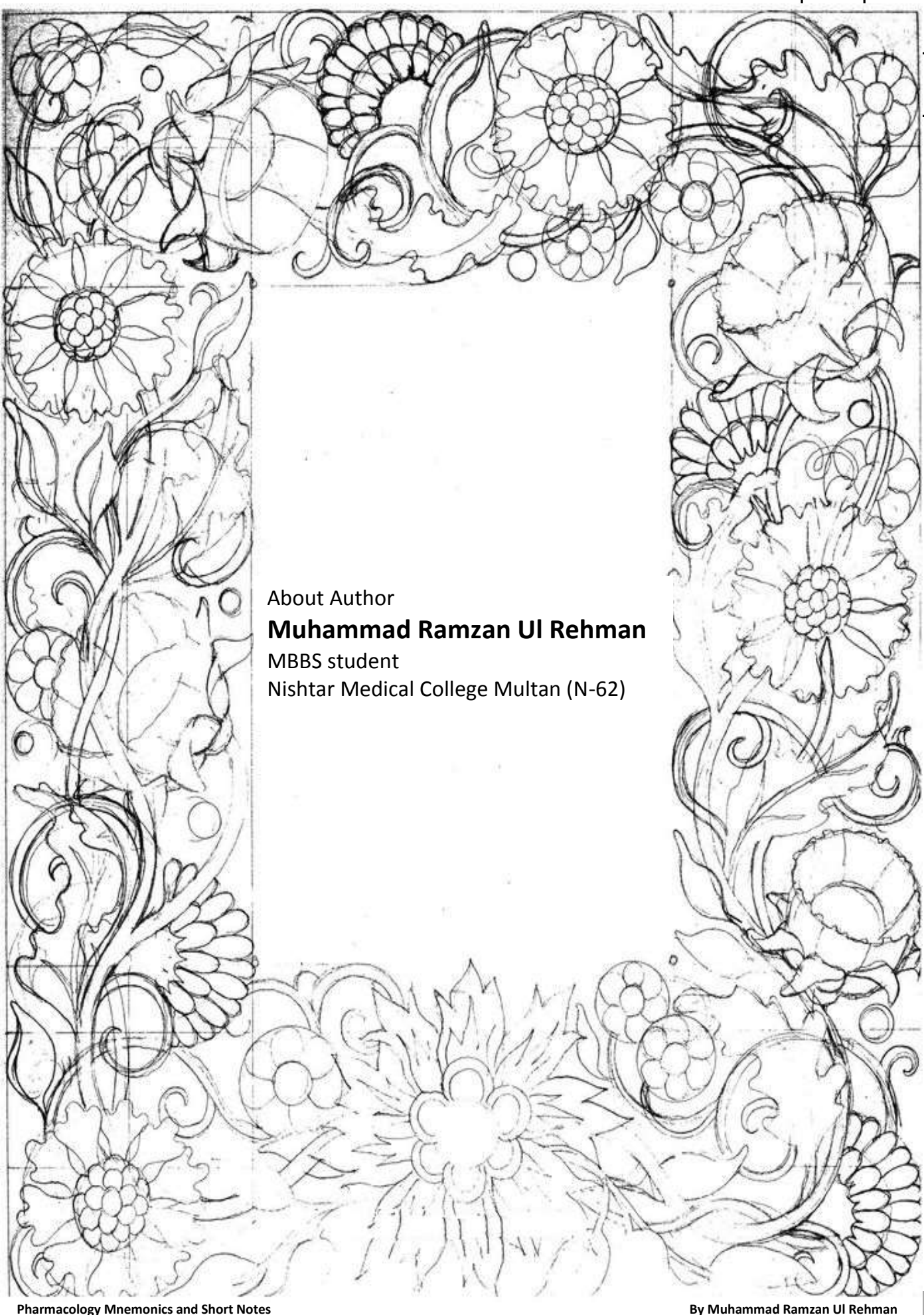

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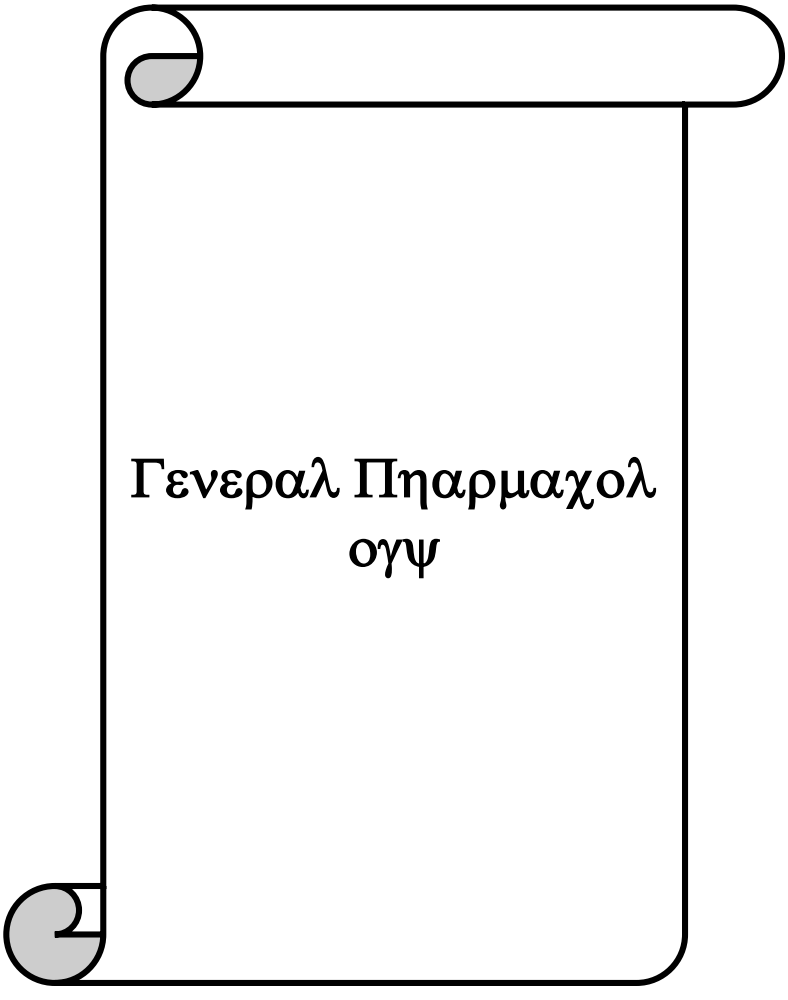

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General Concepts

Pharmacology ➔Study of substance that interact with living systems through clinical processes especially by binding to regulatory molecule

Pharmacopeia➔are the total of all authorized drugs available within the country.

Medication ➔is a substance administered for diagnosis, cure, treatment, mitigation or prevention.

Prescription ➔the written direction for the preparation and the administration of the drug.

The therapeutic effect ➔is the primary effect intended that is the reason the drug is prescribed such as morphine sulfate is analgesia.

Side effect ➔Secondary effect of the drug is one that unintended, side effects are usually predictable and may be either harmless

Drug toxicity➔ deleterious effect of the drug on an organism or tissue, result from overdose or external use.

Drug allergy ➔ is immunological reaction to a drug.

Drug interaction ➔occur when administration of one drug before or after alter effect of one or both drug.

Drug misuse ➔is the improper use of common medications in way that lead to acute and chronic toxicity for example laxative, antacid and vitamins.

Contents

Drug abuse ➔is an inappropriate intake of substance either continually or periodically.

Drug dependence ➔is a person's reliance on or need to take drug or substance there are two type of dependence:

1) **Physiological dependence:** is due to biochemical changes in the body tissue these tissue come to require substance for normal function.
2) **Psychological dependence**: is emotional reliance on a drug to maintain a since of wellbeing accompanied feeling of need.

Pharmacokinetics	• is about how the body deal with drug (effect of body on drug)
Pharmacodynamics	• Is effect of drug on the body (d from dynamic drug on body).
Pharmacotherapeutics	• Is a clinical using of drug.
Pharmacognosy	• The study of natural (plant and animal) drug sources.

Sources of Drugs

1. Plants: such as digitalis (fox glove) and atropine (atropa belladonna)
2. Human and animals: such as epinephrine, insulin and adrenocorticotropic hormone.
3. Minerals: as iron, iodine and zinc

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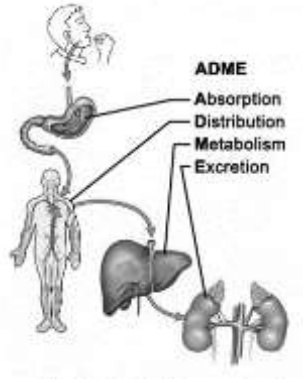
4. Synthetic and chemical substance: as sodium bicarbonate

Pharmacokinetics

Comprises Absorption, Distribution, Metabolism (Biotransformation) and Excretion.

A ➔ Absorption
D ➔ Distribution
M ➔ Metabolism
E ➔ Excretion



Absorption

Absorption is defined as the passage of a drug from the site of administration into the blood stream.

- Most drugs are absorbed (crosses cell membrane) by Passive diffusion (along concentration gradient with no carrier or energy).

Factors That Modify Drug Absorption

1) Factors related to the drug:

a. Lipid solubility

The higher the lipid solubility of the drug the higher the rate of drug absorption.

b. Degree of drug ionization

The greater the ionization, the lesser the absorption.

C. pH of the medium

Ionization depends on pH of absorbing media

Contents

-At acidic pH (stomach) weak acid drugs e.g. Acetyl salicylic acid (Aspirin) become more unionized → more lipid soluble → more absorbable, while weak basic drug e.g. amphetamine become less unionized (ionized) → less lipid soluble → less absorbable.

-At alkaline pH (Intestine) weak basic drugs become more un-ionized, more lipid soluble and more absorbable, while weak acidic drugs become less unionized, less lipid soluble and less absorbable.

d. Valency

Ferrous (Fe^{+2}) salts are more absorbed than ferric (Fe^{+3}), so vitamin C increases absorption of iron.

• Pharmaceutical form: Solutions are better absorbed than suspensions, the smaller the particle size of the powder, the more is the absorption.

e. Concentration at site of administration

2) Factors related to the Patient:

1-Route of Administration:

-Absorption from subcutaneous tissue is more rapid than absorption from mucous membranes EXCEPT pulmonary alveoli.

- Absorption from skeletal muscle is more rapid and complete than from subcutaneous sites.

2-State of absorbing surface

Diarrhea markedly decrease absorption of systemically acting drugs.

3-State of general circulation (Blood Flow)

During hypovolemic shock oral and subcutaneous rout are ineffective and drugs should be given intravenously.

Another way to enumerate these factors is (Modified form)

Chemical properties

- acid or base
- degree of ionization

Contents

- polarity
- molecular weight
- lipid solubility
- partition coefficient

Physiologic variables

- gastric motility
- pH at the absorption site
- area of absorbing surface
- blood flow
- presystolic elimination
- ingestion w/wo food

Routes of drug administration

Routs of Drug administration

Enteral	Non-enteral

Oral	Rectal	Sub lingual	Injection	Inhalation	Topical

Enteral Route of administration

Oral route

Drugs should be stable, non-irritant and adequately absorbed

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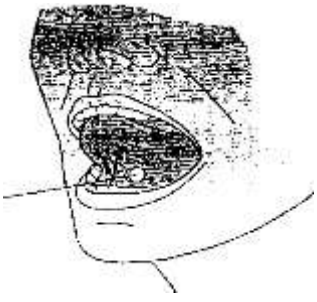
•Advantages (Oral is the most common)

1. Least expensive and most convenient route for most clients.
2. Safe, does not break the skin.
3. Conscious, able to swallow.



•Disadvantages:

1-Variation in rate of absorption.

2-Not in emergencies

3-Not in unconscious patient

4-Not for irritant drugs.

5-Not in GIT disturbances (vomiting and diarrhoea).

6-Not for non-absorbable drugs when systemic effect is needed e.g. streptomycin

7-Not for drugs that undergo complete first pass metabolism e.g. lidocaine.

Governed by ➔surface area for absorption, blood flow, physical state of drug, concentration.

- Occurs via passive process.
- In theory ➔ weak acids optimally absorbed in stomach, weak bases in intestine.
- In reality ➔ the overall rate of absorption of drugs is always greater in the intestine (surface area, organ function).
- Ingestion of a solid dosage form with a glass of cold water will accelerate gastric emptying: the accelerated presentation of the drug to the upper intestine will significantly increase absorption.
- Ingestion with a fatty meal, acidic drink, or with another drug with anticholinergic properties, will retard gastric emptying. Sympathetic output (as in stress) also slows emptying.

Sublingual route

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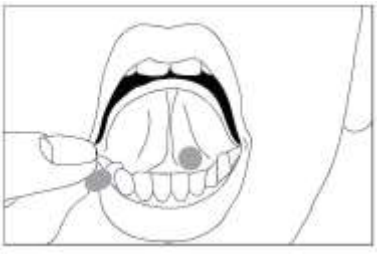
Drug should be absorbed, stable, palatable and effective in small dose.

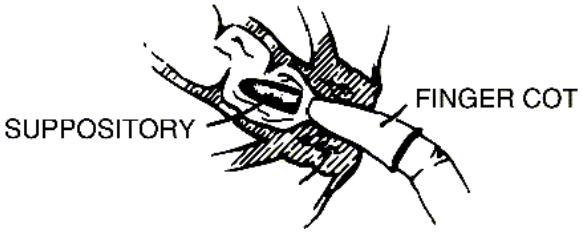


- **Advantages:** Rapid absorption, escape first pass effect and proper control of dose by spitting or swallowing excess of drug.

Nitro-glycerine ➔non-ionic, very lipid soluble. Because of venous drainage into the superior vena cava, this route "protects" it from first-pass liver metabolism.

Rectal route

- May be useful when oral administration is precluded by vomiting or when the patient is unconscious.
- Approximately 50% of the drug that is absorbed from the rectum will bypass the liver, thus reducing the influence of first-pass hepatic metabolism. Incomplete. -irritation.



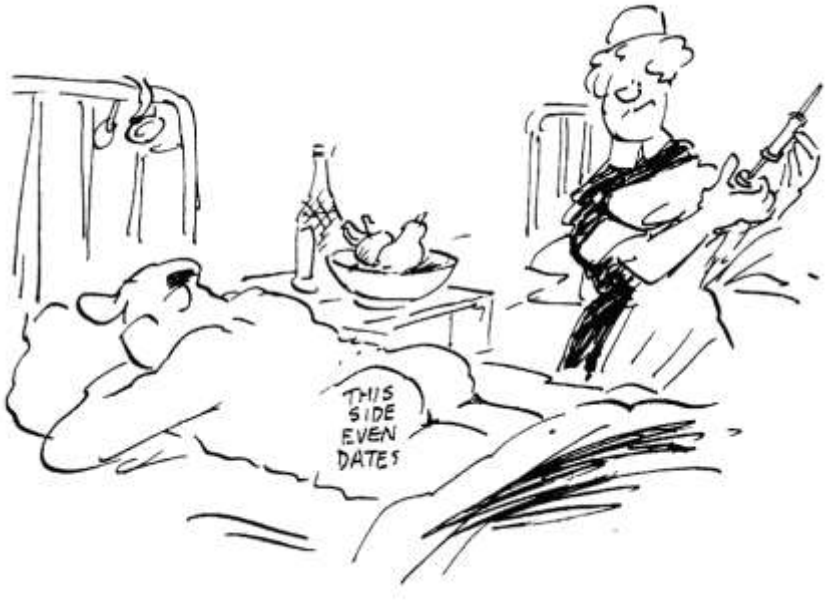
- **Advantages:** Rapid absorption, useful in vomiting, unconscious patient, children, irritant drugs on stomach and drugs that undergo first pass effect.
- **Disadvantages**
  1. Psychological many patients refuse this route.
  2. Rectal inflammation may occur with repeated use.
  3. Absorption can be unreliable, esp. if the rectum is full of stool.
  4. Irregular
  5. Incomplete absorption
  6. Irritation may occur

Parenteral Route of administration

Injections

Injection which should be sterile and are used in the following:

1. Drugs ineffective by other routes.



2. Drugs producing irritation.
3. Emergencies and to increase blood level rapidly.

Injections may be in the following sites:

a. Intradermal e.g., sensitivity tests and vaccination.

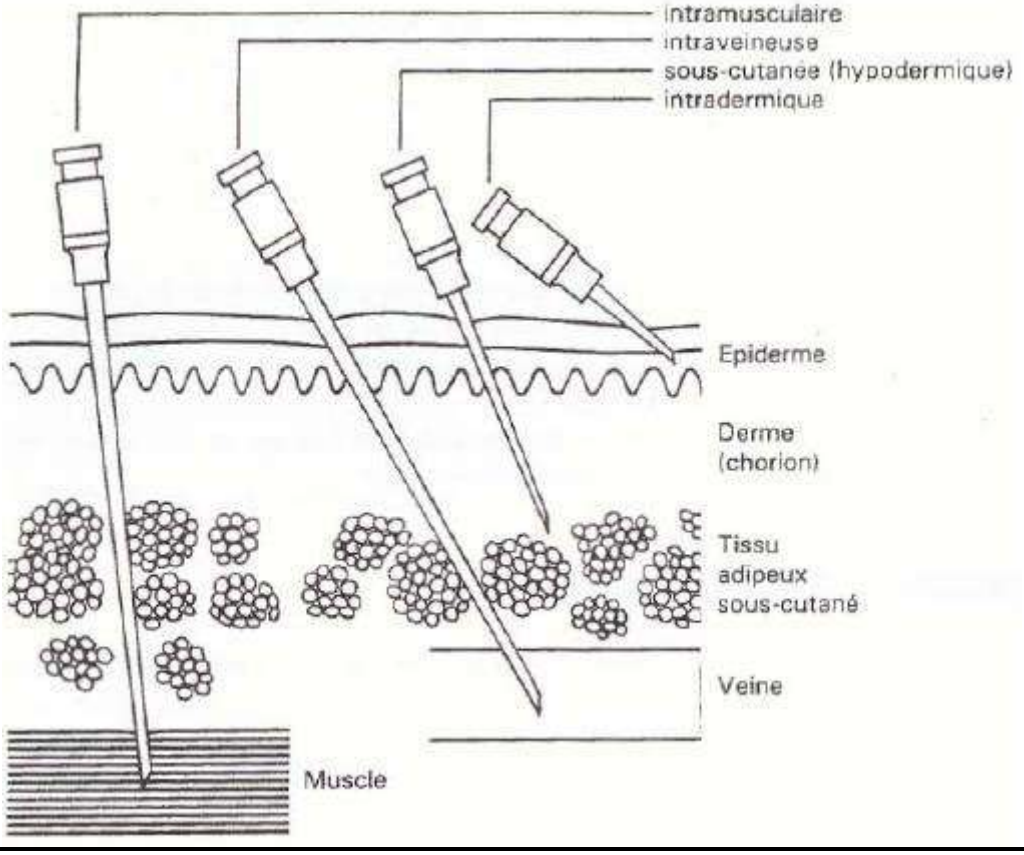
b. Subcutaneous: more rapid and complete than oral and is suitable for non-irritant drugs.

c. Intramuscular: for moderate irritant drugs.

Contents

d. Intravenous: drugs should be aqueous. It is suitable for too irritant drugs and rapidly destroyed drugs (e.g., lignocaine and nitroprusside). Usually has a rapid onset and produce immediate effective blood level.

e. Rare as in bone marrow, intra-arterial, intracardiac, intrathecal, intra-articular, intraperitoneal.



Intradermal

is the administrating of a drug into the dermal layer of the skin just beneath the epidermis, usually small amount of liquid is used for example 0.1ml.

- **Advantage:** absorption is slow (this advantage test for allergy).
- **Disadvantage:** amount of drug administered must be small and Breaks skin barrier

Subcutaneous

Hypodermic into subcutaneous tissue, just below the skin.

Advantage: onset drug action faster than oral.

Disadvantage:

1. Must involve sterile technique because breaks skin barrier.
2. More expensive than oral.
3. Can administer only small doses.
4. Slower than intramuscular injection.
5. Some drug can irritate tissue and can cause pain.

Intramuscular

Into in the muscle.

Advantage:

- Pain from irritating drugs is minimized.
- Can administer large volume of drug.
- Drug rapidly absorbed.

Disadvantage:

- Breaks skin barrier.
- Can be anxiety producing.

Intravenous

Intravenous (IV): allow injection of drugs and another substance directly into bloodstream through the vein.

- **Disadvantages of I.V.**

  * Allergic reaction as anaphylactic shock.
  * Velocity reaction, e.g. if aminophylline is given rapidly it can produce arrhythmia, hypotension and cardiac arrest.
  * Pyrogenic reaction.
  * Disease transmission.
  * Thrombophlebitis.
  * Extravasation (leakage) → severe irritation.

Miscellaneous routes

1-Topical administration

Is useful in the treatment of patients with local conditions, there is usually little systemic absorption. Drugs can be applied to various mucous membranes and skin.

2-Inhalation

Provides a rapid access to systemic circulation; it is the common route of administration for gases and volatile drugs.

3-Subcutaneous pellet implantation

Pellet under skin induces fibrosis around it leading to slow absorption and long duration (e.g. contraceptives, steroid hormones)

4-Transdermal delivery system

By applications of drugs to the skin for systemic effect. The drug is released through a rate controlling membrane into the skin and so into the systemic circulation.

5-Hypospray gun (jet injection syringe)

Very convenient, no need for sterilization, not painful, offers self-medications. Used for giving insulin & for mass immunization.

6-Intranasal

Calcitonin is used in treatment of osteoporosis as a nasal spray.

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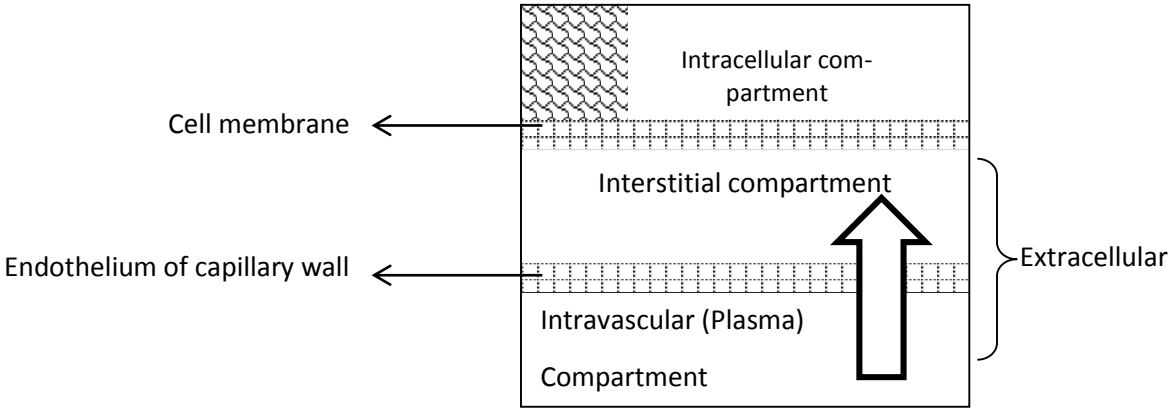
Drug Distribution

Process by which a drug reversibly leaves the circulation and enters the interstitium and cells of the tissue.



Drugs are distributed to the different tissues and body fluids, according to the compartmental models.

***One compartment model (intravascular)**

- E.g. drugs with high molecular weight as heparin has Vd 3-4 L.

***Two compartment model (extracellular distribution)**

- Drug with small molecular weight but ionized e.g. skeletal muscle relaxants have Vd average of 14 L.

***Multicompartmental model (extracellular and intracellular distribution)**

- Drug with small molecular weight and lipid soluble as alcohol has Vd average of 42 L.

***Selective distribution**

- Some drugs have special affinity for specific tissue. e.g. calcium in bones and iodide in thyroid gland.

Apparent volume of distribution (Vd)

Contents

- It is the hypothetical volume of the fluid into which a drug distributed

$$V_d = \frac{\text{Amount of drug in body}}{\text{Plasma concentration of drug}}$$

V_d is not a real volume, small volume indicates extensive plasma protein binding, but large volume indicates extensive tissue binding.

V_d is increased by increased tissue binding, decreased plasma binding and increased lipid solubility.

N.B. in average 70 kg adult, the total body water is 42 liter, extracellular volume is 14 liter and plasma volume is 4 liter.

A-Patterns of Drug Distribution

The drug is transported in the blood in either 2 forms bound form OR free form

Plasma protein bound Drug	Free Drug
Inactive	Active
Non-Diffusible	Diffusible
Cannot be metabolized	Can be metabolized
Cannot be excreted by kidneys	Can be excreted by kidneys

•The protein bound drug acts as a store from which a small amount of free drug is released.

•The protein responsible for binding of most drugs is albumin.

B-Competition for Plasma Protein Binding Sites

One drug may displace another from its binding sites on plasma proteins. The displaced drug will show higher free blood level with enhanced activity & possibly toxicity e.g. Aspirin can displace Warfarin (anticoagulant) → Hemorrhage.

C-Passage of drug to CNS via BBB and to fetus via placental membrane

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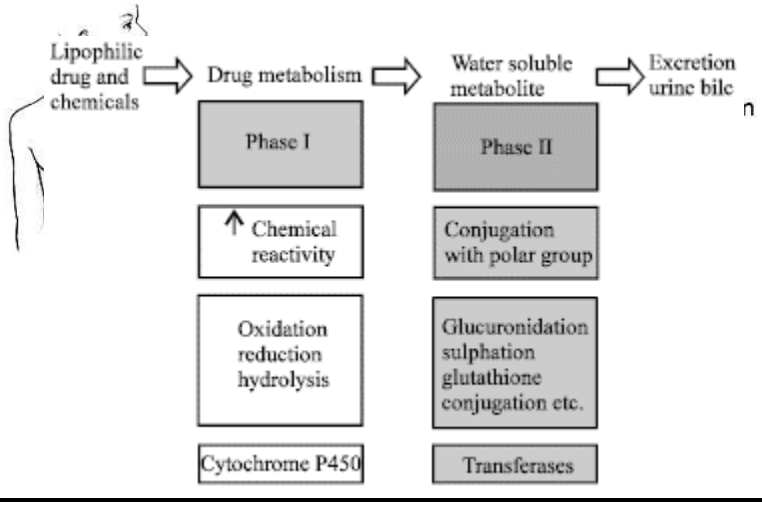
Only un-ionized lipid soluble drugs can pass through BBB and placental membrane to exert central effects and affect the fetus respectively.

Drug Metabolism (Biotransformation)

It aims to eliminate the drugs by converting lipid soluble drugs into more polar and less lipid soluble compounds enhancing their renal excretion.



Phases of biotransformation

Phase I (Non synthetic) reactions ➔ by **oxidation, reduction or hydrolysis**.

- Oxidation
  - Oxidation p450 dependant
    - Hydroxylation ➔ Barbiturates and phenytoin
    - N-dealkylation ➔ caffeine and morphine
    - N-oxidation ➔ Nico ➔ Nicotine
    - Deamination ➔ DA ➔ diazepam
  - Oxidation p450 independent

Contents

  - Amine oxidation ➔ catecholamine (as catecholamine have amine group)
  - Dehydrogenation ➔ ethanol
- Reduction
  - Easters ➔ aspirin
  - Amides ➔ Lidocaine

Phase II (Synthetic) reactions➔ Functional group or metabolite formed by phase I is conjugated with natural endogenous constituent as **glucuronic acid, glutathione, sulphate, acetic acid, glycine or methyl group.**

- Glucouronidation ➔ DAM Gluco
  - D ➔Diazepam and digoxin
  - A ➔ Acetaminophen
  - M ➔ Morphine
- Glycine conjugation ➔ GlyciNe ➔ Nicotine
- Sulphation ➔ methyldopa
- Methylation ➔ Dopamine, epinephrine, norepinephrine and histamine
- Acetylation ➔ isoniazid

Most of drugs pass through phase I only or phase II only or phase I then pphase II.

Results of drug metabolism

1. Conversion of **active** drug into an **inactive** metabolite.
2. Conversion of **active** to another **active** substance.
3. Conversion of **pro-drug** (drug given is inactive) to an **active** metabolite.
4. Conversion to a **toxic** compound.

Liver is the main organ for drug metabolism using **liver microsomal P_{450} enzymes.**

Hepatic Metabolism depends on

1. Hepatic function: diseased liver is unable to metabolize drugs as healthy one.

Contents

2. Nutritional state as vitamins and minerals are cofactors for the metabolizing enzymes.
3. Presence of other drugs

a) Activators (Enzyme Inducers)

Some drugs can increase the activity of microsomal enzymes →their ability to detoxicate drugs.

GPRS Cell phone

G ➔ Grisofulvin
P ➔ Phenytoin
R ➔ Rifampicin
S ➔ Smoking
Cell ➔ Carbamazepine
Phone ➔ Phenobarbitone (Benzodiazepines and barbiturates)

b) Inhibitors (Enzyme Inhibitors)

PC Games

P ➔ P 450 inhibitors
C ➔ Cyclosporine and Cimetidine
G ➔ Grape fruit
A ➔ Antifungals
M ➔ Metronidazole
E ➔ Erythromycin
S ➔ SSRIs

Hepatic First-Pass Metabolism

Metabolism of drugs (usually oral) before reaching the systemic circulation (pre-systemic metabolism).

Locations➔ liver and GIT linings

How to overcome hepatic first-pass metabolism?

1. Give a loading dose (high first dose).
2. Change route of administration e.g. sublingual or rectal.
3. Use alternative drug with less hepatic metabolism.

Drug Excretion and elimination

Drugs are eliminated from the body either unchanged or as metabolites.

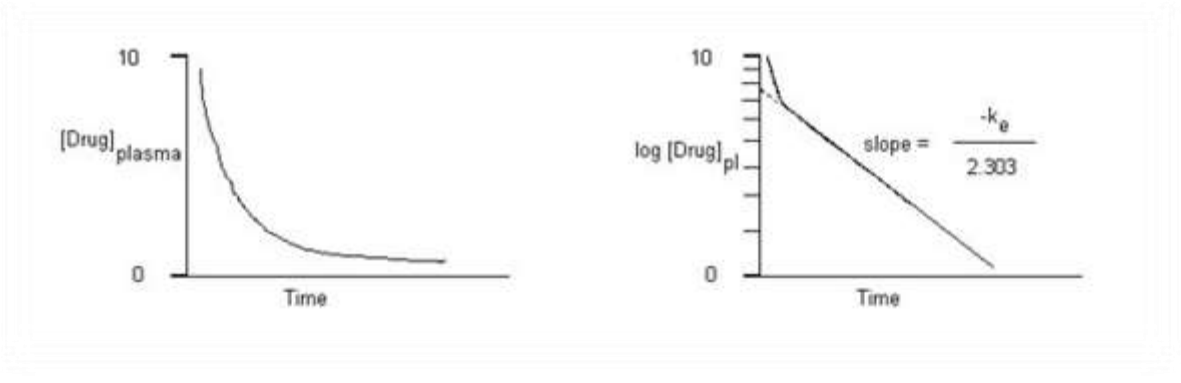
⇨ Kidney is the major organ for drug excretion

- Kidney
  - Acidic urine ➔ Excretion of basic drugs
  - Alkaline urine ➔ excretion of acidic Drugs

First order kinetics

A constant fraction of drug is eliminated per unit of time.

When drug concentration is high, rate of disappearance is high.



Zero order kinetics

Rate of elimination is constant and is independent of concentration

Example ➔ Alcohol

•Other routs of drug excretion include: **Bile**, **Stool**, **Stomach** (Morphine), **Saliva** (Iodides), **Sweat** (rifampicin), **Milk** (amphetamine) and **Lungs** (nitrous oxide).

Other pharmacokinetic Properties

Clearance

Volume of blood or plasma that can be freed of a drug in a specific time is called clearance

Contents

Formula

$$Cl = \frac{\text{Rate of elimination of Drug}}{\text{Plasma concentration of drug}}$$

Rate of Clearance

First order kinetics ➔ constant

Dependence of Clearance

- Blood flow
- Condition of organ eliminating

Clearance of Drug by an organ = extraction capability of that drug x rate of delivery of that drug to that organ

Bioavailability

Is the percent of unchanged drug reaching systemic circulation after administration by any route.

In case of I.V. administration, bioavailability will be 100%.

By other routes

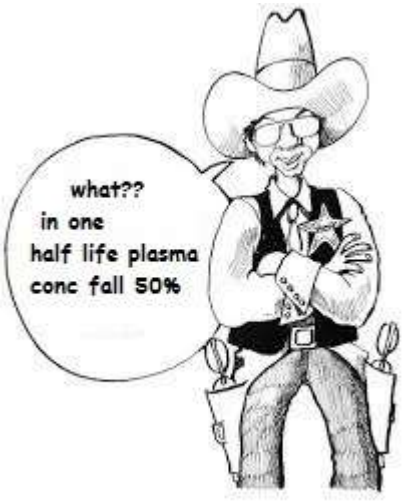
Absorption is less than 100

- Due to incomplete absorption
- Due to first pass metabolism
- Distribution into tissue before drug enters the circulation
- Drug formulation

Bioavailability ➔ measured by area under plasma concentration curve

Plasma half-life (t1/2)

It is the time needed to reduce drug plasma concentration by 50%. The longer the half-life of the drug the lesser the frequency of drug administration.



$$\text{Half-life} = \frac{0.693 \times V_d}{\text{Clearance}}$$

Half-life ➔ determines the rate at which blood concentration rises during constant infusion and falls after stopped

Dosage regimens

A plan of drug administration over a period of time

- Achieve therapeutic level of drug without achieving the minimum toxic level of the drug.

Maintenance Dose

Dose required for regular administration to maintain plasma level

$$\text{Dosing rate} = \frac{\text{CL} \times \text{Desired plasma concentration}}{\text{Bioavailability}}$$

Bioavailability for IV route is 1 so we can say that
Dosing rate = CL x Desired plasma level

Loading dose (Love ➔ mean Loading dose have V_d)

Dose required to achieve specific plasma level with single administration

- Therapeutic concentration must be achieved rapidly at the onset of therapy

$$\text{Dosing rate} = \frac{V_d \times \text{Desired plasma concentration}}{\text{Bioavailability}}$$

Bioavailability for IV route is 1 so we can say that
Dosing rate = V_d x Desired plasma level

- Clearance is not needed here because when clearance will start we will give patient maintenance dose

Adjusted dose for patient with impaired clearance

$$\text{Dosing rate} = \frac{\text{Average dosage x patient's clearance}}{\text{Normal clearance}}$$

Therapeutic window

Safe range between the minimum therapeutic concentration and minimum toxic concentration of a drug is called therapeutic window

- Helpful in designing dosage regimens

Minimum effective concentration ➔ determine the trough level of drug given intermittently

Minimum toxic concentration ➔ determines the peak concentration of the drug

Theophylline ➔ 8 to 16 mg/dL

Pharmacodynamics

Actions of Drug on body

- Mechanism of drug
- Receptor interactions
- Dose response phenomena
- Adverse effects of drug

Mechanism of drug action

a- Physical action, e.g., mannitol induces osmotic diuresis.

b- Chemical action, e.g. $NaHCO_3$ neutralizes excess HCl in hyperacidity.

c- Cytotoxic action (stop cell division) e.g. anticancer drugs.

Contents

d- Interfere with passage of ions as Na^+ entry across cell membrane e.g. local anaesthetics.

e- Interference with normal metabolic pathway, e.g. sulphonamides compete with PABA which is essential for bacterial growth.

f- Enzyme inhibition. Enzyme inhibition could be:

1. Reversible e.g. neostigmine (cholinesterase inhibitor).

2. Irreversible e.g. irreversible anticholinesterases.

g- Action on specific receptors:

Most of drugs are effective because they bind to particular target proteins. Changes of intracellular molecular and biochemical events, responsible for drug action.

Receptors

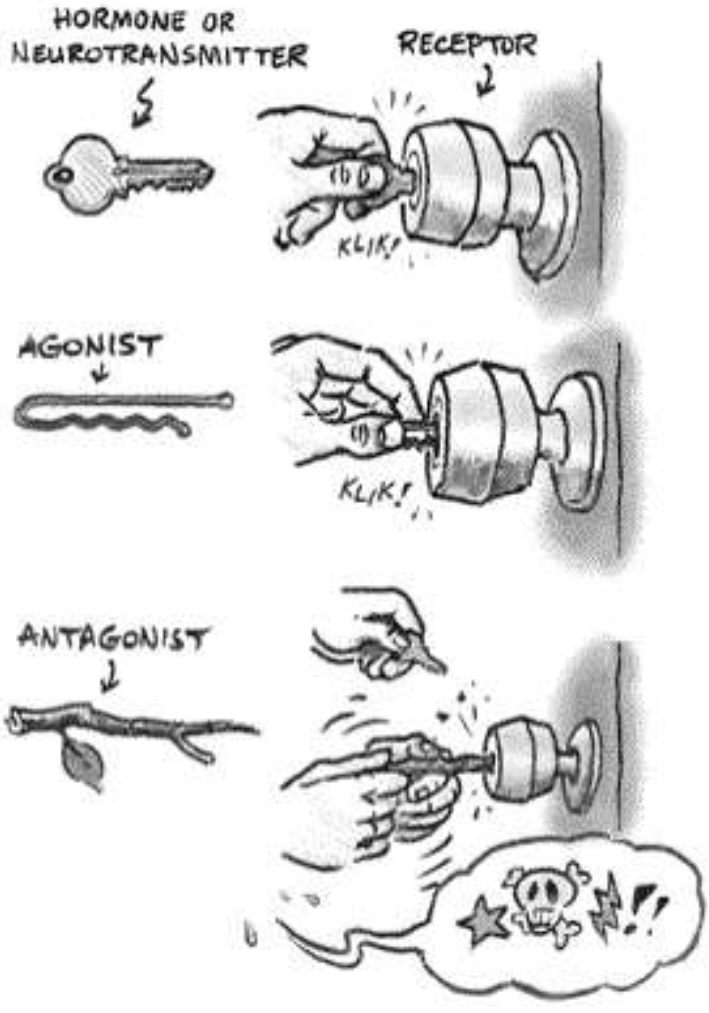
Macro molecular structures present on cell membrane or within the cell that react specifically with ligand (drug, hormone or neurotransmitter) to produce a biological response.

Drug + Receptor $\xrightleftharpoons{\text{Affinity}}$ **D/R complex** $\longrightarrow$ **Response** (Efficacy)

Affinity is the ability of the drug to bind to a receptor forming drug/receptor complex.
Efficacy = response is the ability of drug/receptor complex to produce a biological response or effect.

Receptor interactions

Agonist: A drug having affinity, efficacy and rapid rate of dissociation and is capable of fully activating the effecter system when it binds to the receptor
e.g. adrenaline and acetylcholine.



Antagonist: A drug having affinity, no efficacy and slow rate of dissociation. It blocks the action of an agonist on the receptor e.g. Atropine and propranolol.

Partial Agonist OR Antagonist: A drug having affinity, efficacy less than that of agonist and moderate rate of dissociation. It blocks the action of an agonist on the receptor.

Inverse agonist: agonist have much higher affinity for the inactive state than for activated state and decreases or abolishes the constitutive activity (Activity in the absence of ligand is called **Constitutive activity)**

Dose Response phenomena

Graded Dose Response Relationship

Contents

A graph of increase response to increasing drug concentration

Graded dose response		
Graph between	Graded	Dose response
	Increase of response	Increase of dose of drug

Data derived from this Graph

- Efficacy (E_{max})
- Potency (EC_{50} or ED_{50})

Smaller the EC_{50} greater the potency of drug

Quantal dose response

A graph of fraction of population that shows a specific response at progressively increasing dose

Quantal dose response		
Graph between	Quantal	Dose response
	Fraction of population showing that response	Increase of dose of drug

Data derived from this Graph

- Median effective dose (ED_{50})
- Median toxic dose (TD_{50})
- Median lethal dose (LD_{50}) ➔ in animals

Efficacy ➔greatest effect

is the greatest effect (E_{max}) an agonist can produce if dose is taken to highest tolerated level

Determined by

- Nature of the drug
- Nature of the receptor
- Nature of the effector system associated with it

➔ can be determined by graded response curve not by Quantal response curve

Contents

Potency ➔ amount required to produce required effect

The amount of drug needed to produce a given effect
Determined by

- Affinity of the receptor for drug
- No of receptor available

➔ can be determined by quantal and graded dose response curve

Spare receptors

Spare receptors are present if maximum response is obtained at less than 100% occupation of the receptors

Reasons

- Duration of activation of receptor may be greater than the duration of Drug receptor interaction
- Actual no of receptor may exceeds the no of effectors

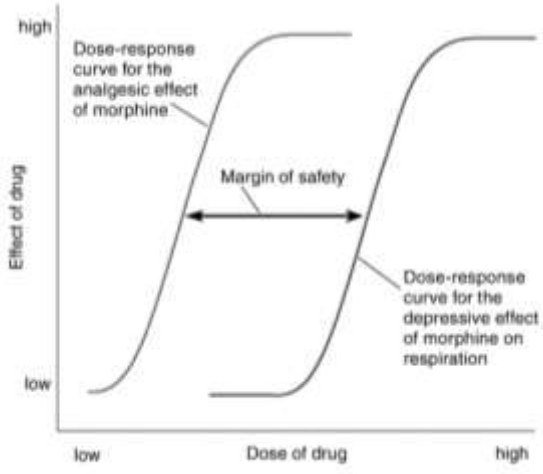
⇨ Spare receptors increase the sensitivity of the receptors to the agonist

Therapeutic Index

This is the ratio of: $\frac{LD_{50}}{ED_{50}}$

- It measures margin of **Safety** for a drug.

Contents



- Safe Drug ➔ very large toxic dose and much small effective dose
- LD_{50} or median lethal dose ➔ is the dose that kills 50% of experimental animals e.g. rats or mice.
- ED_{50} or median effective dose ➔ is the dose that produces a certain pharmacological effect in 50% experimental animals.
- The higher the therapeutic index the safer the drug.
- **Values of therapeutic index:**

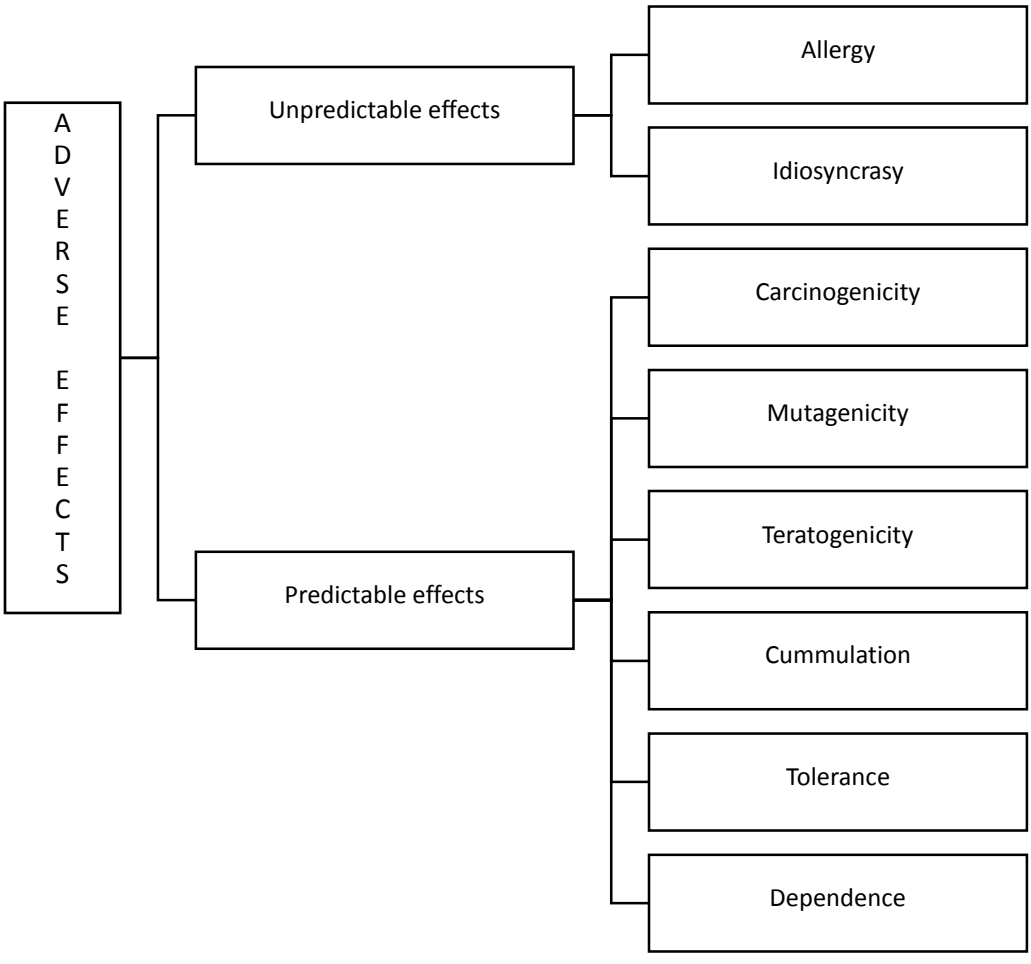
1-So small therapeutic index means that the LD_{50} is just above ED_{50} e.g. digoxin.

2-So great therapeutic index means that it is impossible to kill a patient (the LD_{50} is so great compared with ED_{50} which is so small) e.g. Penicillin.

Adverse Drug Effects

"Each capsule contains your medication,
plus a treatment for each of its side effects."

Contents



Unpredictable

1-Allergy➔the drug is recognized by the immune system as an antigen → allergic reaction e.g. anaphylactic shock in penicillin allergic patients.

2-Idiosyncrasy (pharmacogenetics) ➔ abnormal reaction to the drug due to genetic or enzyme defect e.g.

Contents

1-Hemolysis of RBCs in patients with G6PD deficiency due to administration of certain drugs as aspirin.

Predictable

1. Carcinogenicity➔ drug induced cancer.

2. Mutagenicity➔ drug induced gene mutations in parents or in their offspring.

3. Teratogenicity➔ drug induced foetal defects in utero. Drugs are safely avoided as much as we can especially during the first trimester.

4. Cummulation (Toxicity)➔ drug induced poisoning either due single large dose or several small doses.

5. Tolerance➔ decreased drug response the usual dose on repeated administration of the drug. Tolerance may be congenital (inherited) **OR** Acquired.

1. Congenital:

a) Racial: Negroes are resistant to mydriatic effect of ephedrine.

b) Species: rabbits are resistant to atropine due to presence of atropinase enzyme.

c) Individual variation.

2. **Acquired:** e.g., morphine, ethyl alcohol, nitrates, ephedrine, and amphetamine.

   * It is reversible, so cessation of the drug will lead to loss of tolerance.

   * It may develop to some actions only and not to all actions. Tolerance occurs to analgesia and respiratory depression of morphine, but not to miosis and constipation.

Special types of tolerance

1) Tachyphylaxis

(Acute acquired tolerance) e.g. ephedrine on B.P.

Reasons

- Intracellular molecules block access to G protein s ➔ Beta arrestins in case of beta agonists
- Agonist bound receptor may be internalized ➔ like morphine receptors
- Continuous activation may leads to depletion of some essential substrate required for downstream effects ➔ like depletion of thiol co-factors in case of tolerance to nitroglycerine

2) Cross tolerance (tolerance between related drugs), e.g. between ethyl alcohol and general anaesthesia.

Variation in drug response may be due to

1. **Alteration in drug concentration that reaches the receptors** due to an effect on absorption, distribution or elimination.

2. **Variation in concentration of endogenous transmitters** e.g. β-blockers will slow heart rate markedly in patients with excess endogenous catecholamines.

3. **Alteration in the number or function of receptors**, e.g. thyrotoxicosis increases the number and sensitivity of β-receptors.

   - Long use of agonists may decrease the number of receptors (down-regulation) and this may be responsible for overshoot phenomena which follows withdrawal of some drugs.

   - Long use of antagonists may increase the number of receptors by preventing down-regulation caused by endogenous agonists.

6. Dependence

- Habituation: emotional or psychological dependence on the drug e.g. Tobacco smoking.
- Addiction: both psychological and physical dependence on the drug e.g. Morphine addiction.

Drug Interactions

DRUG-DRUG INTERACTIONS

T tri cyclic anti depressants

H Histamine antagonist

E erythromycin

M MAO inhibitor

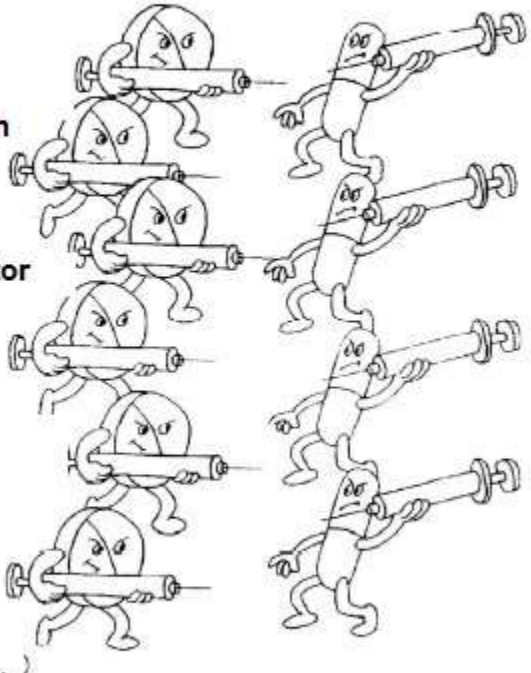
A aspirin

D digoxin diuretics

W warfarin

A zole (antifungals)

R rifampin



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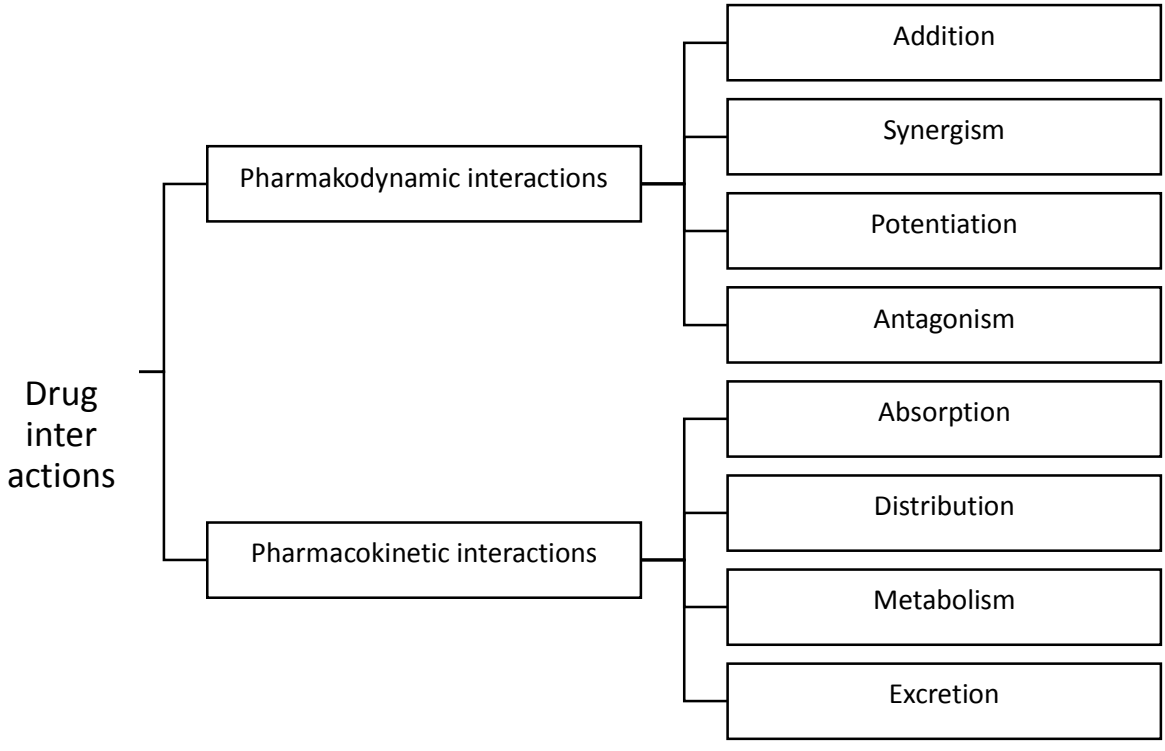
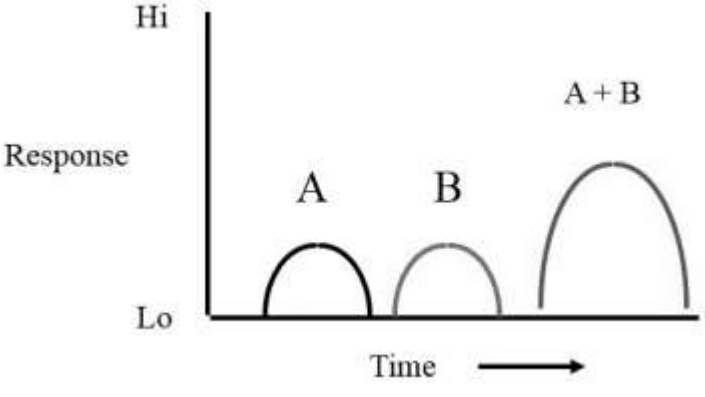


A. Pharmacodynamic Interactions

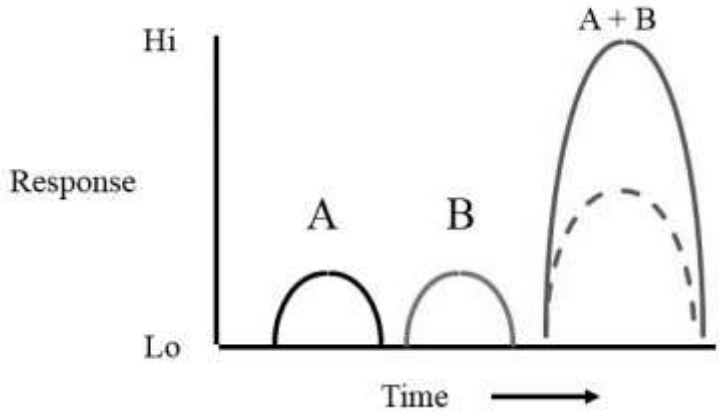
When two or more drugs are combined, one of the following four phenomena may be observed.

I. **Addition or Summation** ➔ the combined effect of the two drugs given together equals the algebraic sum of their individual actions i.e. A = 1, B = 1, A + B = 2.



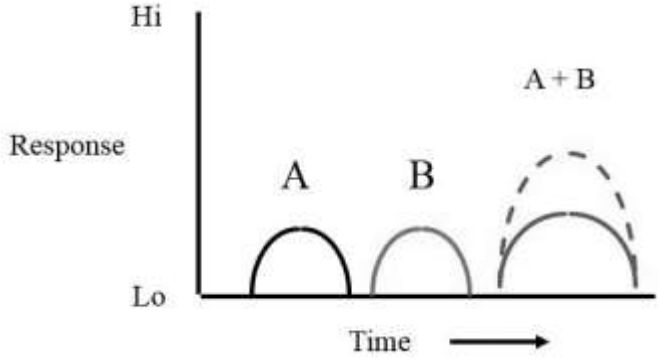
II. **Synergism** ➔ the combined effect of drugs is more than the algebraic sum of their individual actions i.e. A = 1, B = 1, A + B > 2.

Contents



III. Potentiation ➔ one drug has no action on a system but increases the action of another drug on the same system i.e. A = 0, B = 1, A + B > 1.

III. **Antagonism** ➔ several types: (we discuss later after pharmaco-kinetic interactions)

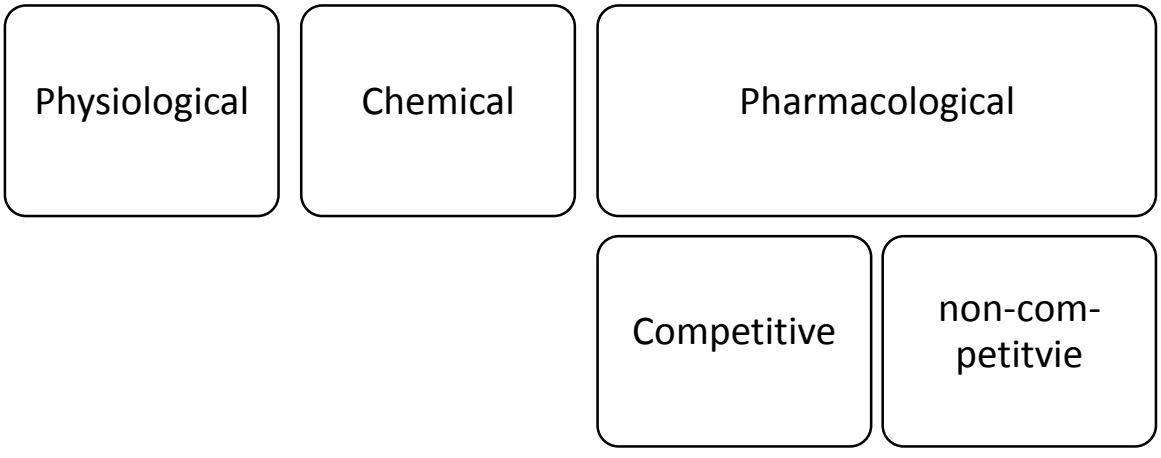


B. Pharmacokinetic Interactions

- **Absorption**➔ Salts of Mg, Ca & Al limit absorption of tetracy-cline.
- **Distribution**➔ displacement from plasma protein binding sites (see interaction between aspirin & warfarin).
- **Metabolism** ➔ enzyme induction and enzyme inhibition (see pharmacokinetics)
- **Excretion** ➔ Probenecid inhibits renal excretion of penicillin.

Antagonism

Antagonism



- **1-Physiological**

  One drug has the opposite pharmacological action to another drug while the two drugs act on different receptors

  ➔ E.g. adrenaline antagonizes the effect of histamine on blood pressure.

- **2-Chemical/Physical**

  One drug chemically or physically combines with another drug and antagonizes its action

  ⇨ E.g. Pralidoxime (antidote for Organophosphates) combine avidly to Phosphorous of organophosphate avidly

- **3-Pharmacological**

  One drug bind to receptor without activating it and prevents the binding of agonist (thus prevent activation by agonist)

  Types

  - Competitive

- Non competitive

Competitive

A pharmacological antagonism in which effect of antagonist can be overcome by increase in concentration of agonist

- There is competition between antagonist and agonist ➔ whose concentration is more will dominate

➔ Drug will closely resemble the agonist and will bind reversibly to the receptor without activating the receptor

Non-competitive

A pharmacological antagonism in which the effect of antagonist cannot be overcome by increase in concentration of agonist

- There is no competition But antagonist bind irreversibly and do not allow the agonist to bind

➔ Drug will bind to receptor irreversibly

ANS Pharmacology

Contents

1. Introduction

Receptors Classification and their location and effects.

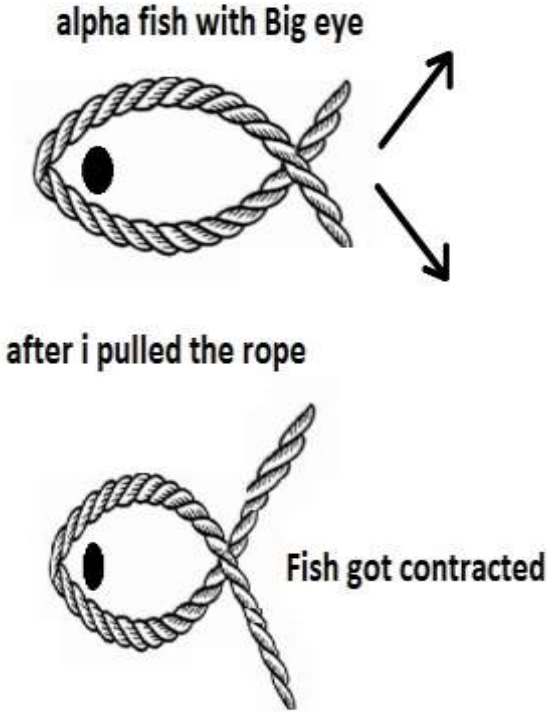
Adrenergic Receptors or sympathetic receptors

Alpha 1 receptors

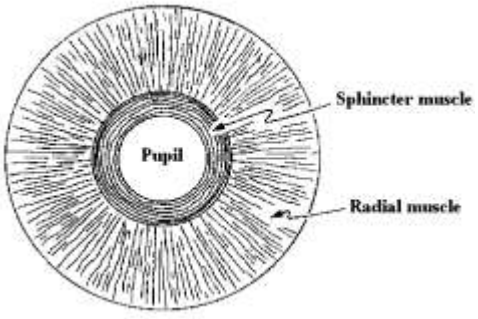
imagine a Fish made of rope with a big Eye. And you pulled the rope and the Fish became smaller.

This means Alpha has big eye and other things generally constricted or contracted. So now we can move to the Functions Performed By Alpha..

- Fish with Big eye ➔ mean sympathetic eye ➔ Dilate Pupil (Mydriasis)



Other all almost will contract or constrict



- **Radial Muscles of eye➔** contract ➔ pupillary dilation
- Blood vessels ➔constrict (skin, Mucous membrane, viscera)
- Bronchi ➔constrict (Minor role as compared to Beta 2 receptors)
- Uterus ➔contract ➔ Baby out
- Sphincters ➔contract
- Erector Pilli➔contract ➔ hair rising
- Seminal vesicles ➔contract ➔ ejaculation of sperms

Another mnemonic for remembering ejaculation and erection is

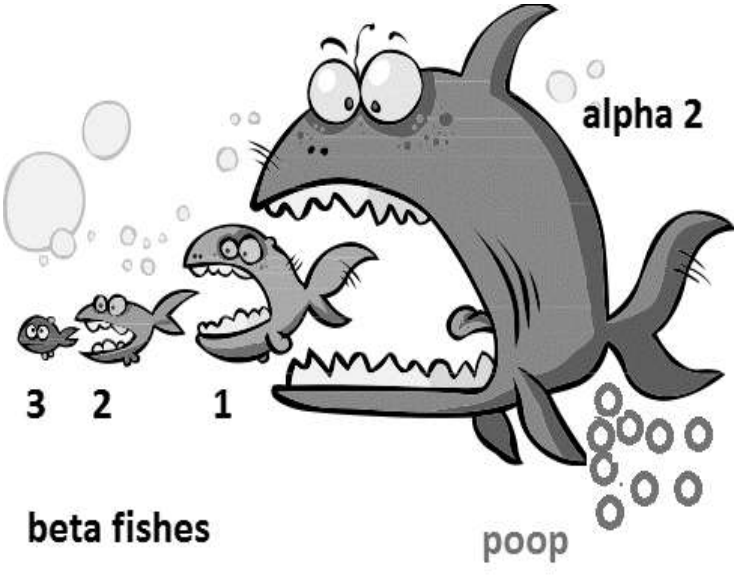
Point and shoot

Point (erection) ➔ parasympathetic

Shoot (ejaculation) ➔ sympathetic

Alpha 2 receptors

Alpha 2 is like a Big fish and Alpha 1 was a small fish. There was rivalry between Alpha and others. Alpha 2 was swimming in water. And his enemies came to finish her. But as she is Big fish and Alpha 1 is too a fish so she recognize that alpha 2 is more powerful



Contents

so Alpha 1 ran away. But Beta 1 2 3 are batmez party so they decided to fight.

In the end Alpha 2 ended up eating all betas and with some poop.

So what happens is Alpha 2 have functions of opposing Batmez Betas

Its functions will be

- Heart rate ➔ decrease
- Secretions (slivery and from other Parts of GIT) ➔ decrease
- Insulin release ➔ decrease
- Weak opposition of effects of Betas because they are eaten up
- Weak favour of effects of alpha 1 because both are fishes
- There was **PooP** too ➔ mean increases platelet aggregation

Beta 1 receptors

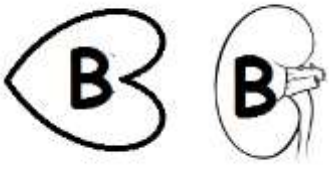
Shape of Beta resemble heart and kidney so

- So effects of Beta will be

  On heart ➔ (betay ko daikh kar man k dil ki dharkan taiz ho gai)

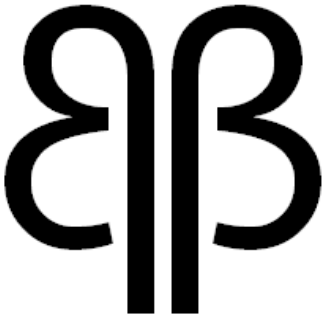
  - Increase heart rate
  - Increase contractility
  - Increase Cardiac out put

  On kidney ➔increase Renin secretion



Beta 2 receptors

Resemble expanding wings of Butterfly (**Things will be expanding or relaxing here)**

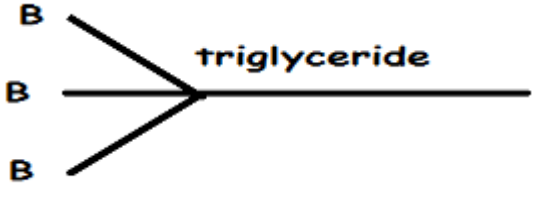


- Relax smooth Muscles ➔ decrease GIT motility
- **Expand Bronchi** ➔ Broncho dilation (Butterfly have two wings just like we have two lungs so Lungs function is important one)
- Expand Blood to Liver and skeletal muscles (vasodilation mean expand blood vessel calibre)
- Expand blood Glucose Level ➔ increase Gluconeogenesis
- Expand uterus ➔ keep baby inside
-
- Increase insulin release

Increase blood glucose mean blood glucose level is increased by them and increase insulin is for increase entry of Glucose into skeletal Muscles so we can fight or flight powerfully in sympathetic stimulation.

Beta 3 receptors

Resembles triglyceride ➔ so its function is in Lipolysis



Cholinergic Receptors or Parasympathetic receptors

M 1 receptor

M one ➔ mean Moan

Contents

M 1 ➔ increase Gastric secretions (increase proportion of water)

M 2 receptor

M 2 is just like M & M chocolate in shape of Heart. And you love them but this time you are having no chocolate.

SO its Functions will be

- Decease heart Rate
- Decrease Force of contraction of Heart
- Decrease Cardiac output

M 3 receptor

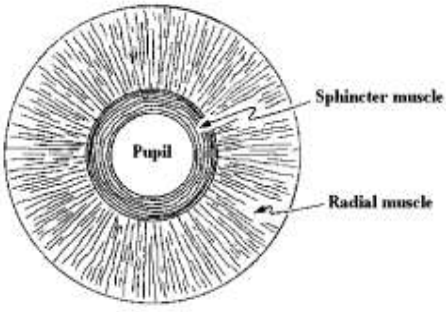
Anything that comes under parasympathetic control and not from M 1 (gastric secretions) and M 2 (Heart depression effects) will come here.

So let's start

Most of the functions are reverse of sympathetic

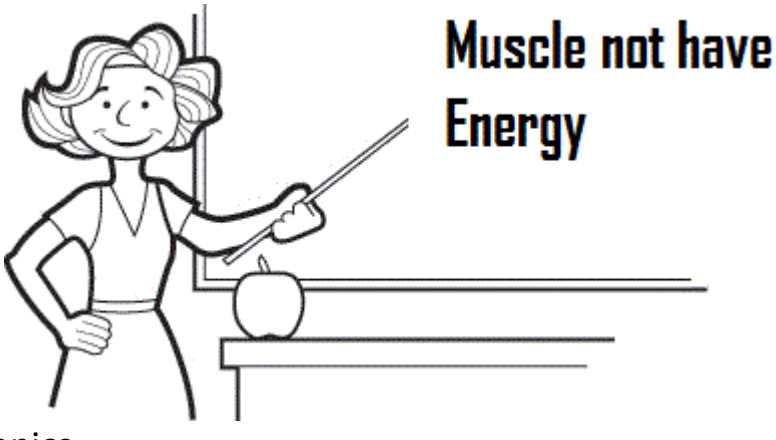
- Relax Sphincters (opposite to alpha 1 that contract them)
- Relax Blood Vessels ➔ vasodilation (opposite to alpha 1 that contract them
- Increase GIT motility (opposite to beta 2 that decrease GIT motility by relaxing smooth muscles)
- Increase secretions ➔ increase water content of saliva (opposite to alpha 2 that decreases secretions)

- Broncho constriction (opposite to Beta 2 that expand bronchi)
- Eye ➔ Pupillary constriction ➔ **Due to contraction of Sphincter muscles** (opposite to Big eyed fish in alpha) Lead to miosis.



Location of these Receptors

You can guess their Location from their effects in which they are working and if you want to remember them separately so here are some mne-



monics

Muscarinic Receptors

- Muscles ➔ muscarinic receptors
- Not ➔ M 1 in Nerve endings (increase IP_3 DAG)
- Have ➔ M2 in Heart (decrease cAMP)
- energy ➔ M3 in Effector cells (increase IP_3 DAG)

Nicotinic Receptors

Nicotinic ➔ N ➔ Nerves

Nicotinic N ➔ ANS ganglia
nicotinic M ➔ neuromuscular end plate (M for muscle)

Mechanisms: they act on Na^+-K^+ ion channels ➔ depolarize and evoke action potential

Adrenergic Receptors

- England ➔ alpha 1 in effector tissues
- Never ➔ alpha 2 in Nerve endings and smooth muscles
- Have ➔ beta 1 in heart
- Some ➔ beta 2 in smooth muscles
- Apology ➔beta 3 in adipose tissue

Dopamine D1 receptor in renal vascular smooth muscles

Mechanisms:

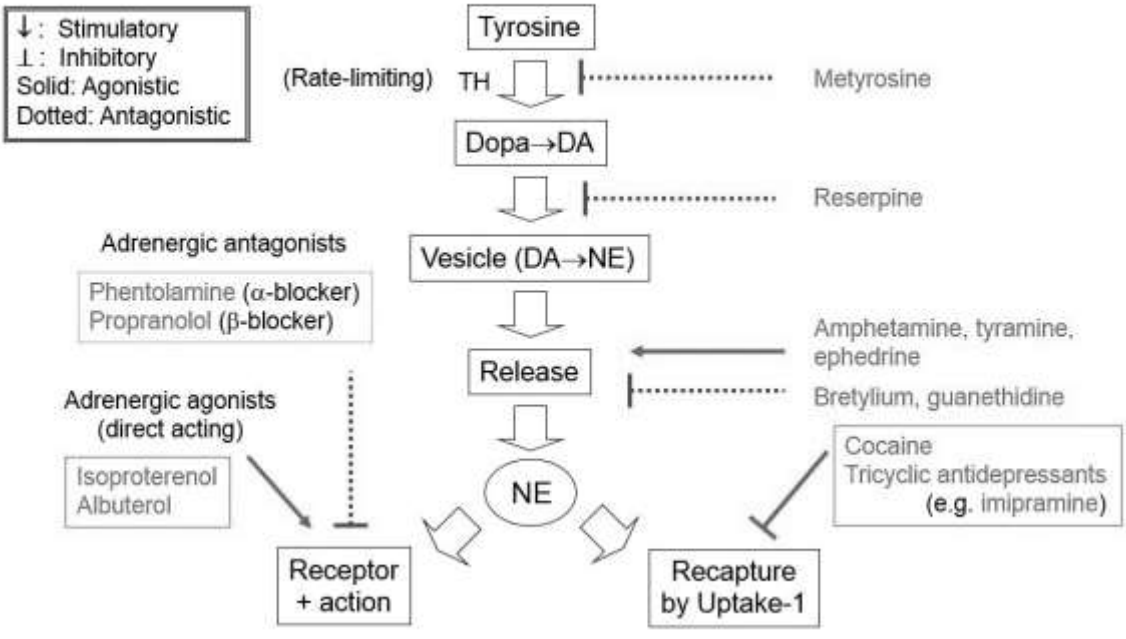
First alpha 1 ➔ increases IP3 DAG (like M 1)

Second alpha 2 ➔ decreases cAMP (like M 2)

Rest betas and dopamine receptors all➔ increase cAMP

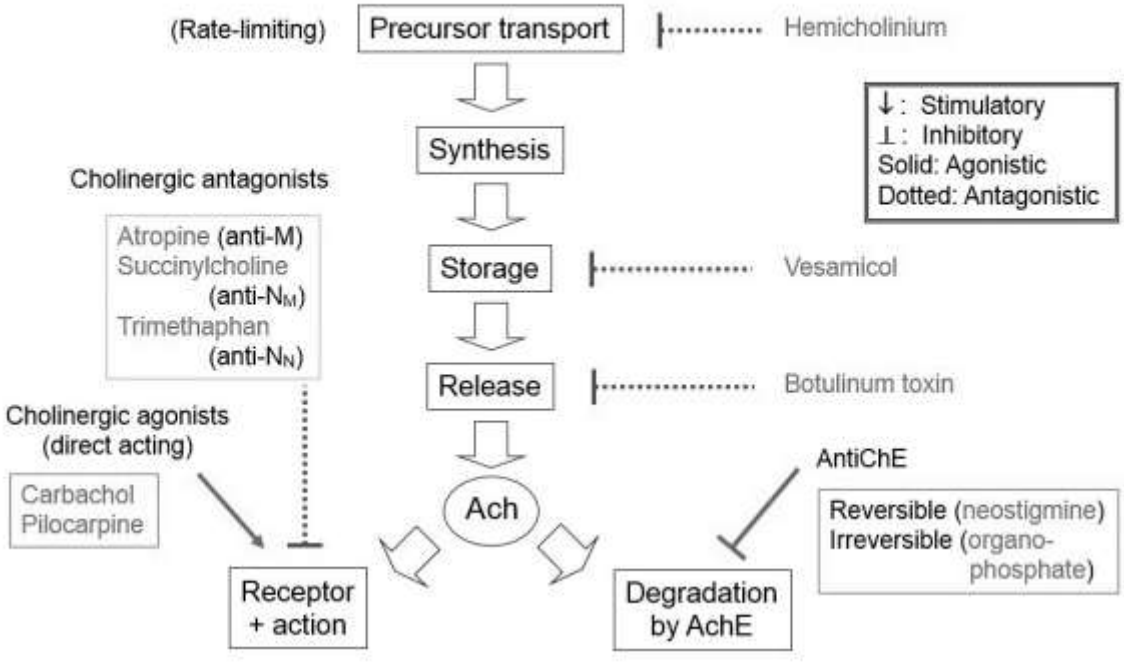
Adrenergic transmission

Drug intervention -- Adrenergic transmission



Cholinergic Transmission

Drug intervention -- Cholinergic transmission



Contents

2. Cholinergic or Parasympathomimetic or Cholinomimetic Drugs

Members& Classification

Direct acting (agonists)

Direct acting cholinomimetics

on Both receptors		Muscarinics		Nicotinic	
Acetylcholine	Carbacol	Bethanecol	Pilocarpine	Nicotine	acetycholine

Mnemonic

Acetyl choline can bath pillow not succinylcholine (or you can use this ➔ aman can beat punon not succy)

Contents

Acetylcholine

Can ➔Carbachol

Bath ➔Bethanichol

Pillow ➔Pilocarpine

Not ➔ nicotine

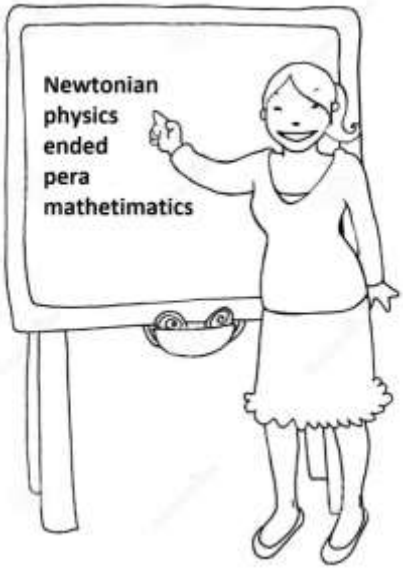
Succinylcholine

indirect acting cholinomimetics

Carbamates		Alcohols	Organophosphates	
Neostigmine	Physostigmine	Edrophonium	Parathion	Malathion

Indirect acting

Mnemonic Newtonian physics ended para Mathematics



Newtonian ➔ neostigmine

Physics ➔physostigmine

Ended ➔edrophonium

Para ➔ parathion

Mathematics ➔malathion

Direct acting cholinomimetics

1 Acetylcholine (both)

Not used therapeutically ➔ because rapidly destroyed by cholines-trase.

2 Carbachol (both)

Glaucoma treatment

Other uses are rare (due to high potency and long duration of ac-tion

3 Bethanichol (muscarinic)

B for Bladder atony

B for Bowel atony

4 Pilocarpine (muscarinic)

- Patient's GCS

G ➔ Glaucoma treatment

C ➔ cystic fibrosis treatment

S ➔sojourn's syndrome

* Glaucoma treatment (increase drainage of aqueous humour)

Chronically➔ Open angle glaucoma (anterior chamber open

Filtration drainage in tissue)

Acutely➔ angle closure glaucoma

*Cystic Fibrosis

Sweat test (to measure Na^+ and Cl^- excreted in sweat)

Indirect acting cholinomimetics

1 Neostigmine New Pump

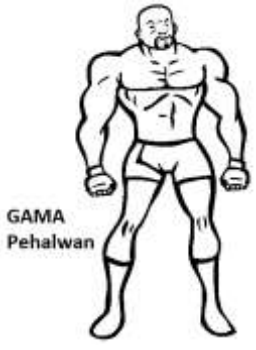
Contents

New ➔ neostigmine

P ➔Pseudo obstruction of colon

U ➔ Urinary retention resulting from General anaesthesia

M ➔Myasthenia Gravis (improve Muscle tone)



P ➔Pregnancy test (provoke menstruation in women with delayed Menstruation.)

2 Physostigmine

Physostigmine is like pehelwan and mashoor pehelwan in

Pakistan was Gama pehelwan

So

G ➔ glaucoma (acute)

A ➔Atropa belladonna poisoning (atropine poisoning)

M ➔Myasthenia gravis

A ➔Alzheimer's disease (improve short term memory)

3 Edrophonium

- Is end diagnosis of myasthenia gravis from cholinergic crisis

  Tension test is performed

Edrophonium is given to the patient and results are observed

- Myasthenia gravis ➔ reduce muscle weakness ➔ because it supply

Ach needed

- Cholinergic crisis ➔ worsen weakness ➔ because Ach is deficient Patient

Side-effects Produced By cholinomimetics

Mnemonic: DUMBLESS

D ➔ Diarrhoea.

U ➔ Urination urgency

M ➔Miosis.

B ➔ Bronchoconstriction

L ➔ Lacrimation

E ➔ emesis & excitation

S ➔ salivation

S ➔ sweetening

From head to toe

System	Effect	Adverse effect
CNS	Excitation	Convulsions
Eye	Miosis	Miosis
Cardiac	Dec heart rate ➔ Dec contractibility Vasodilation	Bradycardia ➔ reflex tachycardia
Bronchi	Bronchoconstriction	Aggravate asthma
GIT	Increase motility➔ Increase secretion➔	Diarrhoea Peptic ulcer
Glands	Sweetening lacrimation	Excessive

Contraindications

CAPI

C ➔ coronary insufficiency (because they dec heart rate) * this C also indicate these are contraindications of Cholinomimetics

A ➔ asthma (because they cause bronchoconstriction so…)

P ➔ Peptic Ulcer (because they cause increase in secretions)

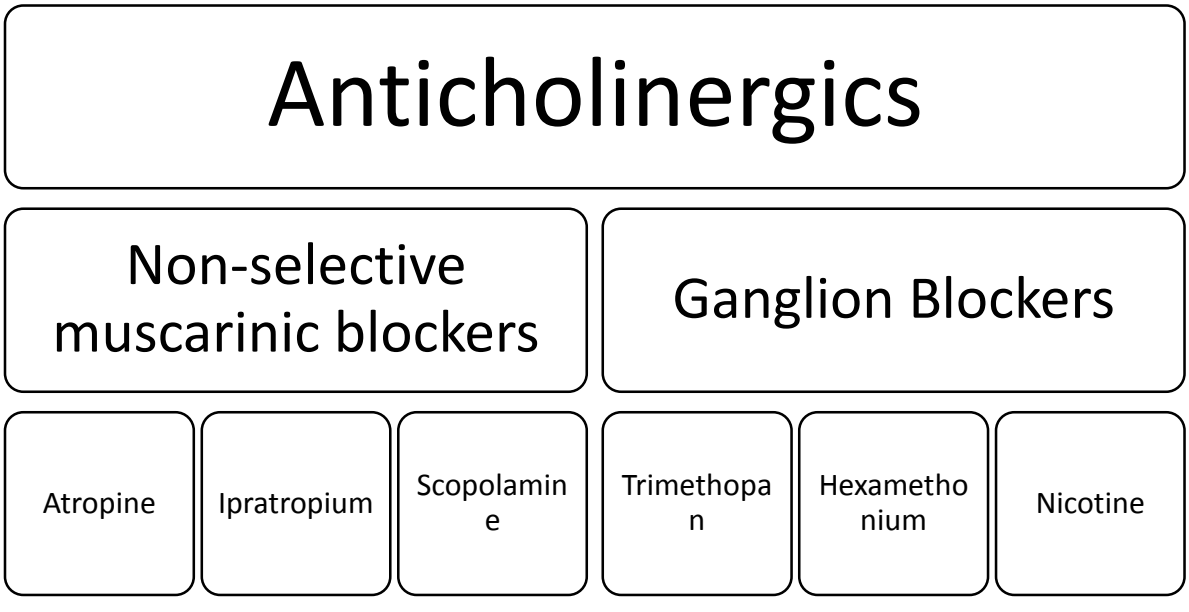
I ➔ intestinal obstruction (they cause increase motility)

3. Cholinoreceptor Blockers and cholinesterase inhibitors

Or Parasympatholytic

Or Anticholinergics

Members and Classification



Mnemonic: <u>Aunty in school trimming her Nails</u>

Aunty➔ atropine (nonselective muscarinic blocker)

In ➔ ipratropium (nonselective muscarinic blocker)

School ➔ scopolamine (nonselective muscarinic blocker)

Trimming ➔trimethopam (ganglion blocker)

Contents

Her ➔Hexamethonium (ganglion blocker)

Nails ➔ Nicotine (ganglion blocker)

Drugs mnemonics
Non selective muscarinic Blockers

1 Atropine

A 4 atropine

A ➔ankh (Eye) ➔mydriatic and cycloplegic (used in measurement of refractory disorders because it will make you pupil big so disorders will be seen easily)

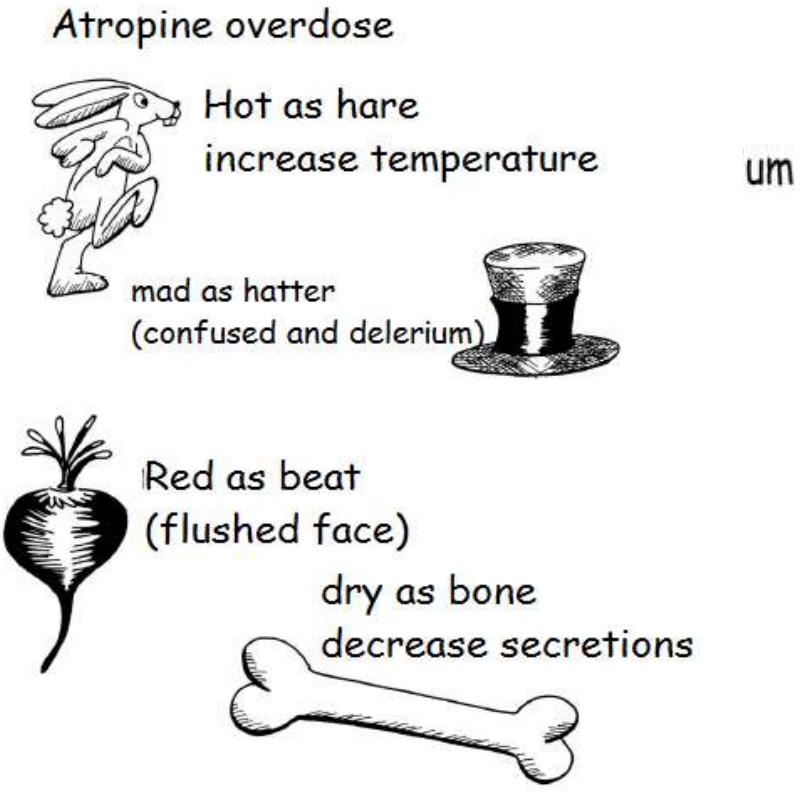
A ➔antispasmodic➔ because they relax GIT and bladder

A ➔antisecretory agent in lower respiratory tract (Preanesthetic use)

A➔ Antidote ➔ in case of cholinesterase inhibitors

Contents

➔Organophosphate poisoning



2 Ipratropium

Asthma (inhaler)

COPD

3 Scopolamine

SMS

S➔ short term memory loss

MS ➔ Motion sickness

Ganglion Blockers

1 Trimethoprim

T for tension

Used in Hypertension caused by pulmonary hypertension

2 Hexamethonium

H for hypertension

Used in hypertension (obsolete)

3 Nicotine

N for no use

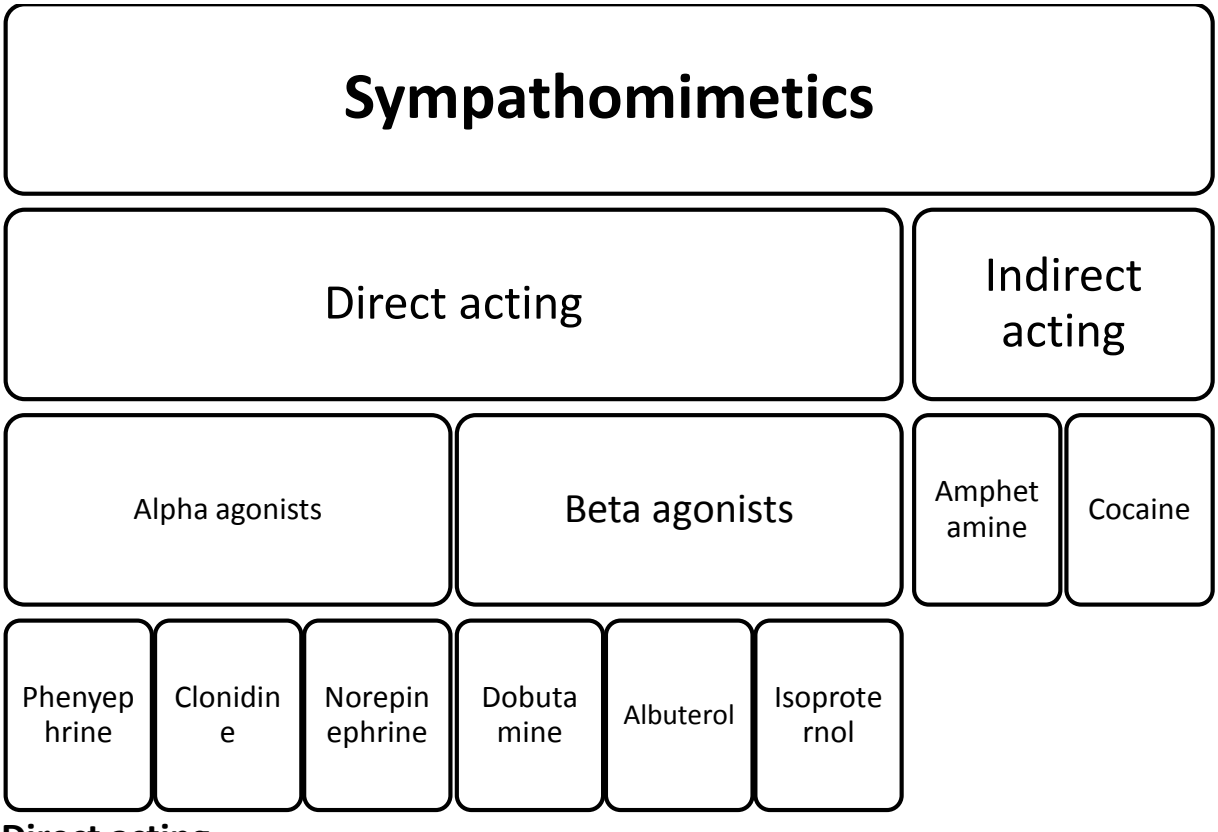
Toxicity

All parasympathetic effects Blocked + sedation + hyperthermia opposite of DUMBLESS

Ganglion Blockers ➔ Block all autonomic effects by Blocking the autonomic ganglia

04. Sympathomimetics Drugs adrenergic Drugs

Members and Classification



Direct acting

Mnemonic: *Please call Noor do all isoproteins*

Please ➔Phenylephrine (alpha 1)

Call ➔ Clonidine (alpha 2)

Contents

Noor ➔ Norepinephrine (alpha non selective)

Do ➔Dobutamine (beta 1)

All ➔albuterol (beta 2)

Isoproteins➔ isoproterenol (beta 3)

Indirect acting

Mra aik friend hay name inam or mujhay wo tab hi yad karta hay jab usko loi kam ho
I remember this as

Inam ko cam (cocam)

Coc➔ cocaine

Am➔ amphetamine

Effects produced from head to toe are

system	Effect produced
CNS	Catecholamines ➔do not enter brain Amphetamine ➔ stimulatory effect
Eye	mydriatic➔ alpha one (Big eyed fish) decrease aqueous humour formation ➔ alpha 2
Bronchi	Alpha 1 ➔ Bronchoconstriction (less marked) Alpha 2 ➔Bronchodilation (more marked)
Heart	Beta 1 and Beta 2 • inc firing of pacemaker • inc force of contraction • inc AV conduction velocity

Contents

GIT	Relation of smooth muscles Sphincters ➔ tone increased
Urinary Bladder	Increase sphincter tone
Uterus	Relaxation (beta 2 mediated)
Vascular effects	Vascular Effect • A ➔ C for contraction (alpha 1 mediated) • B ➔ D for dilation (beta 2 mediated)
Metabolic effects	Beta 1➔ renin secretion Beta 2 • increase gluconeogenesis • increase glycogenolysis • increase insulin secretion (increase uptake of glucose by muscles) Beta 3 ➔ Lipolysis

Drugs Mnemonics

Direct acting Sympathomimetics

1 Phenylephrine (alpha 1)

Two pherends (friends) Humpty dumpty& Super man went on alpha ones party

Pherends➔ phenylephrine

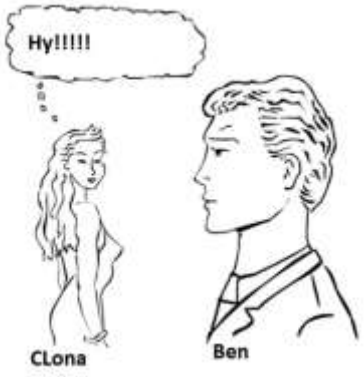
Contents

Humpty ➔ hypertension

Dumpty ➔ nasal decongestant

Super ➔ supraventricular tachycardia

Man ➔mydriatic (ophthalmic use)



2 Clonidine (alpha 2)

Clona said …..Hy two (to) Ben!

Two for alpha 2

Hy➔ Hypertension

Ben ➔ minimize withdrawal symptoms of benzodiazepines

3 Norepinephrine (alpha non selective)

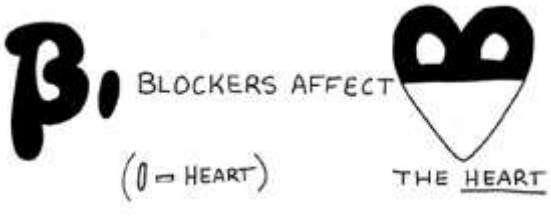
Noor shocked us by her marks

Norepinephrine is basically used in treatment of sock (septic and neurogenic)

4 Dobutamine (Beta 1 ➔ we have one heart in our body)

Used to increase cardiac output in congestive cardiac failure)

- ◈ produces little change in heart rate
- ◈ Do not significantly elevate myocardial oxygen demand (advantage over other sympathomimetic

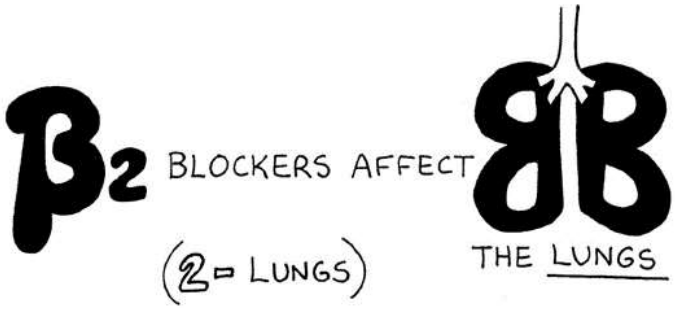


- ◈ Increase AV conduction ➔ caution for atrial fibrillation

5 Albuterol (beta 2➔ we have two lungs)

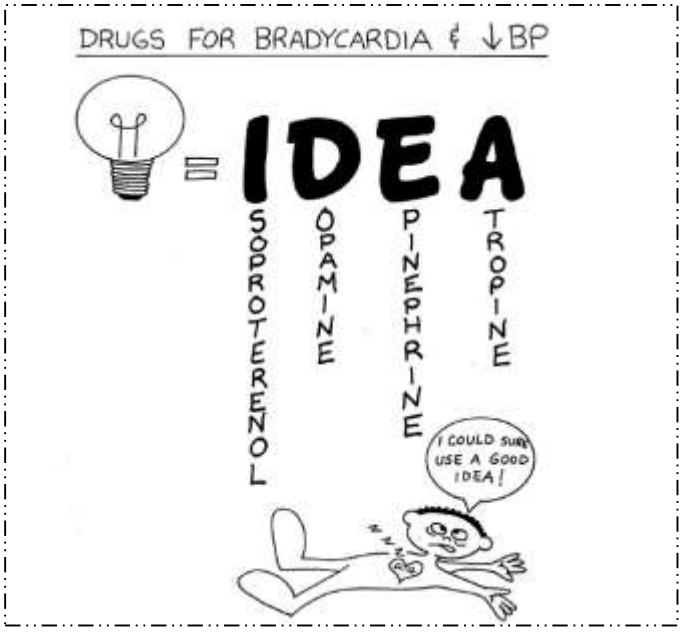
Albuterol lessens bronchospasm

Contents



6 Isoproterenol (beta 1 and beta 2) ➔ we have one heart and two lungs**)**

- Stimulator of heart in emergency conditions
- Nebulizer for asthma (bronchodilator)
- In Bradycardia



7 Epinephrine or adrenaline (alpha and beta receptors)

ABCDE

- A 4 adrenaline
  - Anaphylactic shock
  - Asthma (acute attacks)
  - Anaesthesia (local ➔ increase duration)
  - Asystole
- B ➔ Bronchoconstriction
- C ➔ Cardiac arrest

Contents

- D ➔ dizziness and headache
- E ➔ Eyes (treatment of glaucoma ➔ 2 percent solution is used)

Side effect (C_3)

- CNS ➔disturbance + anxiety + fear + headache + tremors
- Cardiac arrhythmias
- Cerebral haemorrhages (due to elevated Blood pressure)

Interactions

Person having cocaine or suffering from hyperthyroidism and you gave him epinephrine ➔ he will have exaggerated cardiac effects of epinephrine

8 Dopamine (alpha and beta effects)

D for Dil walay

- + Inotropic effects (inward movements mean contractibility)
- + chronotropic effects (chronic time related mean rate of contraction
- Blood flow ➔ increase blood flow to viscera's and kidneys

Used in Shock treatment. As it stimulate heart by beta 1 receptors

- Preferred over norepinephrine because it increases blood flow to viscera's and kidney
- Increases glomerular filtration rate

While nor epinephrine decreases blood flow to kidney may lead to renal shutdown.

Adverse effects

Excessive sympathetic effects

Rapidly metabolized

9 Metoprolol and terbutaline ➔ beta 2 receptor ➔ bronchodilators

- Used in asthma.

Indirect acting Sympathomimetics

1 Amphetamine

Displace stores of nor epinephrine from nerve endings

Uses

A hyperactive naughty child depressed her Ant.

A ➔ amphetamine

Hyperactive ➔ *

Naughty ➔ Narcolepsy

Child ➔ CNS stimulant

Depressed ➔ Depression treatment

Her ➔ Hypotension

Ant ➔ Apatite control

Adverse effects

- Hypertension (sympathetic drug and sympathetic system increase blood pressure by increasing heart pumping)
- Dependence liability high (Amphetamine is like a Fanta bottle when I drink I liked so much that now I am dependent on it)
- Pregnancy ➔ developmental problems in child

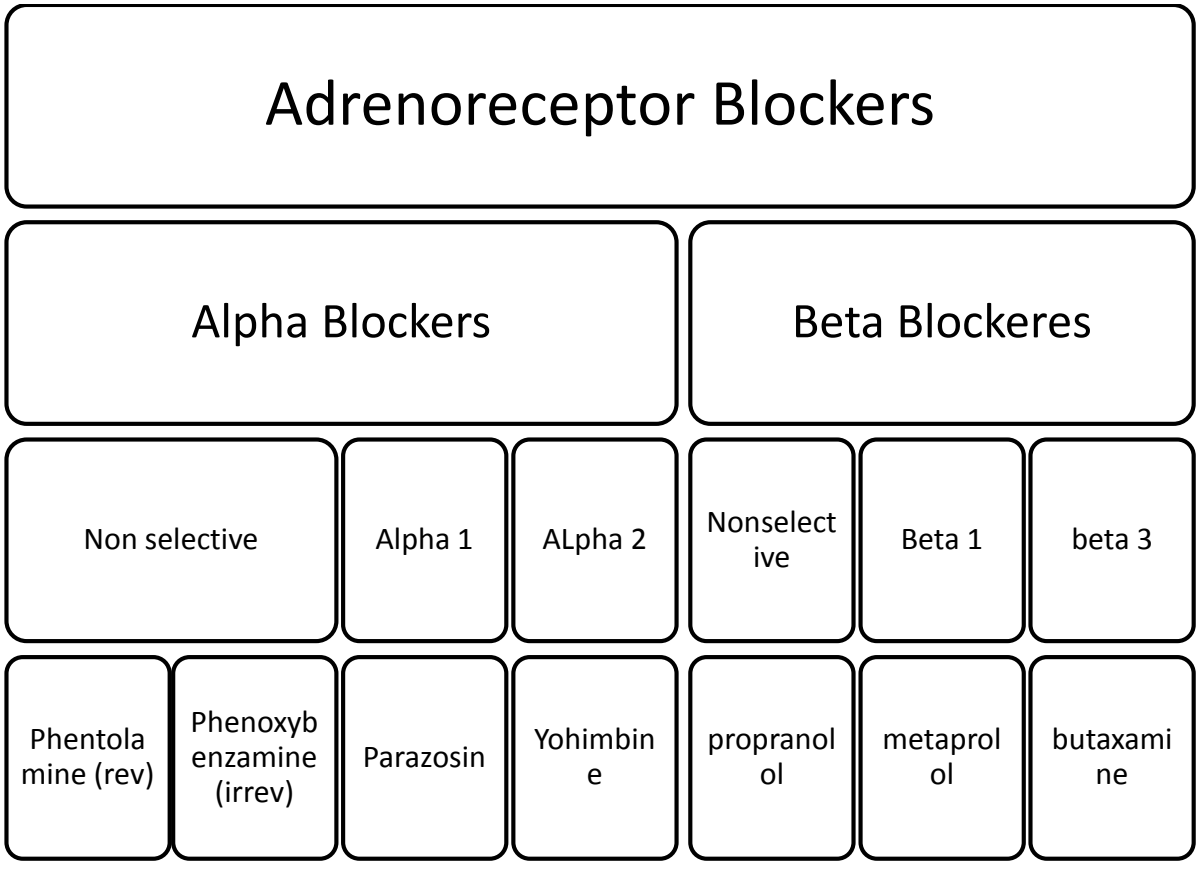
2 Ephedrine

Like amphetamine

- Increase half life
- Less addiction liability.

05. ADRENORECEPTOR BLOCKERS or SYMPATHOLYTICS

Members and Classification.



Mnemonic: pit-bull (dog name) par yonhi pathar maro at buttocks

Pit-bull

- Pit ➔phentolamine (alpha nonselective) reversible

Contents

◈ Pit-bull➔phnoxybenzamine (alpha nonselective) irreversible

Par ➔ parazosin (alpha 1)

Yonhi ➔ yohimbine (alpha 2)

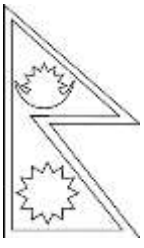
Maro ➔ metoprolol (beta 1)

At ➔ atenolol (beta 1)

Buttocks ➔butaxamine (beta 2)

This was one example from each group

Beta Blockers



The NEPAL prime minister

The ➔timidolol

N ➔Nadolol

E ➔Esmolol

P ➔Pandolol

A➔Atenolol

L ➔Labetolol

Prime ➔ propranolol

Minister ➔metaprolol

TRICK

A to M are Beta 1 Blockers

Rest from N to Z are non-selective Beta Blockers

Beta 2 Blocker ➔Butaxamine (only)

Cardioselective Beta Blockers or Beta 1 Blockers

Beta blockers acting exclusively at myocardium

Contents

Beta blocker➔butaxolol

Acting ➔acebutalol

Exclusively➔Esmolol

At ➔ atenolol

Myocardium➔metaprolol

Effects Produced by Alpha blockers

Most important effects are of CVS effects

- No significant direct cardiac effects are produced by them
- They cause baroreflex mediated tachycardia (reflex activated due to decrease of arterial pressure)

Epinephrine reversal phenomena

Blood Pressure effect of Epinephrine

- Increase of Blood Pressure occurs (alpha mediated more alpha 1) (Presser effect)
- Because epinephrine act both on alpha and beta
  But effect of alpha is more so increase B.P occurs

But if Person is on Alpha Blockers and we gave him epinephrine then

- Decrease of Blood Pressure occurs (Beta mediated as alpha are on Block) (depressor effect)

Effects

A ➔ Alpha	C ➔ Vasoconstriction
B ➔ Beta	D ➔ Vasodilation

Selective alpha 1 blockers are more associated with cardiac symptoms than non-selective alpha blockers

But

Non-selective alpha blockers are more associated with reflex tachycardia than alpha 1 blockers

Clinical Uses of Alpha Blockers

PMDC

P_4

- Pressure ➔ Blood Pressure ➔Hypertension
- Pheochromocytoma
- Penile erection ➔phentolamine and yohimbine mediated
- Peripheral vascular disease

M ➔ Migraine

D ➔ Disorders related to sleep & psychotic disorders

C ➔ Congestive cardiac failure

Drugs Mnemonics

1 Phentolamine (alpha non selective and reversible blocker)

P ➔Pheochromocytoma

And antidote in alpha agonist overdose

2 Phenoxybenzamine (alpha non selective and irreversible blocker)

PCR

P ➔Pheochromocytoma

Contents

C ➔ carcinoid use

R ➔Reynard's disease

3 Parazosin (alpha 1 Blocker)

P for parazosin

◈ Pressure ➔ increase B.P ➔ hypertension

◈ Benign prostate hyperplasia

4 yohimbine (alpha 2 blocker)

Obsolete use for erectile dysfunction

Side effects

OTG (OTG software is an android mobile software used to attach use to mobile) or you can use **GOT**

O ➔ orthostatic hypertension

T ➔ reflex tachycardia

G ➔ gastric distress

Beta Blockers

Clinical uses

Mag took maha

MAG took MAHA

CNS

M ➔ migraine

A➔ anxiety

EYE

G ➔ Glaucoma

Thyroid

Took ➔ thyroid storm

CVS (MAHA) ^{2}

M ➔ Myocardial infarction + Cardiomegaly

A➔ Angina + arrhythmias

H ➔ Hypertension + Heart failure

A➔ Aortic aneurysm + with alpha blockers to treat pheochromocytoma.

Drugs Uses Mnemonics

1 Non Selective Beta Blockers

- Uses are MAG took MAHA.
- Additionally Propranolol is also used in stage fright
- Timolol➔ used in Eyes (Because it lacks local anaesthetic activity)
- Pandolol➔ it is a partial agonist so can be used in asthmatic persons (while others are contraindicated)
- Nadolol➔ longer duration

2 Beta 1 Blockers (Cardioselective beta blockers)(Atenolol)

- Used for MAHA
- Esmolol also used for thyroid storm treatment

3 Beta 2 Blocker (butaxamine)

No use (research purposes)

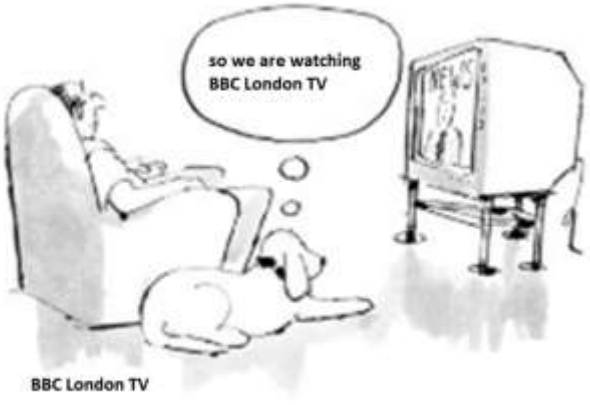
Side effects of beta blockers

(confused and delerium)**BBC London TV**

B ➔ Bradycardia and hypotension

B ➔ Blood Pressure drop

And Bronchoconstriction



Contents

C ➔Cough

London ➔ lipid metabolism disturbance (Beta 3)

T ➔ Tiredness

V ➔ Vivid dreams and yawing

Contraindications for Beta Blockers

ABCDE

A➔ asthma

B ➔ Heart Block

C ➔ COPD and cough

D ➔ Diabetic (as beta 2 releases insulin and we are going to inhibit Beta 2 so patient will be on risk)

E ➔ electrolyte imbalance (hyperkalemic patient at risk)

Usage in Asthma patient

As Beta Blockers are contraindicated in asthmatic person because they causes bronchoconstriction

So there are some beta blockers with slight agonist activity and are going to least effecting asthmatic person so we are to use them they are

- Acebutalol
- Esmolol
- Metoprolol

In fact these are beta 1 selective and beta 1 receptor are only in heart not in lungs so safer for them

Full antagonist like propranolol (beta non selective ➔also have beta Blockage effect on beta 2 receptor present in lungs) causes severe bron-chospasm so contraindicated in asthmatic person

Usage in Glaucoma patient

Drugs lacking local anaesthetic activity like Timolol are used while other drugs causes local anaesthesia and result in loss of reflexes

Drugs acting on Smooth Muscles

Contents

06. Histamine and Seroto-nin and Ergot Alkaloids

Histamine Effects

H ➔HCl Production

I ➔Inflammation

S ➔ Strong vasodilation

T➔ Therapeutic value none

A ➔ Allergy

M ➔ By Mast cells

I ➔Ig E

N ➔ Narrow air ways (bronchoconstriction)

Location of Histamine Receptors

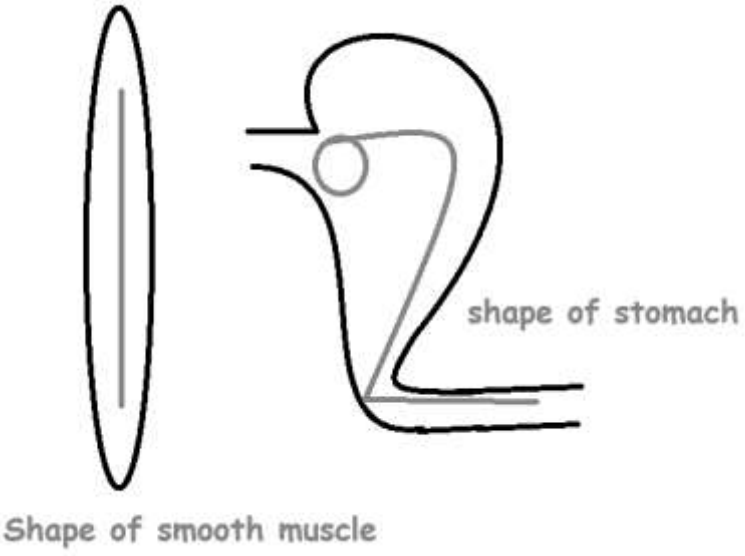
H1 Receptor

Located in smooth Muscle (imagine shape of smooth Muscle just like one for me so H1 is in smooth Muscle)

H2 Receptor

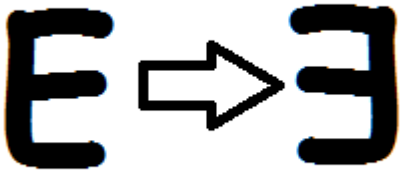
Located in stomach (If I rotate stomach to 90 degree left then it make me shape of 2 so H2 is in Stomach)

Contents



H3 Receptor

Located in Endings of Nerves (Mean in Nerve Endings).



H4 Receptor

Located in Leukocytes (Do you remember Charlie ➔ Char for 4 and lie for Leukocytes

Location of Serotonin Receptors

HT 1D Receptors

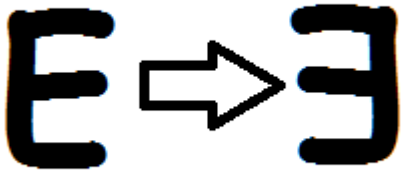
D for Dimag so they are located in Brain

Contents

HT 2 Receptors

Two mean second and second mean smooth Muscles

So second histamine is in smooth Muscles



HT 3 Receptors

Located in Endings of Nerves

And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor Trigger zone.

5HT 4 Receptor

Enteric Nerve endings (khuch khud bhi yad kar lo)

Important Drugs and members from these Groups

H1 Blockers

First Generation

DiDi promotes cycling

Di ➔Diphenhydramine

Di ➔Dimenhydrinate

Promotes ➔ Promethazine

Cycling ➔cyclizine

Didi promotes cycling

&

Didi have mobile NGO

Mechanism

- ❖ Histamine receptor 1 Blockers
- ❖ Structurally resemble muscarinic and adrenergic receptors

Antihistamine + anticholinergic + antiemetics + antitussives

Clinical Uses

DiDi have mobile NGO

Have ➔ hay fever

Mobile ➔ anti motion sickness use

NGO ➔ angioedema

Side effects

DiDi have mobile NGO so stays away from home and many time she have to sleep in an automobile

So she sleeps in automobile

- ❖ Sleepy or sedation
- ❖ Automobile ➔ autonomic side-effects

Second generation

Its member is cetirizine and I remember this as SITRIZINE while so S for second, S for sitrizine this sounds fair

Generation 2 lacks effects on Autonomic receptors and are not Antimotionsickness agent

Another member is LORAtidine

Other all stuff remain same as that of First Generation

Side effects are less

H 2 Blockers

FRaNCeTidine

F ➔Famo + tidine➔Famotidine

R ➔ Rani + tidine➔ ranitidine

N ➔Niza + tidine➔Nizatidine

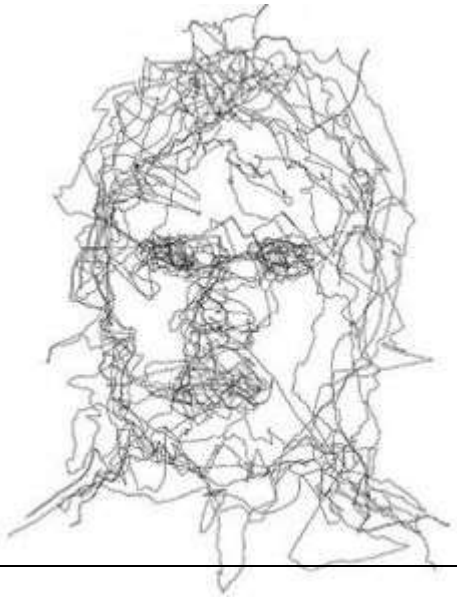
C ➔Cime + tidine➔ Cimetidine

Femo rani niza (Nazia) Cime sounds just

Like Girl name

and tidine in Punjabi we say tid to abdomen so you can remember this as Femo, Rani, Niza and Cime are Girls having Big Tids and there uses will indicate that they are acting on tids

Uses



GPS Dr

G ➔ GERD

P ➔ Peptic ulcer

S ➔ Stress related gastroenteritis

Dr ➔ Dyspepsia

5HT 1 agonists

Suma Riza farva nay zalim nara lagaya (mnemonic from Fozia shafi from Nishtar Med college)

Suma ➔Suma + triptan➔Sumatriptan

Riza➔Riza + triptan➔Rizatriptan

Farva➔Frova + triptan➔Frovatriptan

Zalim➔Zalmo + triptan➔Zalmotriptan

Nara ➔Nara + triptan➔Naratriptan

Or nara itnain zor ka tha k logon k sar main dard ho gia or unk chest main dard shro ho gia

Uses

- Migraine
- Cluster headache

Adverse effect

- Chest pain
- Dizziness

5HT 2 antagonists

Two mean K2 (mountain in Pakistan)

K 2 ➔ketaserine (2 ➔ 5HT2 antagonist)

Uses

Two for tension so used in hypertension

Adverse effect

Hypotension.

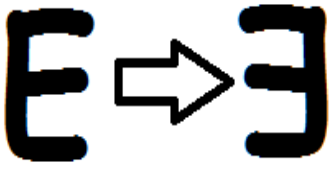
5HT3 Antagonists

Location of HT3 receptor is

HT 3 Receptors

Located in Endings of Nerves

And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor Trigger zone.



So it will have role in vomiting

Contents

And its antagonists will stop vomiting

Use

- ❖ Antiemetic in chemotherapy
- ❖ Post-operative vomiting

Drugs

Imagine Granny is driving a Honda motor cycle and everyone saying hello! Hello!

Granny ➔ Granisetron

hONDA➔Ondasetron

Another member is Alosetron that is used in irritable bowel syndrom

Adverse effect

Arrhythmias.

5HT4 Partial agonist.

5HT4 receptor location is

5HT 4 Receptor

Enteric Nerve endings (khuch khud bhi yad kar lo)

So its use will be somewhere in Git it increases GIT motility so used in Irritable bowel disease and adverse effect will be diarrhoea

Drug➔Tegaserod

Ergot Alkaloids

These are Partial agonists at

- ❖ Alpha adrenoreceptors
- ❖ 5HT receptors
- ❖ Dopamine receptors

Drugs

They are ergot alkaloids and erg comes in their names

- Ergotamine
- Ergonavine
- Another member is bromocriptine

Uses

HOME (I Built two homes in this book one in ergot alkaloids and another in Loop diuretics so you will visit my other Home in
adverse effects of Loop diuretics)

H ➔Hyperprolectenemia (Bromocriptine is release inhibitor of prolactin)

Also used in Parkinsonism

O ➔ Obstetric Bleeding ➔ Ergotamine and Ergonavine erg containing members are used because they causes strong vasoconstriction so they will stop bleeding

M ➔ ergotamine used in migraine in acute attacks and in prophylaxis

E ➔ expel baby out (abortion and miscarriage) ➔ because they produces powerful uterine contractions (Ergonavine is prototype)

Adverse effects

- ❖ Ischemic gangrene (because they produces long lasting vasoconstriction

Contents

- Uterine effects ➔ sensitization of uterus to alkaloids
- Hallucination
- GIT effects

Contents

07. Prostaglandins and other Eicosanoids

Pathways

- Lipoxigenase pathway ➔**L** ➔Leukotrienes
- Cyclooxygenase pathway ➔ others all
  - Prostaglandins
  - Prostacyclin
  - Thromboxane

Mechanism of action

Action are brought about by cell surface G protein coupled receptors

Some inhibitors to be remember

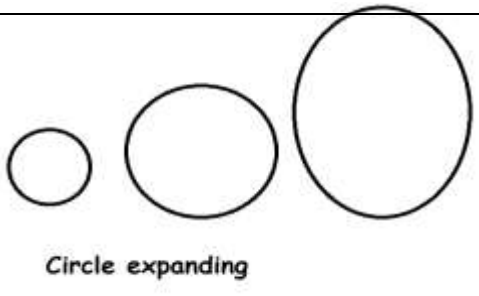
- Corticosteroids ➔ Phospholipase A_2 (convert phospholipid ➔Arachidonic acid)
- NSAIDS ➔ Inhibit COX (cyclooxygenase)
- Zeliuton➔Ze + Li ➔Ze indicate this is Zeliuton and Li indicate it is **li**poxygenase enzyme inhibitor
- Zafirlukast➔zafir+ Luko➔Zafir indicated this is zafirlukast and Leuko indicate that this ihibit**Leuk**otriene receptor antagonist
- Montelukast➔ Brother of zafirlukast

Effects Produced By Eicosanoids.

On Blood Vessels

Imagine a circle expanding

Circle ➔ Prostacyclin (PGI_2)



Circle expanding

Contents

Expanding ➔ PG E_1 and PGE_2

So their action will be vasodilation by expanding the calibre of the blood vessel

On Bronchi

Circle expanding again and here will be Bronchodilation.

On Platelet aggregation

PGI_2 and TXA_2 both are opposition leaders

- PGI_2 ➔ causes Bronchodilation that will help in making blood flow easy so they will decrease platelet aggregation
- TXA_2 ➔ is opposition leader so it will increases platelet aggregation

On uterus

PGE_2 ➔ analogue Dinopreston (have dual action on uterus)

- ⇨ In lower concentration ➔ causes contractions
- ⇨ In higher concentrations ➔ causes relaxation

Di mean two this mean Dinopreston is having dual action.

PGF_2➔its analogue is Latinopreston.

Dinopreston and Latinopreston➔ are used in 2nd trimester abortion

Chemotactic factor

B for Bhago➔ B_4 Bhago➔ LTB_4 is leukocyte chemotactic factor

Clinical Uses

Obstetrics

Dinopreston

and latanopreston➔are used in 2 trimester abortion

Contents

- Dinopreston is PGE_2 analogue
- While Latanoprestone is PGF_2 analogue

So we can say E_2 and F_2 analogues are used in 2nd trimester abortion.

Later stages they induces labour but are not used clinically due to their side-effects.

Paediatrics

PGE_1 (Misoprostol) ➔ used to maintain patent ducts arteriosus before surgrical cessation is done

Miso**P**rostol➔ maintain patent ducts arteriosus

Dialysis

PGI_2 (epoprostenol) ➔ prostacyclin analogue is used to prevent platelet aggregation in dialysis machine due to platelet aggregation antagonist.

Pulmonary use

PGI_2 (epoprostenol) ➔ used in pulmonary hypertension

Peptic Ulcer

PGE_1(Misoprostol) is used

Genitourinary tract

PGE_1 (Misoprostol) is used

Ophthalmology

PGF_2 (Latanoprostol) ➔letina = Lenz + retina.

In glaucoma

Drugs which is which

PGE_2

Dinoprostone➔Di mean two and Die mean Di + E mean 2E

PGE_1

Misoprostol ➔ M for mono so it is 1 and if we rotate M it will Become E so it is 1E

PGF_2

Latanoprost➔Lat mean Laat mean Leg and leg has foot so from foot it is F two

PgI_2

Epoprostenol➔khudyadkaro

Eicosanoid antagonists

1 Leukotriene antagonist

Lipoxygenase inhibitors ➔Zeliuton

- Zeliuton ➔ Ze + Li ➔ Ze indicate this is zeliuton and Li indicate it is **li**poxygenase enzyme inhibitor

⇨ It Blocks the synthesis of leukotrienes

⇨ Used in prophylaxis of asthma

Leukotriene receptor inhibitors ➔zafirlukast and Montelukast

- Zafirlukast ➔ zafir + Luko ➔ Zafir indicated this is zafirlukast and Leuko indicate that this ihibit **Leuk**otriene receptor antagonist
- Montelukast ➔ Brother of zafirlukast

Contents

- ⇨ Block cytoplasmic leukotriene receptors
- ⇨ Used in prophylaxis of asthma

2 Cyclooxygenase inhibitors (NSAIDS)

Nonselective COX inhibitors

- ⇨ Ibuprofen (Reversible)
- ⇨ Indomethacin (Reversible)
- ⇨ Aspirin (Irreversible)

COX2 Selective

- ⇨ Celecoxib (damage produced by cox_1 is prevented

Will discuss NSAIDS in detail in NSAIDS section.

Contents

08. Nitric oxide donors and inhibitors

Nitric oxide synthase inhibitors

NCB (Nation commercial bank's employers) in medical examination.

Isoform 1

N➔nNOS➔neuronal

C ➔cNOS➔ epithelial

B ➔bNOS➔ epithelial

Isoform 2

In ➔iNOS➔ Macrophages

Medical ➔mNOS➔ muscles smooth

Isoform 3

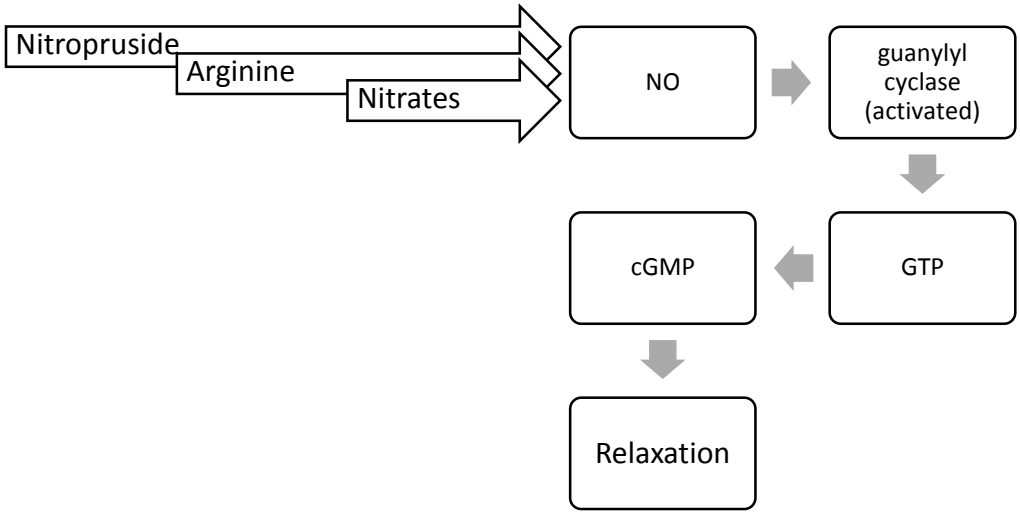
Exam ➔eNOS➔ endothelial

NOS inhibitors

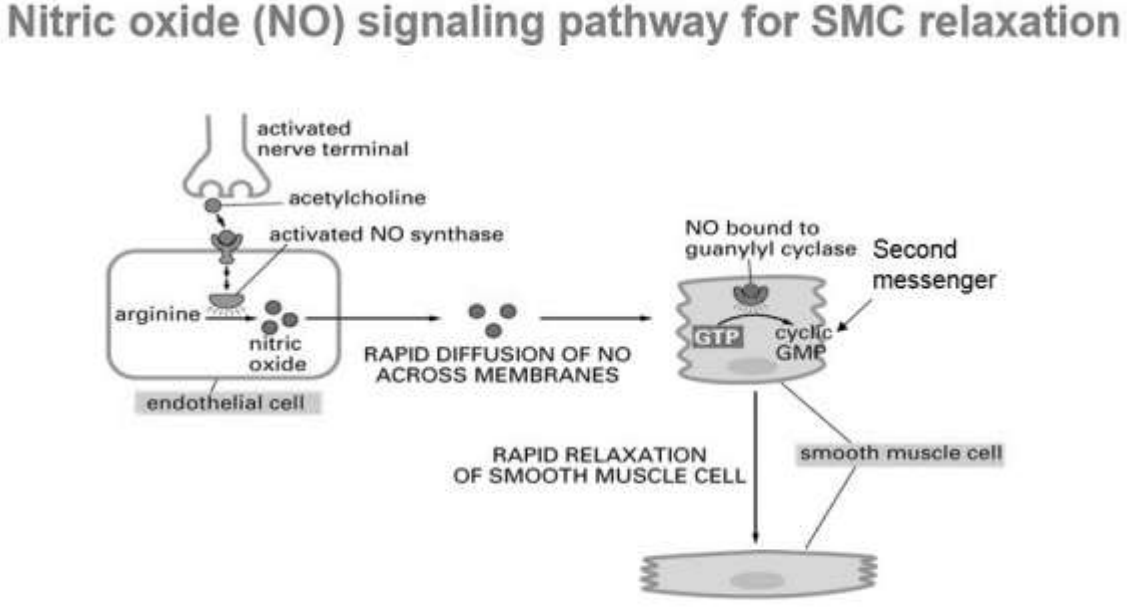
NOS inhibitor is N-methyl arginase

Synthesis of NO can be inhibited by Heme and Hemoglobin

Contents



Effects Produced



- ⇨ Smooth muscles ➔ vasodilator
- ⇨ Cell adhesions ➔decrease platelet aggregation and decrease neutrophil adhesion

Contents

- ⇨ Facilitate inflammation
- ⇨ Act as neurotramitter

Uses

NO papa

NO ➔ uses of NO

P ➔ Pressure ➔ Blood pressure control ➔ hypertension

A➔antianginal➔ nitro-glycerine

P ➔ pulmonary hypertension and in penile erection maintenance in erectile dysfunction

A➔ antioxidant and antithrombic

Risk factors

- ⇨ smokers
- ⇨ Septic shock (may exaggerate)
- ⇨ Hypotensive

Side-effects

TOTM

T ➔ tachycardia ➔ by baroreceptor reflex

O ➔ orthostatic hypotension

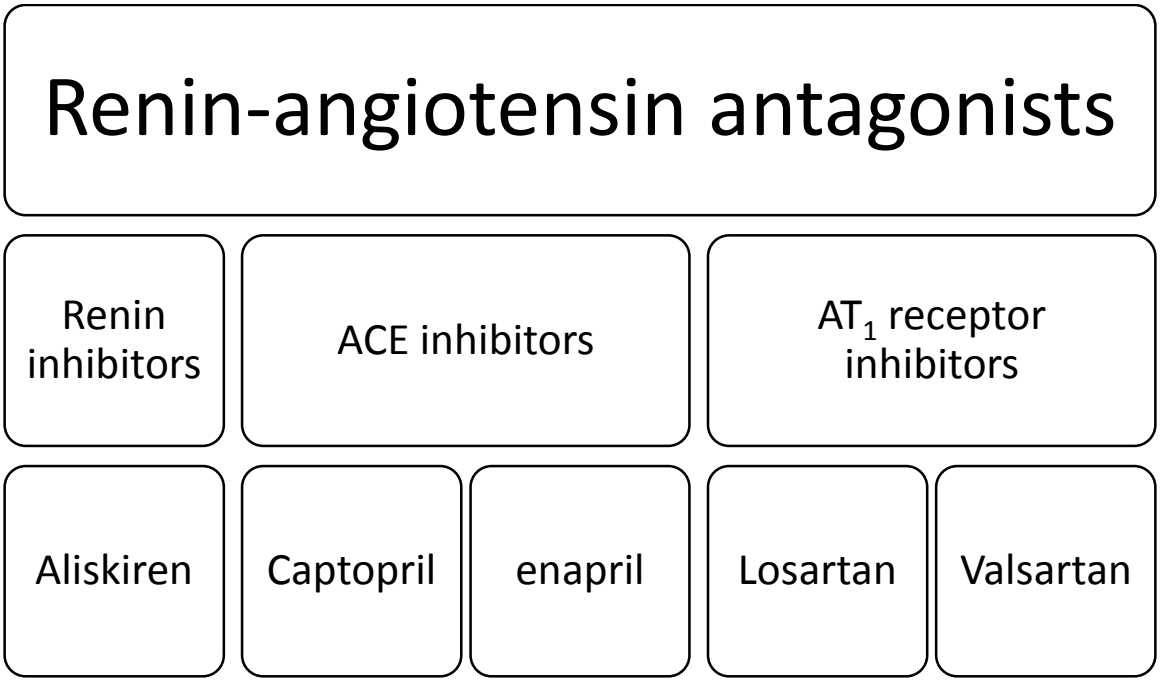
T ➔ throbbing headache

M ➔methmoglobenemia

Contents

09. Vasoactive Peptides

Renin-angiotensin antagonists



Aliskiren

Renin inhibitor ➔ reduce angiotensin 1, 2 and aldosterone

Use

Hypertension

Adverse effects

Angioedema and renal impairment

Contents

ACE Inhibitors

Pril sisters➔ captopril and enapril

- ⇨ Inhibit ACE enzyme ➔decreases AT_2 and aldosterone secretion and increases bradykinin secretion.

Use

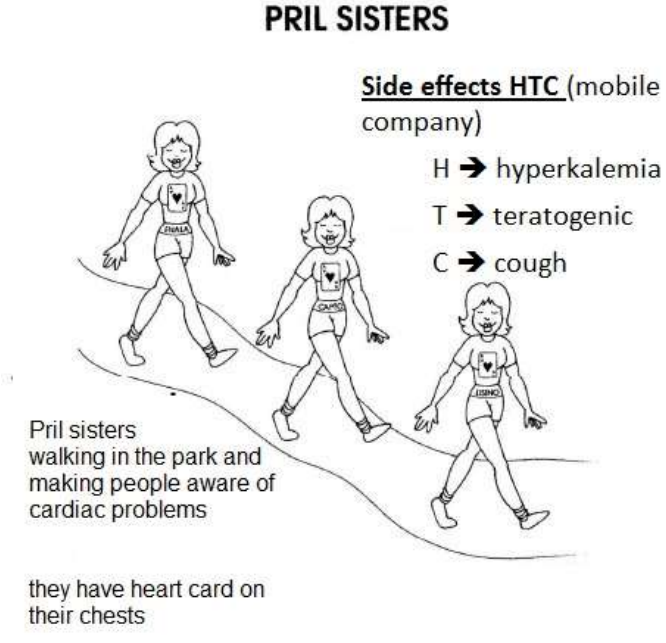
- ⇨ Heart failure
- ⇨ Hypertension

Side effects HTC (mobile company)

H ➔hyperkalemia

T ➔teratogenic

C ➔ cough



AT receptor antagonists

Sartan brothers ➔ Losartan and Valsartan

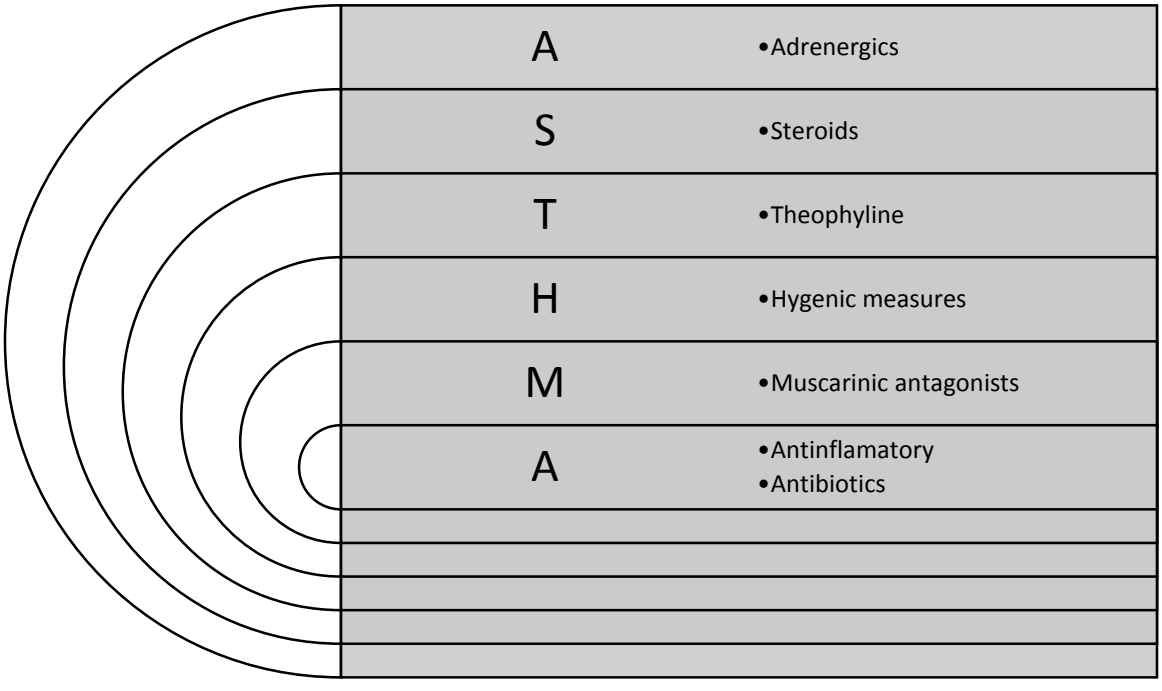
- ⇨ AT_1 receptor inhibitors ➔ reduces effects of angiotensin II

Uses and adverse effects are almost same as Pril sisters

Contents

10. Drugs used in asthma treatment

Drugs used and classification



Adrenergics.

Beta agonists

Asif is asthamatic person want to buy some Beta adrenergic drugs

Contents

A➔albuterol

S ➔salmeterol

I ➔indacaterol

F ➔formoterol

First member Albuterol is short acting while other three are long acting beta agonists

And he run short of money so he goes to **ATM** now he can buy two other short acting beta agonists also.

A➔albuterol

T ➔terbutaline

M ➔metoproternol

Uses

Short acting ➔ in acute treatment

Long acting ➔ in prophylaxis and chronic use

- Long acting are not used in acute attacks because of their slow onset of action

They are first line of treatment in asthma treatment and are used in combination with corticosteroids and are also effective in COPD

Adverse effects

Important adverse effects are

- Skeletal muscle tremors
- If used excess ➔ arrhythmias

Non selective Sympathomimetics

Epinephrine and isoproterenol ➔ were also used previously

Indirect acting Sympathomimetics

Ephedrin➔ release stored catecholamines➔ obsolete use

Steroids➔ **Corticosteroids.**

Birthday party

Inhaled cosrticosteroids

Birth➔bachlomethasone

Day ➔dexamethasonium

Systemic corticosteroids

Party ➔ prednisone (oral) and prednisolone (I/V)

Corticosteroids inhibit phospholipase A_2 that results in decrease formation of inflammatory mediators

- Corticosteroids ➔ Phospholipase A_2 (convert phospholipid ➔ Arachidonic acid)

Side effects

Inhaled

- Pharyngeal candidiasis
- Other effects are minimal because of lesser systemic absorption

Oral and Parenteral

Cushingoid

C ➔ cataract

U ➔ ulcers

Contents

S ➔ skin stria + skin thinning + salt retention

H ➔Hirsutism+ hypertension + hyperglycaemia

I ➔ infections

N ➔ necrosis (avascular necrosis of femoral head)

G ➔ GIT ulcers

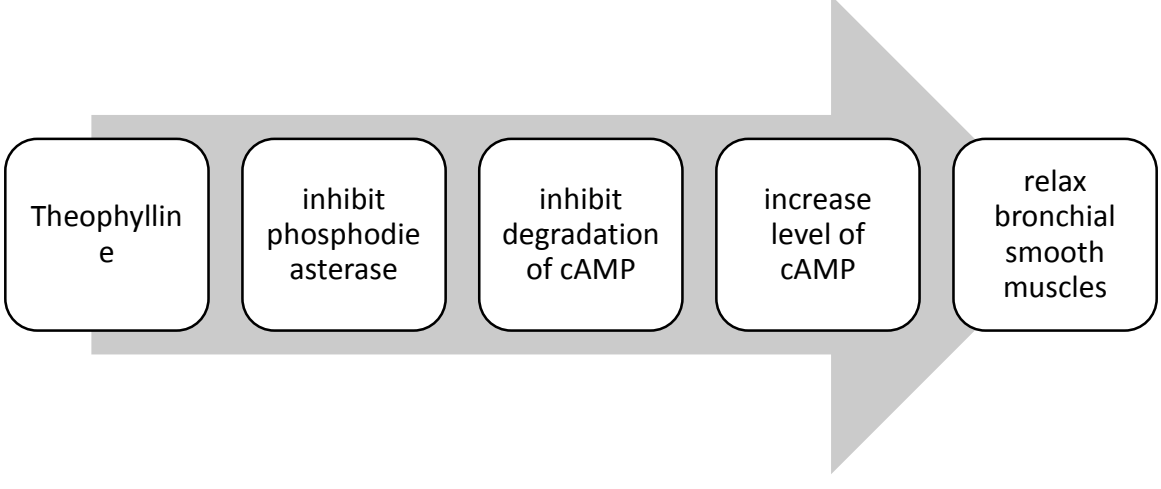
O ➔ obesity (buffalo hump obesity) + osteoporosis

I ➔ immune suppression

D ➔ diabetes mellitus

Theophylline.

(Methylxanthine derivative)



It also inhibit synthesis of leukotrienes and inhibit TNF alpha slowing the inflammatory process

Uses

- Prophylactic agent in asthma treatment

- COPD
- Infant apnea (in premature baby)

Adverse effects

TAAS

T ➔ tremors (T also indicate this drug is theophylline)

A➔ arrhythmias

A ➔ anorexia and asleep

S ➔ seizures

Caffeine also produces similar effects

Hygienic measures.

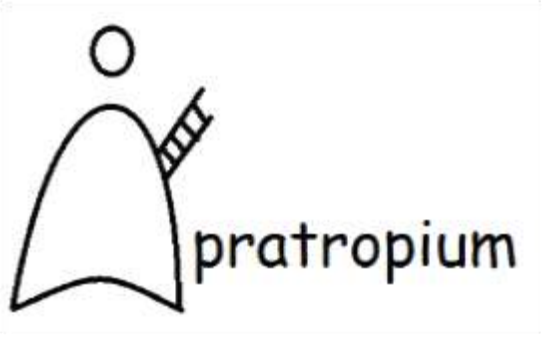
This is just to make word for asthma best method to avoid asthmatic attacks is to avoid trigger (stimulant of asthmatic attacks)

Like allergens, pollutants etc.

Muscarinic antagonists.

Contents

Ipratropium



- Asthma
- COPD

Prevent bronchoconstriction mediated by vagal discharge

⇨ Have no effect on chronic inflammation

Side effects

Minimum side effects of inhaler (minimum atropine like)

Anti-inflammatory agents.

1) Leukotriene antagonists

1 Leukotriene antagonist

Lipoxygenase inhibitors ➔ Zeliuton

❖ Zeliuton ➔ Ze + Li ➔ Ze indicate this is zeliuton and Li indicate it is **li**poxygenase enzyme inhibitor

⇨ It Blocks the synthesis of leukotrienes

⇨ Used in prophylaxis of asthma

Leukotriene receptor inhibitors ➔ zafirlukast and montelukast

❖ Zafirlukast ➔ zafir + Luko ➔ Zafir indicated this is zafirlukast and Leuko indicate that this ihibit **Leuk**otriene receptor antagonist

❖ Montelukast ➔ Brother of zafirlukast

⇨ Block cytoplasmic leukotriene receptors

Used in prophylaxis of asthma

2) Mast cell stabilizers

After a long fight with foreign invaders masto cell got exhausted he started watching cartoon network (CN) to stabilize himself.

C ➔cromolyn

N ➔nedocromil

- They reduce release of inflammatory mediators from sensitized mast cells.
- Used especially in children (as children watch cartoon network profoundly)
- Rarely used for prophylaxis

- Also used in other allergies like ophthalmic, nasopharyngeal and GIT allergies

May cause cough as adverse effect.

3) Antibodies (Omalizumab)

Aik mali tha to usko severe asthma hogia or us nain har kisam ki drug li and no response tu aik dr bola **O mali!** Antibody lay lo us say thk ho jaey ga

Omalizumab➔ Bind to IgE antibodies on mast cells ➔ reduce reaction to allergies

- Used as prophylaxis of severe respiratory asthma not responsive to all other drugs

Precipitating factors of asthma

Diplomat

D ➔ Drugs (Aspirin + NSAIDS + Beta antagonists) and DNA mean genatic factors

I ➔ Infections (URTIs and LRTIs)

P ➔ Pollutants (at work and at home)

L ➔ laughter (emotions)

O ➔Obesity

M ➔ Mites

A➔ activity (exercise) + atopic disease

T ➔ temperature (cold) + Tabaco (smocking)

Causes of asthma

A ➔ Allergens (most of the precipitating factors)

S ➔ small airways

Contents

T ➔ Tracheal obstruction

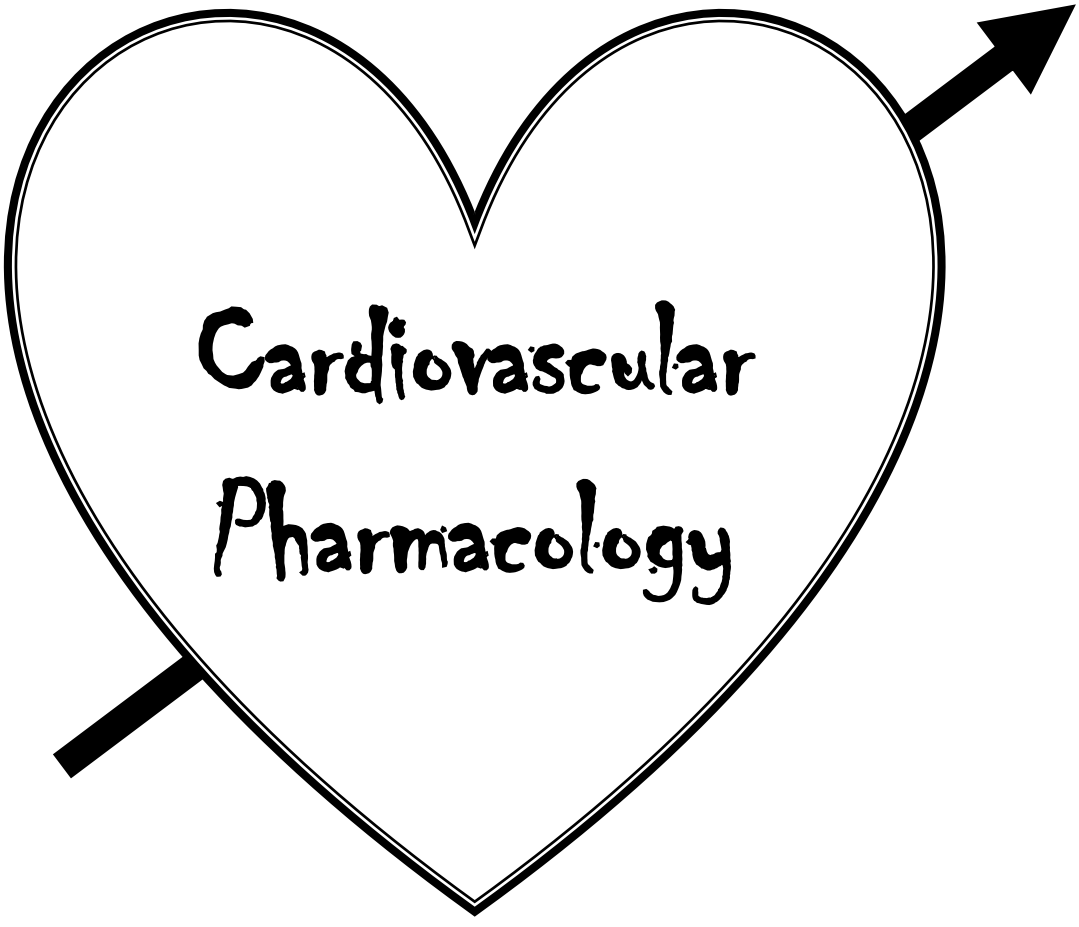
H ➔ heart failure

M ➔mastocytosis

A➔ anaphylaxis

Treatment strategies.

1) Avoidance of antigen or causative factor
2) Twice attacks or less per weeks
    a. Short acting beta agonists (SABA)
3) More than twice a weak
    a. Add inhaled corticosteroids to treatment (ICS)
4) Daily ➔ moderate attacks
    a. Long acting beta agonists added (LABA)
5) Multiple attacks per day
    a. ICS + SABA dose increased
6) Severe multiple attacks per day
    a. Systemic corticosteroids added hospitalized if needed



Contents

11. Drugs used in Hypertension

A	• Adrenergics • ACE inhibitors • Angiotensin receptor inhibitors • Aliskiren
B	• Beta blockers
C	• Calcium channel Blocers
D	• Diuretics
E	• Endothelial antagonists
F	• facilitate Vasodilation
G	• Ganglion blockers

Contents

Adrenergics.

Alpha adrenoreceptor agonists (centrally act on Alpha 2 receptors)

2 Clonidine (alpha 2)

Clonidine said .....Hy two (to) Ben!

Two for alpha 2

Hy ➔ Hypertension

Sudden discontinuation causes rebound hypertension due to salt retention as compensatory mechanism.

Rebound increase in blood pressure can be controlled by reinstitution of the clonidine therapy or administration of alpha blockers such as phentolamine

Contents

Alpha adrenoreceptor inhibitors

3 Parazosin (alpha 1 Blocker)

P for parazosin

- Pressure ➔ increase B.P ➔ hypertension
- Benign prostate hyperplasia

ACE Inhibitors

ACTION– ↓ PERIPHERAL VASCULAR RESISTANCE WITHOUT:

- ∅ · ↑ CARDIAC OUTPUT
- ∅ · ↑ CARDIAC RATE
- ∅ · ↑ CARDIAC CONTRACTILITY

Contents

ACE Inhibitors

Pril sisters' ➔ captopril and enapril

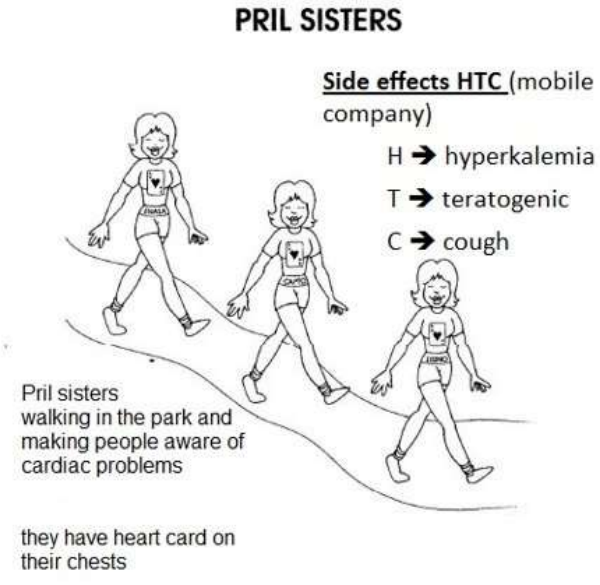
⇨ Inhibit ACE enzyme ➔decreases AT_2 and aldosterone secretion and increases bradykinin secretion.

Use

⇨ Heart failure
⇨ Hypertension

Side effects HTC (mobile company)

H ➔ hyperkalemia
T ➔ teratogenic
C ➔ cough



AT receptor antagonist.

AT receptor antagonists

Sartan Brothers ➔ Losartan and Valsartan

⇨ AT_1 receptor inhibitors ➔ reduces effects of angiotensin II

Uses and adverse effects are almost same as Pril sisters

Contents

Aliskiren.

Aliskiren

Renin inhibitor ➔ reduce angiotensin 1, 2 and aldosterone

Use

Hypertension

Adverse effects

Angioedema and renal impairment

Beta antagonists.

Contents

Beta Blockers

- Reduces cardiac output
- Reduction in renin release

Propranolol atenolol and labetalol are used commonly

CVS (MAHA) [2]

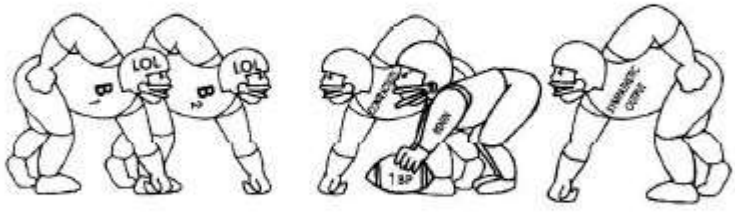
M ➔ Myocardial infarction + Cardiomegaly

A ➔ Angina + arrhythmias

H ➔ Hypertension + Heart failure

A ➔ Aortic aneurysm + with alpha blockers to treat pheochromocytoma.

THE "LOL" TEAM



The "**LOL**" team blocks hypertension by "blocking" (decreasing) the contractility in the heart, the renin release from the kidneys, and the sympathetic output from the vasomotor center of the brain.

For further reading go to chapter of beta blockers

Side effects of beta blockers

(confused and delerium)**BBC London TV**

B ➔ Bradycardia

B ➔ Blood Pressure drop

And Bronchoconstriction

C ➔ Cough

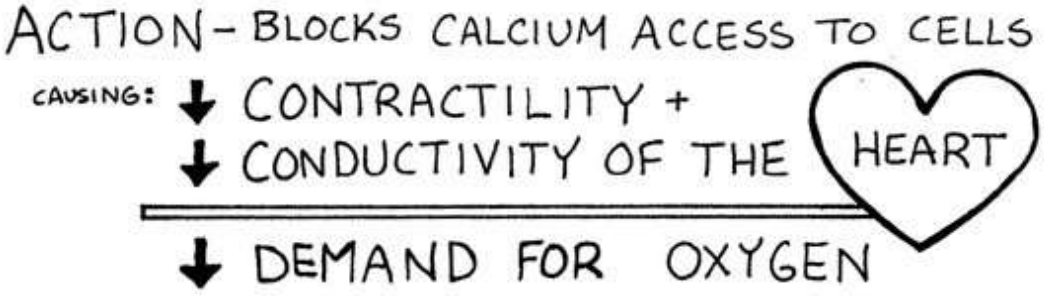
London ➔ lipid metabolism disturbance (Beta 3)

T ➔ Tiredness

V ➔ Vivid dreams and yawing

Ca^{+2} Channel Blockers.

Actions



Uses

Ca mash

C ➔ cerebral vasospasm

A➔angina

M ➔ migraine

A➔ atrial flutter and fibrillation

S ➔ supraventricular tachycardia

H ➔ hypertension

Contents

Adverse effects

Happy Dec. (happy December)

Happy ➔ hypotension and heart failure

D➔ cardiac depression + dizziness

E ➔ pulmonary oedema

C ➔ constipation

Diuretics.

Loop diuretic ➔furosemide (lofer drug)

Thiazide diuretic ➔ hydrochlorothiazide

Both are used in hypertension and heart failure

Endothelial Antagonist.

Busentan (Endothelial A and B receptor antagonist

Use in pulmonary hypertension

Facilitate vasodilation.

drugs those facilitate vasodilation

NO releasers		K^+channel openers		Ca^{+2}channel blocker
Hydralazine (oral)	Nitroprusside (parentral) name have P so.	minoxidil (oral)	Diazoxide (parentral)	detail above

NO Releasers

Hydralazine

Release NO by endothelial cells ➔ NO causes vasodilation

Uses

- Hydralazine is used in hypertensive emergencies
- Also used in heart failure

Nitroprusside

Release NO from drug molecule

Uses

- Hypertensive emergencies
- Cardiac decompensation

⇨ Adverse effects for NO releasers will be TOTM from chapter of NO

K^{+1} channel Openers

Contents

Minoxidil (prodrug)

Open K^+ channels ➔atrial smooth muscles hyperpolarization and vasodilation

Uses

Hypertension and male pattern baldness

Adverse effects

Hirsutism and tachycardia

Diazoxide

Open K^+ channels in smooth muscles and in glands

Uses

Hypertension and hypoglycaemia

Adverse effects

Opposite of use (hypotension and hyperglycaemia)

Ganglion Blockers.

Ganglion Blockers

1 Trimethoprim

T for tension

Used in Hypertension caused by pulmonary hypertension

2 Hexamethonium

H for hypertension

Used in hypertension (obsolete)

Antihypertensive drugs contraindicated in Pregnency

Dr from NASA

D ➔ Diuretics

R ➔ Reserpine

N ➔ Non selective Beta blockers

A ➔ ACE inhibitors

S ➔ sodium Nitroprusside

A ➔ AT_1 antagonists

Doctor from NASA

Contents

12. Drugs used in Heart failure

Cardiac failure

Decrease cardiac function as compared to needs of the body

Homeostatic responses of the body to decrease cardiac output

- By sympathetic nervous system
- By renin angiotensin mechanism

Drugs used in Cardiac failure.

Same drugs as hypertension are used in cardiac failure but finished before F (F mean failure finish) and C there was for Ca^{+2} channel blockers and here C is for Cardiac glycosides

A	• ACE inhibitors • Angiotensin receptor inhibitors
B	• Beta agonists • Beta antagonists
C	• Cardiac glycosides
D	• Diuretics
E	• Endothelial factor releasers

Contents

ACE and angiotensin receptor inhibitors.

Same as hypertension

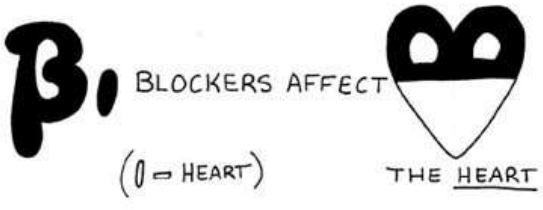
Beta agonists.

Dobutamine

4 Dobutamine (Beta 1 → we have one heart in our body)

Used to increase cardiac output in congestive cardiac failure)

- produces little change in heart rate
- Do not significantly elevate myocardial oxygen demand (advantage over other sympathomimetic



- Increase AV conduction → caution for atrial fibrillation

Beta antagonists.

Contents

Cardioselective beta blockers are used

- Cardevalol and labetalol also

Cardioslective Beta Blockers or Beta 1 Blockers

Beta blockers acting exclusively at myocardium

Beta blocker➔ butaxolol

Acting ➔ acebutalol

Exclusively ➔ esmolol

At ➔ atenolol

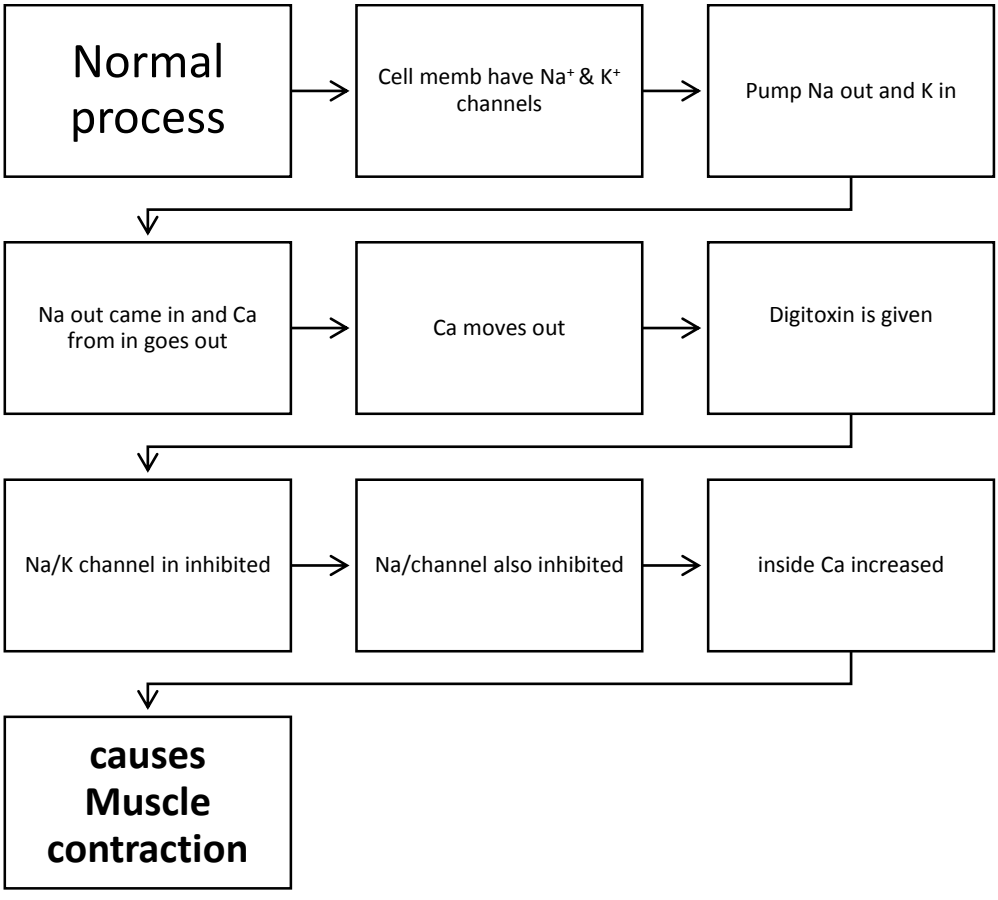
Myocardium ➔ metaprolol

Cardiac Glycosides.

Cardiac glycosides

- Steroid nucleus + Lactone ring + one or more sugars.
- Digitoxin is prototype and is obtained from foxglove plant

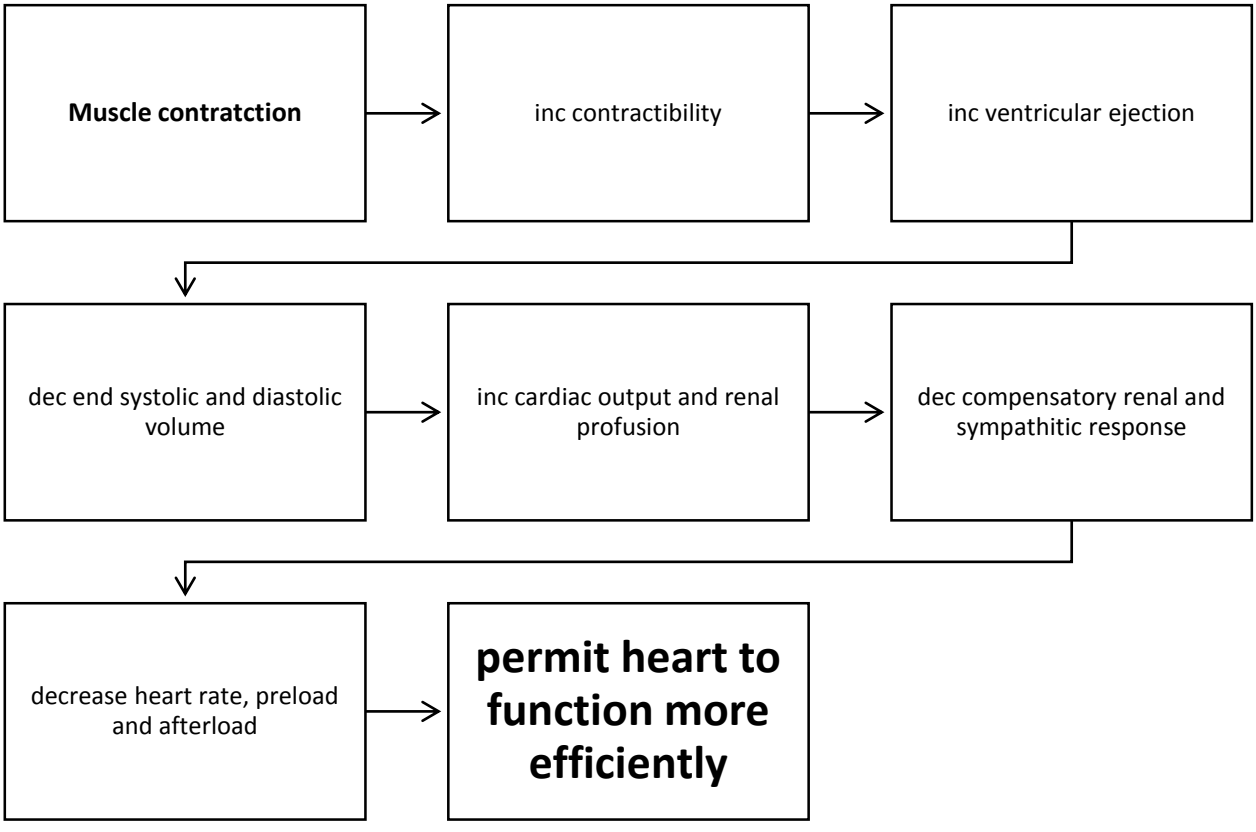
Mechanism



Effects Produced

Mechanical effects

Contents



Electrical effects

Early response (parasympathetic effects)

- Inc PR interval ➔ due to decrease AV conduction velocity
- Flattening of T wave

Toxic effects

- Inc automaticity caused by intracellular Ca^{+2} overload
- Premature ventricular beats

Clinical Uses of cardiac glycosides

Cardiac glycosides

C ➔ congestive cardiac failure

Contents

A➔ atrial fibrillation

Congestive cardiac failure

+ Inotropic effects are produced

⇨ So used in chronic heart failure

Atrial fibrillation

⇨ Dec velocity of conduction

⇨ Inc refractory period

Interactions

- **Factors that increase toxicity**
  - Hypercalcemia + hyperkalemia + hypomegnacemia
- **Digitalis induced vomiting**
  - Loss of Mg ➔ increase toxicity
- **Loop diuretics and thiazide diuretics**
  - Reduce serum Ca^{+2} level ➔Dec toxicity

Toxicity

Very And (very Andy drug)

Very ➔ vomiting + ventricular fibrillation

A➔ arrhythmias + AV node block and SA node block

N ➔ Nausea

D ➔ diarrhoea

Contents

Diuretics.

Same as hypertension

** First line of therapy for cardiac failure**

Endothelial factor releasers.

Hydralazine and Nitroprusside➔ same as hypertension

Non Pharmacological methods.

- Remove non-functional regions of myocardium.
- Resynchronization of left and right ventricles by pacemaker.
- Revascularization of coronary artery

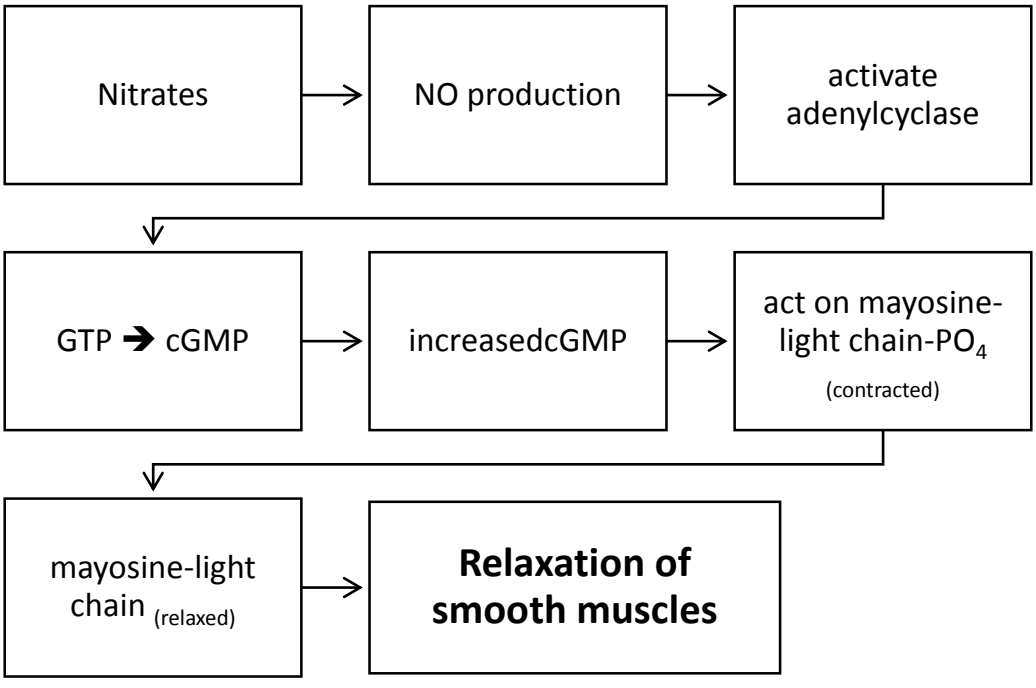
13. Drugs used in Angina pectoris.

N	• Nitrates
C	• Ca^{+2} channel blockers
B	• Beta blockers
Others	• metabolism modifiers

Or you can Use National commercial bank.

Nitrates.

Mechanism



Effects produced by Nitroglycerine

NO VCR

N ➔ nitroglycerine effects

O ➔ reduce oxygen requirements

V ➔ venodilation ➔ veins are more sensitive

R ➔ Reduce cardiac size and preload

Side effects

Totm (same as side effects of NO)

Side-effects

TOTM

T ➔ tachycardia ➔ by baroreceptor reflex

O ➔ orthostatic hypotension

T ➔ throbbing headache

M ➔ methmoglobenemia

Uses of nitroglycerine

A man has spasm

A ➔ angina pectoris

Man ➔ myocardial infection

Has ➔ severe hypertension

Spasm ➔ coronary artery spasm

Interactions

With sidenaphil

- Sidenaphil is used for Erectile dysfunction ➔ act by inhibit break-down of cGMP ➔ result inc of cGMP
- Nitrates ➔ also inc cGMP by increase production by release of NO

⇨ So Net effects produced by cGMP will be more marked

  - And will result high level of hypotension

Cyanide poisoning

Cyanide + iron of cyt P450➔ complex is formed ➔ oxidative metabolism is blocked

Nitrates➔ oxidize Hemoglobin iron (ferrous ➔ ferric) and result methmoglobin formation ➔ cyanide bind to methmoglobin avidly ➔result release of cyanide from cytochrome oxidase

Methmoglobin➔ carry less oxygen ➔ treated with methlyene blue to revert this effect.

Ca^{+2} **Channel Blockers.**

Do this from hypertension

Beta blockers.

Same as hypertension

Uses

- Prophylactic treatment of angina
- Prevent exercise induced angina
- In vasospastic angina
- Combination with nitrates

Other drugs.

Ronalazine

Effects are produced by alteration of intracellular levels of Na^+

roNAlazine ➔ Na^+ channel effects.

- Increase Ca^{+2} expulsion by Na^+ -Ca^{+2} channels
- Moderately effective in angina
    - Dec angina episodes and increase exercise tolerance.

Ivabradine.

Inhibit SA node➔ result hyper polarization➔ dec heart rate

- Symptomatic treatment of angina

Nitrates + Ca^{+2} channel blockers + Beta blockers ➔ reduce oxygen requirements

Nitrates + Ca^{+2} channel blockers ➔increase O_2 delivery also

14. Antiarrhythmic Drugs.

Arrhythmias

Heterogeneous group of conditions in which there is abnormal electrical activity in heart.

Drugs and classification

Sodium beta k calcium channel blockers married

Sodium	• Na^+ channel blockers
Beta	• Beta blockers
K	• K^+ channel blockers
Ca	• Ca^{+2} channel blockers
married	• mischeleneous ➔ adenosine + K^+ + Mg^{+2}

Group 1. Na^+ channel Blockers.

Group 1A

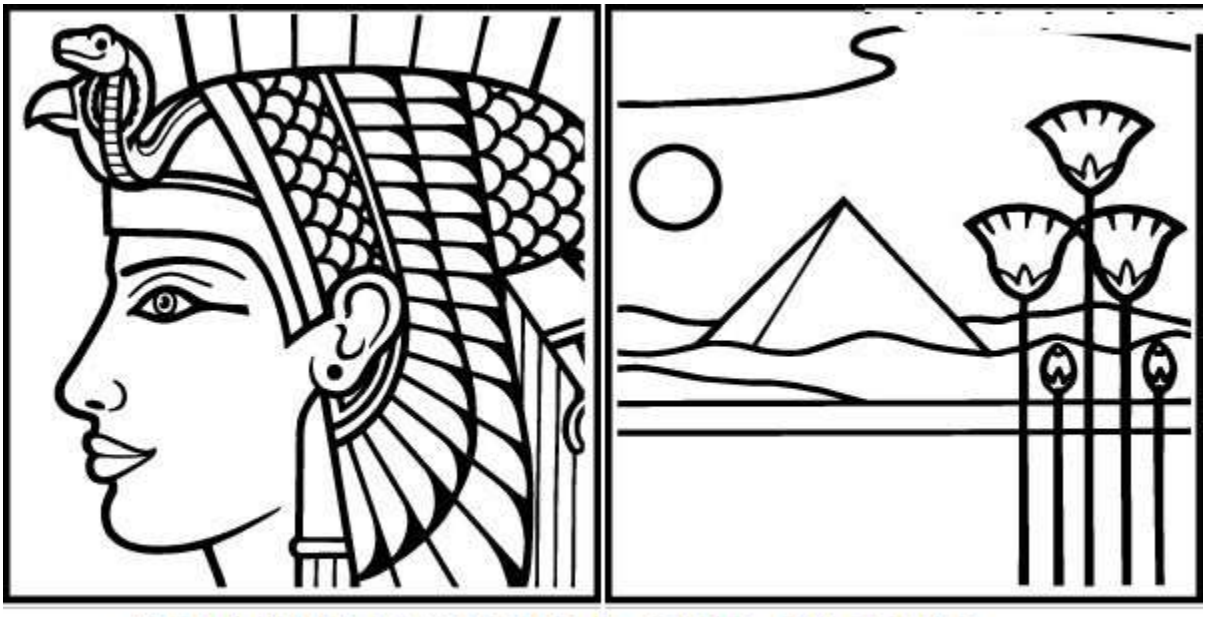
Queen proclaimed this pyramid

Contents

Queen ➔ Quinidine

Proclaimed ➔ procainamide

This pyramid ➔ dispyramide



QUEEN PROCLAIMED THIS PYRAMID

- Queen belongs to royal family so she belongs to first class people.
- A group indicate ➔ these are active people and active people have more potential and this indicate that this group prolongs the action potential (**mechanism**)

⇨ Na^+ channel blockers block channels in abnormal tissue more effectively

  - Use dependent and state dependent they selectively depress tissues that is frequently depolarizing.

Use

Atrial arrhythmia and ventricular arrhythmia

Group 1B

B for Bili ➔ Bi + Li ➔ li mean lidocaine

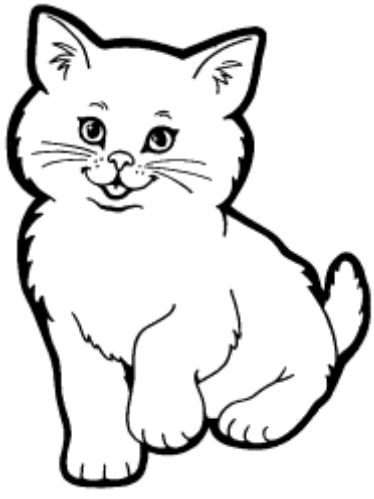
Contents

B for bored ➔bored people are not active people and have less or reduce potential

- Group B people decrease action potential. because they reduces recovery of Na channels from inactivation.**(mechanism)**

Lidocaine

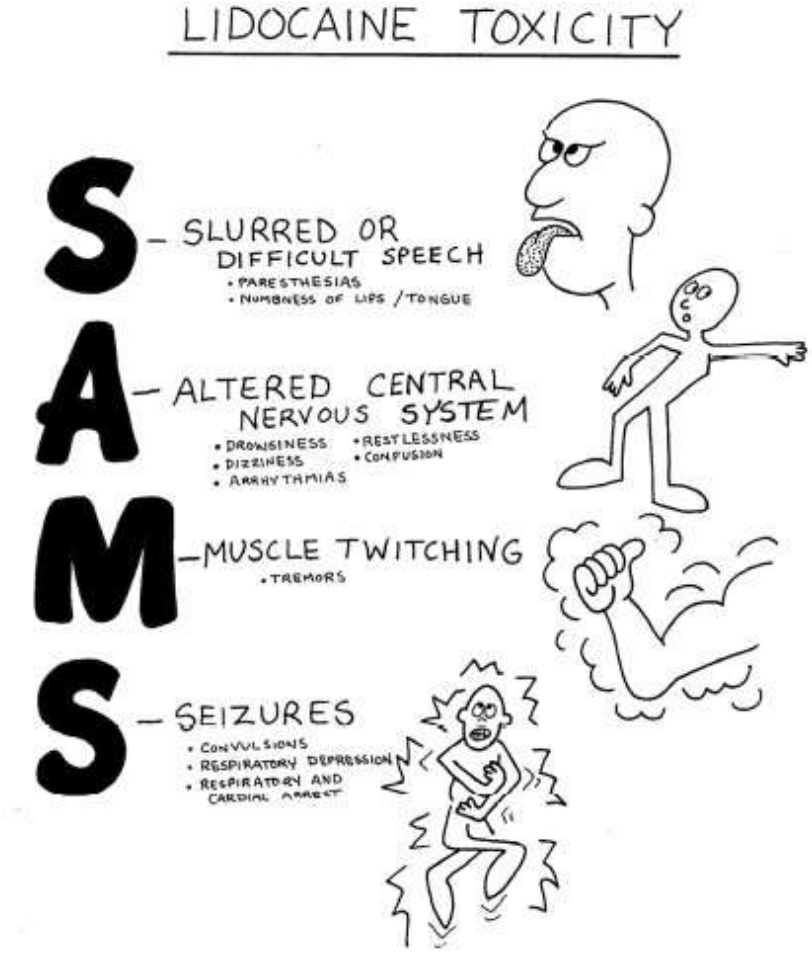
Li ➔ I indicate it is used in ischemic ventricular arrhythmias (for example after MI)



- Orally not administered because of high first pass metabolism and metabolites produced are cardiotoxic

Toxicity

- Local anaesthetic toxicity
- Cardiovascular depression
- Allergy



Drug interaction

Hyperkalemia ➔ increase cardiac toxicity

Group 1C

Ham darwazay ko Cafal kehtay hain tu us hisab say chota darwaza Cafle bana

Cafle ➔ C indicates this is C group and Fle indicates its drug Flecainide

Ab caflee chota darwaza hota hay tu logon k guzarnain k speed kam ho jaey gi

- Group 1C drugs lower conduction velocity
- Have no effect on action potential.

Contents

- They are powerful depressants of Na^+ current and they increase QRS duration

Uses

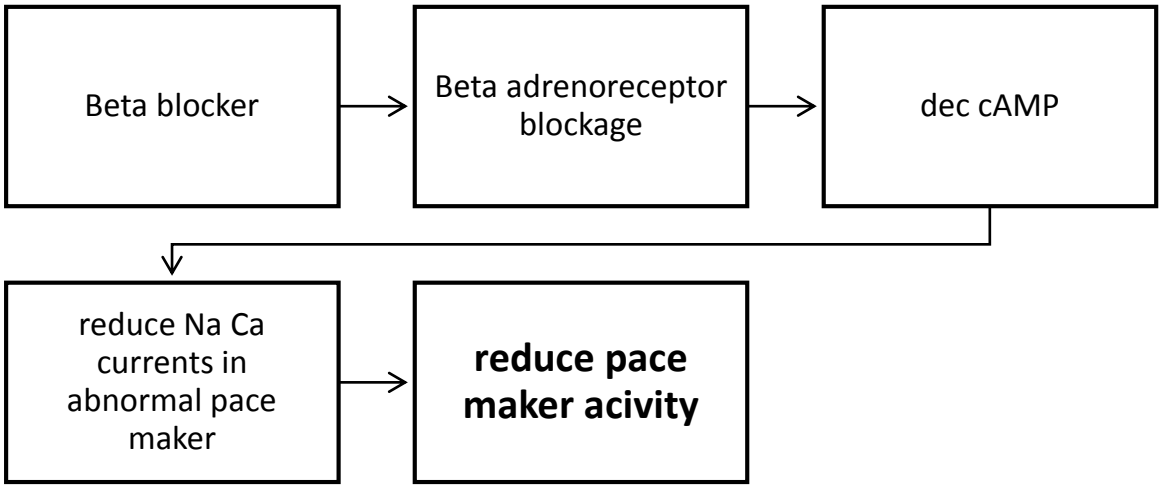
Refractory arrhythmia

⇨ Use is restricted to persistent arrhythmias fail to response other therapies

Group 2. Beta Blockers

Prototype drugs propranolol and Esmolol

Mechanism



- AV nodes are selective to beta blockage
- PR interval is usually prolonged

⇨ Amiodrone and sotalol are from group 3 but have some activity of group 2

Group 3. K^+ channel blockers

Bachy parh nh rhay thy tu **ami sota lai** or sab ki **kutt** laga di

Ami ➔ amiodrone

Sota ➔ sotalol

Contents

Lai ➔ lides ➔ibutilide and dofetilide

Kutt ➔ K channel blockers

Mechanism

Block K^+ channel ➔ result prolongation of action potential and refractory period.

- Also show activity of other groups like sotalol also blocks Beta blocker & amiodrone show activity of group 1 2 and it-self is 3 and of 4

Amiodrone

Most efficacious of all antiarrhythmic drugs

- Block Na^+ channel
- Block beta adrenoreceptor
- Block K^+ channel
- Block Ca^{+2} channel

Use is restricted why?

⇨ Extensive toxic effects are produced ➔ used only where other drugs are not responding

Adverse effects

Micro ppts of amiodrone

Micro ➔microcrystalline deposits

P ➔ pulmonary fibrosis

P ➔ paraesthesia

T ➔ thyroid dysfunction

S ➔ skin sensitivity to light

Dronedrone

Contents

Similar to amiodrone but is toxic and used for atrial flutter and fibrillation.

Group 4. Ca^{+2} channel blockers

Discussed previously.

Uses

- AV nodal arrhythmias (prophylaxis)

Group 5. Miscellaneous.

Adenosine ➔ in acute nodal tachycardia

K^{+} and Mg^{+2} ion ➔ in digitalis toxicity and other arrhythmias

15. Diuretics.

Classification and sites of action

- Diuretics decrease Na absorption at various sites of nephron resulting increase rate of urination

Carbonic anhydrase inhibitors

CIA

⇨ Carbonic anhydrase inhibited by Acetazolamide.

Site ➔Proximal convoluted tubule

Site of action➔ carbonic anhydrase enzyme

Loop diuretics

LEFT

L ➔ Loop diuretics

E ➔ Ethacrinic acid

F➔ Furosemide

T ➔ Torsemide

Site➔ Thick ascending limb of loop of henle

Site of action➔ Na / K / 2Cl channels

Thiazide diuretics

Thiazide came in their names

Hydrochloro**thiazide**

Chloro**thiazide**

Contents

Chloro**tha**lidone

Site➔ distil convoluted tubule

Site of action➔ Na / Cl channel

Potassium sparing diuretics

PotASSium ➔ ASS of diuretics

A ➔ amiloride

S ➔spironolactone

Site➔collecting duct

Site of action➔ aldosterone receptor

Osmotic diuretics

OSMO➔ Mo ➔ manitol

Osmotically retain water in tubule

Site➔ dec absorption of water in dLOH, proximal tubule and CT.

Uses and adverse effects

Carbonic anhydrase inhibitors

Gem made a small dp with zola (acetazolamide)

Use

G ➔ glaucoma (chronic treatment

E ➔ edema with alkalosis & Epilepsy in conjugation with antiepileptic drugs
M ➔ mountain sickness ➔ prophylactic

- They are less used as diuretics because they are less efficient than thiazide and loop diuretic.

Adverse effects

Made ➔ metabolic acidosis (hyperchloremic)

Small ➔ sedation and stone (renal)

D ➔ depletion of K

P ➔ paresthesia

Loop diuretics

Loop have Hope for Home

⇨ (my second home in this book first was in ergot alkaloid uses)

Uses

H ➔ Hypertension

Heart failure

Hypercalcemia (**Loop loose calcium)**

O ➔ oedema associated with heart failure, hepatic cirrhosis and renal impairment

PE➔ Pulmonary edema associated with congested heart

Contents

Adverse effects

H ➔Hyperkalemia ➔ increase exchange of Na for K

Hypovolemia

Hyperuricemia

O ➔ ototoxicity ➔ especially when used with aminoglycoside antibodies.

M ➔ metabolic hypovolemic alkalosis.

E ➔ efficiency decreased by NSAIDS.

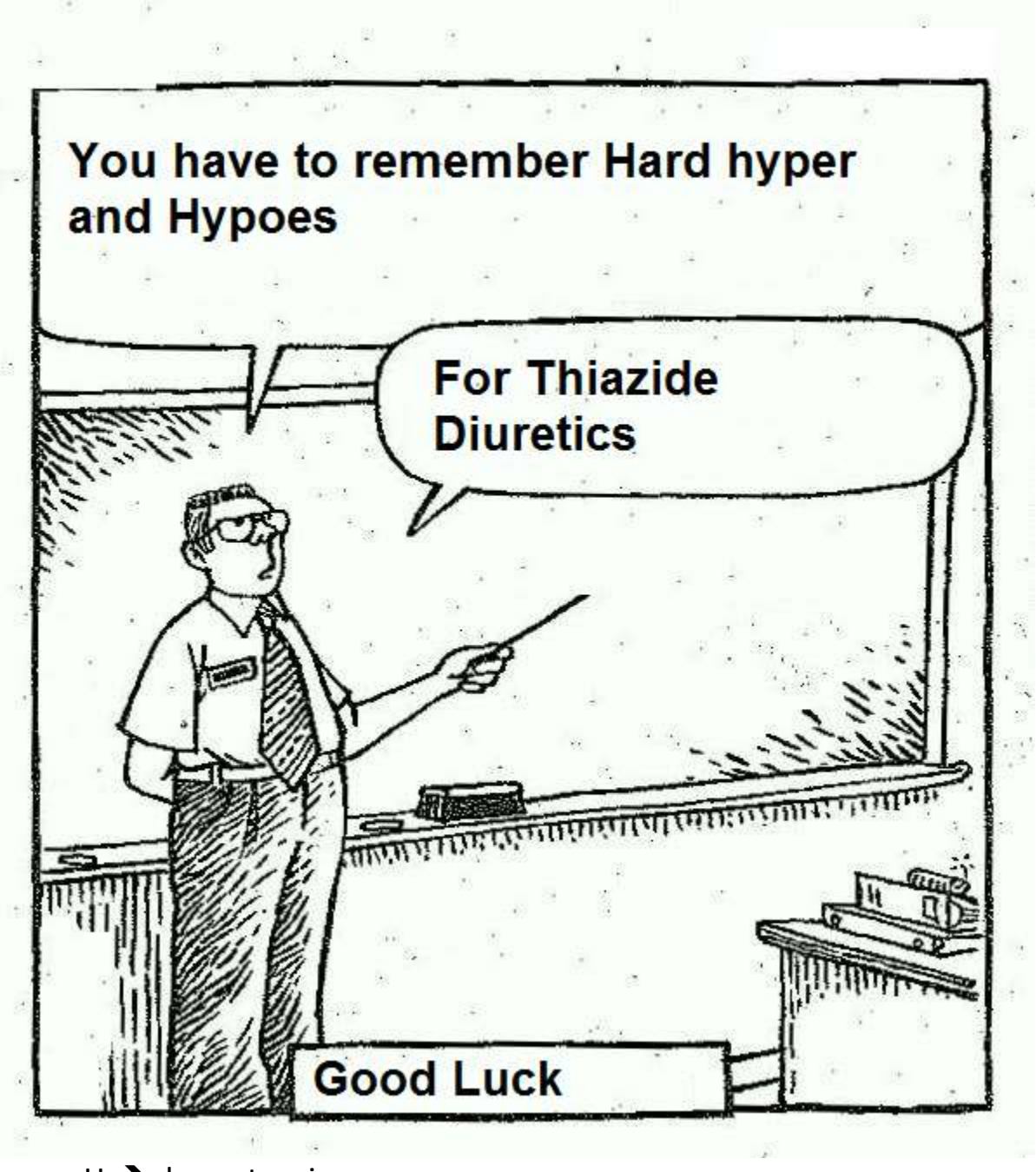
Thiazide diuretics

Hard hyper and hypoes

Uses

Hard

Contents



H ➔ hypertension

Heart failure

Hypercalciuria (dec urinary Ca excretion)

A ➔ syndrome of inappropriate ADH secretion

Contents

R ➔ Renal impairment (nephrotic syndrome accompanied by edema)

D ➔ Diabetes inspidus (produces hyper osmolar urine and urine volume drop from 11 litre to 3 litre per day)

Adverse effects

Hypoes

- Hypovolemia
- Hypokalemia
- Hypernatremia

Hypers

- Hypercalcemia (opposite of Loop)
- Hyperuricemia
- Hyperlipidaemia
- Hyperglycaemia
- Hypersensitivity (vasculitis & dermatitis)

K^+ sparing diuretics

Uses

- Excessive K loss due to other diuretics
- Aldosteronism

Adverse effects

Hyperkalemia

Gynecomastia (spironolactone)

Osmotic diuretics

Uses

Contents

OSMO

O ➔ oedema of brain (due to inc intracranial P)

S ➔ Shock

M ➔ Glauco**Ma**

O ➔ solute Overload

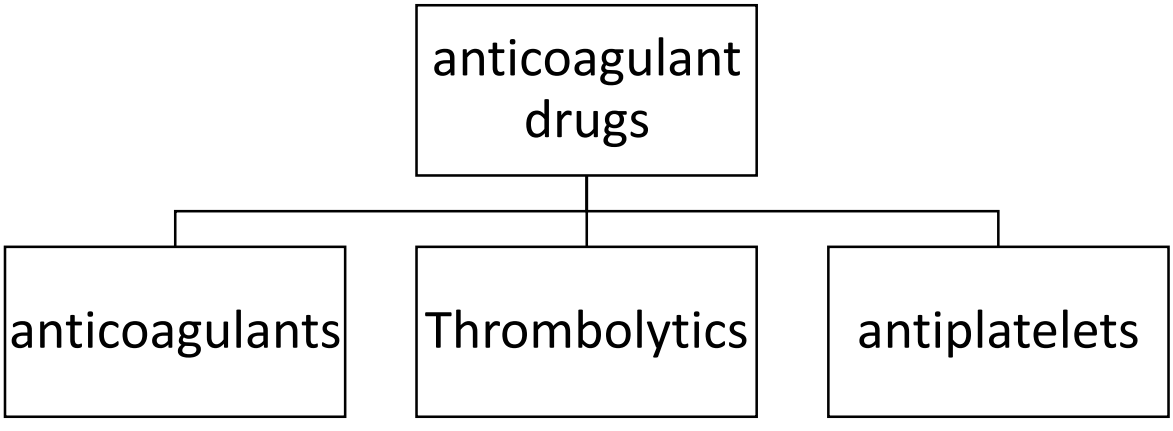
Adverse effects

- Hyponatremia followed by hypernatremia
- Nausea
- Vomit

16. Anticoagulant Drugs.

Anticoagulant drugs

They are classified into three groups



Anticoagulants

Anticoagulant diseased have defective wounds

Diseased ➔ Direct thrombin inhibitors

Have ➔ heparin

Defective ➔ Direct factor Xa inhibitors

Wounds ➔ warfarin

Thrombolytics

Contents

Smart thrombolytics

Smart ➔ streptokinase

Thrombolytics ➔ tPA activators

Antiplatelet drugs

APA g antiplatelet lo

A ➔ ADP inhibitors

P ➔ phosphodiesterase inhibitors

A ➔ aspirin

G ➔ glycoprotein IIB and IIIa inhibitors

Members of each group

1) Direct thrombin inhibitors

Anty thrombin loves BD anatomy

Anty thrombin ➔ antithrombin drugs

Loves ➔ lepirudin

B ➔ bivalirudin

D ➔ dabigatran

Anatomy ➔ argatroban

Anty thrombin loves BD anatomy

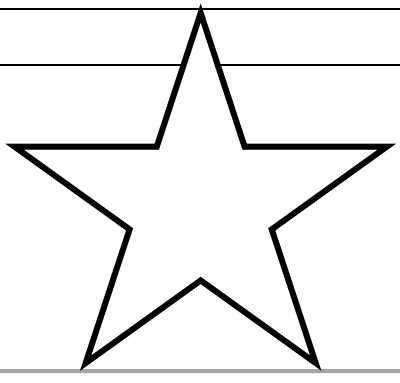
2) Heparin

3) Direct factor Xa inhibitors

Ten A ➔ TA

Mnemonic is TARA

T A ➔ Direct factor Xa inhibitors



R ➔ Rivaroxaban

A ➔ apixiban

4) Warfarin
5) Streptokinase
6) tPA derivatives ➔ Thrombolytic agents

tPA derivatives (Plases)

Alteplase ➔ normal

Reteplase ➔ human mutated form

Tenectiplase ➔ mutated and with increased half life

7) ADP receptor inhibitors

Ticlo

Ticlo ➔ Ticlopidine

Clo ➔ Clopidogrel

8) Phosphodiesterase inhibitors

Phosphodiesterase inhibitors ➔ dieaseterase ➔ Dipyridamole

9) Aspirin
10) Glycoprotein IIb and IIIa inhibitors

GTA vice city (game name)

G ➔ Glycoprotein IIb and IIIa inhibitors

T ➔Tirofeban

A ➔ Abciximab

Detail of each of them

Anticoagulants

1) Direct thrombin inhibitors

Based on Protein hirudin (Leach protein)

Drugs ➔ Anty thrombin loves BD anatomy

- Lipirudin ➔ recombinant form of Hirudin
- Bivaluridin ➔ modified form of hirudin
- Dabigatran ➔ orally active
- Argatroban ➔ small molecule with lesser half life

Mechanism ➔ Bind to thrombin and thrombin substrate (argatroban only to thrombin)

Clinical uses

- t**H**rombin ➔ alternative to heparin in patients with heparin induced thrombocytopenia
- with aspirin in coronary artery angioplasty

Acivity➔measured by aPTT (activated prothrombin time)

Toxicity ➔prolonged bleeding

2) Heparin

Mechanism

High molecular weight Heparin ➔ inhibit thrombin and factor Xa

Contents

Low molecular weight Heparin ➔ inhibit only factor Xa

Uses and adverse effects

Pic Dam hoti

Uses

P ➔pulmonary embolism

And this indicate this drug is positive for Pregnancy (Drug of choice in pregnancy ➔ acidic drug so cannot cross placenta and cane be used)

I➔ immediate coagulation

C ➔ coronary artery stunts

D ➔ DVT treatment

A➔ angioplasty and coronary stunts

M ➔ acute myocardial infarction

Adverse effects

HOTI

H ➔ Heparin induced thrombocytopenia (caused by an immunological reaction that make platelets a target of immunologic response result degradation of platelets leading to thrombocytopenia)

O ➔ osteoporosis

T ➔ two non-haemorrhagic side effects (elevation of serum amino transferase level and Hyperkalemia)

I ➔ increased bleeding time

Antidote ➔ Protamine sulphate

Contents

3) Direct oral factor Xa inhibitors

Members of Drugs ➔ TARA (Rivaroxaban and Apixaban)

Mechanism

Bind to factor Xa free and bound to clotting complex

Uses

Ten A inhibitors

Ten ➔ T ➔ venous thrombosis after Nee (knee) surgery

A ➔ atrial fibrillation

4) Warfarin

Lipid soluble ➔not given in Pregnancy

Mechanism

Vit K Epoxide ➔ activated Vit K under the action of enzyme **Vit K Reductase**

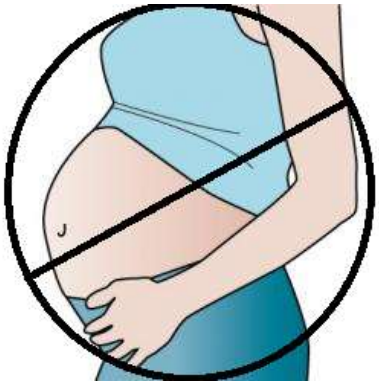
⇨ Activated Vit K involve in the production of clotting Factor 2, 7, 9, 10 (II, VII, IX and X)

Warfarin ➔ inhibit Vitamin K Reductase enzyme ➔ result in loss of production of these factors and Result in antithrombic activity.

Reversal of effects

Effects of warfarin can be reversed by Vit K ➔ will result in synthesis of cofactors in 6 to 24 hours

- For emergency cases fresh frozen Plasma that have normal clotting factors is given



Uses

Warfarin is a chronic anticoagulant in clinical situations Except Pregnancy

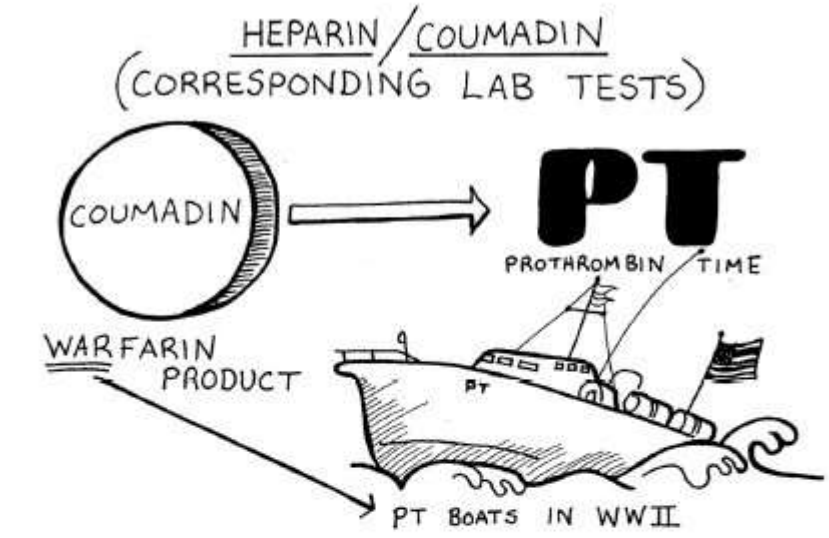
*Warfarin have low therapeutic window

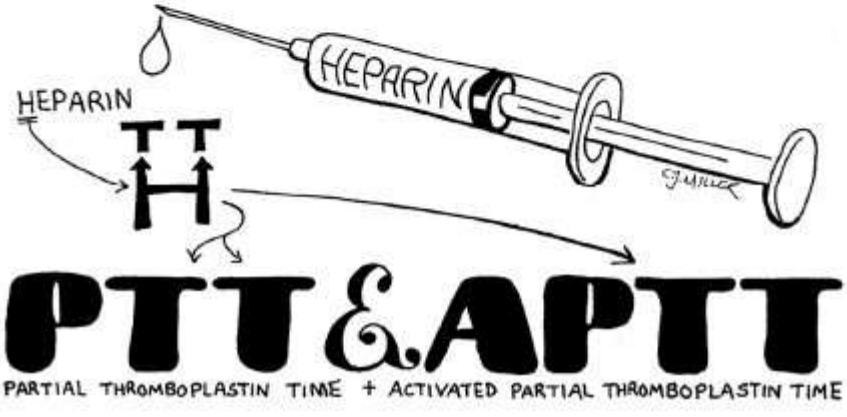
~~Warfarin in Pregnancy~~

Toxicity

- Increase bleeding time
- Dermal and vascular necrosis (it causes deficiency of protein C that is endodermal Vit K dependant anticoagulant

Lab tests for for warfarin and Heparin





Thrombolytic agents

Mechanism

Members

tPA(Tissue plasminogen activator)

- Selective for plasminogen that is already bound to fibrin (convert it into plasmin)

Contents

- Protective layer is form to prevent loss by widespread production of plasmin

Alteplase

- Normal human plasminogen activator

Reteplase

- Mutated form of human tPA (fast + longer duration of action)

Tenectiplase

- Human mutated form with longer half life

Streptokinase

- Obtained from bacteria
- Non selective to fibrin bound to plasmin

Uses

PCR

P ➔ pulmonary embolism

C ➔coronary artery angiography in coronary artery thrombosis

R ➔ recanalize coronary artery

Adverse effects

ABC

A ➔ antibody formation against streptokinase

B ➔ increased bleeding

C ➔ cerebral haemorrhage

Antiplatelet drugs

Contents

1) ADP receptor inhibitors

Ticlo (Ticlopindine and clopidogrel)

Irreversibly inhibit platelet ADP receptor

Uses

Ticlo Cap

C ➔ acute coronary syndrome

A ➔ prevent and treat arterial thrombosis

P ➔ after PCI (percutaneous coronary intervention) to prevent restenosis

2) Phosphodiesterase inhibitors

Dieaseterase ➔ Dipyridamole

- Inhibit adenosine uptake
- Inhibit phosphodiesterase that degrade cAMP.

Uses

- Prevention of thromboembolic complications of cardiac valve replacement
- With Aspirin to prevent secondary ischemic stroke

3) Aspirin

Mechanism

Non-selective irreversible inhibitor of COX enzyme

⇨ Result reduced production of thromboxane A_2 by platelets (TxA_2 is potent stimulator of platelets)

Uses as anticoagulant

- P^o myocardial infarction

Contents

- S^{o} myocardial infarction
- Prevent ischemic attack or stroke
- Prevention and treatment of arterial thrombosis

Uses of aspirin are

⇨ Antiplatelet ➔ conc less than 300 mg/dl

⇨ Antipyretic ➔ conc 300 to 2400 mg/dl

⇨ Analgesic ➔ conc 300 to 2400 mg/dl

⇨ Anti-inflammatory ➔ 2400 to 4000 mg/dl

Adverse effects

Aspirin

Contents

A ➔ asthma

S ➔ salicylism

P ➔ peptic ulcer

I ➔ intestinal blood loss

R ➔ ray's syndrome ➔Aspirin given to children with viral infection (Rapid liver degeneration and encephalopathy)

I ➔ idiosyncrasy

N ➔ noise➔tinnitus

Contraindication

As aspirin belongs to NSAIDS so same contraindications as that of NSAIDS

N ➔nursing and pregnancy

S ➔ severe blood loss

A_3➔ Allergy + Asthma + Angioedema

I ➔ impaired renal function

D ➔ drugs (when patient is allergic to ibuprofen and naproxen), (with warfarin produces intestinal blood loss)

Contents

17. Drugs used in Hyprtlipidemias

Friend drugs

F	• Fibrates
R	• Resins
E	• Ezetimaibe
N	• Niacin
D	• Drugs that inhibit HMG CoA ➔ Statins(most imp)

Treatment strategies

Diet

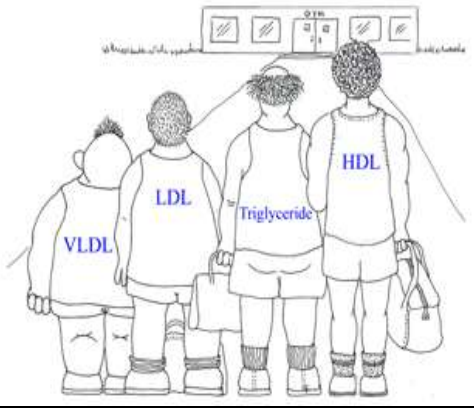
- Dec intake of cholesterol and saturated fats
- Avoid alcohol ➔ as they increase Tg and VLDL

Drugs

- Drugs effective at lowering LDL cholesterol ➔ HMG CoA reductase inhibitors, Resins, Ezetimibe and Niacin.

Contents

- Drugs effective at lowering VLDL and rising HDL cholesterol ➔ Fibric acid derivatives, Niacin and marine Omega 3 derivatives.



Fibrates ➔ Gemfibrozil and fenofibrate

Are ligands for PPAR alpha (peroxisome proliferator activated receptor alpha) ➔ regulate transcription of genes involved in Lipid metabolism ➔ Increase synthesis of **Lipoprotein lipase ➔** associated in capillary endothelial cells ➔ enhanced clearance of Tg rich lipoproteins.

Uses

- Hypertriglyceridemia
- Low HDL cholesterol

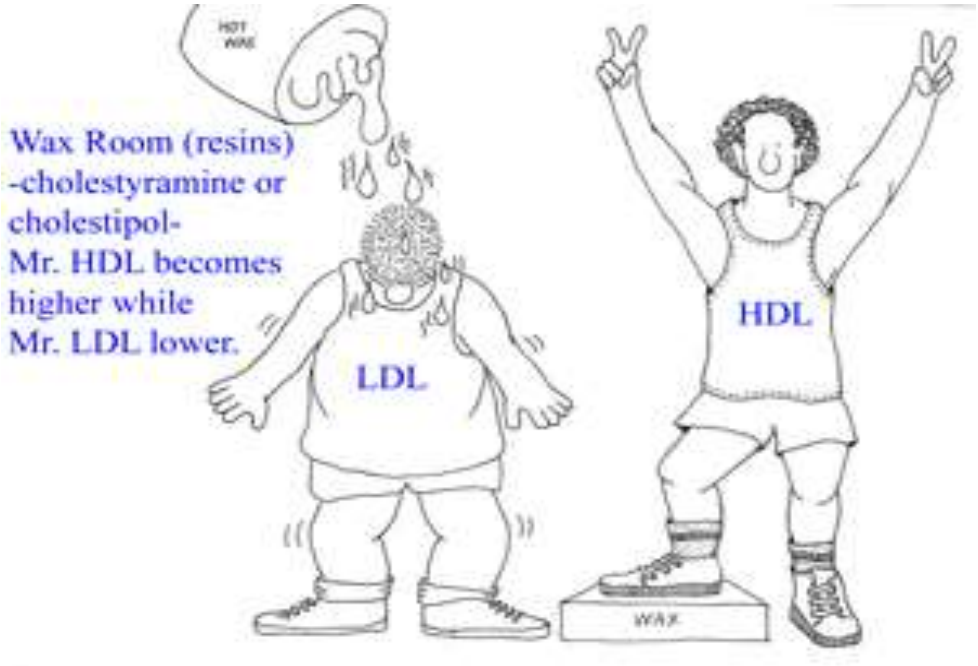
Resins

Also called bile acid binding resins

Colestipol and cholestyramine ➔ are large non-absorbable polymers that bind to bile acids and similar steroids in intestine and prevent their absorption ➔ prevent recycling of bile acids ➔ Divert hepatic cholesterol to Bile acid synthesis resulting in decrease in cholesterol in triglyceride regulatory pool.

- Resins ➔ modest reduction of LDL cholesterol
- No effect on HDL and Triglycerides

Uses



- Hypercholesterolemia
- To reduce pruritus in patients with bile salts accumulation

Niacin

- Reduces VLDL cholesterol synthesis ➔ in turn decreases LDL cholesterol
- Activate signalling pathway in adipose ➔ reduce lipoprotein lipase activity ➔ Decrease plasma free fatty acids and Tg level ➔ LDL formation decreased
- Reduces catabolic rate for HDL

Uses

- Hypercholesterolemia
- Hypertriglyceridemia
- Low level HDL

Toxicity

- Cutaneous flushing
- Git irritation
- Hyperuricemia
- Reduce glucose tolerance

Drugs that inhibit HMG CoA ➔ Statins

Semi loves rose flavour

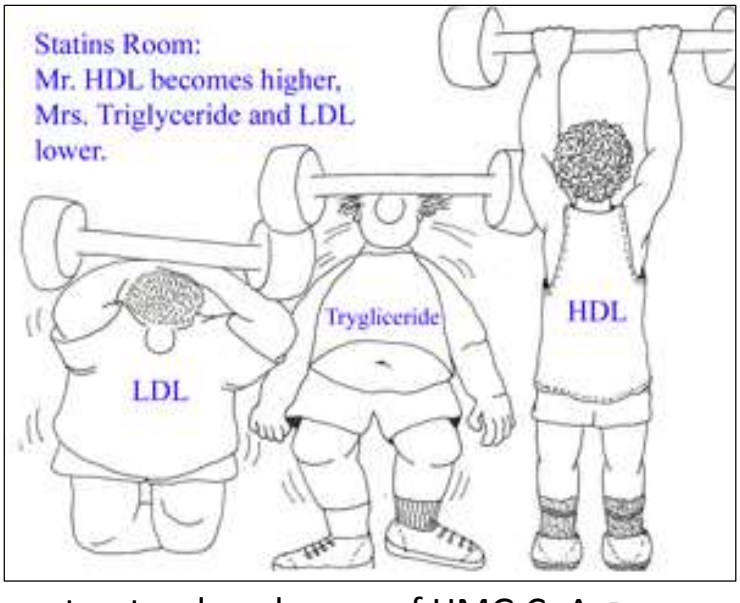
Semi ➔ Simva + statin ➔ Simvastatin

Loves ➔ Lova + statin ➔ Lovastatin

Rose ➔ Rosuva + statin ➔ Rosuvastatin

Flavour ➔ Fluva + statin ➔ Fluvastatin

HMG CoA is formed from acetyl CoA and is converted in to cholesterol under the action of enzyme **HMG CoA reductase,**



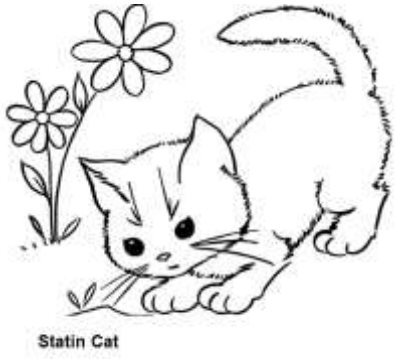
⇨ Statins are structural analogues of HMG CoA ➔ competitively inhibit HMG CoA reductase enzyme.

Uses

- Reduce LDL cholesterol

- Reduce risks of Coronary events
- Reduce mortality in patients with ischemic heart disease
- Reduce risk of ischemic attacks

Toxicity


Statin Cat

Statin cat

C ➔ creatinine kinase increase ➔ release from skeletal muscles

A ➔ elevation of serum aminotransferases

T ➔ teratogenic ➔ should be avoided in pregnancy

Contents

18. NSAIDS and drugs used in treatment of Rheumatoid Arthritis and Gout

NSAIDs

Non-steroidal anti-inflammatory drugs

Mechanism

Inhibit COX (Cyclooxygenase enzyme) ➔ decrease prostaglandin and thromboxane synthesis

COX_1➔ in non-inflammatory cells ➔ normal physiological cells

COX_2➔ in inflammatory cells, activated lymphocytes and poly morphoneuclear cells.

Effects

- **Anti-inflammatory effect** ➔ decrease synthesis of arachidonic acid derivatives (important mediators of inflammation) ➔ reduce manifestations of inflammation and have no effect on underlying tissue and immunological reactions
- **Antipyretic effect** ➔ supress prostaglandin synthesis in CNS ➔ reduces fever
- **Analgesic effect**➔ Reduced production of prostaglandins in injured tissues

Classification

Contents

NSAIDs

N	• negligible anti inflammatory and good analgesics • Acetaminophen
S	•Salicylates •Aspirin •Na salicylates
A	•Acid derivatives •all other than salicylates •Ibuprofen
I	• Indoles ➔ indomethacin
D	• Drugs with long duration ➔ Oxicams
S	• COX_2 selective ➔ celecoxib and meloxicam

Aspirin and other NSAIDs

Most of it is discussed in chapter of anticoagulants

Uses of aspirin are

- ⇨ Antiplatelet ➔ conc less than 300 mg/dl
- ⇨ Antipyretic ➔ conc 300 to 2400 mg/dl
- ⇨ Analgesic ➔ conc 300 to 2400 mg/dl
- ⇨ Anti-inflammatory ➔ 2400 to 4000 mg/dl

Contents

TXA_2 ➔increases platelet aggregation (coagulant effect).

PGI_2 ➔ decreases platelet aggregation (anticoagulant effect).

- Aspirin conc below 100mg/dl ➔ only ThA_2 is inhibited and there is only anticoagulant effects that last upto 300 mg/dl
- TXA_2 is inhibited PGI_2 is also inhibited so anticoagulant effect is cancelled by coagulant effect and there will be no anti-coagulant effect.

Adverse effects

Non selective NSAIDs

- GIT disturbances
- Renal damage

COX2 Inhibitors

- Reduced GIT damage
- Same risk or renal damage
- Increase risks of Myocardial infarction and stroke ➔ have more effect on PGI_2 synthesis than on TXA_2 synthesis ➔ increased risks of thrombosis

Aspirin and Acetaminophen

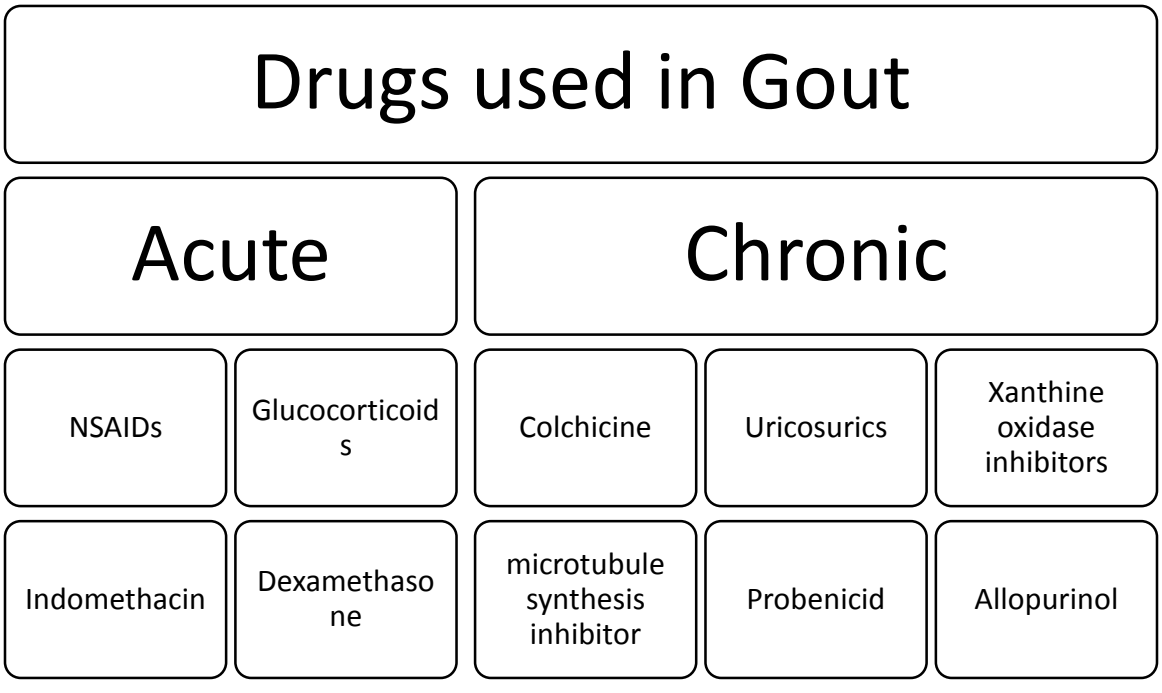
Aspirin	Acetaminophen (peracitamole)
Analgesic	yes
Antipyretic	Yes
anti-inflammatory	Not
Irreversible non selective COX inhibitor	Weak inhibitor of COX_1 and COX_2 (lack anti-inflammatory) COX_3 (in CNS) ➔inhibitors
Anticoagulant	Not

Uses ➔discussed already	Substitute of aspirin ➔ especially in children with viral infection

Toxicity of Acetaminophen

- Therapeutic dosage ➔ negligible toxicity
- Overdose or in patient with liver impairment ➔ Hepatotoxic drug ➔toxic metabolites produced by phase I reaction if substrates of phase II reaction (acetate and glucouronate) are lacking
- Antidote ➔ Acetyl cysteine

Drugs used in treatment of Gout



Treatment strategies

Gout ➔ increase uric acid in serum ➔ deposition of Uric acid crystals in Joints ➔ inflammation

Treatment strategies will be

- Reduce inflammation ➔ Colchicine, NSAIDs or Glucocorticoids

Contents

- Accelerate renal excretion of uric acids ➔ uricosuric drugs ➔Pro-benicid and Sulfinpyrazone
- Reducing conversion of purines into uric acid ➔ by xanthine oxi-dase inhibitors ➔ allopurinol

indian	• indomethacine
Coli (player)	• cochicine
provided	• probenicid
aalu	• allopurinol
to salman	• Sulfinpyrazone

Anti-inflammatory drugs

NSAIDs➔ such as indomethacin ➔ inhibit inflammation of acute gouty arthritis ➔ reduce prostaglandin synthesis and phagocytosis by macro-phages.

Colchicine ➔ inhibit microtubule assembly ➔ reduce migration of leuko-cytes and phagocytosis.➔ Reduce inflammation

Glucocorticoids ➔preferred for treatment of acute gouty arthritis

Uricosuric Drugs

90% of uric acid is reabsorbed in proximal convoluted tubule

Uricosuric drugs ➔ prevent reabsorption of uric acid in PCT

Contents

Mechanism ➔ compete with uric acid in PCT ➔ increase uric acid excretion.

- Used in chronically. No value in acute attacks.

Toxicity

- Uricosuric agents (weak acids) also inhibit the secretion of other weak acids like penicillin and methotrexate.
- Hypersensitivity because they are sulphonamides share allergenicity with other sulphonamides

Xanthine oxidase inhibitors

Mechanism ➔ inhibit enzyme xanthine oxidase (the enzyme that metabolize conversion of hypoxanthine into xanthine and xanthine into uric acid) ➔ result decrease production of Uric acid

- **Allopurinol** ➔ converted into alloxanthine ➔ inhibit enzyme irreversibly
- **Fubuxostat** ➔ reversible inhibitor (more effective drug) (non-purine inhibitor of xanthine oxidase)

Uses

- Chronic gout treatment
- In combination with colchicine or NSAIDs in acute attacks
- Adjunctive in treatment of cancer therapy ➔ slow the formation of uric acid from purines by death of neoplastic cells.

Toxicity

- GIT upset + rash + peripheral neuritis + bone marrow dysfunction + aplastic anemia

19. Drugs used in GIT Disorders

Acid peptic disease.

Drugs used in acid peptic disease are Hy papa

hy	• H_2 inhibitors
P	• Proton pumb inhibitors
A	• Ant acids
P	• Protectivegents
A	• Antibiotics

H_2 inhibitors

Contents

H 2 Blockers

FRaNCeTidine

F ➔ Famo + tidine ➔ Famotidine

R ➔ Rani + tidine ➔ ranitidine

N ➔ Niza + tidine ➔ Nizatidine

C ➔ Cime + tidine ➔ Cimetidine

Mechanism

Blockage action of histamine on parietal cells

Uses

Uses

GPS Dr

G ➔ GERD

P ➔ Peptic ulcer

S ➔ Stress related gastroenteritis

Dr ➔ Dyspepsia

Proton pump inhibitors

OLPER + parazole

O ➔ Ome + prazole ➔ Omeprazole

L ➔ Lenzo + prazole ➔ Lenzoprazole

P ➔ Pento + prazole ➔ Pentoprazole

Contents

E ➔ esmo + prazole ➔ Esmoprazole

R ➔ Rabe + prazole ➔ Rabeprazole

Mechanism

Lipophilic weak bases that diffuses into parietal cell canaliculi.

- Irreversibly inhibit the parietal cells H/K ATPase the transporter that is primarily responsible producing stomach acid.

Uses

Uses

GPS Dr

G ➔ GERD

P ➔ Peptic ulcer

S ➔ Stress related gastroenteritis

Dr ➔ Dyspepsia

In GERD and peptic ulcer these agents are more potent than H_2 receptor antagonists

Pharmacokinetics

- Oral formulations are enteric coated to prevent destruction in stomach
- Half-life of 1-2 hours and effects last for 1 day and 3-4 days are required to achieve full effectiveness

Adverse effects

TIDA proton

T ➔ Vit B twelve (B_{12}) deficiency ➔ because of decrease absorption (need acidity for absorption)

Contents

I ➔ inc risk of respiratory and enteric tract infections

D ➔ Diarrhoea and sar dard (headache)

A ➔ Abdominal pain

Antacids

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

- These are weak bases that react with protons in GIT
- Also stimulate protective function of gastric mucosa

$Mg(OH)_2$ ➔ this is also found in syrup milk of magnesia that is a laxative

So this causes strong laxative effect

$Al(OH)_3$➔ show constipating effect opposite to $Mg(OH)_2$

$CaCO_3$ and $NaHCO_3$ can also be used they are also weak bases

Uses

GPS dr with burning hurt

G ➔ GERD

P ➔ Peptic ulcer

S ➔ Stress related gastroenteritis (less used)

Dr ➔ Dyspepsia

Burning hurt ➔ heart burn

Adverse effects

- Excess Calcium absorption from milk and Calcium rich foods ➔ result in milk alkali syndrome

- Regular intake may lead to alkalosis
- Chemical reaction between antacid and acid ➔ production of CO_2➔ distended abdomen
- May cause headache
- $Al(OH)_3$ ➔ constipation
- $Mg(OH)_2$ ➔ laxative
- $Al(OH)_3$ ➔ neurotoxic and contraindicated in pregnancy
- $Mg(OH)_2$ ➔ in renal failure patients body Mg level increase Mg ➔ hypermagnecemia

Protective agents

Protective MSc

Protective ➔ protective agents

M ➔ misoprostol

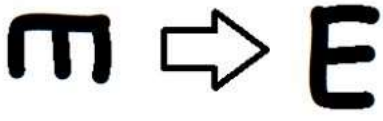
S ➔ sucralfate

C ➔ colloidal bismuth

Misoprostol

PGE_1

Misoprostol ➔ M for mono so it is 1 and if we rotate M it will Become E so it is 1E



Peptic Ulcer

PGE_1(Misoprostol) is used

Actions

Contents

- Inc. mucosal protection
- Dec. acid secretion

Uses

- Effective in Ulcers by NSAIDS

Not used widely because of multiple doses and poorly tolerated adverse effects

Side effects ➔diarrhoea + GIT upset

- Should not be taken by pregnant women ➔ increase uterine contractions may cause abortion
- With mifepristone used vaginally ➔ to terminate pregnancy

Sucralfate

⇨ Aluminium sucrose sulphate

- Poorly soluble molecule that polymerise in acidic environment of stomach and bind to injured tissue
  - form protective covering over ulcer beds
  - accelerate healing of the ulcer
  - Reduce reoccurrence rate
- Systemic effects are very less ➔ too insoluble

⇨ Toxicity very low

Colloidal bismuth

⇨ Formation of protective covering on the ulcerative tissue

⇨ Stimulation of mucosal protection mechanism

Antibiotics

Chronic infection with H-Pylori (present in most of the patients with reoccurrence, Non NSAID induced peptic ulcer.

Dosage regime

Proton pump inhibitor + Clarithromycin + amoxicillin

⇨ Metronidazole is given for penicillin allergic persons.

Motility Promoters

Mnemonic for this is MMDC (Multan medical and dental college)

M	• motility promoters
M	• Metocloperamide
D	• Domperidone
C	• Cholinomimetics (Neostigmine)

Metoclopramide and Domperidone

Dopamine D_2 antagonist that increase the GIT motility

- Prevent emesis after surgical anaesthesia

⇨ Chronic use of metoclopramide causes symptoms of parkinsonism and other extrapyramidal side effects

Cholinomimetics

Neostigmine ➔ is used for GERD and Gastropresis.

Drugs used in irritable bowel syndrome

Contents

Sir Alu said to aunty chalo chalain lubi k pas irritation ho rhi hay.

Sir ➔ serotonin antagonist ➔ alosteron

Aunty ➔ anticholinergics

Chalo chalain ➔ chloride channel activator ➔ Lubiproston

Serotonin antagonists

Alosteron

- Potent $5HT_3$ antagonist

Drugs

Imagine Granny is driving a Honda motor cycle and everyone saying hello! hello!

Granny ➔Granisteron

hONDA➔Ondasteron

Another member is Alosteron that is used in irritable bowel syndrom

Used in treatment of women with severe IBM and diarrhoea

Side effect ➔ constipation and colitis

Anticholinergics

Hayoscyamine ➔ also known as dhaturine (an antispasmodic drug)

Antispasmodic ➔ drug or herb that depress muscle spasm and relieve abdominal pain

Hayoscyamine ➔ is an anti-muscarinic drug

Uses

- Peptic ulcer
- Irritable bowel syndrome
- Pancreatitis and colitis

Side effects same as of atropine but weaker

Chloride channel activators

Lubiproston ➔ Chloride channel activator type 2

⇨ Treatment of women with IBS and constipation

Drugs for inflammatory bowel disease

Central intelligence agency of America

central	• Corticosteron
intelligence	• immunosuppresants
agency	• 5-aminosalisalic drugs
america	• anti TNF drugs

Corticosteroids

Glucocorticoids are used

- Inhibit prostaglandin synthesis
- Inhibit leukotriene synthesis

Immunosuppressants

Methotrexate' azathioprine are used

Depress immune system

5-aminosalisalate inhibitor drugs

Used for topical therapy of inflammatory bowel disease

Mechanism

- inhibit synthesis of prostaglandins
- inhibit synthesis of inflammatory mediators
- interfere with the production of inflammatory cytokines

Generic name for 5ASA is Mesalamine

Adverse effects ➔ GIT upset, headache, nausea, bone marrow suppression and hypersensitivity reactions

Anti TNF drugs

⇨ Natalizumab

Block integrins on circulatory leukocytes

- Used in severe Crohn's disease

Antiemetic drugs

H_2Canada

H	• $5HT_3$ blocers
H	• H_1 blockers
C	• corticosteroids
A	• anti-muscarinics
N	• Nurokinin receptor antagonists
A	• aaaaaaaaa
D	• D_2 blockers
A	• aaaa

5 HT_3 antagonists

Go to $5HT_3$ antagonists in chapter of histamine and serotonin

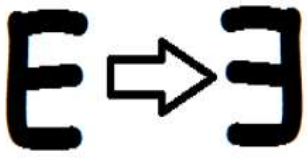
Contents

Location of HT3 receptor is

HT 3 Receptors

Located in Endings of Nerves

And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor Trigger zone.



So it will have role in vomiting

And its antagonists will stop vomiting

Use

- Antiemetic in chemotherapy
- Post-operative vomiting

Drugs

Imagine Granny is driving a Honda motor cycle and everyone saying hello! hello!

Granny ➔Granisteron

hONDA➔Ondasteron

H_1 blockers

Go to chapter of histamine and serotonin for more details

Contents

H1 Blockers

First Generation

DiDi promotes cycling

Di ➔ Diphenhydramine

Di ➔ Dimenhydrinate

Promotes ➔ Promethazine

Cycling ➔ cyclizine

Didi promotes cycling

&

Didi have mobile NGO

Mechanism

- ❖ Histamine receptor 1 Blockers
- ❖ Structurally resemble muscarinic and adrenergic receptors

Antihistamine + anticholinergic + antiemetics + antitussives

Corticosteroids

Dexamethasone is used ➔ anti-inflammatory and immunosuppressant

For further readings read in Corticosteroids chapter

Anti-muscarinics ➔ scopolamine

3 Scopolamine

SMS

S➔ short term memory loss

MS ➔ Motion sickness

Neurokinin receptor antagonists ➔ apirepitant

- Chemotherapy induced nausea vomiting used

D_2 blockers ➔ prochlorperazine

Contents

Antiemetic treatment of nausea and vomit

Antidiarrheal drugs

- Loperamide
- Colloidal bismuth compounds
- Pectin and Kaolin absorbent compounds

Loperamide

Activate opioid mu receptors ➔ decrease tone of longitudinal muscles.

Colloidal bismuth compounds

Subsalicylate and citrate salts ➔ effective in travellers' diarrhoea

Pectin and Kaolin ➔ absorbent compounds

Laxatives

- $Mg(OH)_2$ and other nonabsorbant s
- Bulk forming compds ➔ methyl cellulose and psyllium
- Stool surfactants ➔ mineral oils
- Stimulants ➔ cenna
- chloride channel activators ➔lubiprostone
- Opiod receptor inhibitors

Drugs acting on CNS.

Contents

20. Sedative and Hypnotics

Benzodiazepines

Members and Classification

Benzodiazepenes		
Short acting	Intermediate acting	Long acting
TOM	Steal	chloro floro carbon drugs

Short acting

Contents

TOM

T ➔ Triazolam

O ➔ oxazepam

M ➔ Midazolam

Intermediate acting

STEAL

S ➔ skip

T ➔ Teniazepam

E ➔ Estazolam

A ➔ Alprazolam

L ➔ Lorazepam

Long acting

Chloro floro carbon drugs

Chloro ➔ Chlorazepam

Floro ➔ Flurazepam

Carbon ➔ Chlordiazepoxide

Drugs ➔ Diazepam

Benzodiazepines not metabolized by the liver

Outside the live

Outside ➔ oxazepam

The ➔ tempazepam

Liver ➔ lorazepam

They can be used in patient with liver disease

Actions of Benzodiazepines

Ben SCAM not by brain but by muscles

Ben ➔ actions of benzodiazepines

S ➔ sedation and hypnosis (used in insomnia)

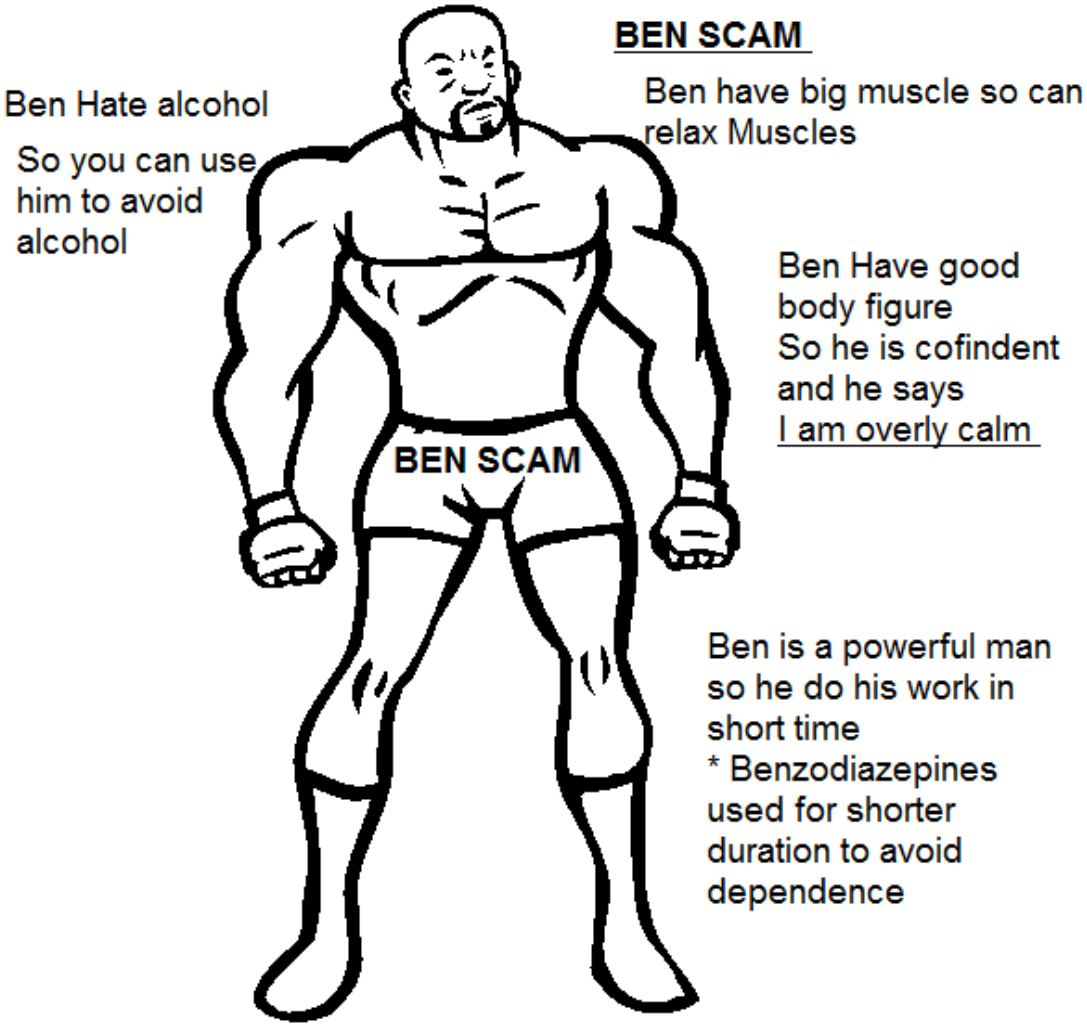
C ➔ anti-**C**onvulsant (used in seizures)

A ➔ anti-anxiety (used in panic disorders and Generalized anxiety disorders)

- Also produces short term amnesia (used in premedication for medical procedures)

Contents

M ➔ Muscle relaxants (used to relieve muscle spasm)



Other way you can use to remember this is

SAM said Aaaah

S ➔ Sedation ➔ relief of anxiety

A ➔ Anti-convulsants ➔ in seizures

M ➔ medullary depression ➔ lead to respiratory and cardiac depression

Said ➔ Sleep onset ➔ hypnosis

Aaaah ➔ Anaesthesia ➔ amnesia + conscious loss + Reflex loss

Side effects

ABCDE

A ➔ Ataxia

Dec alertness

B ➔ behavioural disturbances

C ➔ coma

Decreased concentration

Decreased co-ordination

D ➔ Depression (resp and CNS)

Drowsiness

Diplopia

E ➔ Decrease erection

Antidote

Ben is off with flu (Ben ko flu tha is liay chuti par hay)

Effects of benzodiazepines are reversed by Flumazenil.

Barbiturates

Members and classification

Meray father ka name Boota hay. Jab wo chotay thay to aam k darakht par charh gaey or whan say aik second main 5 aam tor kar phenkay

So mnemonic will be

Bootay nain aik sec main 5 aam phenkay

Contents

Bootay nain	• Buta + Barbital ➔ butabarbital
aik Second	• Seco + barbital ➔ secobarbital
5	• penta + barbital ➔ pentabarbital
Aam	• Amo + barbital ➔ Amobarbital
phenkay	• pheno + barbital ➔ Phenobarbital

Contents

Mechanism

Bootay nain aik sec main 5 aam phenkay

Barbi**DURATES** ➔ Duration

Contents

- Barbiturates increase the duration of Cl^- channel opening thus decrease neuron firing

Effects

Effects will be same as benzodiazepines except muscle relaxant effects

S ➔ sedation (Sedation at lower doses to anaesthesia at higher doses)

C ➔ anti-Convulsants

A ➔ anxiolysis and hypnosis

Other uses

- Physician assisted suicide
- Capital punishment by lethal injection
- Na-Pentothal➔ truth serum
- Weak analgesia

Side effects

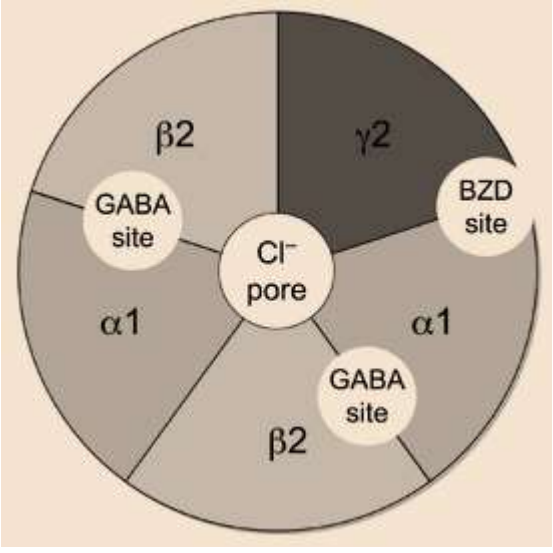
- Children are annoying (hyperkinesia + irritability + Insomnia + Aggression)
- Adults are sleepy (Sedation Dizziness and Drowsiness)
- **Or you can use same side effects here ABCDE.** Benzodiazepines and Barbiturates have similar effects.

Contraindications

- Pregnant women ➔ foetus
- Babies ➔ see side effects
- Aged person ➔ difficult to remove from body
- Breast feeding ➔ can came in Breast milk

Contents

Mechanism of Benzodiazepines and Barbiturates



GABA mediated chloride channel have 5 subunits two alpha, two beta and on gamma subunit.

Benzodiazepines and newer hypnotics (like zolpidem)

Binding at single site between alpha and gamma subunits

- Benzodiazepines antagonist Flumazenil also bind to this site

Barbiturates

Bind to sites on alpha and beta subunits

GABA

Bind to site between alpha and beta subunits

Tolerance

- Decrease responsiveness when used chronically in larger amount.
- Reduction in drug effect to amount of drug that was previously effective

Cross tolerance

Cross tolerance occurs when a person is tolerant to effects of a Drugs and he also develop tolerance to another drug

- This happens with two drugs with similar functions or effects for example acting on same cell receptor

Contents

- Cross tolerance also present in sedative and hypnotics (Benzodiazepines and barbiturates)

Physiological dependence

Dependence that involves persistent physical–somatic withdrawal symptoms

- (fatigue, anxiety, tremors and/or persistent insomnia depending on substance)

Psychological dependence

Dependence that involves emotional–motivational withdrawal symptoms.

- Loss of comfort
- Loss of pleasure etc.

Physiological and psychological dependence ➔ result in compulsive use of these drugs

⇨ Tolerance, Cross tolerance, physiological and psychological dependence are common with sedatives and hypnotics

Atypical sedatives and hypnotics

Buspiron

- Minimal CNS depressant effects (it does not affect driving skills)
- No anticonvulsant and muscle relaxant properties

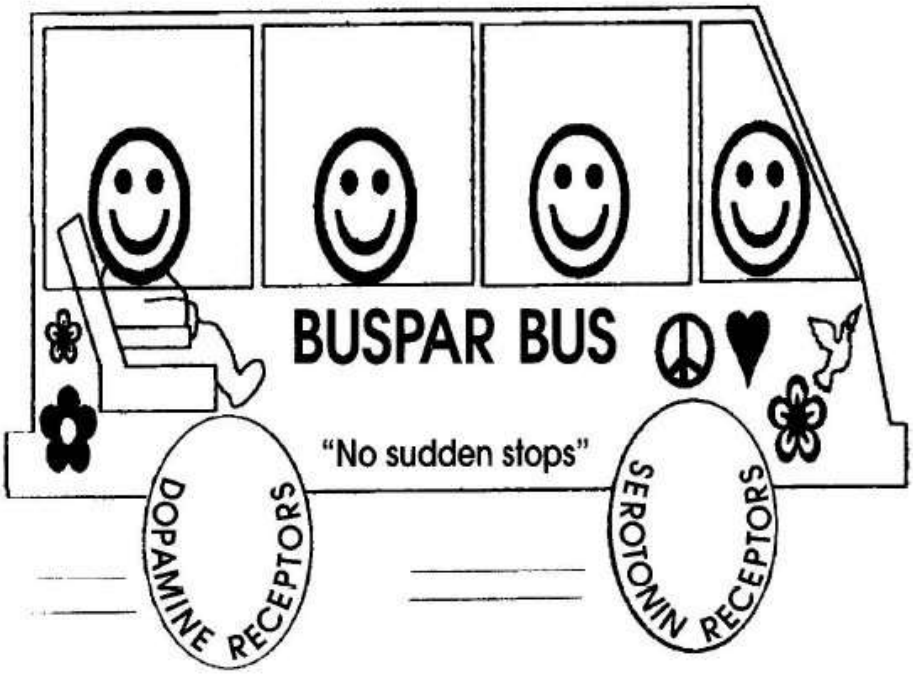
⇨ Partial agonist at 5HT and D_2 receptor

Good things about this

- Development of tolerance with chronic use is minimal
- Little rebound anxiety and withdrawal symptoms

Contents

BUSPAR BUS



Get on the Buspar Bus to decrease ansiety. The seats recline for the undesirable effect of dizziness and drowsiness. Smiles can be seen after taking the drug for a week.

- Safe in pregnancy

Adverse effects ➔GIT distress + Tachycardia + pupil constriction

Ramelton

- Activate melatonin receptors in suprachiasmatic nuclei of the CNS
- Decrease latency (delay) of sleep with minimal rebound insomnia and withdrawal symptoms

Good things about this

- Minimal dependence liability

- Minimal abuse liability

Adverse effects ➔ dizziness, fatigue and endocrine changes

21. Alcohols

Metabolism

Ethanol ➔ Acetaldehyde ➔ Acetate

Ethanol ➔ Acetaldehyde

- Concentration below 100mg/dl

  Alcohol dehydrogenase is active

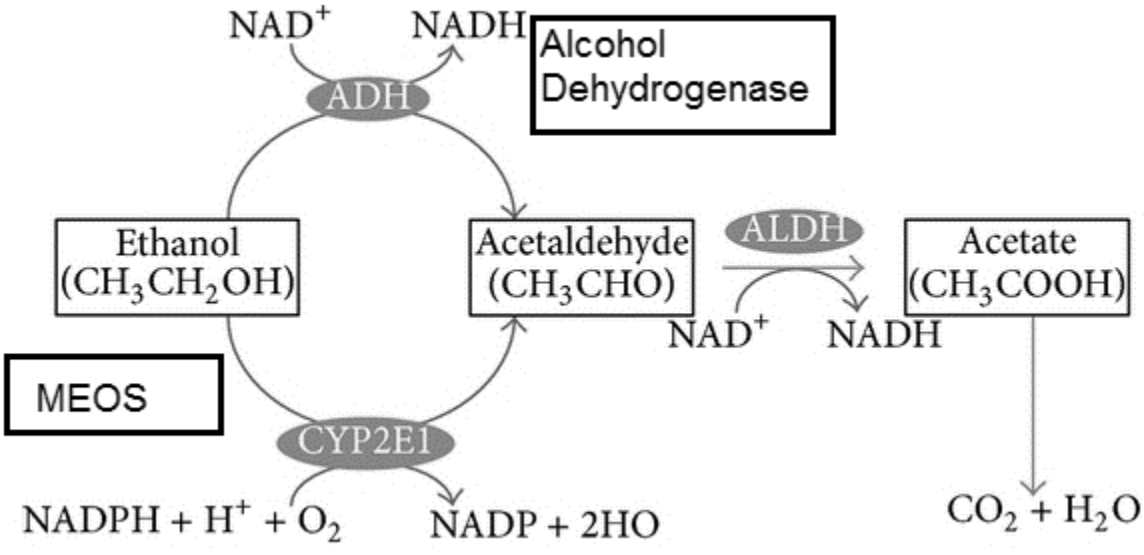
  - Alcohol dehydrogenase is inhibited by **Fomipizol**
- Concentration above 100mg/dl

  Microsomal ethanol oxidizing system is active

Acetaldehyde ➔Acetate

- Aldehyde dehydrogenase is working
  - Aldehyde dehydrogenase is inhibited by **Disulfiram**

Contents



Effects Produced by ethanol

- Acute effects
- Chronic effects

Acute effects

- 60 to 80 mg/dl ➔ impairment of driving ability
- 120 to 160 mg/dl ➔ Gross drunkenness
- More than 300 mg/dl ➔ Loss of conscious, anesthesia and coma
- More than 500 mg/dl ➔ Lethal
- **Other effects**
    - Sedation
    - Sedation, inhibition loss, impaired judgment and slurred speech
- CNS effects mg/dl ➔ produce due to modulation of signalling proteins

Contents

- Heart mg/dl ➔ depressed
- Blood vessel mg/dl ➔ vasodilation
- Smooth muscles ➔ relaxed

Chronic effects

- **Tolerance**

  Tolerance develop due to

  - Due to CNS adaptations
  - Due to faster metabolism
- **Fatty liver** ➔ irreversible hepatitis, cirrhosis and liver failure
- **GIT** ➔ irritation, inflammation and bleeding
- **CNS** ➔ most common effect ➔ peripheral neuropathy
- **Thiamine deficiency** ➔ Wernicke Korsakoff syndrome ➔CAP ➔ confusion, ataxia and paralysis extraocular muscles
- **Endocrine** ➔ gynecomastia and testicular atrophy
- **CVS** ➔ Hypertension, anemia and cardiomegaly
- **Immune system** ➔ increase inflammatory effects

Foetal alcoholic syndrome

Alcohol in pregnancy ➔ teratogenic

- If used ➔ can lead to

⇨ Alcohol in MUG

  - M ➔ mentally retard and microcephaly
  - U ➔ underdeveloped mid face
  - G ➔ Growth deficiencies

Treatment

Ethanol.

- Used as antidote in methanol and ethylene glycol poisoning.

Methanol poisoning.

- Leads toxic level of formate ➔ visual disturbances, coma and seizures
- Death due to respiratory failure
- **Fomipizol**➔ used in treatment of methanol and ethylene glycol poisoning
- Inhibit alcohol dehydrogenase **Fomipizol**➔ used in treatment of methanol and
    - Inhibit the formation of toxic metabolites (formaldehyde and formate)
        - Fomipizol ➔ F ➔ formaldehyde and formate

Ethylene glycol poisoning.

- Toxic aldehydes and oxalates ➔ kidney damage and severe acidosis

Treatment of Acute ethanol withdrawal.

1) Benzodiazepines

- If Liver is working fine➔ Long acting ➔ diazepam
- If liver is abnormal➔Drugs metabolized outside the liver are used
    - Lorazepam is used (outside the liver * From benzodiazepines)
- **Use** ➔ prevention and treatment of acute ethanol withdrawal syndrome

2) Thiamine (B_{12})

- Coenzyme required for thiamine phosphatase

Contents

- **Use** ➔ to prevent Wernicke korsakoff's syndrome

Drugs used in treatment of chronic alcoholism.

1) Opioid receptor antagonist

- Naltrexone used ➔ non-selective competitive antagonist of opioid receptors
    - Reduce risks of relapse

2) Enzyme inhibitors

- Disulfiram ➔ inhibit aldehyde dehydrogenase ➔ accumulation of acetaldehyde ➔ increase acetaldehyde major cause of hangover
- Prevention of relapse in individuals with alcohol disorders
- **Symptoms**

  Symptoms include flushing of the skin, accelerated heart rate, shortness of breath, nausea, vomiting, throbbing headache, visual disturbance, mental confusion, postural syncope, and circulatory collapse.

3) Others

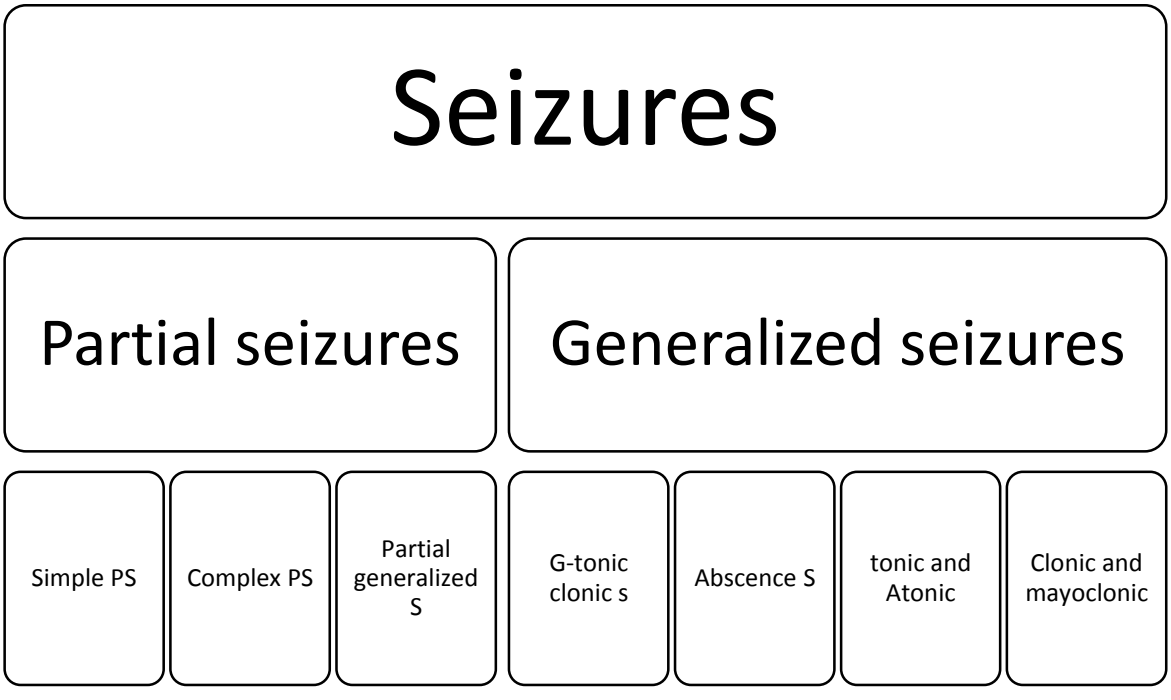
- **Acamprostate** ➔ block NMDA receptor
    - Reduce risks of relapse

Treatment of methanol poisoning

- Maintenance of vitals
- Administration of thiamine (for thiamine deficiency)
- Electrolyte (for electrolyte imbalance)
- Treatment of alcohol withdrawal syndrome ➔ by benzodiazepines
- Treatment of alcoholism ➔ by Disulfiram

22. Anti-seizure Drugs

Antiseizure Drugs



Pharmacokinetics

- They are used for long time
- All have hepatic metabolism (except gabapentin and vigabatrin)

Classification of Drugs

Contents

Antiseizure Drugs

Partial and tonic clonic seizures	Abscence seizures	Mayoclonic seizures	Backup drugs
VLC players	VE	VLC	Lela feto got Vig

Partial seizures and tonic clonic seizures

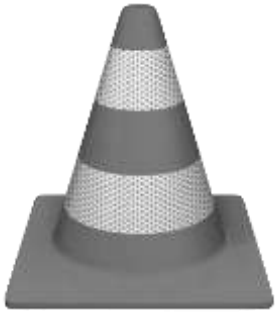
VLC player

V ➔ Valproate

L ➔ lamotrigine

C ➔ Carbamazepine

Player ➔ phenytoin Na



Absence seizures

Valproate and ethosuxamide are used

Myoclonic seizures

V ➔ valproate

L ➔ Lamotrigine

C ➔ Carbamazepine

Backup and adjunctive drugs

Contents

Lela fato got Wig (hairs wali)

Lela ➔ lamotrigine

Fe ➔ Felbamate

To ➔ Topiramate

Go ➔ Gabapentin

T ➔ Taigabine

Vig ➔ Vigabatrin

Lela feto got a vig

Sites of Drug action & Uses

Na^+ channel blockers

Zoni found a car lamozin

Zoni ➔ zonisamide

Found ➔ phenytoin

Car ➔ carbamazepine

Lamozin➔ lamotrigene

Zoni Found a car lamozin

Uses

- Tonic clonic seizures
- Partial seizures

Ca^{+2} Blockers

Cave

Ca ➔ Ca channel blockers

V ➔ Valproate

Contents

E ➔ Ethosuxamide

Uses

- Myoclonic seizures
- Absence seizures

GABA related targets

Baba G took vegan

Ba ➔ benzodiazepine

Ba ➔ Barbiturate

G ➔ GABA-pentin

Took ➔ Tiagabine

Vegan ➔ Vigabatrin

Baba G took Vagan

Uses

- Tonic clonic seizures
- Partial seizures

Phenytoin

Mechanism

Na^+ Phenytoin ➔ this Drug block Na^+ channels in neuronal membranes

Clinical uses

Drug of choice in

- Generalized tonic clonic seizures
- Partial seizures

⇨ Elimination of Drug ➔ dose dependant

Contents

Adverse effects

Phenytoin

P ➔ P450 interactions

H ➔ Hirsutism

N ➔ Nystagmus

Y ➔ yellow brown skin

T ➔ teratogenic

O ➔ Osteomalsia

I ➔ Interfere B_{12} metabolism (anemia)

N ➔ Neuropathies

Carbamazepine

Mechanism

Block voltage gated Na^+ channels ➔ decrease glutamate release

Uses

- Generalized tonic clonic seizures
- Partial seizures

Adverse effects

Carbon on hand

Carbon ➔ Carbamazepines

H ➔ Headache

A ➔ Ataxia

N ➔ Nausea

D ➔ diplopia

Lamotrigine

Mechanism

Block Na^{+} and Ca^{+2} channels

Uses

- Generalized seizures
- Partial seizures
- Myoclonic seizures

Adverse effects

- Dizziness
- Diplopia
- Headache
- Rash

Valproate

Mechanism

- Block Ca^{+2} channels (T type)
- Beta block high frequency firing

Uses

- Used in all types of parkinsonism

Adverse effects

Valproate

V ➔ Vomiting

A ➔ Alopecia

L ➔ Liver (Hepatotoxic)

P ➔ Pancreatitis

R ➔ Retention of fat (obesity)

Contents

O ➔ Oedema

A ➔ Appetite increase

T ➔ Teratogenicity

E ➔ enzyme inducer

Ethosuxamide

Mechanism ➔ decrease Ca^{+2} current (T type)

Uses ➔ Absence seizures

Adverse effects ➔ GIT distress and CNS effects

Gabapentin

Analogue of GABA

Mechanism ➔ Block Ca^{+2} channels

Uses

- Generalized tonic closure seizures
- Partial seizures

Adverse effects ➔ ataxia and dizziness

Benzodiazepines

Mechanism ➔ Bind GABA receptor subunit ➔ opening of Cl^- channels (increase frequency of opening of channels)

Uses

- All except absence seizures (Generalized tonic clonic, Partial and myoclonic seizures) [Clonazepam]

Barbiturates

Phenobarbitone

Contents

Mechanism ➔ Opening of chloride channels like benzodiazepines (increase duration of opening)

Uses

- Same as barbiturates

GABA pentin

Analogue of GABA

- Uses and adverse effects as barbiturates and benzodiazepines

Vigabatrin

Mechanism ➔ inhibition of GABA transaminase

V for vegan and vegan is used for transport So Transaminase is inhibited here

Uses

- Generalized tonic clonic seizures
- Partial seizures

Side effects

D_2O

- Drowsiness
- Dizziness
- Ocular side effects

Tiagabine

Tiagabine ➔ T ➔ inhibit GABA Reuptake by transporter

Uses ➔ Partial seizures

Side effects ➔ Dizziness, Depression and seizures

Contents

23. General anaesthetics

Stages of Anaesthesia.

Also called Guedel's signs

Anny did some mistakes (or you can use this Annay di serial maan)

Anny	• Analgesia
Did	• Disinhibition
some	• surgical anaesthesia
mistakes	• Medullary depression

Stages of anesthesia

1) **Analgesia**

   Decrease awareness of pain

2) **Disinhibition**

anny did some mistakes

Contents

Delirious and exited

3) **Surgical anesthesia**

Unconscious + no pain reflexes

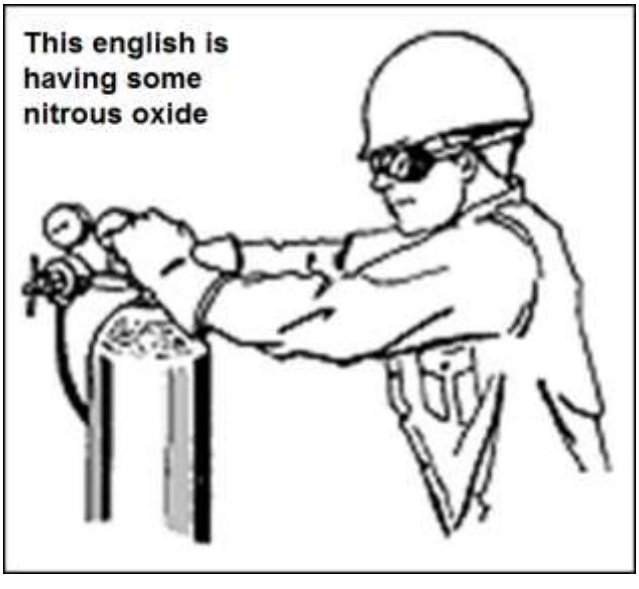
4) **Medullary depression**

Severe respiratory and CNS depression

⇨ Dangerous stage

Inhaled anesthetics.

This English is having some nitrous oxide, ether and chloroform.



This	• Disfluran
English	• Enfluran
Is	• Isofluran
Having	• Halothane
some	• sevofluran
Nitrous oxid	• nitrous oxide

Others either and chloroform were previously used not now.

Mechanism

FAN

F ➔ Facilitate GABA mediated inhibition

A ➔ Ach receptor blockage

N ➔ NMDA receptor blockage

Elimination

Elimination of drugs through lungs for inhalational anaesthetics

Halothane ➔ liver metabolism (H for hepatic)

Side effects

- Increase ICP
- Respiratory depression
- CNS depression
- Cardiac depression

Contents

Intravenous anaesthetics

Barbie doll in Pacific Ocean

Bar	• Barbiturates
Bie	• benzodiazepenes
doll	• Dissociatives
in	• imedazole
pacefic	• phenols
ocean	• opoids

Barbie doll in pacefic ocean

Barbiturates

Thiopental, Thioamylal and methohexital

Contents

Effects (high lipid solubility and shorter duration of action)

- Respiratory and CNS depression
- Decrease ICP

Side effects

CNS depression extensions

Benzodiazepines

Midazolam, diazepam and lorazepam are used

Effects

- Less depression than barbiturates
- Shorter onset and longer duration of action than barbiturates

Side effects

- Respiratory depression

Dissociative ➔ Ketamine

Block excitation by NMDA receptor

- NMDA ➔ N methyl D aspartate

Effects

- Analgesia
- Amnesia
- Catatonia ➔ neurogenic motor immobility
- CVS stimulation

Dissociative anaesthesia

Dissociative are a class of hallucinogen in which distort perceptions of sight and sound and produce feelings of detachment (dissociation) from the environment and self.

- Complete unconsciousness is not present
- Generalize anaesthesia ➔ characterized by catalepsy, catatonia and amnesia.

Opioids

Morphine and alfentanil

Mechanism ➔ interact with mu, kappa and delta for endogenous opioid peptides.

Effects

Analgesia and respiratory depression

Side effects

Respiratory depression

Effects produces by General anaesthetics

Effects produced by general anaesthetics are A_6

A ➔ anaesthesia ➔ hypnosis and conscious loss

A ➔ analgesia ➔ loss of pain sensation

A ➔ Amnesia ➔ Memory recall loss

A ➔ Autonomic areflexia ➔ sympathetic Nervous control loss

A ➔ Areflexia ➔reflex loss

A ➔ anxiolysis ➔ anxiety control

Contents

24. Local anaesthetics

Classification

<table>
<tr><td colspan="6">Local anesthetics</td></tr>
<tr><td colspan="4">Easters</td><td colspan="2">Amindes</td></tr>
<tr><td>Short term</td><td>Long term</td><td colspan="2">Surface action</td><td>Medium action</td><td>Long action</td></tr>
<tr><td>Procaine</td><td>Tetracaine</td><td>Cocaine</td><td>Benzocaine</td><td>Lidocaine</td><td>Bupivacaine</td></tr>
</table>

Easters

Pakistan tele communication board

- Pakistan ➔ Procaine
- Tele ➔ Tetracaine
- Communication ➔ Cocaine
- Board ➔ Benzocaine

Easters

Contents

All members have one i in them examples ➔ Procaine, Tetracaine, cocaine and Benzocaine

Amides

All members have two i in them examples ➔ Lidocaine, Bupivacaine and Ropivacaine.

Mechanism

Local anesthetics ➔ block voltage gated Na^+ channels ➔ prevent depolarization ➔Block conductance of action potential

- Higher concentration of K^+ in extracellular environment elevate their local activity
- Higher concentration of Ca^{+2} in extracellular environment antagonise the action of Local anesthetics

Clinical uses

S_6

- Minor surgical procedures
    - Mostly combined with vasoconstrictor (epinephrine)
        - Lee bleeding
        - Less dose of anethetic required
        - Action prolonged
        - Less toxicity due to lesser systemic absorption
- Spinal anesthesia➔ abdominal surgery
- Analgesia after surgery (post-operative analgesia) (slow epidural low concentration infusion)
- Surface anesthesia ➔ in dentistry and eye surgery
- Shoulder and arm surgery ➔ plexus anesthesia

- Surgery of skin ➔ topic anesthesia

Adverse effects

Sheda in L.A (Los Angeles)

S ➔ seizures

H ➔ hypotension

E ➔ CNS exited

D ➔ vasodilation

A ➔ arrhythmias

I ➔ localized impairment of Nerve

L ➔ Localized adverse effects ➔ prolonged anesthesia (numbness) and paresthesia (tingling, feeling pins)

A ➔ arrhythmias

Sheeda in los Angeles

Cocaine

Causes vasoconstriction and hypertension while for others effects remain the same

Contents

25. Skeletal Muscle Relax-

Skeltal muscle relaxants

Neuromuscular blockers

non-depolarizing drugs		Depolarizing drugs
Long acting	Short acting	succynylcholine
tubocurarine	mivacurium	

Neuromuscular Blocking drugs

Block transmission on neuromuscular end plate of skeletal Muscle

Non-depolarizing drugs

Antagonists and non-competitive

- Less anesthetic is required to produce muscle relaxation

Mechanism of action

At Low doses

Contents

Non-depolarizing neuromuscular blocker ➔ prevent attachment of acetylcholine to nicotinic receptor ➔ prevent depolarization of muscle cell membrane ➔ inhibit muscle cell contraction

- Effects overcome by increase Acetylcholine ➔ by administration of cholinesterase inhibitors.

At higher doses

➔Block the ion channel of the end plate ➔ further weakness of neuromuscular transmission.

- Effects not overcommed by increase of acetylcholine ➔ because the ion channel is **Blocked**

Actions

Muscle relaxation from smaller to larger muscles

⇨ Diaphragm Muscles are last to paralysed.

Therapeutic usage

Adjuvant drugs in anesthesia ➔ less anesthetic is needed to produce muscle relaxation

Classification

- Tubocurarine
- Mivacurium
- Metocurium
- Desocurium
- Rocuronium

Vacuronium and rocuronium ➔ are deacetylated in liver ➔ clearance is prolonged in hepatic disease.
LVR ➔ liver

Drug inter actions

1) **Cholinesterase inhibitors**

   Neostigmine and physostigmine overcome action of nondepolarizing neuromuscular blockers

2) **Halogenated hydrocarbon anesthetics**

   Increase neuromuscular blockage ➔ like halothane

3) **Aminoglycoside antibiotics**

   Gentamicin and toberamicin ➔ inhibit Acetylcholine release by inhibiting Ca^{+2} release

4) **Ca channel blockers**

   Increase neuromuscular blockage

Depolarizing neuromuscular blockers

Succinylcholine.

Mechanism

Attaches to Nicotinic receptors ➔ persist at high concentration in synaptic cleft and remain attached to the receptor for longer time ➔ provide constant stimulation.

Phase I

Membrane depolarization result in initial discharge which produces transient fasciculations followed by flaccid paralysis

Phase II

Full neuromuscular blockage is achieved and receptor is desensitized to effect of acetylcholine

- Now receptor is resistant to depolarization (closed or blocked)

Actions

Sequence of paralysis little different.

- Respiratory muscles are paralysed in last

Initially produce short lasting fasciculations ➔ followed within minute by paralysis

Therapeutic usage (rapid onset and short duration)

- When rapid endotracheal intubation is required ➔ to avoid aspiration of gastric contents to be avoided during intubation
- Electroconvulsive shock treatment

Adverse effects

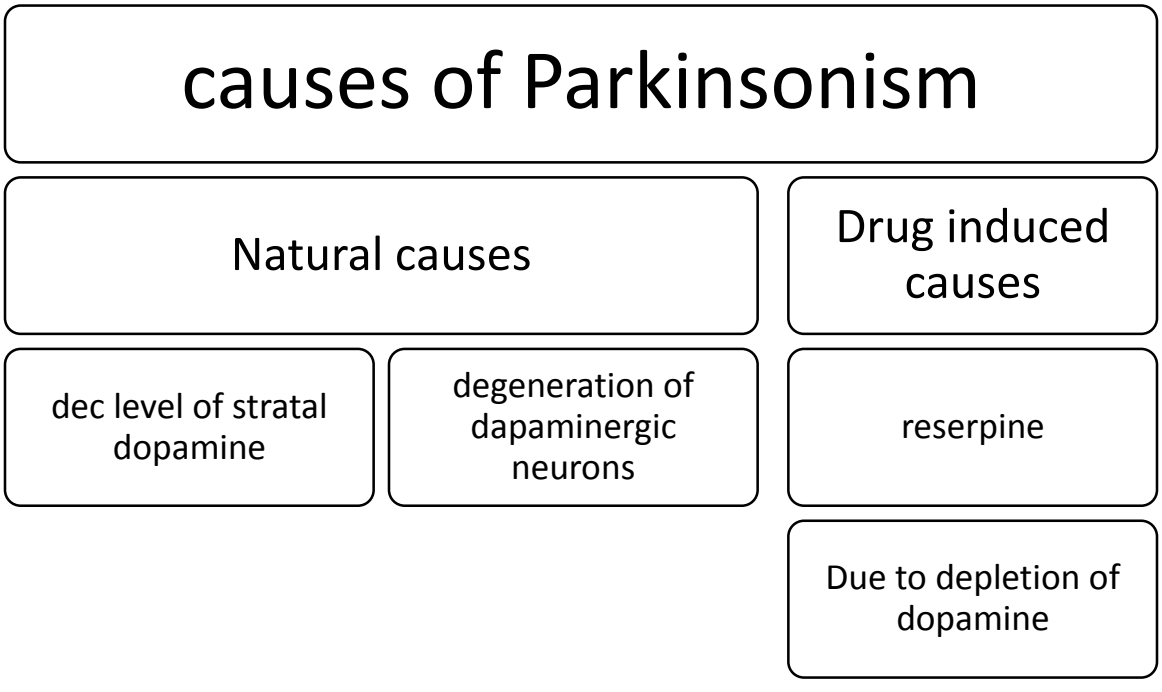
- Hyperthermia
- Apnoea

Contents

26. Drugs used in Parkinsonism

TREATMENT OF PARKINSONS DISEASE

Causes of Parkinsonism



Contents

Symptoms of Parkinsonism

RAFT

- R ➔ rigidity of skeletal muscle
- A ➔ akinesia (bradykinesia)
- F ➔ flat face (expression less)
- T ➔ tremors at rest

DRUGS USED IN PARKINSONISM

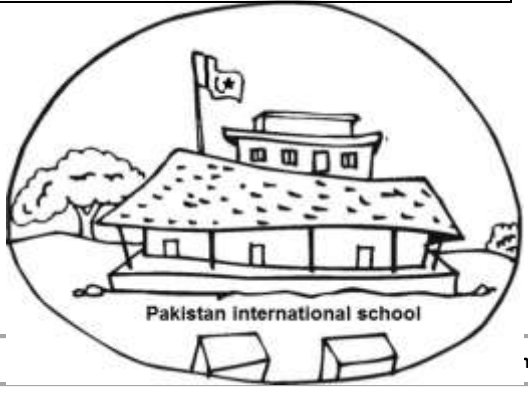
Mamu dp.com

Parkinsonism Drugs				
Ma	Mu	dp	Dot	Com
MAO inhibitors	Muscarinic inhibitors	dopamine precursors	dopamine agonists	COMT inhibitors

MAO inhibitors

ISP or Pakistan international school

- I ➔ isocarboxazid
- S ➔ selegeline



P ➔ phenelezine

Mechanism

- Inhibit MAO (Monoamine oxidase enzyme) ➔ catabolism of amines (Dopamine) inhibited
- Used as adjuncts with levodopa in treatment of parkinsonism

Muscarinic Inhibitors

Muben ➔ Mu + ben ➔ Muscarinic inhibitors ➔ durug is benztropine

Mechanism

- Block muscarinic receptors

Uses

- Improve tremors and rigidity but not bradycardia

Adverse effect

- Muscarinic inhibitors (ANS section for side-effects)

Dopamine precursors

Levodopa and Carbidopa are used

- Levodopa ➔ metabolic precursor of dopamine and this restores the dopamine level in extrapyramidal centres
    - Provide symptomatic relief that last only when drug is present in body
- Carbidopa ➔ inhibit peripheral metabolism of Levodopa

Mechanism

Parkinsonism ➔ decrease level of dopamine in specific regions of brain

Dopamine ➔ cannot cross blood brain barrier

Levodopa ➔ immediate precursor of dopamine & can cross blood brain barrier

Carbidopa ➔ inhibit peripheral metabolism of Levodopa and cannot cross blood brain barrier SO metabolism inside brain will not be effected ➔ Lower dose of levodopa to 4 to 5 folds and decrease severity of side effects

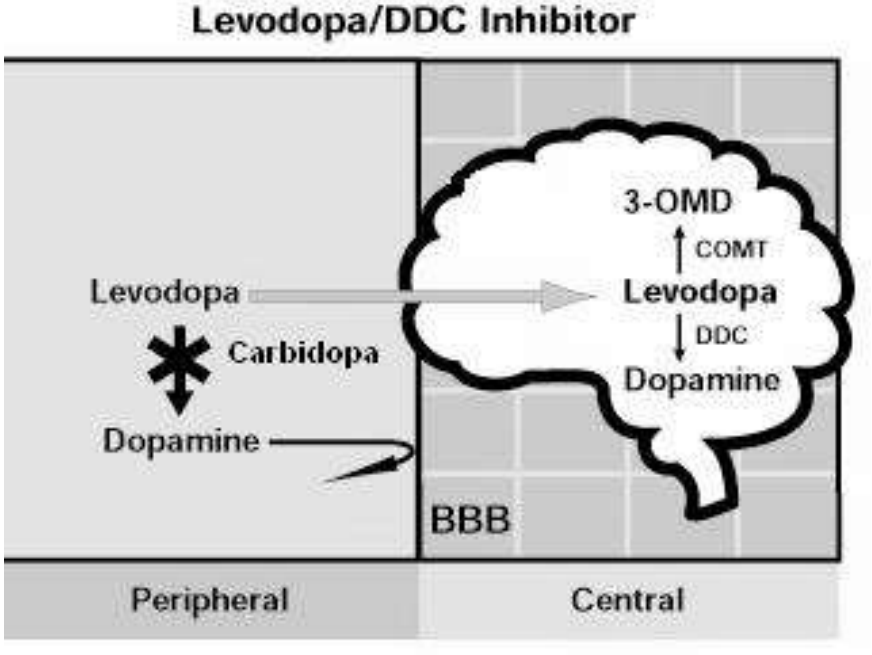
Therapeutic uses

Levodopa in combination with Carbidopa is potent and efficacious drug regime currently available

- Decrease severity of disease for few years

Absorption and metabolism

- Absorbed rapidly from small intestine
- Half-life 2-3 hours



Contents

- Fluctuations in plasma concentration produces ➔ Fluctuations in motor response (ON OFF phenomena) ➔ sudden loss of mobility and tremors

Dietry interactions

- High protein meal ➔ interfere transport of levodopa (leucine and isoleucine compete with this drug for absorption and transport.
- Taken empty stomach 45 min before meal

Adverse effects

LEVODOPA

L ➔ lower blood pressure and loss of hairs

E ➔ emesis ➔ stimulate emetic centre

V ➔ ventricular extrasystole

D ➔ dyskinesia

O ➔ (^{o}I^{o}) ➔ o resemble eye ➔ Visual and auditory hallucinations

P ➔ protein interference with Levodopa ➔ nausea

A ➔ Anorexia

Interactions

- **Vit B_{12}** ➔ increase peripheral breakdown of levodopa
- **Antipsychotic drugs** ➔ contraindicated in patients of parkinsonism ➔ exacerbate symptoms

Dopamine agonists

Bromocriptine (D_2 agonist) and pramipexol (D_3 agonist)

Uses

- Used in early treatment of parkinsonism
- Adjuncts to levodopa in treatment of parkinsonism

Contents

COMT inhibitors (catechol o methyl transferase)

Capones

- Entacapone
- Tolcapone

Mechanism

- Block levodopa metabolism in periphery

Uses

- Prolong levodopa actions

Tourette's syndrome

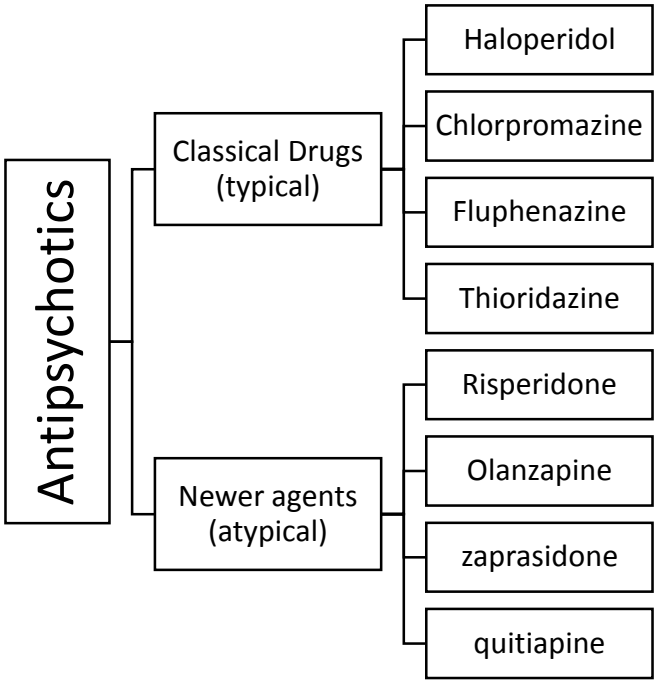
- Haloperidol ➔ D_2 blocker
- Clonidine ➔ alpha$_2$ blocker

Use

- Reduce vocal and motor tic frequency

27. Antipsychotics and Lithium

Antipsychotics.



Classical agents ➔ D_2 receptor affinity

Chlorine said! Hallo tharki fluorine

Chlorine ➔ Chlorpromazine

Hallo ➔ Haloperidol

Tharki ➔ Thioridazine

Fluorine ➔ Fluphenazine

Newer agents ➔ $5HT_2$ affinity

Contents

Roz (rose) from Quetta came

R ➔ Risperidone

O ➔ Olanzapine

Z ➔ Ziprasidone

From ➔ says ➔ $5HT_2$ receptor affinity

Queta ➔ Quetiapine


Roz (rose) from Quetta came

USES

Antipsychotics ➔ AntiPSychotics

A ➔ treatment of agitated state

P ➔ Psychosis

S ➔ Schizophrenia

PHARMAKOKINETICS

- Lipid soluble readily enter CNS
- Hepatic metabolism

Mechanism of action

⇨ Dopamine hypothesis (older)
⇨ Serotonin hypothesis (new)

1) Dopamine hypothesis

- Schizophrenia ➔ is due to excess of functional activity of neurotransmitter dopamine in specific brain tracts
  ⇨ **Dopamine tracts (**multinational technical college)
  - Mesocortical & mesolimbic pathway
  - Nigrostriatal tract
  - Tuberoinfundibular tract
  - Chemoreceptor trigger zone

Contents

DOPAMINE receptors ➔ G protein coupled receptors

2) Serotonin hypothesis

These antipsychotics Block serotonin $5HT_2$ receptor and also D_2 receptors

Clinical Uses of Antipsychotics

PAKISTANI BATS

Pakistani Bats

- Pakistani ➔ psychotic and neurological disorders
- B ➔ bipolar disorders
- A ➔ antiemetic
- T ➔ Tourette's syndrome
- S ➔ schizophrenia treatment

Side effects of Antipsychotics

Ramzan SHADED a new painting

Ramzan ➔ reversible neurologic effects (Bradykinesis, rigidity)

S ➔ sedation

H ➔ hypotension

A ➔ anticholinergic (autonomic effect)

D ➔ dermatologic effects

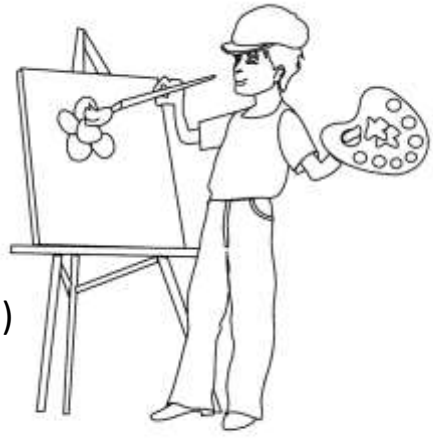
E ➔ endocrine (increased prolactin)

Extra pyramidal effects

D ➔ deposits in rating

New ➔neuroleptic malignant syndrome

Painting ➔ Parkinsonism



Ramzan SHADED a new painting

Contents

Lithium.

Uses

Lithium ➔ ends on M ➔used in manic phase of bipolar disorder

- Prevention and treatment of manic and depressive episodes

Mechanism

- Inhibit several enzymes involved in recycling of neuronal membrane phosphatides.
  ⇨ Result Suppress IP3 and DAG signaling

Adverse effects

Lithium

L ➔ leucocytosis

I ➔ inspidus (diabetes)

T ➔ tremors and teratogenic

H ➔ hypothyroidism

I ➔ increased weight

U ➔ v ➔ vomit

M ➔ regular monitoring (because Li interfere Na^+ and H_2O levels in body

Other used as antipsychotic (VLC)

V ➔ valproic acid

L ➔ lamotrigine

C ➔ carbamazepine

Contents

28. Antidepressants

Members and Classification

Maria tanver sweet sweet hay

Maria	• Mao inhibitors
Tanver	• TCAs
Sweet	• SSRIs
Sweet	• SNRIs
hay	• 5HT2 antagonists

MAO inhibitors.

⇨ Used in treatment of atypical depression

Contents

⇨ **Last line of treatment ➔** due to lethal drug dietary interactions

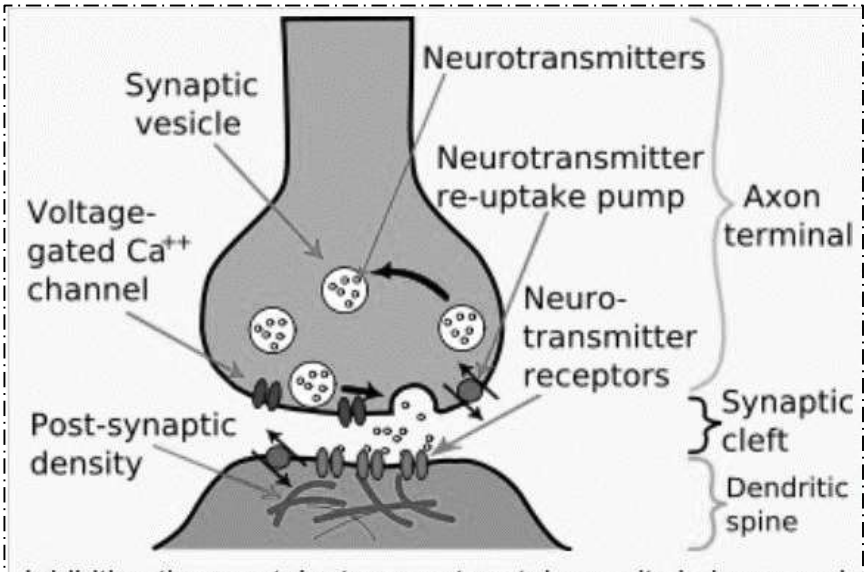
Mao in ISP (international school of Pakistan)

I ➔ isocarboxazid

S ➔ selegeline

P ➔ phenlezine

Mechanism



Inhibiting the reuptake transport protein results in increased concentrations of serotonin and norepinephrine in the synaptic clefts, leading to improvement of depression symptoms.

Inhibit MAO enzyme (two isoforms A & B) ➔ prevent breakdown of mon-oamine neurotransmitters (example serotonin, dopamine and melatonin) ➔ increase their availability

Uses

In atypical depression.

Interactions

- **Catabolism of dietary amines is inhibited**
  - Food containing amines (cheese effect)

Contents

- Hypertensive crisis are produced (tyramine displaces norepinephrine from storage vesicles) (or causes accumulation of catocholamines)
- Examples ➔ liver, soyabean and aged cheese

- Food containing tryptophan ➔ hyperserotonemia ➔ fatal serotonin syndrome developed
- Should not be combined with other antipsychotics ➔ certain combination may prove lethal ➔ like with SSRIs and tricyclics
- Addictive potential of Nicotine (component of tobacco) is increased➔ result difficulty in cessation of smoking.
- Cause hypertension with sympathomimetics

Tricyclic antidepressants

CIA is after cyclics

C ➔ Clomipramine

I ➔ imipramine
A ➔ amitriptyline

Mechanism

Block nor-epinephrine and 5HT transporter

Uses

- Major depressive disorders
- Bipolar disorders
- Generalized anxiety disorders
- Post-traumatic stress disorders
- Body dysmorphic disorders
- Eating disorders (anorexia nervosa and bulimia nervosa)

- Borderline personality disorders
- Mood disorders
- Panic disorders
- Phobias (social phobias)

Interactions

TCAs are metabolized by cyt P450 ➔ drugs that inhibit cytP450 ➔ result increase TCA level and their toxicity is enhanced

Side effects

(TCAs)[3]

T ➔ Thrombocytopenia
Tachycardia
Tremors

C ➔ Cardiac (arrhythmias, MI and stroke)
Comma
Convulsions

A ➔ Anticholinergic effects
Adipose ➔ obesity
Appetite change

S ➔ Sedation
Sweatening
Seizures

Selective serotonin reuptake inhibitors

Sir Pera cita flu (or you can use this Pakistan chocholate factory)

Sir ➔ sirotonin ➔ serotonin

Contents

Pera ➔ paroxetine

Cita ➔ citalopram

Flu ➔ fluoxetine and fluvoxamine

Mechanism

Block 5 HT transporter only

Clinical applications

Same from TCAs list

- In stroke
- Sidenaphil ➔ improvement in ejaculatory delay and sexual satisfaction

Side effects

SSRIs

S ➔ serotonin syndrome (It is a predictable consequence of excess serotonin on the CNS and/or peripheral nervous system.) (Symptoms ➔ increased heart rate, shivering, sweating, dilated pupils, myoclonus etc.)

S ➔ Stimulant CNS

Stimulate CVS ➔ tachycardia

Shorten weight (weight loss)

Shorten appetite

R ➔ Reproductive dysfunction in males

I ➔ insomnia

S ➔ suicidal risks (usage is associated with increase suicidal risks in children and adults)

Selective norepinephrine reuptake inhibitors

SNRIs

Father and son ice-cream khanain gaey. Son nain two ice-creams li and father said

Son vanilla day do

Son ➔ SNRIs

Vanilla ➔ vanela ➔ vanla + fexine ➔ vanlafexine

Day ➔ des + vanlafexine ➔ desvenlafexine

Do ➔dulextine

Mechanism

- Block norepinephrine reuptake
- Block 5HT transporter

Clinical applications

Major ➔ depression

Others from SSRIs

- Chronic pain (neuropathic pain)
- Anxiety disorders

Side effects

Same as SSRIs

- Less severe as compared to SSRIs

Sexual effects (decrease libido and difficulty to reach climax)

- Major cause of decrease compliance for both SNRIs and SSRIs

Contents

Additional side effects due to nor-epinephrine are

- Urinary retention
- Mydriasis
- Hypertension
- GIT motility

$5HT_2$ antagonists

Also called SARI (Serotonin antagonist and reuptake inhibitors)

Imagine ap nain 300 ki aik book kharedi and 313 ki baech di apko **tera** rupay ka **nafa** hoa

Tera + zodone ➔ terazodone

Nafa + zodone ➔ nafazodone

Mechanism

Block $5HT_2$ receptor

Inhibit reuptake of serotonin and nor-epinephrine

Clinical applications

Same depression

Adverse effects

- Sedation
- Blurred vision
- Headache
- Fatigue
- Anticholinergic effects

29. Opioids

Opioids

Agonists

Strong	moderate	weak
morphine methadone meperidine	codeine oxycodone	propoxyphene

Antagonists

Naloxon	naltrexon

Metabolism

To inactive glucouronide conjugates before excretion by kidney.

Opioid Receptors

Contents

mu receptors	endorphins	respiratory depression
Kappa receptors	dynorphins	sedative action
dalta receptors	enkephlins	tolerance development

Functions of receptors

Mu Receptors

- Analgesia ➔ produced by all types
- Mu cares
  - M ➔ miosis
  - U ➔ euphoria
  - C ➔ constipation ➔ decrease GIT motility
  - A ➔ analgesia
  - R ➔ respiratory depression
  - E ➔ emesis
  - S ➔ sedation

Kappa receptors

- Analgesia ➔ produced by all type of receptors

Contents

- Kappa kiss
  - K ➔ kappa receptor
  - I ➔ inhibition of ADH
  - S ➔ Sedation
  - S ➔ stress
  - Other effects of mu receptor also weakly

Delta receptor

- Analgesia ➔ as others
- D dalta
  - Dependence
  - Antidepressant

Location of opioid Receptors

Located on

- On Primary afferents
- Spinal cord pain transmission pathways
- Neurons in midbrain and medulla
- That involved in altering activities are located in Basal ganglia, hypothalamus and cerebral cortex

Endogenous opioids

Opioid-peptides that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins

Ionic Mechanisms

Presynaptic membrane (all receptors)

- Decrease Ca influx ➔ decrease neurotransmitter release

Postsynaptic membrane (mu receptor)

- Increase K conduction ➔ inhibitory post synaptic potential develop d

Members and classification

Strong agonists

Max effects ➔ M ➔ morphine, methadone and meperidine

Moderate agonists

Cods ➔Codeine and oxycodone

Weak agonists

Propoxyphene ➔ partial mean weak

Effects produced

Acute effects


BAD AMERICANS

BAD Americans

B ➔ Bradycardias and hypotension

A ➔ Analgesia
[treatment of moderate to severe pain]

D ➔ Dependence

A ➔ anorexia ➔ poor appetite and release of ADH hormone

M ➔ miosis (characteristic of all opioids **except meperidine**)

E ➔ euphoria ➔ state of excitement

Contents

R ➔ Respiratory depression

I ➔ increase smooth muscles activity ➔ biliary tract constriction (by increase contraction of biliary tract smooth muscles)

C ➔ constipation ➔ dec GIT motility ➔ effects of opioids on enteric nervous system(Used as antidiarrheal agents)

A ➔ antitussive ➔ suppression of cough reflex ➔ by inhibiting respiratory centres ➔ with decrease response to CO_2 challenge

N ➔ nausea and vomiting ➔ activate chemoreceptor trigger zone

S ➔ sedation and mental clouding (at higher doses)

Clinical Uses

- Analgesia ➔fentanyl and morphine are used (Strong agonists)
- Cough suppression ➔ cods are used ➔ codeine
- Treatment of diarrhoea ➔ diphenoxylates are used
- Management of acute pulmonary edema ➔ morphine is used
- Anesthesia ➔ preoperative medicines are used

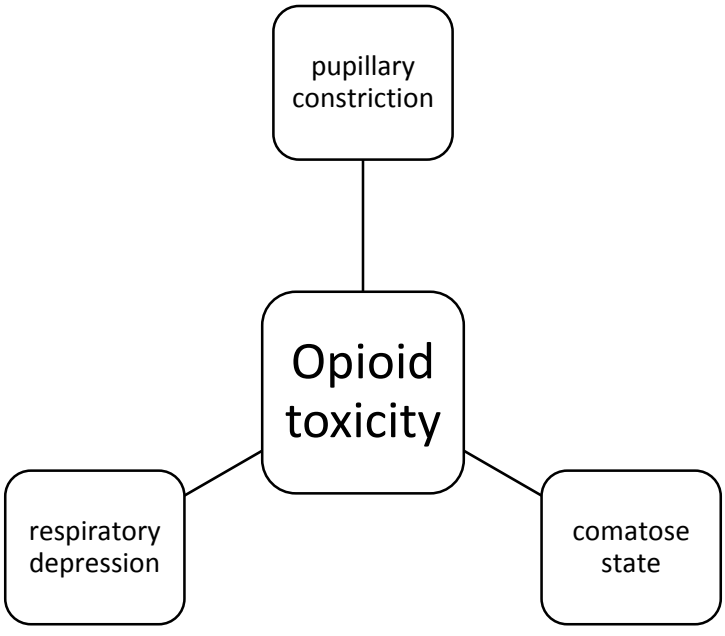
Opioid dependence

Methadone (longer acting opioids) ➔ used to manage withdrawal states of opioids and maintenance program in addicts.

- Prolonged usage of methadone ➔ block euphoric effects produced by short acting opioids (like heroin and morphine)

Side effects

Triad of toxic effects of opioids



Other effects

MORPHINE

M ➔ Miosis and mouth dryness

O ➔ out of it ➔ sedation

R ➔Respiratory depression

P ➔ aspiration pneumonia

H ➔ Hypotension

I ➔ infrequent urination

N ➔ Nausea

E ➔ Emesis ➔ vomiting

Opioid antagonists

Morph ran away with nelo

Contents

Morphine antagonist ➔ naloxone, naltrexone and nalmefene (antagonise opioid receptors)

- Treatment of opioid overdose
- Dependence maintenance

Morph ran away with Nelo

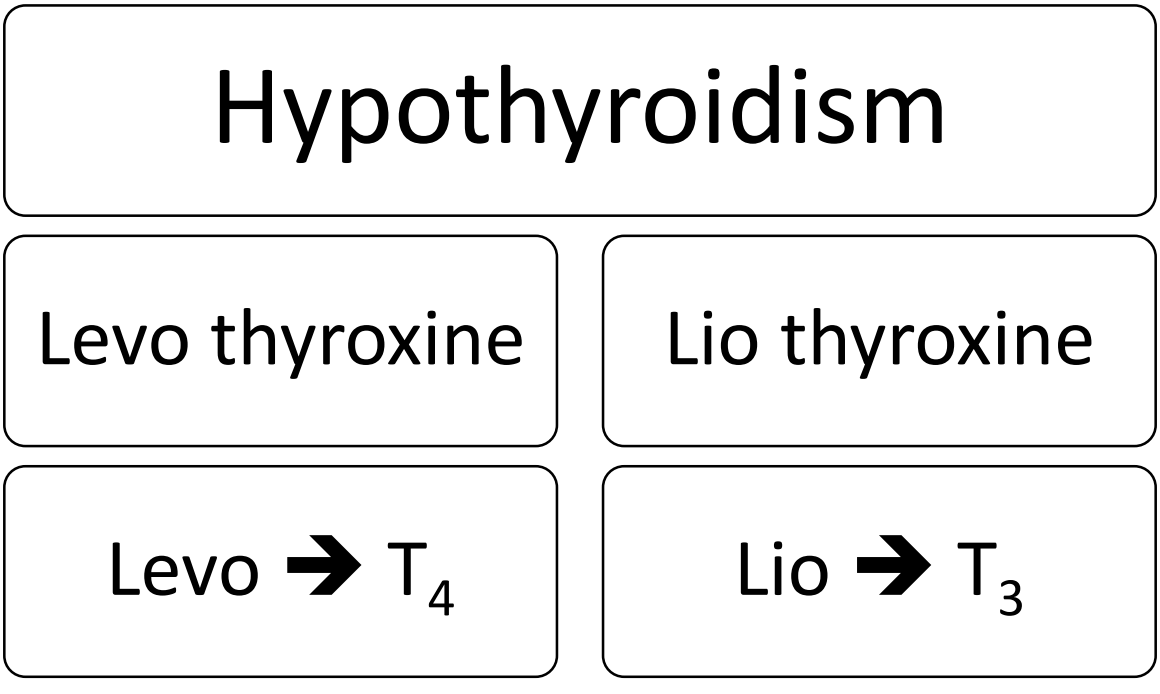
Contents

Endocrine Drugs

Contents

30. Thyroid and Antithyroid Drugs

Hypothyroidism



Levo ➔ have 4 letters ➔ T_4 (Drug of choice for hypothyroidism)

Lio ➔ have 3 letters ➔ T_3 (fast acting, shorter half-life and expansive)

Grave's disease

Beta lymphocytes produces antibodies ➔ that activates TSH receptors ➔ result in production of thyroid hormone

- While TSH level in blood is low

Contents

T_3

T_3 is 10time more potent than T_4

T_4

Converted into T_3 in target cells ➔ liver and kidney are examples of target cells

Liothyroxine and Levothyroxine

They activate nuclear receptor ➔ gene expression ➔ effects of Thyroid hormones are produced

⇨ Used in treatment of hypothyroidism

Adverse effects

Thyroidism

T ➔ tremors and tachycardia

H ➔ increase heart rate

Y ➔ yawing

R ➔ Restlessness

O ➔ Oligomanuria
I ➔ heat intolerance

D ➔ diarrhoea

I ➔ irritability

S ➔ sweat

M ➔ muscle wasting

Antithyroid drugs

Bitar

Thioamides	• PTU • Propylthiouracil • Methemazol
Anion inhibitors	• Thiocyanate • Perchlorate
Radioactive iodine	• ^{131}Iodine
Beta blockers	• Propranolol
Iodide	• Lugol solution

Contents

Tioamides

Mechanism

- Inhibit thyroid hormone synthesis
    - Block peroxide that catalyse iodination of thyroglobin
    - Block coupling of thyroglobin
    - Block coupling of MIT and DIT (mono iodo thyroxine and di iodo thyroxine)
    - Inhibit peripheral conversion of T_4 ➔ T_3
- **Methemazole** ➔ preferred because can be administered per day
- **PTU (propylthiouracil)** ➔P ➔ preferred in pregnancy + do not cross placenta + do not come in milk

Toxicity (reversible)

Rash + vaculitis + agranulocytopenia + liver dysfunction

Anion inhibitors

Thiocyanates and perchlorates

- Block uptake of iodide

Adverse effect ➔ aplastic anemia

Radioactive iodine

Taken up by gland

Dose ➔ is large enough to cause destruction of Gland

- Permanent treatment without surgery

Beta Blockers

Control tachycardia and other cardiac abnormalities produced by thyro-toxicosis

- Also inhibit peripheral conversion of T_4 into T_3

Contents

Use ➔ thyroid storm

Adverse effect ➔ BBC London TV (go to Side effects of beta blockers)

Iodide salts

They inhibit iodination and inhibit thyroid hormone release

- Result decrease size of the Gland

Escape

Thyroid gland escapes from iodide block after several weeks of treatment

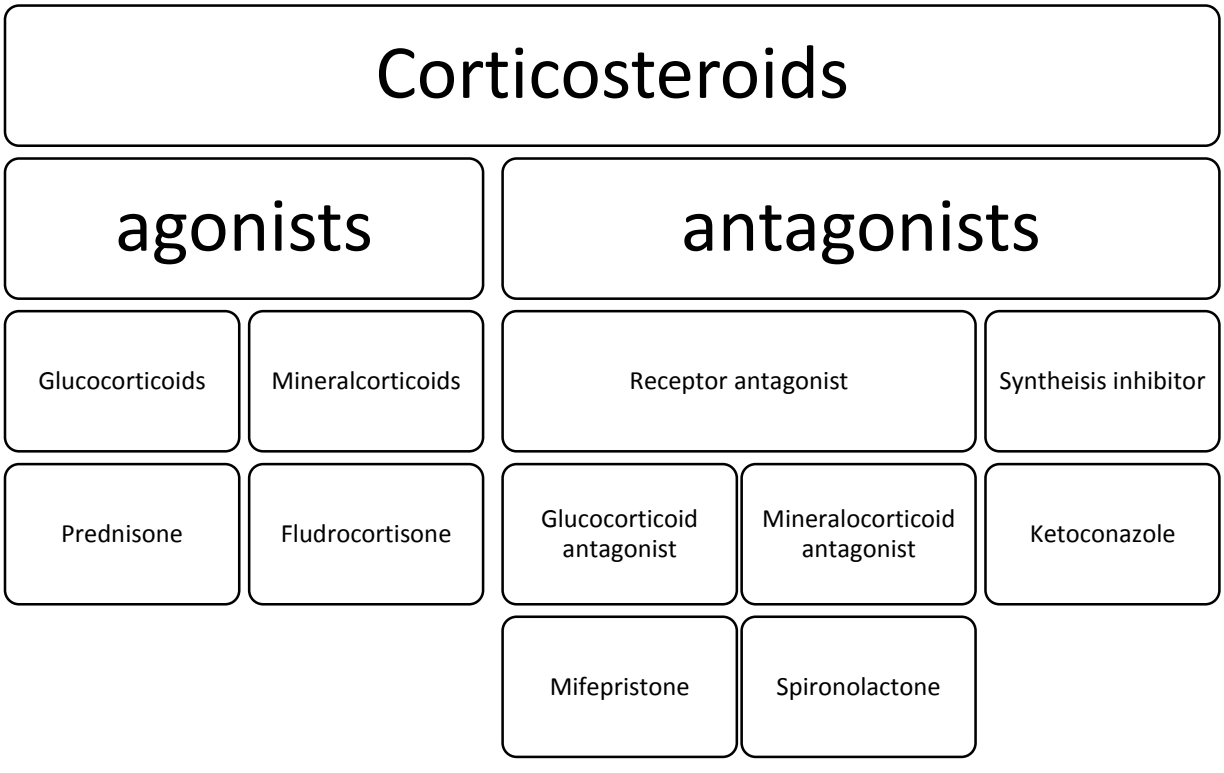
Uses

- Thyroid storm
- Prepare patient for surgical resuscitation

Adverse effects ➔ rash + drug fever + metallic taste + rarely allergy

31. Corticosteroids and antagonists

Members and Classification



Mechanism

Enter the cell ➔ bind to cytosolic receptor ➔ transport corticosteroid into nucleus ➔ alter gene response by binding to gene response element ➔ specific response is made

Organ and tissue effects

- Stimulate gluconeogenesis

Contents

- Blood glucose rises
- Muscle protein is catabolized,
- Insulin secretion is stimulated
- Lipolysis and lipogenesis are stimulated ➔ with net deposition of fat in face, shoulder and back.

Catabolic effects

- Muscle protein catabolism
- Lymphoid CT, fat and skin wasting under the influences of high concentration of steroids
- Can lead to osteoporosis

Immunosuppressive effects

- Inhibit cell mediated immunological functions
- Delay rejection reaction with organ transplant

Anti-inflammatory effects

- Increase neutrophils
- Decrease neutrophils, basophils and monocytes
- Migration of leukocytes is also inhibited

➔ Induce synthesis of an inhibitor that decrease synthesis of Phospholipase A_2

- Decrease synthesis of inflammatory mediators

Clinical uses

1) **Adrenal disorders.**

- Chronic adrenal cortical insufficiency (Addison's disease) Mineralocorticoids are used

- Congenital adrenal hyperplasia ➔ in which synthesis of hormone is stimulated by ACTH➔ administration ➔ decrease synthesis of abnormal steroids

2) Non-adrenal disorders

- Inflammatory disorders and immunological disorders ➔ like asthma, transplant rejections, rheumatic diseases etc.
- Bachlomethasone ➔ hasten maturation of lungs in premature labour

Cushing syndrome ➔ Cortisol is Cushing

Addison's disease ➔ cortisol do not add up

Adverse effects of corticosteroids

Cushingoid

C ➔ cataract

U ➔ ulcers

S ➔ skin stria + skin thinning + salt retention

H ➔Hirsutism+ hypertension + hyperglycaemia

I ➔ infections

N ➔ necrosis (avascular necrosis of femoral head)

G ➔ GIT ulcers

O ➔ obesity (buffalo hump obesity) + osteoporosis

I ➔ immune suppression

D ➔ diabetes mellitus

CUSHINGOID

Contents

Antagonists

Receptor Antagonist

1) Glucocorticoid antagonist ➔ mifepristone

Mifepristone ➔ pharmacological antagonist of Glucocorticoid and progesterone antagonist

- Use ➔ medical abortion and rarely in Cushing syndrome

2) Mineralocorticoid antagonist ➔ Spironolactone

Spironolactone ➔ pharmacological antagonist of mineralocorticoid receptor

- Use ➔ aldosteronism + hypokalemia due to other diuretics

Synthesis inhibitor

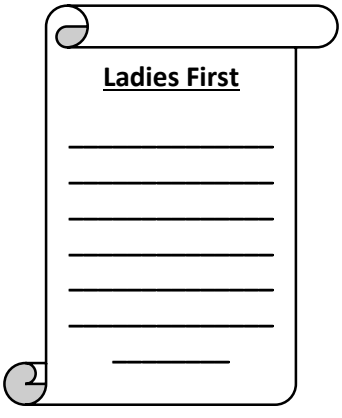
Ketoconazole

Block fungal and mammalian Cyt P 450 enzyme

- Use ➔ inhibit mammalian steroid hormone synthesis and fungal ergosterol synthesis.

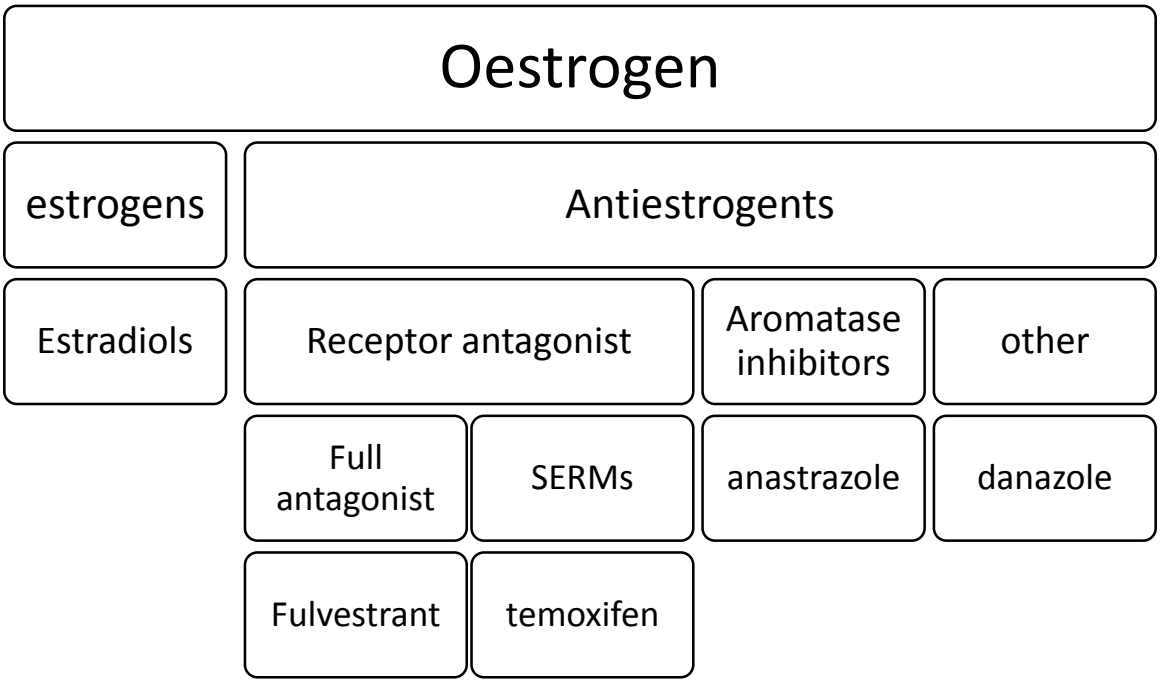
Contents

32. Gonadal hormones and Inhibitors



Female Hormones

- Oestrogen
- Progesterone



Oestrogen

Major is estradiol (have low oral bioavailability)

- Transdermal patches
- Vaginal creams
- IM injections are available

Oestrogen with max bioavailability ➔ Mestranol (max mean Mestra)

Effects

- Normal female reproductive development
  - Growth of genital structures
  - S^{o} sexual characters
  - Growth spurt associated with puberty

Estrogen builds strength in bones (reducing bone loss) and protects the heart from cardiac disease. Estrogen also has been linked to the prevention of Alzheimer's. Estrogen helps maintain the functioning of the female reproductive system.

- Metabolic effects

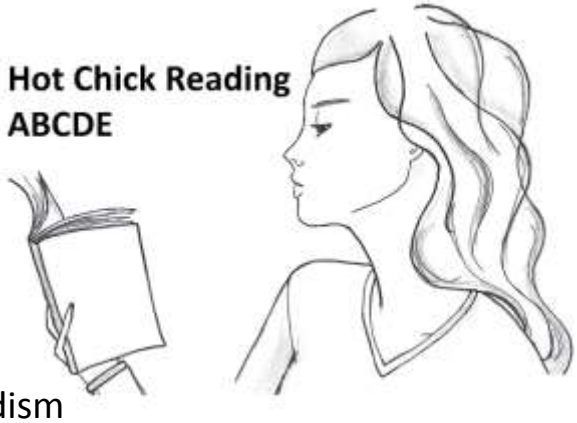
Contents

- Dec Bone resorption
- Inc Coagulability
- Inc plasma Tg
- Dec LDL
- Inc HDL

Continuous administration result dec gonadotropin from anterior pituitary.

Uses

Hot Chick



H ➔ HRT ➔ hormone replacement therapy

O ➔ Osteoporosis and prevent bone loss

T ➔ Tiny gonads ➔ hypogonadism

Chick ➔ contraceptive ➔ component of hormonal contraceptives

Adverse effect

Hot Chick reading ABC.

A ➔ adenocarcinoma ➔ vaginal adenocarcinoma.

B ➔ Breast cancer ➔ in post-menopausal women.

C ➔ cardiovascular events ➔ in post-menopausal women.

D ➔ DVT.

E ➔ endometrial cancer and in premature closure of epiphyseal lines (short stature).

Progesterone

Oral and vaginal creams

Contents

Effects

- Secretory changes in endometrium
- Maintenance of pregnancy
- Do not alter plasma proteins
- Result deposition of fats
- Suppression of gonadotropin secretions

Uses

PEC

P ➔ Promote and maintain pregnancy

E ➔ prevent endometrial cancer induced by oestrogen

C ➔ contraceptive with oestrogen

Toxicity

Lower than that of oestrogen

- Inc Blood pressure
- Dec HDL
- Decrease bone density

Hormonal contraceptives

Preparations ➔ progestin only and combination of progestin and oestrogen

Formulations ➔ Oral pills, transdermal patches, injections and vaginal rings

Preparations

- **Monophasic preparations** ➔ constant dosage throughout the menstrual cycle

Contents

- **Biphasic preparations** ➔ oestrogen and progesterone doses changes during month in two phases
- **Triphasic preparations** ➔ oestrogen and progesterone doses changes during month in three phases
- Progestin only preparations

Post coital Contraceptives

- These are emergency contraceptives that prevent pregnancy if administered within 72 hr of unprotected sex
- Preparations ➔ progestin only and combination preparations

Mechanism of action of contraceptives

- Primary ➔ inhibition of ovulation
- Effect glands (in cervix, uterine tubes) ➔ decrease likelihood of fertilization and implantation
- Progestin only ➔ do not inhibit ovulation ➔ act by other mechanisms
- Post coital ➔ by decrease survival of zygote

Other clinical uses of Contraceptives

Rida have hope (Rida umeed say hay)

R ➔ rheumatic arthritis

I ➔ iron deficiency anemia

D ➔ Dysmanuria

A ➔ acne treatment

Have ➔ Primary hypogonadism

H ➔ Hirsutism

O ➔ ovarian cyst & ovarian cancer


Rida have Hope

Contents

P ➔ pelvic inflammatory disease

E ➔ endometrial cancer

Toxicity

TB have (patient) some blood in mucous

T ➔ thromboembolic effects

B ➔ breast cancer

Have ➔ headache

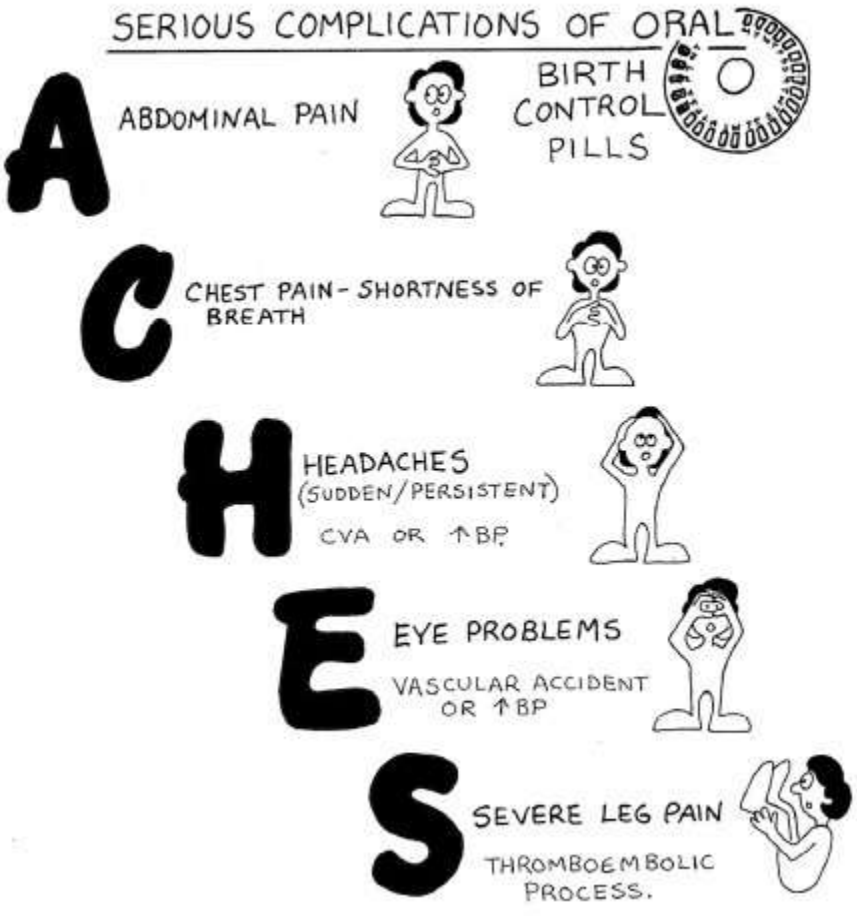
Some ➔ skin pigmentation

Blood ➔ nausea

Mucous ➔ heavy menstrual bleeding

- Older preparation have high androgens (also causes acne, hirsutism and weight gain)

Other adverse effects may be



Anti-estrogens.

Contents

antiestrogens

- Receptor inhibitors
  - full antagonists
    - fulvestrant
  - SERMs
    - tamoxifen
- Aromatase inhibitors
  - anastrazole
- Others
  - Danazole

Fulvestrant

Estrogen receptor antagonist in all tissues

Full receptor antagonist ➔ full ➔ fulvestrant

Use

- Adjuncts in hormone responsive breast cancer fail to response first line antiestrogen therapy

Adverse effects

- Hot flushes + headache

SERMS ➔ selective estrogen modulators

Tamoxifen

- Estrogen action in breast tissue and CNS
- Agonist effects in liver and bone

Uses

- Prevention and treatment of responsive breast cancer

Contents

Adverse effects

- Hot flushes
- Endometrial hyperplasia
- Thromboembolism

Tormifene ➔ same as tamoxifen

Raloxifene ➔ for osteoporosis and breast cancer prevention

Clomiphene

- Induces ovulation ➔ used in fertility

Anastrazole

Reduce estrogen synthesis by inhibition of aromatase enzyme

Aromatase ➔ A ➔ anastrazole

Use

- Adjuncts in hormone responsive breast cancer

Adverse effects

- Hot flushes
- Decrease bone mineralization
- Joint problems (arthralgia, arthritis etc.)

Danazole

Inhibit cyt P450 weakly and act as gonadotropin receptor antagonist

GnRH agonist ➔ Danazole

Uses

- Endometrial fibrotic breast disease

Adverse effects

- Act as partial agonist of androgens ➔ hirsutism , acne and weight gain
- Partial agonist of progestin ➔ menstrual disturbances

Antiprogestins

Mifepristone (progestin antagonist)

Mifepristone

Progestin and glucocorticoid receptor antagonist

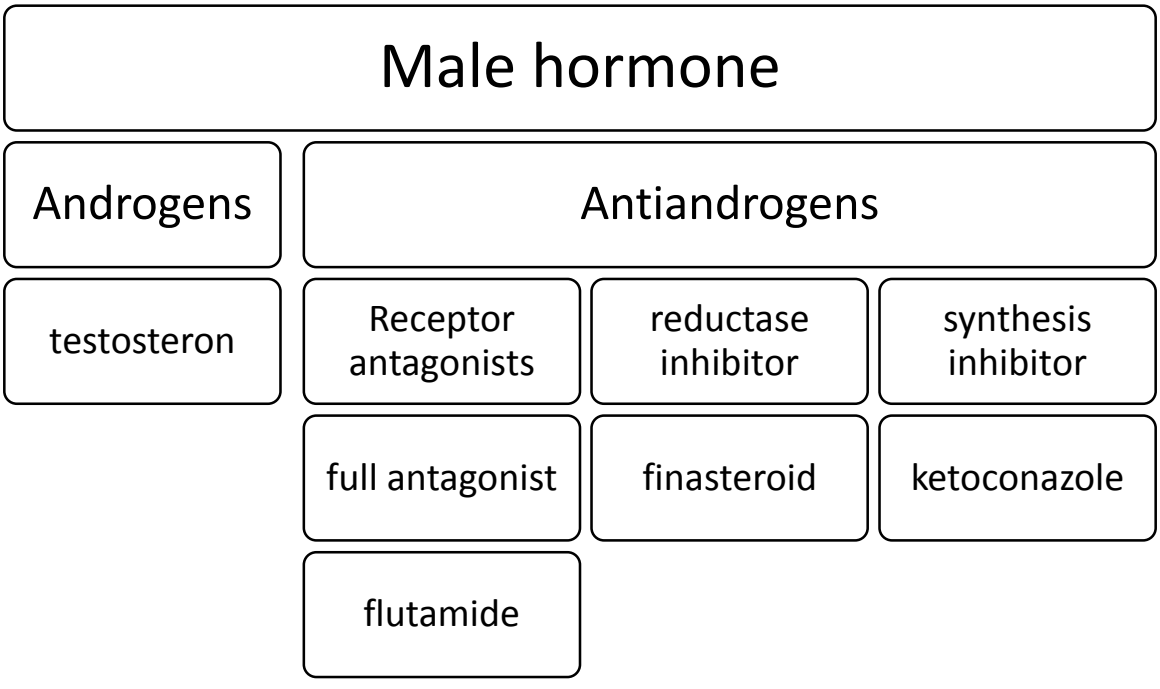
Use

- Combination with misoprostol for medical abortion

Adverse effects

- GIT disturbances
- Vaginal bleeding
- Atypical infections

Male hormones



Androgens

Uses

- Male hypogonadism
- Weight gain in patients with wasting syndrome

Antiandrogens

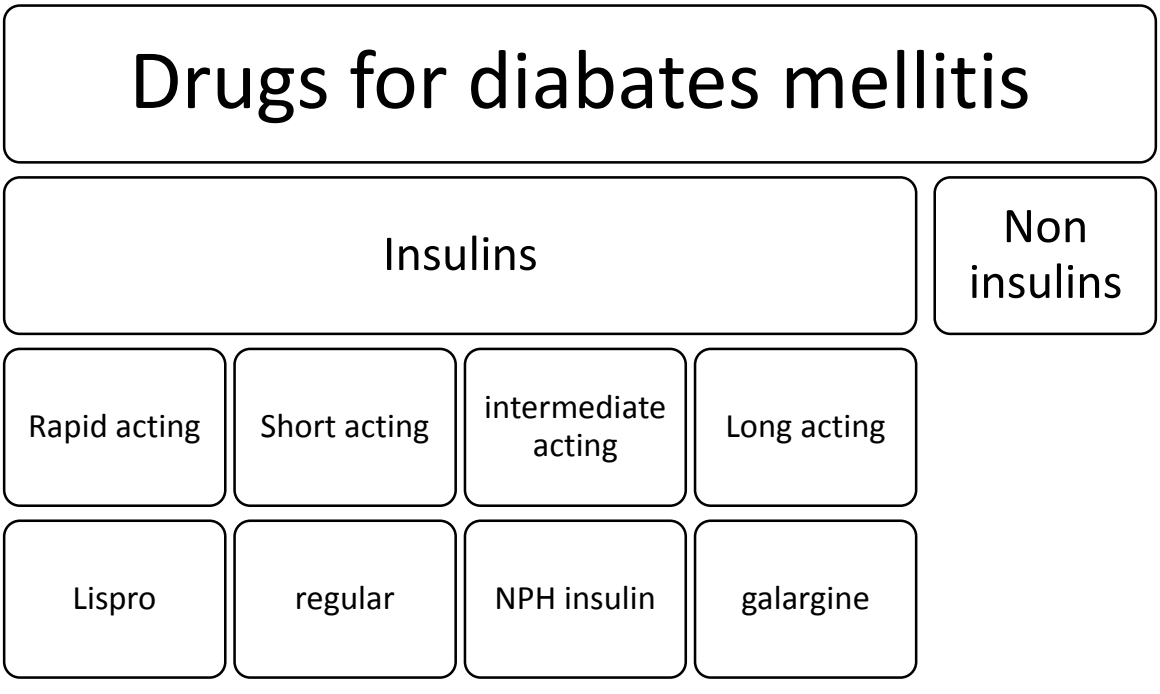
Uses

- Benign prostate hyperplasia (reductase inhibitors➔ finasteride)
- prostatic cancer (receptor antagonist ➔ flutamide)
- Ketoconazole ➔ used in advanced prostatic cancer that is resistant to first line anti androgen drugs
- Male pattern hair loss

Contents

33. Pancreatic hormones and antidiabatic agents

Diabetes management drugs



Insulin preparations

Rapid acting

Lispro, Aspart and Gluline insulins

- Taken just before meal
- Rapid onset and early peak activity

Contents

- In emergency treatment of diabetic ketoacidosis.

Short acting

Regular insulin

- Taken hour or more before meal
- Subcutaneous administered in ordinary maintenance regeims

Intermediate acting

NPH insulin ➔Neutral protamine Hagedorn insulin

Long acting

Galargine insulin

Production ➔ By bacterial recombinant DNA technology

Mechanism

Same as insulin (tyrosine kinase receptor)

Insulin toxicity

- Hypoglycaemia ➔ excessive insulin effect
- Insulin induced immunologic complications ➔ formation of anti-bodies to insulin
- Allergic reactions

Non-insulin anti-diabetic drugs

Non insulin anti diabetic drugs

Insulin secretagogues	Biguinides	alpha glucosidase inhibitors	Thiazolidinediones

Insulin secretagogues

⇨ Stimulate endogenous insulin release ➔ by premature closure of K^+ channels in the pancreatic beta cell membrane

Insulin secretogogues → closes K^+ channels → depolarized the cell → release of insulin

Most of them belong to **Sulfonylureas**

<u>Second generation sulphonylureas</u>

Gly (My pride – my bride)

Gly + My Pride ➔ Glimepiride

Gly + Pride (Pizide) ➔ Glipizide

Gly + Bride ➔ Glyburide

Contents

Older sulphonylureas

Tolbut and Cleopatraan old couple

Tolbut ➔ tolbutamide

Cleopatra ➔ chlorpropamide

Rapid acting

(Rapa + nate) + Glinide ➔ Rapaglinide and Nateglinide

- Rapid onset and short duration of action

Adverse effect

- Can precipitate hypoglycaemia
- Allergic reactions and weight gain

Biguinides ➔ metformin

- Inhibit gluconeogenesis in liver and kidney
- Decrease absorption of Glucose in GIT
- Stimulation of glucose uptake in periphery

Metformin ➔ decrease insulin production ability by increasing insulin sensitivity

- Do not increase weight

First choice in

Overweight patients or in Diabates type II

Thialidinediones

Thai rose payo (in Urdu will be Thailand k rose dalna)

Thai ➔ thialidinediones

Rose ➔ Rosi + Glitazone ➔ Rosiglitazone

Payo ➔ pio ➔ Pio + Glitazone ➔ Pioglitazone

Mechanism

Activate PPAR gamma receptor ➔ activate transcription of gene ➔ proteins encoded that are involved in carbohydrate and lipid metabolism.

- ⇨ Increase glucose uptake in muscles and adipose
- ⇨ Inhibit hepatic gluconeogenesis

Reduce both fasting and post prandial hyperglycemia and are shown to reduce risks of diabetes in high risk patients

- PPAR ➔ peroxisome proliferator activated receptor

Alpha Glucosidase inhibitors ➔ Acarbose

Acarbose

Inhibit alpha glucosidase ➔ Glucose is not formed from more complex carbohydrates ➔ Less absorption of carbohydrates

Alpha glucosidase

Enzyme in conversion Oligosaccharides or disaccharides ➔ monosaccharaides in intestinal cells

- And monosaccharaides are absorbed into blood

Comparison of type 1 and 2 diabetes		
Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults

Body size	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	~10%	~90%
Drugs	Insulin required	• Non-insulin anti diabetic agents • Later stages also require insulin

Contents

Chemotherapeutic Drugs

Contents

34. General concepts

Antimicrobial chemotherapy

Is the clinical application of antimicrobial agents to treat infectious disease

Types of antimicrobial chemotherapy:

- Antibacterial chemotherapy➔ the use of antibacterial drugs (antibiotics) to treat bacterial infection
- Antifungal chemotherapy➔ the use of antifungal drugs to treat fungal infection
- Antiviral chemotherapy ➔ the use of antiviral drugs to treat viral infection

Antimicrobial

- An agent that kills microorganisms or inhibits their growth

Types of Antimicrobials

- Microbicidal
- Microbiostatic

Microbicidal

Agents that kill microbes

Microbiostatic

Agents that inhibit their growth of microbes

Contents

Antimicrobial chemotherapy

The use of antimicrobial medicines to treat infection

Antimicrobial prophylaxis

The use of antimicrobial medicines to prevent infection.

Disinfectants

Nonselective antimicrobials such as bleach which kill a wide range of microbes on non-living surfaces to prevent the spread of illness

Antiseptics

Which are applied to living tissue and help reduce infection during surgery

Antibiotics

Which destroy microorganisms within the body

- Antibiotics are also called antibacterial

Classification of antibacterial drugs

- Bactericidal agents, which kill bacteria
- Bacteriostatic agents, which slow down or stall bacterial growth.

Bactericidal drugs ➔ irreversible

Very finely proficient at cell murder

Very ➔ vancomycin

Finely ➔ fluoroquinolones

Proficient ➔ penicillin

Contents

At ➔ aminoglycosides

Cell ➔ cephalosporins

Murder ➔ metronidazole

Bacteriostatic drugs ➔ reversible

ECSTaTiC

E ➔ erythromycin

C ➔ Clindamycin

S ➔ sulphonamides

T ➔ tetracycline

T➔ Trimethoprim

C ➔ Chloramphenicol

Criteria for choosing antibiotic

- Pharmacokinetics of drug
- Sensitivity to microorganism
- State of the patient
- Availability of the drug

MIC (minimum inhibitory concentration)

Minimum amount of drug needed that can inhibit growth within 15 to 20 hours

Concentration dependant killing

- Concentration of drug and killing ability of drug are proportional to each other below MIC

- Aminoglycosides

Time dependant killing

- Time for which drug remains above MIC is proportional to killing ability of drug
  - Penicillin and cephalosporin

Unwanted effects of antibiotics

- Reactions due to toxic effects of antibiotic
- Hypersensitivity reactions
- Super infections (second infection superimposed on earlier one)

Spectrums of Drug

Broad spectrum

Antibiotic that acts against a wide range of disease-causing bacteria.

- Tetracycline, chloramphenicol etc.

Narrow spectrum

Agents that act on a single or limited group of microorganisms

- Isoniazid against mycobacteria

Extended spectrum

Agents that are effective against gram (+) as well as gram (-) bacteria

- Ampicillin

Drug Combinations

Most infections can be treated with a single agent.
Situations in which combinations are prescribed

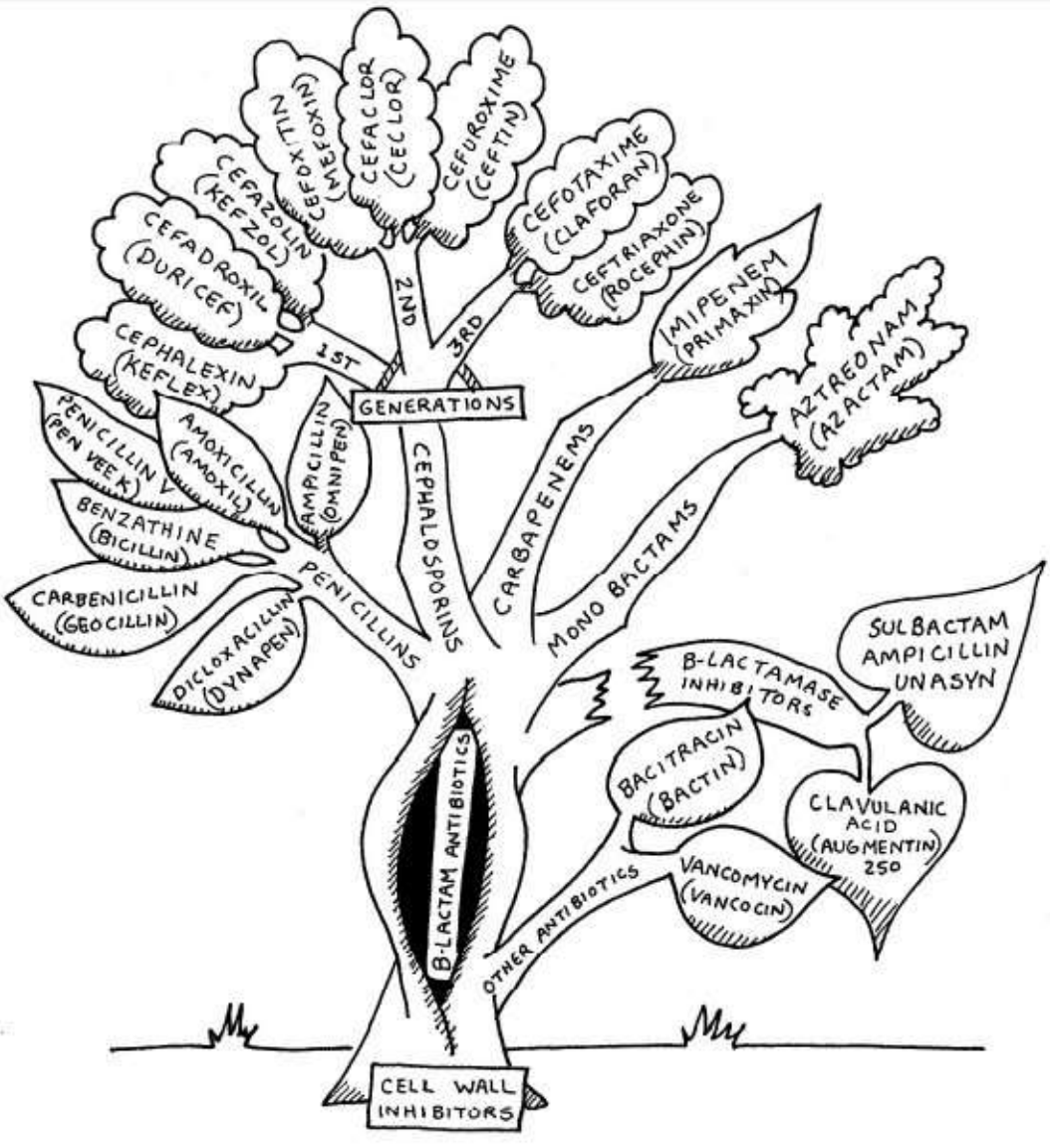
- **To achieve broad antimicrobial activity**
  E.g. **aminoglycoside** plus a **penicillin** to treat septicaemia
- **To treat mixed bacterial infections**

Contents

E.g. following perforation of the bowel)

- **In cases where no single agent would affect all of the bacteria present**
- **To prevent the emergence of resistance**
  E.g. in treating tuberculosis
- **To achieve an additive or synergistic effect**
  E.g. use of **co-trimoxazole** in the treatment of *Pneumocystis carinii* pneumonia

Antibiotic tree



THE ANTIBIOTIC TREE

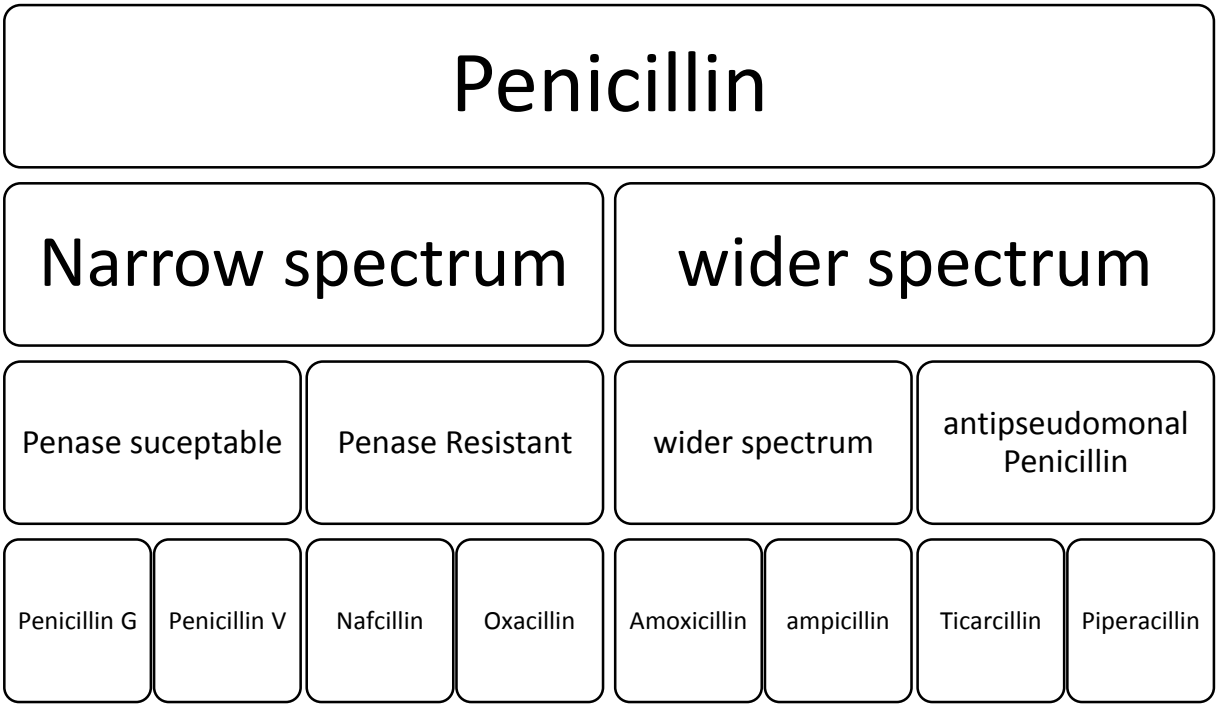
Contents

35. Bacterial cell wall synthesis Inhibitors

Bacterial cell wall synthesis inhibitors ➔ Beta lactams

Penicillin

Derivatives of 6-aminopenicillanic acid



Mechanism

- Binding to specific proteins (penicillin binding proteins)

Contents

- Inhibition of transpeptidation reaction (cross linking of peptidoglycans is inhibited)
- Produce lesions in bacterial cell wall by activation of autolytic enzymes

Mechanism of resistance

- Formation of beta lactamases (penicillinases)
- Structural changes in penicillin binding proteins (PBPs)
- Changes in porin structure in outer cell wall

Narrow spectrum

- **Penase susceptible**(Penase ➔ penicillinases)

  Mean penase is working here so Drugs will be with P

  P ➔ Penicillin G

  P ➔ Penicillin V ➔ oral drug mainly used in oropharyngeal infections

  Spectrums

  - Gram (+) ➔ streptococci
  - Gram negative cocci (-) ➔ Neisseria
  - Spirochetes

  ⇨ Penicillin ➔ no Longer suitable for Gonorrhoea

  ⇨ For syphilis ➔ first line of treatment

- **Penase resistant**

  Means drug is resistant to penase enzyme ➔ enzyme have **NO** action on drug

  N ➔ Naficillin

  O ➔ Oxacillin

  Spectrum

- This drug will be effective in those bacteria that are producing penase
  - Staphylococcal infections (antistaphylococcal penicillin)

Wider spectrum

Wider spectrum of antibacterial activity but remain susceptible to penase

- Everything need ATP and mnemonic here is ATP

A ➔ ampicillin and amoxicillin

Spectrum

- Similar to penicillin G
- For other **HELP**

  H ➔ Haemophilus influenza

  E ➔ E.Coli

  L ➔ Listeria monocytogenes

  P ➔ Proteus mirabilis
- When used with Penase inhibitors its antibiotic activity is even more enhanced

- **Antipseudomonal Penicillin**

  T ➔ Ticarcillin

  P ➔ Piperacillin

  ⇨ Still they are susceptible to penase

  Spectrum
  - Pseudomonas
  - Enterobacter
  - Klebsella

Penase inhibitors

- Inhibit penicillinases enzyme ➔ salbactam, tazobactum and clavulanic acid

Toxicity

- Allergic reactions (SAAF)
    - S ➔ joint swelling
    - A ➔ Hemolytic anemia
    - A ➔ Anaphylaxis
    - F ➔ fever
- GIT disturbances

Naficillin ➔ N ➔ neutropenia

Ampicillin ➔ AM ➔ allergic reaction maculopapular skin rash

Cephalosporins

Derivatives of 7-amiocephalosporanic acid

Mechanism

- Bind to penicillin binding proteins (PBPs) ➔ similar to penicillin (But structure is different from penicillin)

Resistance

- Decrease in membrane permeability
- Change in structure of PBPs

Contents

⇨ Methicillin resistant bacteria are resistant to Cephalosporins

Classification and generations
First-generation drugs

Mr.Fazol (ce**fazol**in) is a lorry driver (cepha**lori**dine). He works very hard and so became thin (Cephalo**thin**. He has Red (cepha**radine**) Lux (Cepha**Lexine**) soap.

Mr.Fazol ➔Ce + fazol + in ➔ cefazolin

Larry driver ➔Cefa + Lori + dine ➔cefaloridine

Thin ➔Cefalo + thin ➔Cefalothin

Red ➔Cef + Radine ➔ Cefradine

Lux soap ➔Cefa + lexine ➔cefalexine

Contents

- In first generation drugs cef can also be spelled by ceph both are correct

Spectrum

Gram (+) ➔ more effective ➔ Activity against penicillinases-producing, methicillin-susceptible staphylococci and streptococci.

Gram (-) ➔ PEcK

- P ➔ proteus mirabilis
- E ➔ E.Coli
- K ➔ Klebsella pneumonia

Methicillin resistant ➔ not effective

Contents

Second-generation drugs

Mr.Foo (Ce**fo**tetan) wearing fox (ce**fox**itin) fur (ce**fur**oxime) coat came into the party.

Mr.Foo ➔Ce + Fo + tetan ➔ Cefotetan

Fox ➔Ce + Fox + itin ➔ Cefoxitin

Fur ➔Ce + fur + oxime ➔Cefuroxime

Spectrum

Gram (+) ➔ less effected

Gram (-) ➔ extended spectrum (HEN PEcK)

- H ➔ H.Influenze
- E ➔ Enterobacter
- N ➔ Neisseria
- PEcK ➔ from first generation

Contents

Third Generation Drugs

Mr Aziz taking his ox in a taxi for slaughter and for this he have three oxon blades

Mr. Aziz (Ceft**azi**dime) is taking his ox (ceftizi**ox**ime) in a taxi (Cef**taxi**me) to slaughter. For this purpose he have three axon (cef**triaxon**) blades

Mr.Aziz ➔Ceft + azi + dime ➔ Ceftazidime

Ox ➔Ceftiz + ox + ime ➔ ceftizioxime

Taxi ➔ Cefa + taxime ➔ Ceftaxime

Three axes ➔ Cef + tri + axon ➔ Ceftriaxon

Spectrum

Gram (+) ➔ less effected

Gram (-)➔extended spectrum

- HEN PEcK

Contents

- And PINS
  - Providentia
  - Influenza
  - Neisseria
  - Serratia

Fourth generation Drugs

Mr.Fazol invited Mr.Aziz to coffee

Coffee ➔ Cefipime

Spectrum

Extended spectrum of activity against Gram-positive and Gram-negative bacteria, with greater activity against both types of organism than third-generation agents.

Gram (+) ➔ similar activity as 1st generation (Mr.Fazol is on coffee)

Gram (-) ➔ effective against wider spectrum of 3rd generation (Mr. Aziz is on coffee)

- Beta lactamase stable

<u>Cephalosporins are not effective against</u>

Lame

L ➔ Listeria

A ➔ Atypicals (mycoplasma)

M ➔ Methicillin resistant staph aureus

E ➔ Enterococci

<u>Adverse effects of Cephalosporins</u> (ADP)

- Allergic reactions
  - Skin rash to anaphylactic reactions

- But less frequent that that of penicillins
- Cross reactivity between penicillins and cephalosporins is incomplete (penicillin allergic can be treated with them but anaphylactic to penicillin should not be treated with cephalosporin)

- Drugs containing methylthiotetrazole group may cause Disulfiram like reactions (Cefamandole and Cefotetan)
- Pain at site of injection (I/M)

Carbapnems

(Imi boli dor maro) + Penem

Imi ➔ Imi + penem ➔ Imipenem

Boli ➔ thses are broad spectrum antibiotics

Dor ➔ Dori + penem ➔ Doripenem

Maro ➔ Mero + penem ➔ Meropenem

Spectrum

- Against penicillin resistant staphylococci
- Not against methicillin resistant strains
- Gram negative rods

- Have partial cross reactivity with penicillins

Monobactams

Mono ➔ Mano

M ➔ monobactum group

A ➔ aztreonam Drug

Contents

No ➔ active against gram (-) bacteria (like pseudomonas and klebsiella)

Glycopeptides

Peptide mean ➔ active against gram (+) bacteria (even against penicillin and methicillin resistant strains)

Mnemonic for this is Red Guava (Gava)
Ga indicate this is glycopeptide and Va indicate its member Vancomycin

Red ➔ indicates this cause's Red man syndrome

- Given parentally for Clostridium deficile colitis

Lipopeptides

Peptide mean ➔ active against gram (+) bacteria

Lipo mean Lipid ➔ D at the end of Lipid indicate its member Daptomycin

- All other groups in this chapter inhibit synthesis of cell wall but Lipopeptide (daptomycin) destabilizes the bacterial cell membrane

Contents

36. Bacterial Protein synthesis inhibitors

Protein synthesis inhibitors

Broad spectrum (TC)	Moderate spectrum (KM)	Short spectrum (L_2S)

Tetracyclins	Chloramphenicol	Macrolide	Ketolide	Lincosamide	Streptogramins	Linezolide

Mechanisms

Tetracycline

Tetracycline ➔ tRNA ➔ tries but cannot bind

- Prevent the amino acyl transfer RNA from attaching A site on ribo-some.

ChloramPhenicol

Chloram + Phenicol ➔ Phenicol ➔ Peptide

- Inhibit the peptide bond formation by peptidyl transferase

Contents

Macrolide

Macro ➔ movement

- Prevent movement of ribosome
    - Prevent translocation

Clindamycin

Clinda ➔ Cling

- Make ribosome cling to mRNA
    - Prevent translocation

Streptogramins

Strepto ➔ sliped (in bathroom)

- Slipping of nacent polypeptide chains from ribosome

Linezolid

Line ➔ if you count lines in A_4 paper of a registor they will be 23 (may differ but in my register they were 23)

- Bind to 23S RNA of 50S subunit

Tetracycline ➔ thirty ➔ 30S

Others ➔ on 50S

Details of Each group

Tetracycline

Members

Tetra doxy minor tigers

Tetra ➔ Tetracycline

Contents

Doxy ➔ doxycycline

Minor ➔ Minocycline

Tigers ➔ Tigecycline (Tiger have broadest spectrum and resistance is less common)

Uses

Tetracycline vacum her bed room

Tetracycline ➔Tularaemia

V ➔ vibrio cholera infections

A ➔ acne

⇨ Alternative in treatment of syphilis

C ➔ chlamydia infections

U ➔urea plasma infections

M ➔ mycoplasma pneumonia

Her ➔ H-Pylori infection

Bed ➔ brucecella infections

Room ➔ Rickettsia infections

Doxycycline

- alternative to Macrolide in community acquired pneumonia
- Lyme disease
- Malaria

Tigecycline ➔also used in case of those organisms resistant to oter tetra-cycline

- Penicillin resistant ➔ yes
- Methicillin resistant ➔ yes

- Vancomycin resistant ➔ yes

Resistance

- Development of efflux pumps (for active extrusion)
- Formation of ribosomal protection proteins (interfere tetracycline binding)

⇨ But there is least resistance to tigecycline

Pregnancy contraindicated

Side effects

Kapil DeV

K ➔ kidney toxicity (fanconi's syndrome ➔ Disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine)

A ➔ Anabolic effect on body

P ➔Phototoxicity

I ➔ increase ICP (intracranial Pressure)

L ➔ Liver toxicity

De ➔Dental ➔ enemal problems

V ➔ vestibular problems

Others

- GIT effects (nausea, diarrhoea, enterocolitis etc.)
- Teratogenic ➔ to be avoided in pregnancy

Contraindications

Tetra + cycline ➔ Cycle ➔ C_4

Children ➔ bone and teeth mineralization problems

Child birth ➔ Teratogenic (liver dysfunctions)

Chelates ➔ form chelates in the presence of divalent ions in food ➔ decrease oral absorption

Candidiasis ➔ super infections

Chloramphenicol

Wide spectrum drugs

Backup Drugs for severe infections

- RMP

Contents

R ➔ rickettsia infection

M ➔ meningitis

P ➔ pneumonia

Not used in chlamydial infection

Resistance

- Plasmid mediated ➔ formation of acetyltransferase that inactivates the drug

Adverse effects

Smart boy in girl's hostel

Smart ➔ super infection

Boy ➔ bone marrow infection

In ➔ irritational effects

Girls ➔ Grey baby syndrome ➔ this occurs in infants characterized by decrease RBCs, cyanosis and CVS collapse

Hostel ➔hypersensitivity

smart boys in Girls hostel

Clindamycin (Lincosamide)

Uses

PAST PAST

P ➔ Peritonitis and prophylaxis of endocarditis in valvular disease

A ➔ Aspiration pneumonia, Acne and Anaerobic infections

S ➔ Strep aureus infections

T ➔ AIDS related toxoplasma

Adverse effects

P ➔ Pseudomembranous colitis

A ➔ Abdominal pain

S ➔ Skin infections and rash

T ➔ Toxic mega colon

And Gray baby syndrome

Macrolides

Mr Aziz telephoned Rfida.

Mr. Aziz Telephoned Rfida

Mr ➔ Group is macrolide

Aziz ➔ Azithromycin

Tele-phoned ➔ telithromycin

Contents

R ➔ RBC ➔ erythrocyte ➔ Erythromycin

Fida ➔ fidaxomycin

Macro mean big ➔ act on big subunit ➔ 50S

Uses

$(PC)^2$

P ➔ pertussis

C ➔ corynebacteria infection

P ➔ Pneumonia

C ➔ Chlamydia infection

- Azithromycin is effective in gonorrhoea alternative to Ceftriaxone
- Azithromycin is effective in syphilis alternative to Penicillin G

⇨ Cross resistance between macrolides is complete

Resistance

- Formation of drug metabolizing easterase

Adverse effects

Macro GRAPES

G ➔ Gastric discomfort

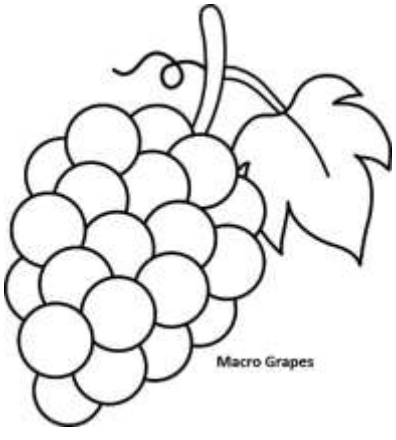
R ➔ Rash

A ➔ acute cholestatatic hepatitis

P ➔ prolonged GT

E ➔ eosinophilia

S ➔ sensitivity



Linezolid

Uses

- Penicillin resistant ➔ yes
- Methicillin resistant ➔ yes
- Vancomycin resistant ➔ yes

Resistance

Decrease affinity of linezolid for binding site

Adverse effects

STN

S ➔ Serotonin syndrome

T ➔ Thrombocytopenia

N ➔ Neutropenia

Contents

37. Aminoglycosides

Members and Classification

STANG

- S ➔ Streptomycin
- T ➔ Tobramycin
- A ➔ Amikacin
- N ➔ Neomycin
- G ➔ Gentamycin

Mechanism ➔ on 30S subunit of ribosome

Aminoglycoside ➔ A is first letter of ABC

- Block the initiation step ➔ by blocking the formation of initiation complex

Other mechanisms

- Inhibit translocation
- Misreading of code on mRNA

amiNOglycosides

NO ➔ no protein synthesis

NO ➔ effective again Negative organisms

NO ➔ Not used in Pregnancy

NO ➔ Neomycin oral ➔ Neomycin use is restricted to oral use to eliminate bowel flora) (topical can also be used)

Contents

NO ➔ Not used alone (used in combinations with Beta lactams)

NO ➔ Nephrotoxic and Ototoxic

Uses

- HEN Peck (see from cephalosporins)
- Streptomycin combination with penicillin ➔ effective in enterococcal carditis , tuberculosis, plague and tularaemia
- Netilmicin ➔ for treatment of infection resistant to other aminoglycosides

Resistance

- Streptococcus pneumonia and enterococci ➔ Resistant due to failure of drug to penetrate the cell
- Primary mechanism ➔ Plasmid mediated formation of inactivating enzymes ➔ Group transferases that catalyse the acetylation of amine functions and transfer of phosphoryl or adenylyl group to oxygen atoms of Hydroxyl groups on aminoglycosides
    - Group transferase produced by enterococci ➔ resistant to gentamycin and toberamycin but not to streptomycin

Adverse effect

- Nephrotoxic
- Ototoxic
- Neuromuscular blockage
- Skin reactions

Contents

38. Sulphonamides, Trimethoprim and Fluoroquinolones

Sulphonamides and trimethoprim ➔ interfere folic acid synthesis

Fluoroquinolones ➔ inhibit microbial nucleic acid metabolism

Sulphonamides

Chemical nucleus resemble PABA (P amino benzoic acid)

- Less soluble in acidic urine

Trimethoprim

Structure similar to folic acid

- Weak bases and are trapped in urine

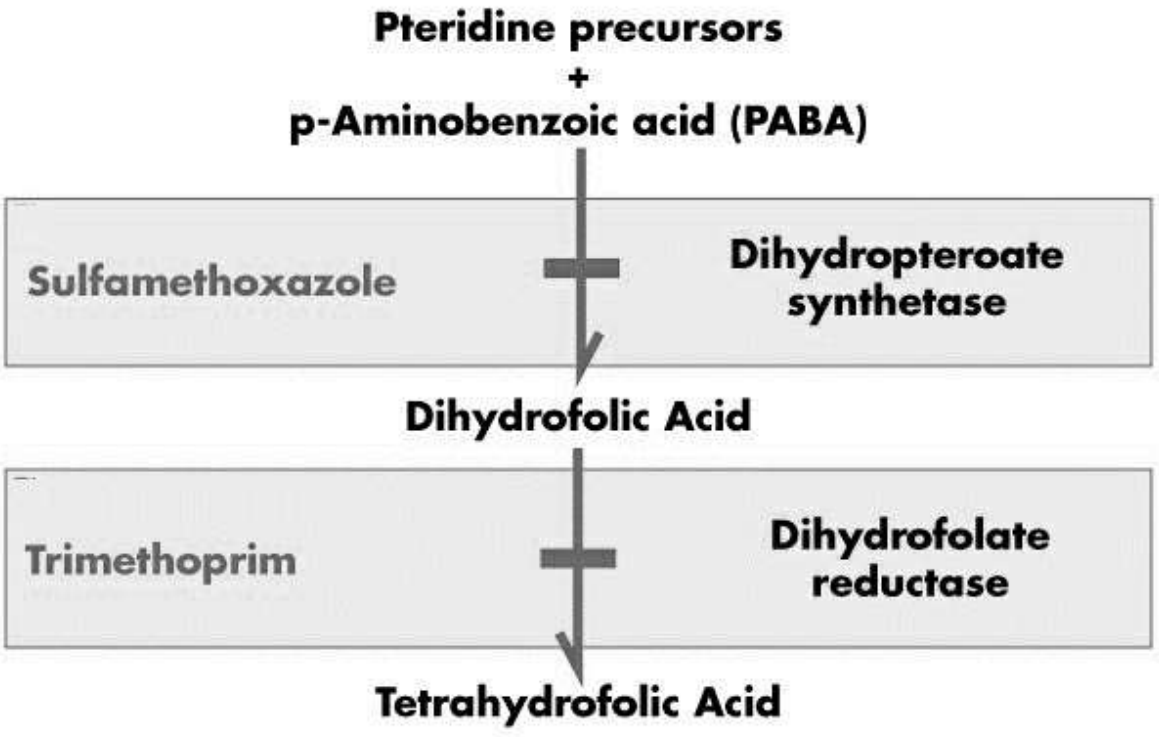
Reisistence

Sulphonamides ➔ Decrease affinity of enzyme for drug + Decrease accumilation of drug

Trimethoprim ➔ Decrease affinity of enzyme for drug

Mechanism

Contents



Members and classification

Antimetabolites			Trimethoprim
Sulphonamides			trimethoprim sulfamethazole
Long acting	Intermediate acting	Short acting	
sulfadoxine	Sulfamethoxazole	sulfasoxazole	

Contents

Sulphonamides

- Long acting ➔ dair tak act karta hay ➔dair ➔ sulfa + doxine ➔

sulfadoxine

- Intermediate acting ➔ mediaum ➔ Sulfa + methoxazole ➔ Sulfameth-oxazole
- Short acting ➔ short ➔ Sulfa + soxazole ➔sulfasoxazole

Clinical uses

- Gram (+)➔ yes
- Gram (-)➔ yes
- Norcardia ➔ yes

Simple urinary tract infection

Urine ➔ came out of sex organs ➔ soxa used

- Sulfasoxazole

Ocular infection

Aankh (eye) ➔ actamide is used

- Sulfaacetamide is used

Ulcerative colitis

Coli Sala

Sulfa + Sala + zine ➔ sulfasalazine is used

Contents

Trimethoprim sulfamethoxazole

Luse

L ➔ Lungs ➔ respiratory tract infections

U ➔ Urinary tract infections

S ➔ sinusses infections

E ➔ Ears infections

- Drug of choice for Norcardia infection

Backup drug

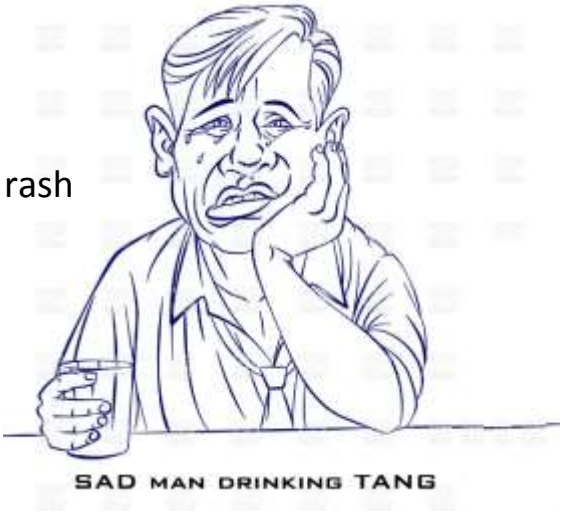
Tv set

T ➔ typhoid

V ➔ vibrio cholera infection

Set ➔ Shigallosis

Toxicity of Sulphonamides



SAD Tang

S➔ sulphonamide side effects + Skin rash

A ➔ aplastic anemia

D ➔ drug interactions

T ➔ thrombocytopenia

A ➔ acidic urine

N ➔ nephrotoxic (crystaluria and hematuria)

G ➔ GIT side effects (Nausea, diarrhoea and vomiting)

Drug interactions

BMW

B ➔ Displace bilirubin from proteins ➔ kernicterus in neonates if used in pregnancy

M ➔ Methotrexate ➔ compete with this for plasma proteins

W ➔ Warfarin ➔compete with this for plasma proteins

Adverse effects of Trimethoprim

The male garments

The ➔ indicate these are side effects of trimethoprim

Ma ➔ magaloblastic anemia due to folate deficiency

Le ➔ leukocytopenia
Garments ➔ granulocytopenia

Trimethoprim and sulfamethoxazole

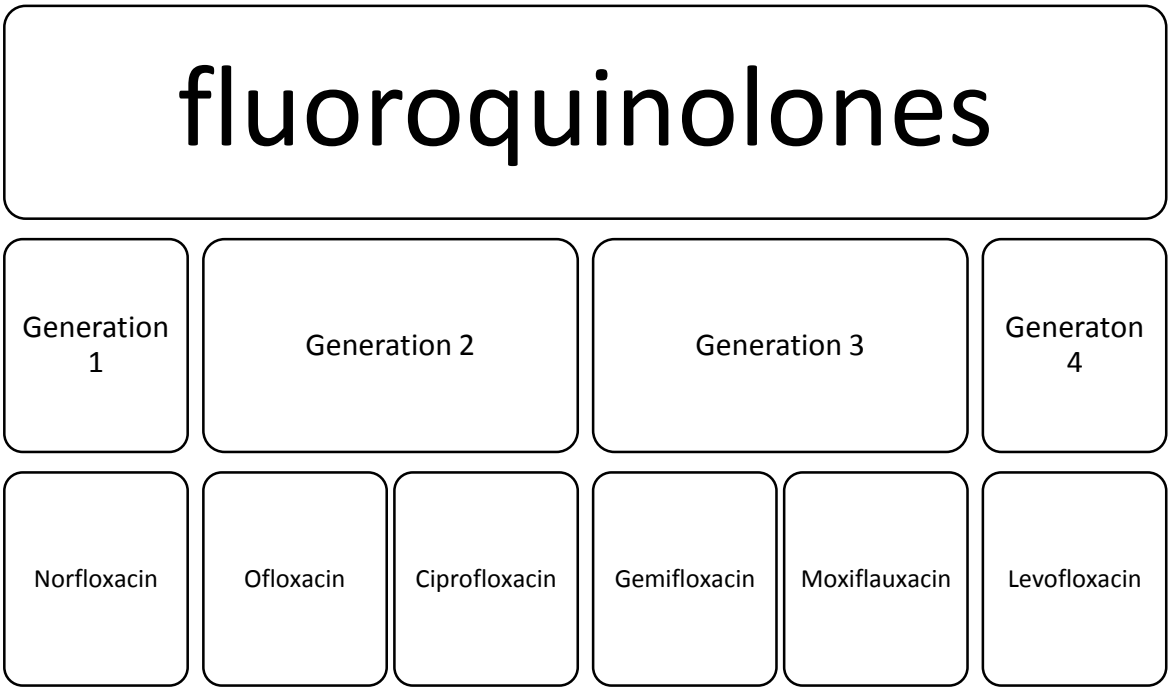
Same from sulfonamides
* alse called ***Cotrimoxazole***(sulfamethoxazole)

Fluoroquinolones

Contents

Drugs and classifications

Noor ciped orange and gemi loves maxico



Generation 1

Nor ➔ Norfloxacin

Generation 2

Ciped ➔ciprofloxacin

Orange ➔ Ofloxacin

Generation 3 and 4

Gemi ➔ gemifloxacin

Loves ➔ levofloxacin

Maxico ➔ Moxifloxacin

1st and last belong to 3rd genrations and levo belongs to 4th generatios

Generation 1 ➔ Norfloxacin

Derived from Nalidixic acid

Contents

One is also called uni ➔ so they are used in urinary tract infections

Generation 2 ➔ ciprofloxacin and Ofloxacin

Use against

Gram (+)➔ yes

Gram (-)➔ no

- Used in atypical pnemonia (mycoplausma pnemonia)

Genration 3 and 4 ➔ gemifloxacin, levofloxacin and moxifloxacin

Less active than generation 2 and have greater activity against gram (+) cocci

Effective against

- Strep pneumonia aureus
- Methicillin resistant staphylococci

⇨ Also called respiratory fluoroquinolones

Pharmakinetics

Norfloxacin ➔Nor Not ➔ Donot achieve adequate plasma level in most of infections

Moxifloxacin ➔ Eliminate also by bile Given in case of renal impairment

Mechanism

Queen on top

Fluoroquinolones ➔ inhibit topoisomerase

- Topoisomerase II ➔ in gram (-) (negative can be drawn between two dots)
- Topoisomerase IV ➔ gram (+) (positive can be drawn between four dots)

Contents

Topoisomerase II ➔ also called DNA guyrase

DNA guyrase ➔causes relaxation of supercoiled DNA during replication and duplication (**This step is inhibited by Fluoroquinolones)**

- Inhibition of Topoisomerase causes death of bacteria

Post antibiotic effect

Fluoroquinolones and aminoglycosides show post antibiotic effects ➔ Growthy is inhibited even after the plasma concentration of Drug is fall below Minimum inhibitory concentration

Resistance

- Efflux pumps ➔ Decrease intracellular accumulations
- Change in structure of porins ➔ in gram (-) organisms
- Change in sensitivity to target enzyme via point mutations

Clinical uses

Fluorquinolone surg

S ➔ Skin infections

U ➔ Urogenetal tract infections

R ➔ Respiratory tract infections

G ➔ GIT infections
Examples
PEcK infections

P ➔ Pseudomonas auregenosa

E ➔ enterobacter and E.coli

K ➔ Klebsella pneumonia

- Should not use them unless no other safe drug is available to avoid development of resistance

Adverse effects

Boxer's LAMP

Boxer ➔ Black boxer warning ➔ Tendinitis and Tendon rupture

L ➔ abnormal Liver function test

A ➔ Allergic reactions (Rash and phototoxicity)

M ➔ Exacerbation of myasthenia gravis

P ➔ Prolongation of QT interval

Contraindications

CAP

C ➔ CNS inflammation

A ➔ Arrhythmias

P ➔ Pregnancy ➔ if used in first trimester abnormalities are developed

Contents

39. Anti-mycobacterial Drugs

First line Drugs

International formula

2HREZ/4HR$_3$

H ➔ Isoniazid

R ➔ Rifampicin

E ➔ Ethambutol

Z ➔ Pyrazinamide

- HREZ daily for 2 months and then HR 3 times a week for 4 months

Second line Drugs

Cape

C ➔ Ciprofloxacin ➔Fluoroquinolone

A ➔ Amikacin ➔ Aminoglycoside

P ➔ P amino salicylate

E ➔ Ethionamide ➔ thioamide

Isoniazid

Mechanism

Inhibit mycolic acid (mycolic acid essential component of bacterial cell wall)

Contents

Resistance

Kat G gene ➔ encodes the catalase ➔ required for bioactivation of drug

- This Gene is deleted to develop resistance

INH-A Gene ➔ encodes the target enzymes

- This Gene is deleted to develop resistance

Pharmacokinetics

Drug ➔ penetrate inside the cell to act on intracellular mycobacteria

Clinical uses

- Prophylaxis of Tuberculosis
- Most important Drug in Tuberculosis regimes
- Given to persons in contact with diseased person

Toxicity

Jim Loves haseena

J ➔ jaundice

I ➔ Insomnia

M ➔ inhibit metabolism of Drugs in liver

Loves ➔ Abnormal Liver function Test

Haseena ➔ Hepatotoxic

Hepatitis

Hemolysis in G6P deficient persons

Jim Loves Haseena

Rifampicin

Derivative of Rifamycin

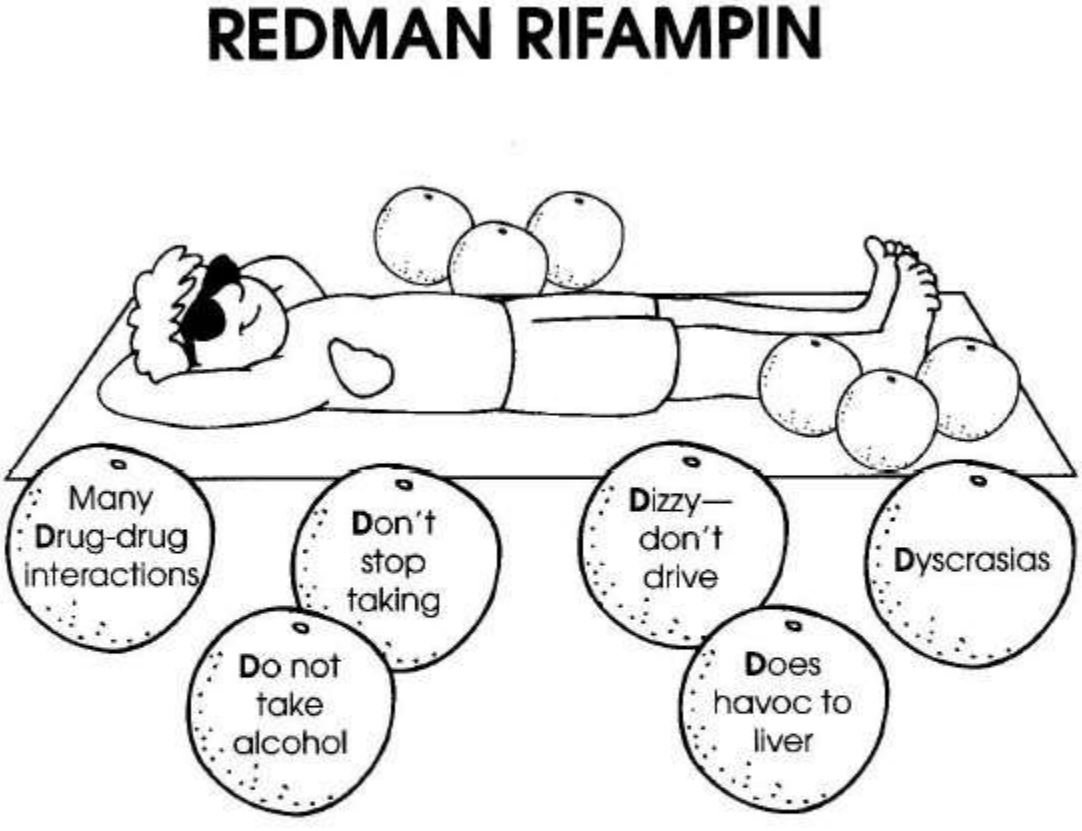
Mechanism

Rifampicin ➔ R ➔ RNA ➔ inhibit RNA polymerase

Resistance

Change of drug sensitivity to polymerase

Pharmacokinetics ➔ enterohepatic recycling and orange metabolites are eliminated in feces



Meet Mr. Redman Rifampin. He is taking some r & r (rest and relaxation) and is at the beach eating many oranges. He has had so many oranges his pee and tears are orange. Rifampin is hard on the liver, so it has gotten larger. The oranges will help you recall the 6 D's of rifampin.

Clinical uses

- Tuberculosis ➔ combination with others

Contents

- Prophylaxis tuberculosis
- Persons in close contact with Tuberculosis person
- Leprosy ➔ delay emergence of resistance
- With Vancomycin ➔ Methicillin resistant staph aureus

Toxicity

Rifampicin in NEPAL

N ➔ Nephritis
E ➔ Excite P450 metabolizing enzyme
P ➔ Proteinuria
A ➔ Anemia
L ➔ Liver dysfunction

Ethambutol

Mechanism

Inhibit arabionosyl transferase (encoded by emb [ab] gene)

Resistance

Emb gene mutation

Uses

- Tuberculosis in combination with others

Toxicity

- Ethambutol ➔ E ➔ Eye
    - Visual disturbances
    - Optic neuritis
    - Red green colour blindness

Pyrazinamide

Require bioactivation

Contents

- Pyrazinamide ➔ Pyrazoic acid
- Bacteriostatic

Uses

- Component of many regimes

⇨ Avoided in pregnancy.

Adverse effects

Parazina + Mide ➔ $(PM)^2$

P ➔ phototoxicity and porphyria

M ➔ Maculopapular rash and myalgia

40. Anti-Fungal Drugs

Antifungal drugs

Alter cell membrane permiability (ATP)			Block nucleic acid synthesis	Disrupt microtubule function	cell wall synthesis inhibitors
Azoles	Terbinafine	Polyenes	Flucytosine	Griseofulvin	Echinocandins

Azoles

Used for systemic mycosis **Members**

Itra and imeda ko bht flu hay

Itra ➔ itra + conazole ➔ itraconazole

Imeda ➔ imeda + conazole ➔ Imedaconazole

Ko ➔ keto ➔ Keto + conazole ➔ Ketoconazole

Bht ➔ very ➔ Vori + conazole ➔ Voriconazole

Contents

Flu ➔ Flu + conazole ➔ Fluconazole

Itra and ameda ko bht flu hay ---wo dr kay pass check up k liay gai hn

Mechanism

Azoles are pzoles

Azoles ➔ inhibit cty p450 ➔ disrupt synthesis of ergosterol

- P450 enzyme ➔ produces 14 alpha demethylation of lanosterol that is converted into ergosterol component of fungal cell membrane

Clinical Uses

For all members

- Systemic mycosis
- Conazole ➔ candidiasis

Ketoconazole

- Ket ➔ Cut ➔ cutaneous ➔ mucocutaneous candidiasis
- Systemic mycosis as other azoles

Fluconazole

- Fluid flows in CNS ➔ so used in meningitides ➔ Cryptococcal meningitides
- If someone engulf his flu secretion it will first go to his oropharynx then into oesophagus
    - Oropharynx ➔ Oropharyngeal Candidiasis
    - Oesophageal ➔ Oesophageal candidiasis

Itraconazole

It is used in ABC

A ➔ Aspergillus infection

B ➔ Blastomycosis infection

C ➔ Chromoblastomycosis & Candidiasis

Voriconazole

Vori ➔ invasive aspergilosis resistant to other drugs

Posaconazole

P ➔ used in prophylaxis of fungal infections

Toxicity

Voriconazole ➔ Visual disturbances

Ketoconazole ➔ munday ko kuri bna deti hay

- Interfere synthesis of adrenal and gonadal hormones
    - Gynecomastia (enlarged breast in male)
- In females ➔ menstrual disturbances

For all ➔ Diarrhoea, vomit, Rash and hepatotoxic

- They all inhibit Cyt p450

Terbinafine

To remember this
Time square

Time ➔ terbinafine

Square ➔ inhibit squalene epoxide

- Time duration ➔ terbinafine is used in dermatophytosis

Toxicity

- Terbinafine and Grisofulvin ➔ both accumulates in Keratin
- Terbinafine ➔ Taste disturbances
- Others ➔ GIT upset and headache

Polyenes ➔Amphotericin B

Used in systemic fungal infections

Mechanism

amphoTERIcin ➔ Amphotericin tearing cell membranes of Fungi

- Amphotericin ➔ produces holes in fungal cell membrane

Bind with ergosterol ➔ form transmembrane channels that leads to movement of ions (Na, K and Cl) ➔ leads to cell death

Clinical Uses

ABCD

A ➔ Aspergillus infection

B ➔ Blastomycosis infection

C ➔ Candida albicans infection

D ➔ Dermatophytosis

Contents

Adverse Effects

Amphotericin

A ➔ Anemia

M ➔ Muscle spasm

P ➔ Phlebitis

H ➔ Headache and hypertension

O ➔ Ooh

T ➔ Thrombocytopenia

E ➔ Emesis

R ➔ Respiratory infections

I ➔ increase temperature

C ➔ Chills

I ➔ immune suppression

N ➔ Nephrotoxic (Most important side effect)

Or you can use this mnemonic

Amna ka blood pressure fall ki waja say fever chill or vomit hoi or uski red kamez neli ho gai

Amna says ➔ this is amphotericin B

Infusion related side-effects

- Blood pressure fall
- Fever
- Chill
- Vomit

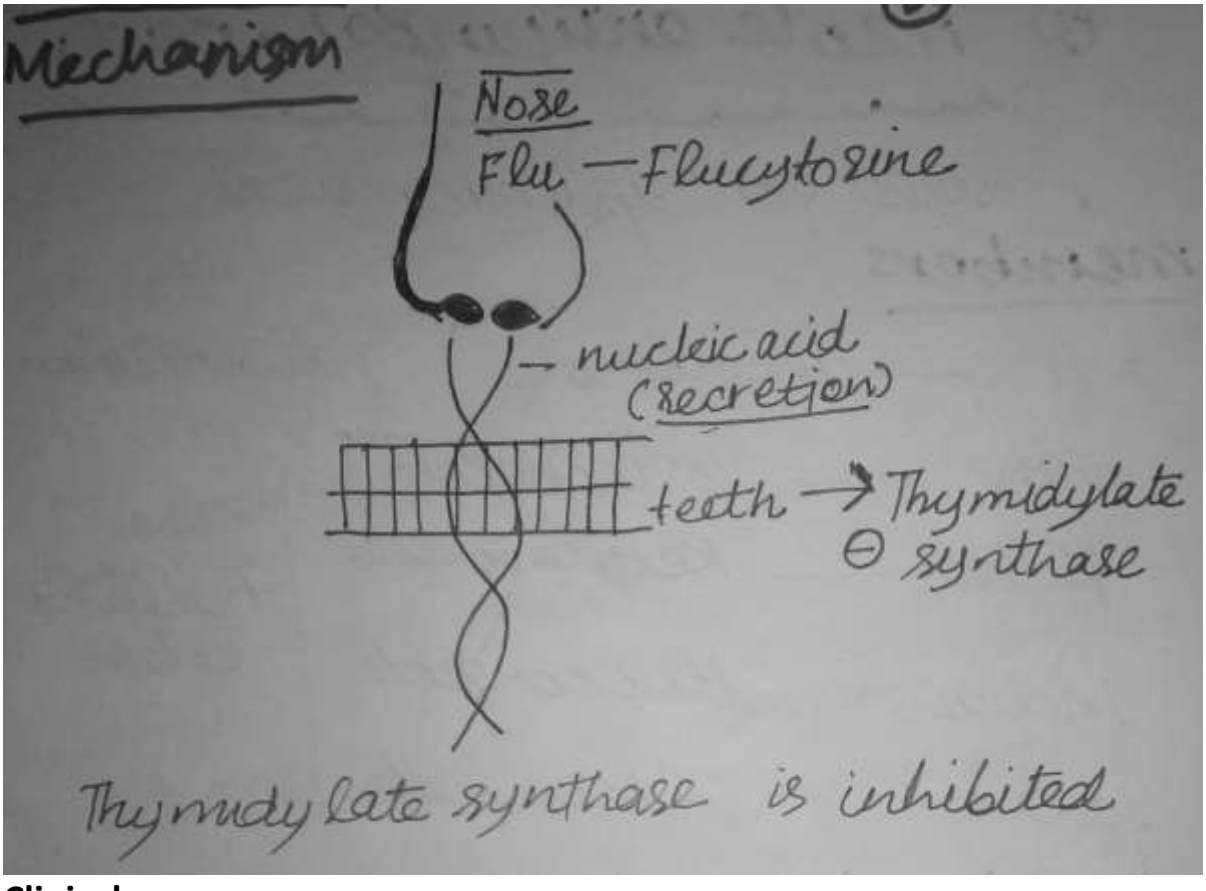
Dose limiting side-effects

- Red ➔ Renal acidosis
- Kamez ➔ K ➔ potassium wasting
- Neli ➔ Nephrotoxic and neurotoxic

Flucytosine

Mechanism

Thymidylate synthase is inhibited by it ➔inhibit nucleic acid synthesis



Clinical uses

As this Drug inhibit Nucleic acid synthesis and Nucleic acid is present in Chromosomes so for its uses C is used

C ➔ in combination with other antifungal Drugs in ABCD (above)

Contents

C ➔ Cryptococcus neoformans

C ➔ Chromoblastomycosis

Toxicity

- Bone marrow depression
- Liver dysfunction

Grisofulvin

Mechanism

Grass like microtubules

- They interfere the Microtubule synthesis (are fungistatic)

Use

Dermatophytosis

Side effects

P5

P ➔ Peripheral neuropathy

P ➔ Porphyria

P ➔ P450 interactions (Activator)

P ➔ Photosensitivity

P ➔ Potentiation of alcohol (Disulfiram like reaction)

Other ➔ GIT disorders, Nausea and confusion

Echinocandin

Candin ➔ Din ➔ Gin ➔ Glycan inhibitors

Contents

- Caspofungin
- Micofungin

Mechanism

They inhibit the synthesis of Beta 1 2 glycan

- Glycan ➔ component of Bacterial cell wall

Clinical uses

Caspofungin ➔ C ➔ Candida infections irresponsive to Amphotericin B

Micafungin ➔ Mico

- Mi ➔ Mucocutaneous candidiasis
- Co ➔ prophylaxis of candidiasis

Echinocandins ➔ candy ➔ Candidiasis

Toxicity

Diarrhoea, vomit, rash and Headache

- Micafungin ➔ release of histamine

Systemic Drugs for Superficial Infections

GTA (Grand theft auto games like vice city)

G ➔ Griseofulvin

T ➔ Terbinafine

A ➔ Azoles

- These are used orally for Dermatophytosis of skin, hairs and nails

Topical for superficial Treatment

Needed for

- Candida infections
- Dermatophytosis

Nystatin➔ polyene

Bind to ergosterol (Polyene so mechanism resemble Amphotericin B)

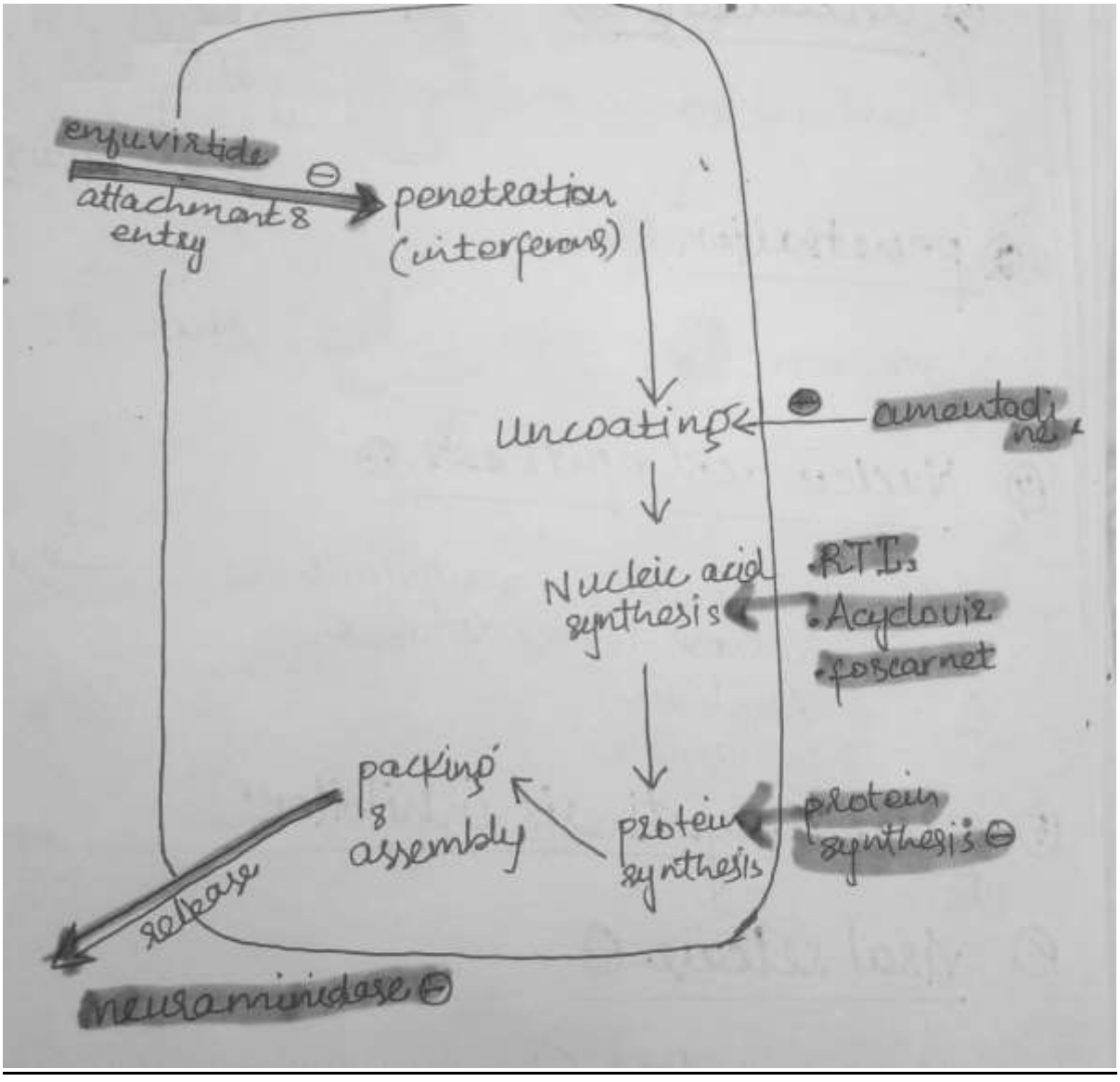
- Cutaneous, vaginal and mucosal candida infections (use)
- Nausea, diarrhoea and rash (side-effect)

Others

Miconazole and Clotrimazole are also available (azoles)

41. Anti-Viral Drugs

Mechanisms



Entry inhibitors

- Entry ➔ en ➔ Enfuveritide

Contents

Uncoating inhibitors

- Amantadine ➔ aam ka chilka just like coat of virus (a covering)

Penetration inhibitors

- Penetration ➔ mean movement in ➔ IN ➔ INF alpha (interferon)

Nucleic acid synthesis inhibitors

Far Far Drugs

F ➔ Foscarnate

A ➔ Acyclovir

R ➔ they inhibit Reverse transcriptase enzyme

Protein synthesis inhibitors

Viral release inhibitors

- Release ➔ Nikalna ➔ Neuraminidase inhibitors

Drugs for Herpes

Her father got a cycle

Her ➔ Drugs for Herpes

Father ➔ Foscanate

Got ➔ Guanithidine

A cycle ➔ Acyclovir

If you reverse order then it will be choice based order

Her father Got a cycle

Acyclovir

Mechanism

Far far Drug ➔ inhibit nucleic acid synthesis

- It is competitive substrate for DNA Polymerase
- Also produces changes in DNA polymerase (alteration of structure)

Pharmacokinetics ➔ short half live ➔ multiple doses per day

Clinical Uses

- Mucocutaneous herpes
- AIDS
- Immunocompromised persons

Adverse effects

Cycle have two new designs

Cycle ➔ Acyclovir side effects

Have ➔ Hypertension

Two ➔ Tremors

New ➔ Nephrotoxicity

Designs ➔ Delirium

Ganciclovir

Guanine derivative

Mechanism

Phosphorylated by thymidine kinase to produce nucleotide that inhibit DNA polymerase

- Inhibit DNA Polymerase ➔ Inhibit nucleic acid synthesis

Uses

- In herpes as from above
- In DNA G pairs with C ➔ G= C so
    - C ➔ Cytomegalovirus infection s

- Prophylaxis
- Treatment
- Treatment by this in immunocompromised persons

Adverse effects

Bloody Effects

- Thrombocytopenia
- Neutropenia
- Leukopenia

Also causes hepatic dysfunctions

Cidofovir

- Acyclovir and Ganciclovir ➔ both are activated by viral enzyme thymidine kinase
- Cidofovir ➔ activated by host cell kinase and do not require viral kinase
    - Used where resistant to first two ➔ to treat herpes

Uses

- Cidofovir ➔ C ➔ CMV viral infection treatment

Foscarnet

Phosphor formate derivative

- Does not require phosphorylation for activity

Used where resistance to other drugs has been developed

Mechanism

fosca**RNA**t ➔ inhibit RNA polymerase & also inhibit DNA polymerase (Like previous discussed drugs)

Uses

- Herpes treatment
- Resistant Herpes in AIDS
- FosCARnet ➔ Car ➔ CMV virual infections

Anti-AIDS Drugs

No new Indian entered Pakistan

No	• Non neucleoside reverse transcriptase inhibitors
new	• Nucleoside reverse transcriptase inhibitor
Indian	• Interase strand trasnferase inhibitors
entered	• Entry inhibitors
Pakistan	• Protease inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs)

Mechanism

Inhibit RNA dependant DNA polymerase (Reverse transcriptase)

Inhibit conversion of single stranded RNA into double stranded DNA

- Activate Host cell kinase ➔ Triphosphates are formed ➔ inhibit reverse transcriptase enzyme

Contents

- Act as chain terminators ➔ block attachment of next nucleotide

Members

Abay ka veer Lamba zidi hay

- Abacavir
- Lamivudine ➔ hep B and HAART (highly active antiretroviral therapy)

- **Zidovudine**

  Also called azidothymidine (AZT)

  - Uses
    - First Drug to be discovered for treatment of AIDS
    - Post exposure prophylaxis
    - Pregnancy prophylaxis
  - Side effects
    - Zid ➔ zero RBCs ➔ Causes anemia (megaloblastic anemia) ➔ because this causes bone marrow suppression
    - Other effects ➔ GIT distress, CNS effects (headache) and hepatotoxic

Non-Nucleoside reverse transcriptase inhibitors

Mechanism

- Site of action different from NRTIs
- They doesnot require phosphorylation for activation
- Non-nucleoside ➔ do not compete for Nucleoside phosphate
- **Resistance** ➔ develop rapidly if used alone (monotherapy)

Adverse effects

- GIT distress (ulcers), CNS effects
- Nephrotoxic
- Electrolyte imbalance

Protease inhibitors

Mechanism

Aspartate protease ➔ enzyme that convert precursor polypeptides into final structural Proteins of Mature Virion

- They are used in combination with other Drugs

Drunavir

- Daro na ➔ used where resistance to other drugs is developed

Fosamprenavir

- Hydrolysis to produce Amprenavir
- Not used in children and pregnant women

Indinavir

- Good oral bioavailability (except in the presence of food)
- Side effects ➔ Indina ➔ India ➔ baharat
    - India ➔ insulin resistance
    - Baharat ➔Increase Bilirubin (jaundice)

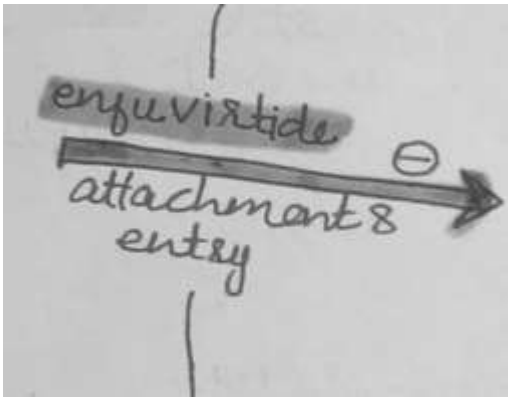
Effects Produced by Protease inhibitors

- Disorders of carbohydrate and lipid metabolism
- Insulin resistance
- Sex hormone abnormality ➔ gynecomastia

Entry inhibitors

Entry inhibitors ➔ en ➔ Enfuvirtide

- Attach to Gp41 unit of viral envelop ➔ prevent conformational changes required for cellular fusion



Other anti-viral Drugs

Fomivirsen

- FOM ➔ Bind to mRNA of CMV ➔ Block initial step of protein synthesis
- Injected IV for treatment of CMV retinitis

Etravirin

- Newest drug ➔ effective against HIV resistant strains

Nevirapine

- Metabolized by cyp3A4
- Nevirapin ➔ N ➔ Neonates ➔ Prevent vertical transmission of HIV when given in single dose to mother at the onset of the labour

Anti-Influenza Drugs

1) **Amantadine and Rimetadine**

Contents

A man dine (Deen) ➔ deen is bat ki ijazat nh deta k naked hon kisi k samnain

- Prevent Virus from being naked ➔ Prevent uncoating of virus ➔ as a result inhibit replication because viral Nucleic acid will not be re-leased until uncoating

Uses

Amantadine ➔ A man ➔ prophylactic against influenza A

- Reduce duration of symptoms if given within 24 hours

2) Oseltamivir and Zanamivir

Ozone ➔ O and Z inhibit Neuraminidase release in influenza A and B

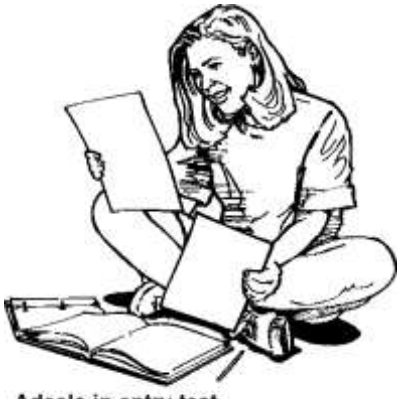
Uses

- Alleviation of influenza symptoms
- More effective if used within 24hrs
- Prophylactic ➔ decrease influenza incidence

Agents used in Viral Hepatitis

Drugs used in treatment of Hepatitis B

Adela in entry test



Ad ➔ Adefovir

La ➔ Lamivudine

In ➔ IFN (interferon) alpha

Entry ➔ entecavir

Test ➔ tenofovir (newer drug)

Drugs used in Hepatitis C

Rabia in chakwal

Rabia ➔ Ribavirin

In ➔ IFN alpha

Chakwal ➔ these drugs are effective against Hepatitis C

Details of Each Drugs

Adefovir

Mechanism ➔ competitively inhibit HBV DNA polymerase

aDefovir ➔ D ➔ Inhibit DNA polymerase

- Need phosphorylation for activation of drug

Uses

- Supress replication of HBV

Side-effect ➔ nephrotoxic

Lamivudine

Nucleoside inhibition of HIV reverse transcriptase

Uses

- Supress replication of HBV
- Used in HAART (highly active acute antiretroviral therapy)

IFN alpha

Interferon alpha

Mechanism

- Activates JACK & STATS ➔ formation of antiretroviral proteins is activated
- Activates host cell ribonuclease ➔ Degrade viral mRNA

Pharmacokinetics ➔elimination ➔ proteolytic hydrolysis in kidney

Uses

- Hep B ➔ alone or in combination with others
- Hep C ➔ Combination with ribavirin to reduce progression
- CMV infection
- Herpes zoster infection

Entecavir

Guanicine nucleotide ➔ inhibit DNA polymerase

Use ➔ effective against HBV

Contents

Adverse effect ➔ fatigue, nausea and headache

Tenofovir

NRTIs (nucleoside analogue reverse transcriptase inhibitor)

Use ➔ effective against HBV

Ribavirin

Mechanism

Make the native nucleoside drug resemble adenosine or guanosine, depending on its rotation ➔ incorporated into RNA, as a base analogue of either adenine or guanine➔inducing mutations in RNA-dependent replication in RNA (Hypermutation) ➔lethal to RNA viruses.

- **Ribavirin** ➔ R ➔ incorporated into RNA ➔ lethal mutations

Uses

- Adjuncts in chronic hepatitis C infection with IFN alpha
- Monotherapy not effective

Toxicity

Ribavirin ➔ R ➔ effect RBCs ➔ Dose dependant haemolytic anemia

- Teratogenic ➔ so contraindicated in pregnancy

Contents

42. Anti-Protozoal Drugs

Antimalarial Drugs

Prima queen celebrated many festivals

Prima	• Primaquine
Queen	• Quinine
Celebrated	• Chloroquine
Many	• Maflaquine
Festivals	• Antifolates

Prima ➔ only tissue schizonticide

Others ➔ Blood schizonticide

Primaquine ➔ synthetic 8-amino quinoline

Quinine ➔ alkaloid

Chloroquine ➔ 4-amino quinoline derivative

Mafloquine ➔ 4-quinoline derivative

Quinine ➔ Quinoline + Quinuclidine

Prima queen celebrated many functions

Contents

Chloroquine

Mechanism

Chloroquine ➔ accumulate in food vacuole ➔ Prevent polymerization of Heme into hemozin ➔ accumulation of Heme ➔ Cytotoxic to Parasite

Resistance

- Decrease intracellular accumulation by increased activity of membrane pumps
- Intravascular accumulation of Chloroquine via transporter encoded by pfcrt (Plasmodium falciparum Chloroquine resistance transporter)

Uses

- Non falciparum and sensitive falciparum malaria Treatment and prophylaxis
- In autoimmune diseases (rheumatic arthritis)
- Radiosenstizing in anticancer therapy

Adverse effects

G Rana sahib

G ➔ GIT irritation

R ➔ Renal damage

A ➔ Auditory damage

N ➔ Neuropathies

A ➔ attacks of porphyria

Sahib ➔ Skin rash and skin lesions

Quinine

Mechanism

Complexes with Double stranded DNA to prevent strand separation ➔ Block DNA Replication and transcription of RNA

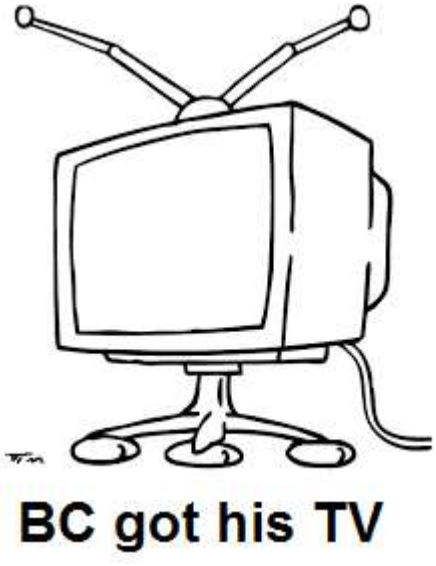
Clinical use

- P falciparum infections resistant to chloroquine
- Used with doxycycline and clindamycin (to shorten duration of toxicity and limit toxicity
- Should not be used for prophylaxis (to delay resistance emergence)

Toxicity

BC got his TV

- Black water fever ➔ Hematotoxic effects
- Cinchonism
  - Got ➔ GIT disturbances
  - His ➔ headache
  - T ➔ tinnitus (ringing in ears)
  - V ➔ Vision blurred



Mefloquine

- First line of drug taken for prophylaxis in all geographical areas with chloroquinine resistance
- Alternative to quinine in acute attacks
- In uncomplicated infection resulting from p falciparum

Toxicity

Psycho cat have some Gastric disease

Psycho ➔ psychiatric diseases

Cat ➔ CVS disorders

Have ➔ headache

Some ➔ skin rash

Gastric ➔ GIT disturbances

Disease ➔ dizziness

Psycho cat have some gastric diseases

Primaquine

Form Quinoline quinone metabolites ➔ electron transferring redox compounds ➔ cellular oxidants ➔ killing of gametes of plasmodium

- Tissue schizonticide ➔ Gametocide

Clinical use

- Eradicate Liver stages of p vivax and P ovale
- Used in conjugation with blood schizonticides (Not active alone)
- 14day treatment of primaquine is standerd after treatment with chloroquine
- Alternative for primary prevention

Anti-folate drugs

Pyrimethamine, Proguanil, sulfadoxine and dapsone are used

Mechanism

Act as antimetabolites of PABA and inhibit synthesis of folic acid

Clinical uses

- Blood schizonticide against p falciparum

- Pyrimethamine + sulfadoxine ➔ Fensidar (used in Chloroquine resistant p-falciparum
- Proguanil + atvaquone ➔ Malarone (chemoprophylaxis of chloroquine resistant malaria)

Adverse effects

Anti-folate HINGE

H ➔ hemolysis

I ➔ Drug interactions (competition with plasma proteins)

N ➔ Nephrotic damage

G ➔ GIT distress

Other Antimalarial Drugs

Doxycycline ➔ Tetracycline ➔ chemoprophylactic

Amodiaquine ➔ used against chloroquine resistant p-falciparum (Low cost drug)

Atovaquone ➔ Quine derivative (Disrupt mitochondrial electron transport) ➔ Chemoprophylaxis and treatment of p-falciparum malaria

Halofantrine ➔ Halo > whole ➔ active against erythrocytic stages of all 4 forms of malaria

Artemisinins ➔ only drug reliably effective against Quinine resistant strains

Travellers Malaria

1) Chloroquine is used as prophylaxis
2) Chloroquine resistant ➔ Mefloquine

Contents

3) Multidrug resistant ➔ doxycycline and Malarone

4) Primaquine ➔ for terminal prophylaxis of p-ovale and p-vivax

43. Anti-Microbial Drugs

Metronidazole

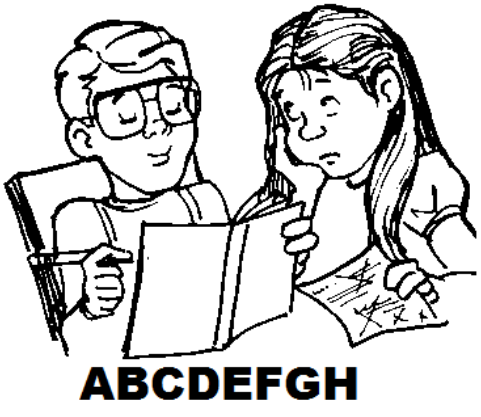
Imidazole Derivative

- Active against Protozoa and Bacteria

Mechanism

Reductive bioactivation of nitro Group by Ferridoxin ➔ and form reactive cytotoxic products

Clinical Uses



ABCDEFGH

A ➔ Amebiasis and Anaerobic streptococci infections

B ➔ Bacteroids infection

C ➔ Clostridium perferenges infection

D ➔ D-medinensis infection

E ➔ pseudomembranous enterocolitis and Entameba infection

F ➔ Fusobacterium infection

Contents

G ➔ Giardiasis and gardenerela infection

H ➔ H pylori ➔ ulcer

For antiprotozoal use GET

- G ➔ Giardia infection
- E ➔ Entameba infection
- T ➔ Trichomonas infection

Side effects

DAD loves sexy girl parveen

DAD loves sexy girl parveen

D ➔ Dark colour faeces and dark urine and Dizziness

A ➔ ataxia

D ➔Drug interactions with other drugs by competing with plasma proteins

Loves ➔ Leukopenia

Sexy ➔ Sar dard and stomatitis

Girl ➔ Gastrointestinal irritations

Parveen ➔ p in start and n in end ➔ Pregnancy not used (contrain-dicated) ➔ if to be used then with caution

- One other side effect is Metallic taste

Contents

44. Anti-Helminthic Drugs

Drugs used in Nematodes infections

Nematode hate AMP

A	• Albendazole
M	• Mebendazole
P	• Pyrantel pamoate

Mechanisms

Albendazole ➔ inhibit microtubule assembly

Mebendazole ➔ inhibit microtubule assembly

Pyrantel pamoate ➔ Stimulation of nicotinic receptors ➔ Depolarization ➔paralysis.

Uses

Worm infections

- Round worm infection
- Thread worm infection
- Hook worm infection
- Pin worm infection

Contents

Drugs used in Cestode infection

Nikalo AMP

nikalo	• Niclosamide
A	• Albendazole
M	• Mebendazole
P (change)	• Pyraziquental

Mechanisms

Niclosamide ➔ uncoupling of oxidative phosphorylation or by activating ATPase

Pyraziquental ➔ increase permeability of Ca^{+2} ➔ contraction ➔ paralysis ➔ vacuolization ➔ death

Uses(CFTs)

- Cestodes infection
- Flukes and systomiasis
- Trematodes infections
- Schistosomiasis

Drugs used in trematode infections

Who put the trematode into the BOMP

B	• Bithinol
O	• Oxaminiquine
M	• Metrifonate
P	• Pyraziquental