Pharmacology

INTRODUCTION TO GENERAL PHARMACOLOGY AND ROUTES OF DRUG ADMINISTRATION

Introduction

00:00:46

Pharmacology :
Word of Greek origin. pharmakon → drug, logos → study of.
It is the study of drugs and their

- Structure.
- Uses.
- Mechanism of action.
- Side effects etc.

Pharmacotherapeutics :
Word of Greek origin. pharmakon → drug, therapia → in service of (a disease).
Example : Enalapril (drug) 5mg OD (dose) given orally (route of administration) to treat mild/moderate hypertension (stage of disease).

Pharmacognosy : Study of drugs from plant source. Eg : morphine, quinine, reserpine, digoxin.

Pharmacy : Branch dealing with compounding (mixing) and dispensing (giving away to patients) of drugs.
Nowadays, compounding is not done as drugs are already pre mixed in the form of tablets/capsules.

Chemotherapy : Deals with use of drugs for treatment of infections and cancer.

Drug : A chemical with a known structure that alters the pathophysiology for therapeutic gain.
Eg : Enalapril alters RAAS by blocking it (pathophysiology) and results in decrease in BP (therapeutic gain).

Source of the drugs 00:10:47

- Chemicals :

1. Natural :
   a. Plants : Morphine, quinine, digoxin, insulin
   b. Animals : unfractionated heparin from porcine intestinal mucosa. Previously insulin was derived from pork but nowadays human insulin is used.
   c. Micro-organisms : Antibiotics (penicillin etc.)
2. Semisynthetic : A natrural drug is chemically changed to get a new drug.
   Eg : Morphine (from papever somniferum) → Apomorphine.
3. Synthetic :
   Derived by the process of rational drug designing.
   Eg. A disease (HTN) is being studied and a target receptor is found where a ligand attaches and increases the BP. Since BP needs to be decreased, a drug is designed which is complementary to the structure of the receptor, binds and inhibits the receptor resulting in decrease in BP.

- Genetic engineering :
  A gene is introduced to a cell line which gives a product (if useful) → Drug (E.coli can be used as a cell line).
  Eg : Human insulin gene was introduced into a cell line which gave human insulin (regular insulin), as porcine insulin was expensive with limited source.

Types of drugs 00:18:49

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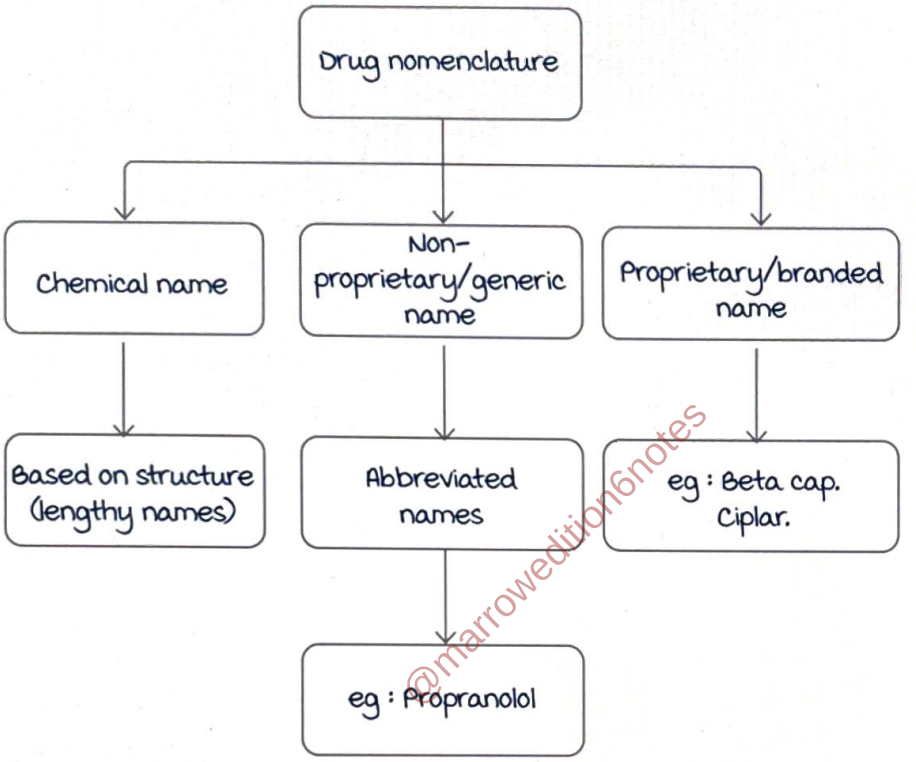
- Prescription/legend drugs :
  Drugs that cannot be sold without prescription.
  These drugs are present under Schedule H.
- Over the counter/OTC drugs :
  Drugs that can be sold without prescription
  Eg : antacids, vitamins.
  Any drug which does not belong to Schedule H/G/X.
- Orphan drugs :
  Drugs used for treatment of rare diseases.
  (Orphan receptor : A receptor without a known ligand).

- Illicit/street drugs : These are the drugs of abuse (eg : cocaine, heroin etc).
- Spurious drugs : These are counterfeit drugs (unoriginal).
  Eg : Dextrose powder sold as remdesivir.
- Prototype drugs : Parental/MC used drug in a class.
  Eg : Morphine in opioids.

Drug nomenclature 00:27:36



Non-proprietary/generic names should be used in the prescription.
Same suffix is usually used for same class. E.g lol : for beta-blockers, pril : for ACE inhibitors, prazole : PPI etc.

Drug compendia 00:32:32

Books having comprehensive and organized data about drugs.

- Indian pharmacopoeia : made by pharmacists.
  Includes drug structure, purity, storage etc → used by drug manufacturers.
  Drug manufacturers are checked by drug regulating authorities.
- Drug formulary : made by doctors.

Includes drug uses, dose, side-effects, contra-indications etc. → used by doctors for clinical practice.

Rational use of drugs

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Use of appropriate/right drug for an appropriate

- Disease
- Patient
- Dose/duration/route
- Dispensation
- onitoring

e.g for trichomoniasis, drug of choice is metronidazole in a patient with no contra-indications.
The appropriate dose would be 2gm given once orally.
The patient would be warned not to take the drug with alcohol as it might cause a Disulfiram-like reaction.
Liver function tests would be monitored.
Price is not a part of rational use of drugs.

Benefit :

- Timely cure.
- Decreased hospitalizations.
- Decreased cost of treatment.
- Decreased morbidity and mortality.
- Decreased risk of resistance to drugs.

Important Drug Schedules in India	
Drug Schedules	
Schedule G	List of drugs that requires a mandatory text on label "Caution : It is dangerous to take this preparation except under medical supervision". Eg. antihistaminics, metformin, insulin, anticancer drugs, antiepileptics etc.

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Schedule H	List of drugs that can be sold only when a prescription is produced. Most drugs belong to this category. The drug label display the next "Rx" in black colour and "Schedule H drug. Warning : To be sold by retail on the prescription of a Registered medical practitioner only".
Schedule HI	Introduced in 2013 to deal with unauthorized sale of antibiotics. Drugs are labelled with "Rx" in red.
Schedule X	List of narcotic and psychotropic drugs which need special license for manufacture and sale. Drugs are labelled with "NRx" and prescription copy should be retained by the retailer for minimum of 2 years. Eg : Amphetamine, methylphenidate etc.
Schedule P	It is about drug expiry period i.e. maximum period till which drug can be used with intact potency.
Schedule W	List of drugs marketed under generic names only.
Schedule Y	Guidelines on clinical trials, import and manufacture of new drugs.

Schedule H/G/HI/X cannot be sold without prescription.
Others are called OTC drugs.
Schedule H is added while writing Schedule G/X in the prescription.

Pregnancy Drug Categories		
Categories	Significance	Examples
Cat A	No risk to fetus in human studies	Levothyroxine potassium mgSO4
Cat B	Animal studies show no risk. Human studies are lacking.	Penicillins Cephalosporins Macrolides Brimonidine
Cat C	Animal studies show positive teratogenic risk. Human studies are not available	Albuterol Zidovudine CCB Morphine Atropine

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Cat D	Human and animal studies show positive teratogenic risk.. May be used in pregnancy as benefits are greater than risk.	Corticosteroids Azathioprine Carbamazepine Valproate Methotrexate Lithium
Cat X	Human and animal studies show positive teratogenic risk Absolutely contraindicated in pregnancy because of greater risk than benefits.	Thalidomide Isotretinoin Fluoroquinolones Tetracyclines Chloramphenicol Warfarin ACE inhibitors

Category A/B/C are safe in pregnancy (Cat : A > B > C).
Category D/X are teratogenic.
The fetus must be aborted due to high risk of teratogenicity in Category X.

Routes of drug administration

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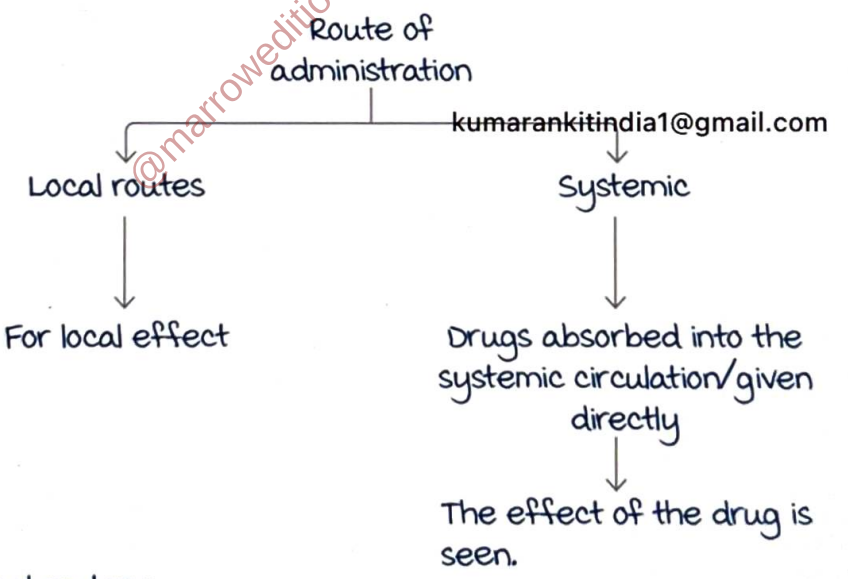

Local routes :

Route	Comments	Drugs
Topical	For local effect	• Cutaneous : Steroids (psoriasis, lichen planus) • Ocular : Anti glaucoma drugs, steroids. • Mucosal : Anticancer drugs in bladder cancer/nasal decongestion.

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Intrathecal	Preferred if rapid or local effect in CNS is required or the drug poorly crosses blood brain barrier (e.g. Aminoglycosides)	• Methotrexate in childhood leukemia • Anesthetic agents like bupivacaine • Baclofen in muscle spastic disorders • Aminoglycosides in CNS infections
Intraarticular	For local effect	• Steroids in rheumatoid arthritis (1-2 joint involvement)
Intraarterial	For local effect on a particular organ supplied by an artery. Limited exposure decreases toxicity and there is lesser first pass metabolism as well	• Anticancer drugs in hepatocellular and head and neck cancer

Intrathecal route : The drug is given in subarachnoid space by lumbar puncture.

All local routes decreases systemic side effects.

Systemic routes :

Routes	Benefit	Drawback	Drugs
Oral (m/c route)	Cheapest Convenient Safest	First pass metabolism. Most variable absorption due to various factors like lipid solubility, food intake, digestive enzymes etc.	Most drugs
Sublingual	No first pass metabolism and faster effect as drug is absorbed directly in to SVC. Drug can be spitted out after desired effect	Tooth discolouration and decay. Cardiac side-effects.	Nitroglycerine IDN Nifedipine Ephedrine Ergotamine Buprenorphine

Rectal	50% lesser first pass metabolism as from rectum 50% blood directly drains into ivc bypassing liver. Unpleasant and irritant drugs can be given	Unreliable absorption because of fecal matter presence, first pass metabolism.	Diazepam for febrile siizures in children
Intravenous	100% bioavailability Fastest acting (Preferred in emergency) Irritants can be given.	Increased chances of acute toxicity. Drugs in oily medium cause hemolysis and hence are contraindicated.	IV Drugs of choice Nicardipine : Hypertensive emergency Furosemide : Pulmonary edema Adenosine : PSVT Lorazepam : Status epilepticus
Intramuscular	Drugs in oily medium and irritants can be given. Self administration possible. NE is contrainidicated as it can cause muscle necrosis due to potent vasoconstriction.	Drugs in oily medium cause pain on injection.	Im drug of choice Adrenaline : Anaphylactic shock
Subcutaneous	Prolonged duration of action due to slow absorption	Irritants cannot be given as pain and skin necrosis can be seen	Insulin Contraceptives Adrenaline
Pulmonary	Faster effect due to rapid absorption by huge capillary network. No first pass metabolism. Local effect possible as in BA or COPD	Irritants can precipitate bronchospasm.	Insulin (Afrezza) Zanamivir Tobramycin for psudeomonas. SABA in bronchial asthma. Anticholinergics in COPD ICS
Transdermal	Longer duration of effect. Slow acting. Patch should be applied 3-4 before.	Only lipid soluble drugs can be given	Nitroglycerine Fentanyl Scopalamine Nicotine Contraceptives HRT
Intranasal	Rapid absorption and faster effect. Bypasses BBB. Ease of administration. Preferred for peptides (cannot cross BBB)	Possible only for potent drugs (as limited dose only can be given) Variable absorption.	Desmopressin GnRH agonists Calcitonin Fentanyl

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Large size drugs (proteins) → e.g drugs ending with

- tide (ocreotide, teriperatide).
- ase (pegloticase, asparaginase, rasburicase).
- mab (trastuzumab).

cannot be given by oral route because of poor absorption.

Sublingual route :

The drug is placed under the tongue and patient is asked not to chew.

Drug passes through sublingual circulation → Absorbed into SVC → Heart.

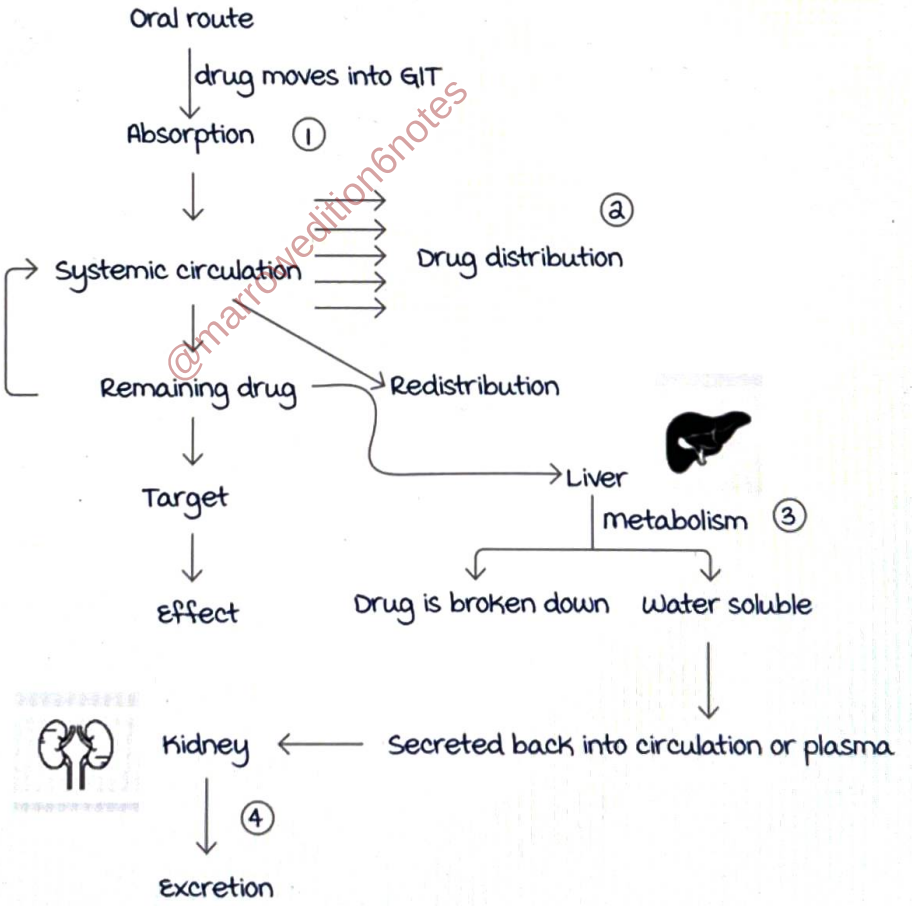
Subcutaneous route is not used in patients with shock as cutaneous blood supply is minimized (majority of blood is moved towards central organs).

PHARMACOKINETICS : ABSORPTION

Pharmacokinetics and Pharmacodynamics 00:00:46

Dervied from greek words.

Pharmacokinetics	Pharmacodynamics
Pharmakon : Drug. Kinesis : Movement. Movement of drug in the body.	Pharmakon : Drug. Dynamos : Change. Drug induced changes in the body.



Remaining drug reversibly binds to the target. It will be redistributed to all the tissues.

To get redistributed :

- Drug must have very high lipid solubility.
- Drug should be very short acting (if drug was not

undergoing redistribution, it would have stayed bound to the target and become long acting).
eg : Thiopentone is purposefully combined with sulphur to make it lipid soluble. Hence, it produces quick effect and is also short acting.

In the kidneys, plasma + any water soluble substance are filtered. Thus, the water soluble drug is filtered along with the drug in the plasma.

Pharmacokinetics : It is what the body does to the drug.
Mnemonic : ADME

1. Absorption
2. Distribution.
3. Metabolism.
4. Excretion.

Pharmacodynamics : It is what the drug does to the body.

- Drug.
- Target.
- Effect (eg : change in HR, RR).
- Efficacy is a part of pharmacodynamics.

Pharmacokinetics

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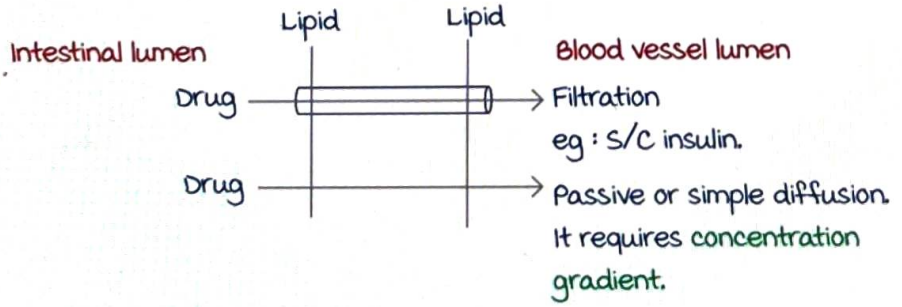
Absorption :

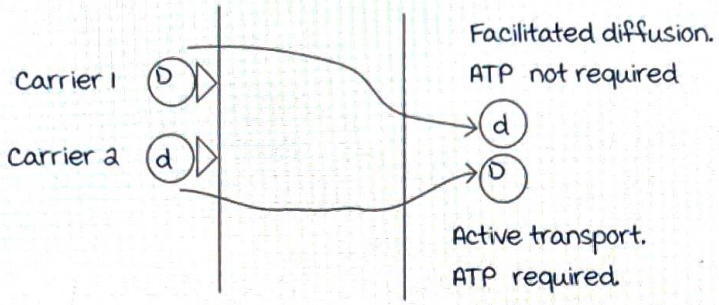


Lipid refers to biological membranes.
S/C insulin gets filtered into capillaries through aqueous channels.
Passive/simple diffusion happens across a semi permeable membrane.

Carrier mediated transport :

Receptors or pumps present in the lipid layer are called carriers.

Drugs bind to the carriers → takes the drug into the circulation.



d : lesser conc.

D : Higher conc.

Facilitated diffusion/passive diffusion : Happens with concentration gradient.

Active transport : Acts _____

eg : P-glycoprotein pump (pgp).

Only difference between facilitated diffusion and passive diffusion is the involvement of a carrier.

For absorption of glucose :

GLUT receptors : Facilitated receptors.

SGLT 1 & 2 receptors : Active transporters.

Whenever glucose is consumed :

- SGLT-1 in intestine absorbs glucose against concentration gradient.
- SGLT-2 in Kidney reabsorbs glucose against concentration gradient.
- GLUT-4 in skeletal muscles allows glucose uptake depending upon the concentration gradient.

m/c mechanism of drug absorption : Passive or simple diffusion.

Drug given by oral route

↓

Enters the intestinal lumen

Active space

↓

Distributed to tissues along concentration gradient by passive diffusion

↓

P-glycoprotein pump moves the drug out against concentration gradient.

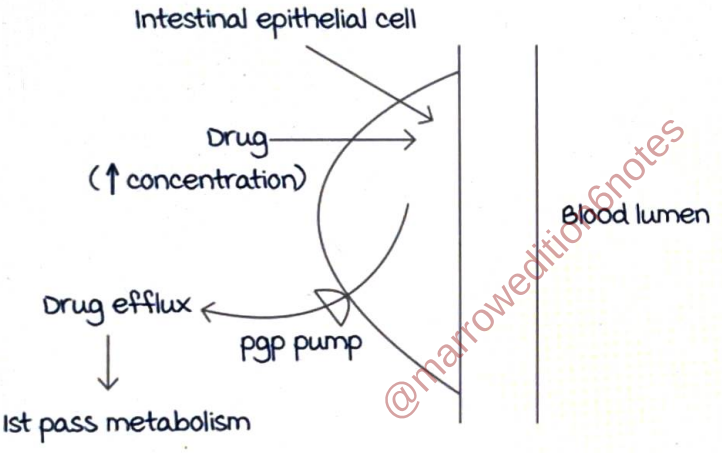
This is **Drug efflux**

This implies that the drug is eliminated before it reaches the systemic circulation.

Pgp causes 1st pass metabolism/Pre systemic elimination.

1st pass metabolism is a misnomer.

Seen in : Liver and intestines.



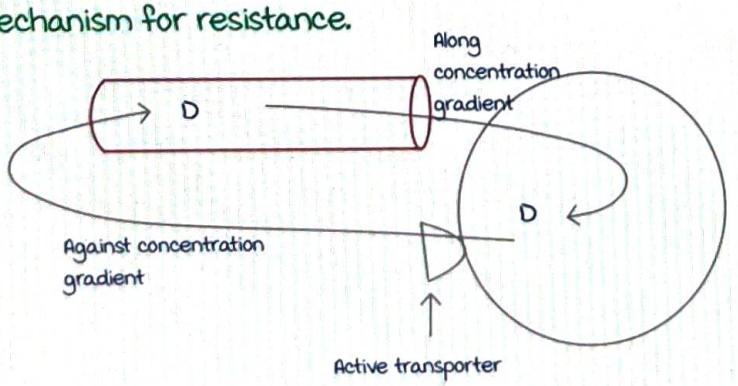
Pathological application of active transporters :

eg : cancer cell or bacteria.

Drugs enter the cancer cell or bacteria only based on concentration gradient.

But cancer cells or bacteria move the drug back to lumen using active transporters (against concentration gradient).

Active transporters in bacteria or cancer cells acts as mechanism for resistance.



Active space

P-glycoprotein pump

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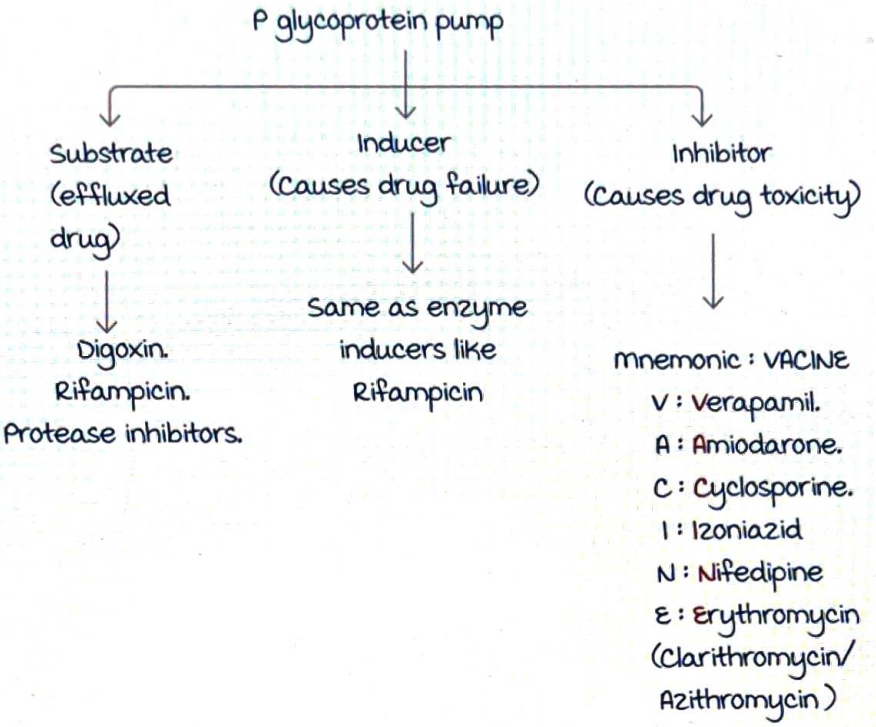
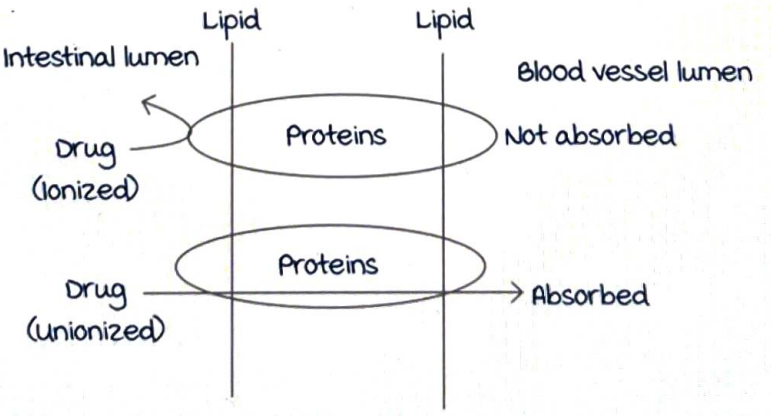


Inhibitors can cause toxicity of drugs that are substrates of pgp like digoxin.

Erythromycin, clarithromycin, azithromycin are the antibiotics causing digoxin toxicity (decrease digoxin dose).

Passive diffusion :

Happens from intestinal lumen to blood vessel lumen.



Lipids & proteins refer to those on the biological membranes.

Proteins are ionized (charged molecule).

Drugs can be either charged or uncharged i.e. ionized and unionized.

Active space

If the drug is ionized, it cannot cross the lipid barrier and is not absorbed. Called Lipid insoluble/Water soluble/Polar.
This criteria is required for excretion.
Lipid soluble drugs are reabsorbed back and water soluble drugs are excreted.

If the drug is unionized, it crosses the lipid barrier and is absorbed. Called Lipid soluble/nonpolar.

No one drug is 100% ionized/unionized.

To get absorbed, drug must be small in size.
Oral absorption is affected by large size of the drug.

Larger sized drugs :
Protein containing drugs ends with 'tide' : eg. Nesiritide, Octreotide etc.
Enzymes end with 'ase' : e.g. Pegloticase, Asparginase etc.
Monoclonal antibodies end with 'mab' : Omalizumab, Abciximab etc.
These drugs cannot be given by oral route due to their large size.

Ionization and unionization of drug 00:36:04

pH of the medium and pH of the drugs are unequal → majority of the drug is ionized.
Eg. acidic drug in basic medium.

pH of the medium and pH of the drugs are equal → majority of the drug is unionized.
Eg. acidic drug in acidic medium.

- Acidic medium in GIT : Stomach.
- Basic medium in GIT: Small intestine.

Unioinization : pH of the drug and pH of the medium should be same.

Maximum absorption of any drug occurs in small intestine (because of its large surface area).

Maximum unionization of acidic drug occurs in stomach.

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For Ionization/excretion to happen, pH of the drug and pH of the medium should be different : Acidic drug in a basic medium or vice versa.

In case of toxicity of acidic or basic drug : change the urine pH.

i.e. acidic drug toxicity → change urine pH into basic → increases the urinary excretion.

eg :

- Aspirin or Phenobarbital or MTX toxicity → alkalinize the urine with bicarbonate.
- Amphetamine toxicity → acidify the urine with ammonium chloride (urine acidifier).
  Urine acidifiers : Ammonium chloride, Vitamin c and cranberry juice.

Henderson-Hasselbalch equation 00:45:15

1. Acidic drug : $\log \frac{[u]}{[i]} = pK_a - pH$.

   pH : pH of the medium.
   pK_a : Specific value of a drug.

2. Basic drug : $\log \frac{[i]}{[u]} = pK_a - pH$.

pK_a of drug is that pH of the medium at which 50% of the drug is ionized and 50% is unionized.

If pKa value of a drug = pH of the medium.

$$\log \frac{[u]}{[i]} = 0 \longrightarrow (\log[1] = 0) \longrightarrow \frac{[u]}{[i]} = 1$$

[u] = [i] = 50% unionized and 50% ionized.

Active space

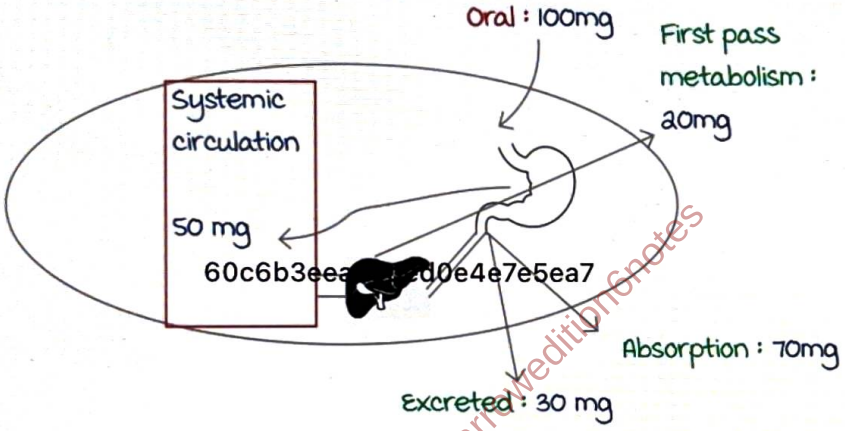
eg : acidic drug with pKa of 4, and stomach with pH of 2.
Calculate how much is ionized and unionized in a drug?

$$\log \frac{[U]}{[I]} = 4-2 \longrightarrow \log \frac{[U]}{[I]} = 2 \longrightarrow \log 10^2 = 2.$$

$$\frac{[U]}{[I]} = \frac{100}{1} = 99\% \text{ unionized and } 1\% \text{ ionized.}$$

Bioavailability 00:50:31

Definition : Fraction of unchanged drug that reaches systemic circulation.

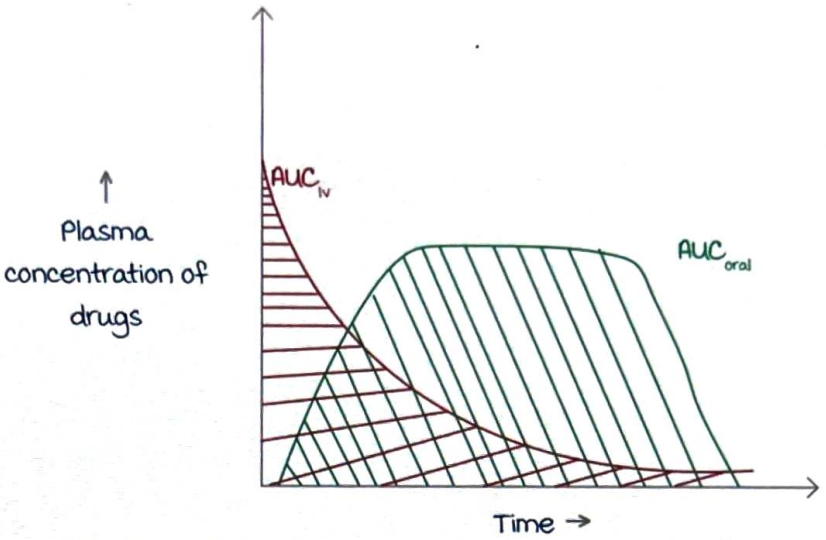


Moxifloxacin undergoes 100% absorption and most of the drugs do not undergo 100% absorption.

50 mg in the systemic circulation is the unchanged drug →
50% = 0.5
Bioavailability = f = 0.5
Range of bioavailability : 0 to 1.
Only route with bioavailability of 1 is Intravenous route i.e. 100% bioavailability.
It depends on 2 factors : Absorption & 1st pass metabolism.

Calculation of bioavailability :
Drug is given by both oral and intravenous route at different times to a person and concentration time curve is plotted.

Helps to study the change in plasma concentration with time.



$$f = \frac{AUC_{oral}}{AUC_{IV}} \times 100$$

f → Bioavailability

Auc → Area under curve

Plasma concentration is maximum at time 0 with IV route.
Area under the curve of a drug denotes bioavailability of a drug.

Bioequivalence 01:00:36

Definition : Two pharmaceutically equivalent compounds with similar rate (time taken for absorption) and extent of absorption (amount of drug absorbed).
It is required for drug manufacturing companies.

Branded drug : One which is invented. Patented for 20 years.
Generic drug : Legal copy of a drug. Done after patent expires.

Normal range : 20% more or less of the branded drug.
Generic drug approval requires a bioequivalence certificate of minimum 20%.
Benefit of generic drugs is that they are cheaper (as they don't need research & development).

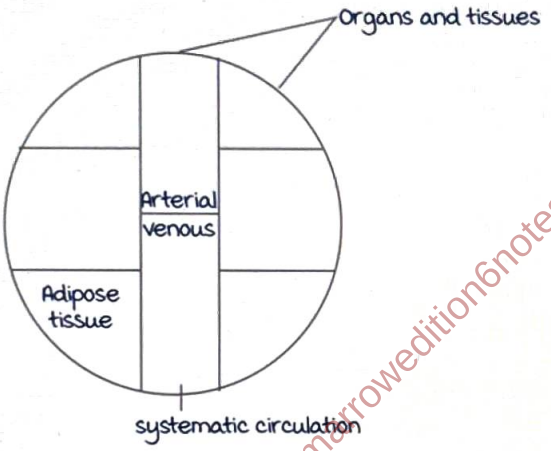
Active space

PHARMACOKINETICS : DRUG DISTRIBUTION

Apparent volume of distribution (AVD) 00:00:15

Volume is measured in litres & distribution of drug in mg.
AVD uses the probable litres of plasma to calculate how many mg of drug is distributed across the body (hypothetical).

AVD is a measure of drug distribution across organs & tissues.



When a drug is said to have high volume of distribution → the drug concentration is more in the organs than in the plasma.
For eg :
1gm of an intravenous drug is administered.
Plasma concentration is 5mg/L.
As the organs and tissues are solid components, same unit as plasma (mg/ml) cannot be used to measure drug in them.

For effective comparison, it is assumed that all the organs and tissues are a homogenous medium (similar to plasma).
This helps in comparing between drug concentration in plasma & tissues.

Suppose that the concentration of drug in adipose tissue is 50 mg/mL,

- Concentration of the drug is 10 times that of plasma.

Active space

To equate plasma & tissue concentration of a drug, dilute the tissue by adding plamsa.
This implies : more the plasma needed for dilution, means more is the amount of drug in the tissue.
Using this, we can calculate plasma required for dilution so that concentration of drug is same in both plasma & tissues.

AVD is the total plasma required to accommodate the administered drug in the whole body at plasma concentration.
Unit is litres.

If AVD > 5L, the drug is present more in organs and tissues.
If AVD < 5L, the drug is present more in plasma.

For eg : AVD is 100L.
100/5 = 20 i.e. drug is 20 times more in plasma.

Drugs with high volume of distribution	Present mostly in organs and tissues i.e. extravascular compartment.
Drugs with low volume of distribution	Present in systemic circulation, i.e. intravascular compartment.

Calculation 00:12:58

If D mg of drug is administered intravenously and a plasma concentration of C mg/mL is achieved.
AVD is the total plasma required to accommodate D mg of drug in C mg/mL concentration.
For C mg → 1mL is required.

For 1 mg → $\frac{1}{C}$ mL.

For D mg → $\frac{D}{C}$ mL.

AVD for intravenous drugs = $\frac{D}{C_0}$ mL, where C_0 is the initial plasma concentration.

AVD for any other route = $\frac{D \times f}{C_0}$ mL, considering the bioavailability of the drug.

D = AVD × C_T, where C_T is the target plasma concentration.

- C_T is specific for treatment, i.e. a constant.
- For a drug with high volume of distribution, as C_T is a constant, the dose is increased.
- Loading dose = AVD × C_T (for iv route).

Loading dose :

High dose given to maintain the target plasma concentration for drugs with high volume of distribution.

It depends on AVD.

For any other route :

$$AVD = \frac{D \times f}{C_T}$$

$$\text{Loading dose} = \frac{AVD \times C_T}{f}$$

Factors that determine AVD 00:19:10

1. Lipid solubility (pKa) α volume of distribution. Pka denotes ionization of the drug.
2. Fat content α volume of distribution.
   Obesity increases volume of distribution.
   Athletes have decreased volume of distribution of drugs.
   Females > males, as females have more fat content.
3. Plasma protein binding $\alpha \frac{1}{\text{volume of distribution}}$

   Higher plasma protein binding, lesser the distribution.
4. Specific tissue binding increases volume of distribution.
   eg : Digoxin binds to skeletal tissue Na^+-K^+ ATPase pump and has high volume of distribution.

Dialysis is not effective for drugs with high volume of distribution.

Dialysis can only clear the drugs in plasma & not those distributed in the tissues.

Mnemonic for dialysis ineffective drugs : BAD DOC

Drugs not cleared by dialysis	Antidote of choice
Benzodiazepines	Flumazenil
Beta blockers	Glucagon
Amphetamines	Ammonium chloride
Digoxin	Digibind
Opioids	Naloxone
Organophosphates	Atropine
Calcium channel blockers	Calcium gluconate

Plasma protein binding

00:25:33

Drugs bind to two types of plasma proteins.

- Albumin : Binds to acidic drugs.
- α_1 acid glycoprotein : Binds to basic drugs.

Albumin binding drugs	α_1 acid glycoprotein binding drugs
All CNS drugs except opioids and tricyclic antidepressants. Antibiotics : Sulfonamides (kernicterus in newborn). Warfarin. Aspirin.	Opioids. Tricyclic antidepressants. Antiarrhythmics : • Beta blockers. • Amiodarone. • Lidocaine.
In conditions with decreased albumin like nephrotic syndrome, CKD and liver cirrhosis : Risk for drug toxicity is high (more free drug).	In conditions with increased α_1 acid glycoprotein like rheumatoid arthritis, inflammatory bowel disease, myocardial infarction : Effect of drug is decreased due to high plasma protein binding.

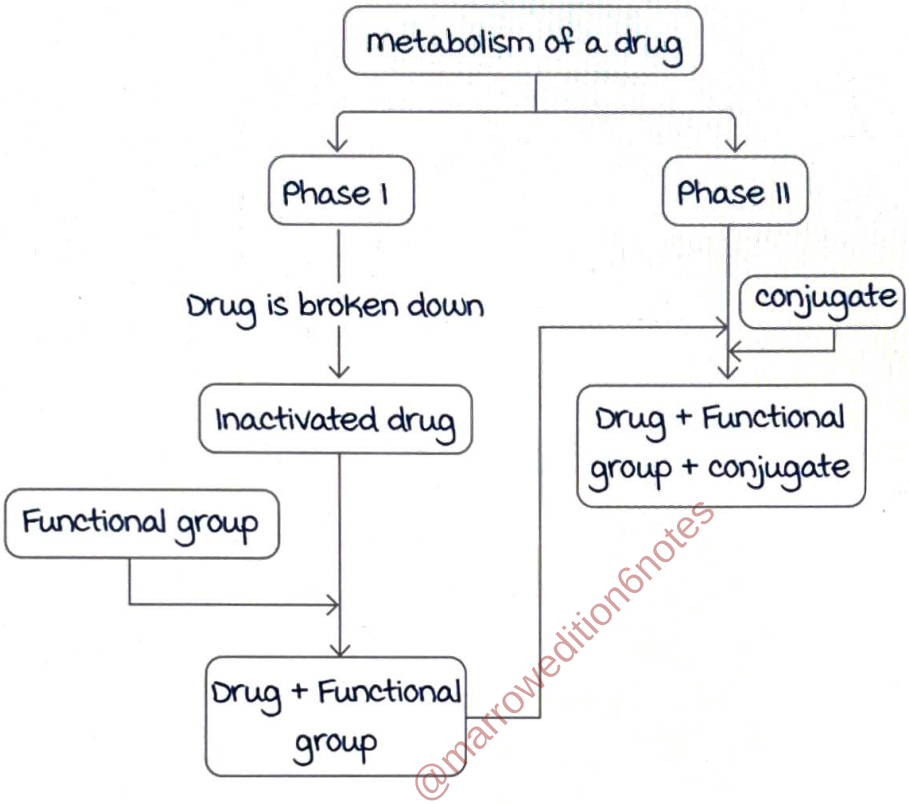
Warfarin and Aspirin are contraindicated with each other.

- Will displace each other from albumin.
- Increases the chances of bleeding.

PHARMACOKINETICS : METABOLISM

Metabolism

00:00:20



Phase I :

Primary function → Inactivation of the drug as structural integrity is lost.

Here prodrugs are activated (as prodrugs are inactive drugs). This is an exception to phase I reaction.

- Levodopa.
- Clopidogrel.
- Proguanil.
- All ACEI except Captopril and Lisinopril.

A functional group is added to the inactivated drug. This can also make the drug water soluble.

Purpose of phase I reaction : Drug inactivation > drug activation > increasing water solubilitiy.

Phase II (Conjugation) :

(Drug + Functional group) moiety becomes negatively charged /ionized by the addition of a conjugate to the functional group. Makes the drug water soluble (primary purpose).

Reactions of metabolism

00:04:47

Phase I reactions	Phase II reactions
Mnemonic : ORCHAD. Oxidation. Reduction. Cyclization. Hydrolysis. Aliphatic hydroxylation. Aromatic hydroxylation. Deamination.	Depends on the conjugate. Mnemonic : GAMS. Glucuronidation (glucuronyl transferase). Glycination. Glutathionation. Acetylation (acetyl/acyl transferase). Methylation. Sulfation.
Most common : Oxidation	Most common : Glucuronidation
Are enabled by CYP450 enzymes (microsomal enzymes in endoplasmic reticulum).	All are enabled by non-microsomal enzymes except glucuronidation, which is enabled by a microsomal enzyme.

CYP450 enzymes

00:08:53

- CY : Cytochrome (Heme protein that binds oxygen).
- P450 : Enzymes were first discovered in a plant pigment that absorbed light of 450nm wavelength.

Types of CYP450 enzymes.

Eg : CYP1A2.

1 → Denotes the family.

A → Denotes the subfamily.

2 → Denotes the gene isoform number.

Drugs metabolized in phase I by CYP450	Drugs metabolized in phase II
CYP1A2 : Paracetamol, Tacrine, Theophylline	Glucuronidation : Atazanavir, irinotecan Estrogen
CYP2B6 : Cyclophosphamide, methadone	Acetylation (mnemonic : HIPS) Hydralazine, INH, Procainamide, Sulfonamides, Dapsone,
CYP2C9 : Phenytoin, Warfarin	methylation : 6 mercapto Purine, methyldopa
CYP2C19 : Omeprazole Activates Clopidogrel	Sulfation : Steroids
CYP2D6 : Psychiatric drugs, Opioids, Beta blockers	
CYP2E1 : Enflurane, Ethanol	
CYP3A4 : metabolizes > 50% of drugs. Rifampicin, Digoxin, Mifepristone, Estrogen, Erythromyan	

Omeprazole and clopidogrel, if given together, competitively inhibit each other (2 substrates & 1 enzyme). Omeprazole,thus, decreases the effect of clopidogrel.
Most common enzyme required for drug metabolism : CYP3A4.

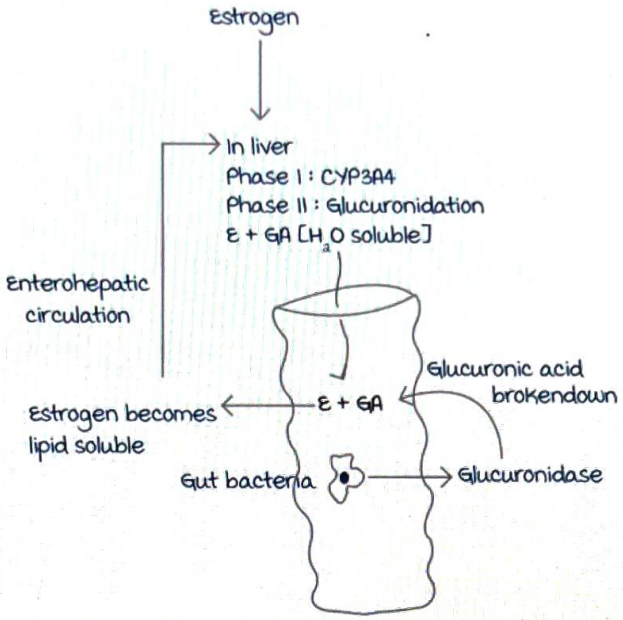
Atazanavir and Irinotecan are contraindicated in Crigler Najjar syndrome (Glucuronidation is affected in the condition).
Atazanavir can cause steven-johnson syndrome & Irinotecan can cause toxicity as it is an anti-cancer drug.

Estrogen (important component of OCP) is metabolized by :

- CYP3A4 in phase I.
- Glucuronidation in phase II.

The water-soluble form after conjugation is secreted into the intestine.
Normal $t_{1/2}$ of estrogen is increased by enterohepatic circulation.

Active space



- Estrogen is reabsorbed from the colon, after the intestinal bacteria breaks glucuronic acid. Estrogen becomes lipid soluble and is taken up.

In a female on OCPs, if antibiotics are given, they kill the gut bacteria (gut sterilization) → Decreases normal $t_{1/2}$ of OCPs → OCP failure.

Drug interaction

00:18:40

Seen due to microsomal enzyme induction or inhibition.

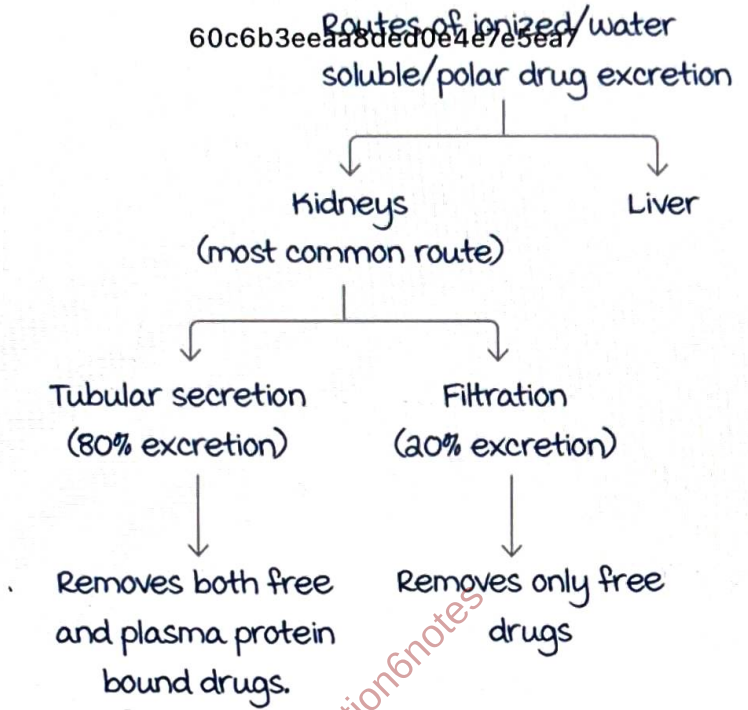
Enzyme inducers	Enzyme inhibitors
Increase in enzymes cause drug failure. eg : OCP failure because of Rifampicin.	Decrease in enzyme causes drug toxicity. eg : Theophylline toxicity with erythromycin/clarithromycin/ azithromycin (contraindicated).
Griseofulvin. Rifampicin. Alcohol. Benzopyrene (toxin). Phenytoin. Phenobarbital. Carbamazepine. St. John's wort (plant. Its water is boiled and consumed to treat depression).	Quinidine. Isoniazid. Cimetidine. Ciprofloxacin. Ketoconazole. Valproate. Erythromycin > Clarithromycin > Azithromycin. Grapefruit juice. Diethylcarbamazine.

Enzyme induction : Increase in number of enzymes increases metabolism and decreases plasma concentration.

Enzyme inhibition : Decrease in number of enzymes decreases metabolism and increases plasma concentraion.

Theophylline can cause cardiac arrhythmias. When Erythromycin is given, there is high risk of ventricular tachycardia, ventricular fibrillation, cardiac arrest & death.

PHARMACOKINETICS : DRUG EXCRETION



Filtration removes only limited amount of drug because it is dependent on GFR.
Filtration cannot remove protein bound drugs as both proteins & glomerulus are charged.

Rate of drug elimination (RDE) 00:02:53

Amount of drug that is eliminated per unit time (mg/hour).
As RDE can not be directly calculated, it is done with the help of two parameters.

- Drug clearance (ml/hour) :
  Amount of plasma that is cleared off the drug per unit time/per hour.
  That is, if D mg of drug is uniformly distributed in the plasma, it is the volume (in mL) of plasma that is completely drug free per unit time.

- Plasma concentration (mg/ml).
  Concentration of drug present in each ml of plasma.

Active space

Therefore, RDE can be calculated by :

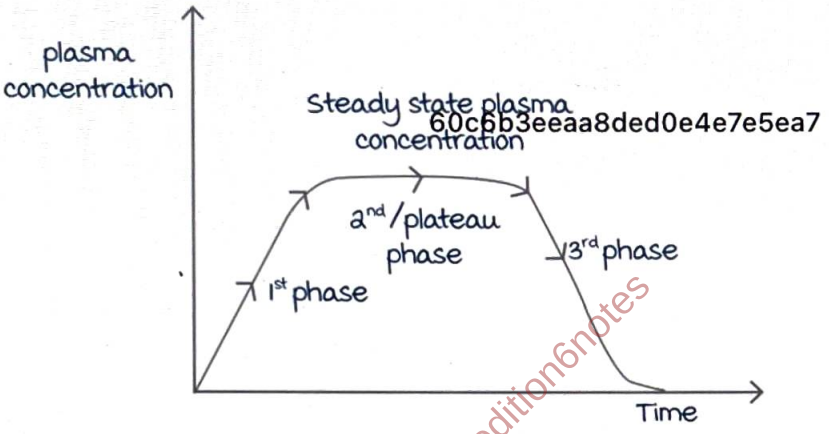
RDE = Drug clearance (Cl) x Plasma concentration (PC).

$$\frac{ml}{hour} \times \frac{mg}{ml} = \frac{mg}{hour}$$

mg/hour = Amount of drug eliminated/hour.

Clinical application :

1. Used to calculate infusion rate/dosing rate, whenever a drug is given by continuous IV infusion.



For an oral drug :

Phase 1 : Concentration of the drug progressively rises.

The amount of drug absorbed into the body is more than its elimination (as plasma concentration is increasing exponentially).

Phase 2 : concentration of the drug is constant.

- Called steady state plasma concentration (SSPC).
- The amount of drug absorbed and eliminated are same.

Phase 3 : concentration of the drug is progressively declining.

The amount of drug eliminated is more than what is absorbed.

To maintain steady state plasma concentration, infusion rate should be equal to rate of drug elimination.

Mnemonic : IPC.

Infusion rate = RDE = PC x Cl.

Infusion rate depends on the clearance.

Steady state plasma concentration is achieved by 4– 5 half lives (5 half lives > 4 half lives).

2. Intermittent dosing :

Maintenance dose (MD).

Amount of drug to be given to the patient after a time interval, following the loading dose, to maintain the drug level at SSPC.

Amount of drug eliminated should be the amount of drug given to maintain SSPC.

MD = RDE x time.

MD = PC x Cl x time.

MD is dependent on drug clearance.

Kinetics of drug elimination 00:15:15

Depends on the order of plasma concentration : zero order or first order.

When the dose of a drug is constant, clearance is constant.

$$RDE = [PC]^1 \times Cl$$

Zero order kinetics	First order kinetics
RDE = PC x Cl. For zero order kinetics: RDE = $[PC]^0$ x Cl. RDE = 1 x (constant). RDE is constant. Amount of drug eliminated per unit time is a constant. Constant amount of drug is eliminated per unit time.	RDE = PC x Cl. For first order kinetics : RDE = $[PC]^1$ x Cl. RDE = PC x (constant). RDE α PC. Amount of drug eliminated per unit time α to plasma concentration. Constant proportion of drug is eliminated per unit time.

What happens when the dosage of drug is not constant ?

Half life of a drug depends on two parameters.

- Volume of distribution (Vd).
- Clearance (Cl)

$$t_{1/2} \alpha \frac{Vd}{Cl} \quad t_{1/2} = 0.693 \times \frac{Vd}{Cl}$$

Zero order Kinetics	First order Kinetics
Eg : drug A is taken. RDE is 20mg/hour. Dose is 100mg. 100mg (1hr) → 80mg (1hr) → 60mg (0.5hr) → 50mg. $t_{1/2}$ = 2.5 hours. Dose increased to 200mg. 200mg (1hr) → 180 (1hr) → 160 (1hr) → 140 (1hr) → 120 (1hr) → 100mg. $t_{1/2}$ = 5 hours. Increase in dose, increases $t_{1/2}$ and decreases clearance.	Eg: drug B is taken. RDE is 20%/hour. Dose is 100mg. 100mg → 80mg → 64mg → ~50mg. 1hr 1hr 1hr. $t_{1/2}$ = 3 hours. Dose increased to 200mg. 200mg → 160mg → 128mg → ~100mg. 1hr 2hr 3hr. $t_{1/2}$ = 3 hours. $t_{1/2}$ and clearance are constant despite change in dose.

Zero order and first order clearance

00:27:48

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Zero order Kinetics	First order Kinetics
Followed by drugs with early saturation of elimination. Eg : Drug with maximum rate of elimination at 5mg/min. Dose : 50mg. Therefore, until the maximum rate of elimination is reached, the rate of elimination is proportional to the concentration. Plasma concentration : rate of elimination 1mg : 1mg. 2mg : 2mg. 3mg : 3mg. 4mg : 4mg. 5mg : 5mg. 6mg : 5mg. 7mg : 5mg. 10mg : 5mg.	Followed by drugs with late saturation of elimination. Eg : Drug with maximum rate of elimination is 500mg/min. Dose : 250mg. Here, the rate of elimination is proportional to the plasma concentration. If taken at high doses, the drug follows zero order kinetics. Dose : 750mg 1000mg. Drug eliminated : 500mg 500mg. Followed by most drugs.

Until maximum rate of elimination is reached, the drug follows first order kinetics. These are called Pseudo zero order drugs. Mnemonic (Zero ATP Has made weak) : Alcohol. Theophylline, Tolbutamide. Phenytoin. Heparin. methanol. Warfarin.	

Only drug that follows true zero order kinetics is alcohol.

If a patient consumes high dose of a zero order drug (eg : phenytoin) and first order drug (eg : carbamazepine), the one with zero order will have more toxicity.

PHARMACODYNAMICS : POTENCY, EFFICACY AND DRC

Affinity, Efficacy & Potency 00:00:18

Pharmacodynamics :

Drugs ⟶ Targets ⟶ Effect

Affinity | Efficacy

Affinity :

- Tendency of a drug to bind to a target.
- Dose required to bind to receptors.

Efficacy :

- Maximum clinical effect produced under controlled conditions.
- Effect produced.

Potency :

- Relative dose of a drug required to produce a particular effect.
- α 1/Dose

Eg : 10 mg, Drug A : decreases BP by 10 mmHg.
20 mg, Drug B : decreases BP by 10 mmHg.
Drug A is more potent.

Dose Response Curve (DRC) 00:08:02

Graded

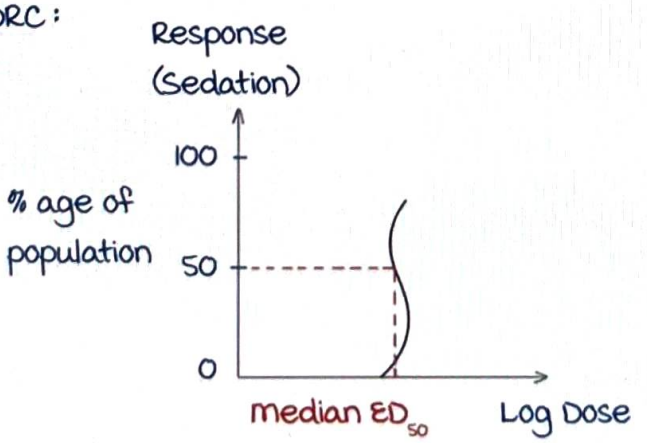
- DRC in an individual.
- Response : Graded

Quantal

- In a population.
- Response : Binary (Yes/ No)

Eg : Sedation.
Pregnancy.

Quantal DRC :

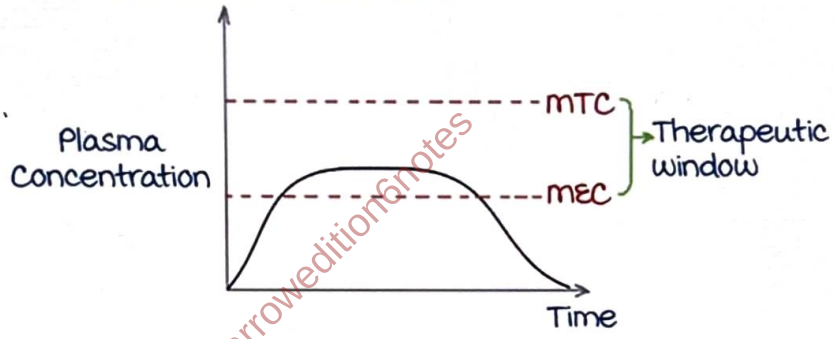


- median ED_{50} (Effective dose) :
  Dose required to produce effect in 50% population.
  marker of drug potency.

- median TD_{50} (Toxic dose) :
  Dose required to produce toxicity in 50% population.
- median LD_{50} (Lethal dose) :
  Dose required to kill 50% animals.
  Describes toxicity.
- Therapeutic index (Drug safety index):

$$= \frac{LD_{50} \longrightarrow \text{Toxicity}}{ED_{50} \longrightarrow \text{Potency (dose)}}$$

  measure of drug safety range.
- Therapeutic window :
  A concentration-time curve :



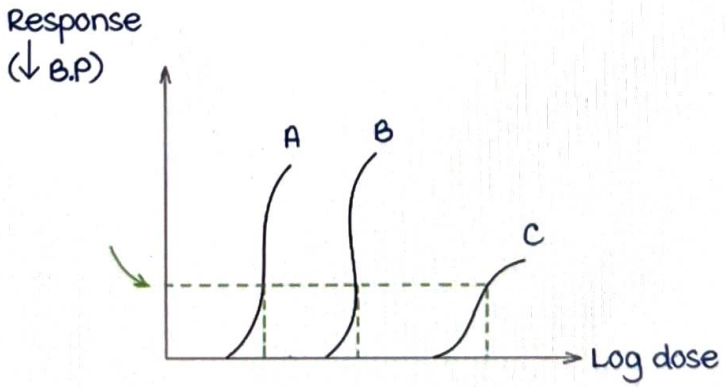
MEC (minimum effective concentration) : Effect is seen only if plasma concentration is above this.

MTC (minimum toxic concentration) : Toxicity begins to precipitate beyond MTC.

The aim is to maintain the plasma concentration between MEC & MTC.

Graded DRC

00:20:26



Efficacy : B > A > C (Height or slope of DRC) : Taller graph → Higher Efficacy.

Potency : A > B > C (Position of DRC on dose axis : less distance from the Y axis, more potent).

Affinity : A > B (Affinity can be compared only if the drugs act on the same target → DRCs are parallel).

Eg :

A : Enalapril (ACE inhibitor).

B : Captopril (ACE inhibitor).

C : Nifedipine (Ca^{2+} channel blocker).

Response : Same for all 3 drugs (Decrease in BP).

Potency & efficacy : Can be compared, even if targets are different.

Affinity : Cannot be calculated (different targets).

PHARMACODYNAMICS : DRUG RECEPTOR INTERACTION

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Types of Interactions 00:01:37

For E.g. We have β_1 receptor & four drugs (A, B, C, and D)
β_1 maintains the heart rate at 70/min. [Drug induced max HR : 200/min, min HR : 40/min]

- Drug A : increases HR to 200/min → Full agonist
- Drug B : increases HR to 150/min → Partial agonist
- Drug C : HR remains 70/min → Antagonist
- Drug D : decreases HR to 50/min → Inverse agonist

Full agonist : A drug that on binding produces the maximal effect. IE : +1.

Partial agonist : A drug that on binding produces the sub-maximal effect. IE : 0 to +1.

Antagonist (MC) : A drug that on binding produces no effect (net effect by preventing agonist action). IE : 0. Most drugs are antagonist.

Inverse agonist : A drug that on binding produces an opposite effect. IE : 0 to -1.

Intrinsic efficacy (IE) : Mathematical representation of effect.
Max effect : +1.
No effect : 0.
Min effect : -1.

Types of Antagonism 00:08:54

Pharmacokinetic	Chemical	Physiological
Antagonize by acting on pharmacokinetics. Eg. Charcoal – Alcohol. Rifampicin – OCP.	Antagonize by binding & neutralizing the effect. E.g. Protamine sulfate (+ve) : Heparin (-ve). Chelating agent : Iron/Copper.	Antagonize by producing an opposite effect on different receptors. E.g. Histamine (H1) : Bronchoconstriction. Adrenaline on (β_2) : Bronchodilation.

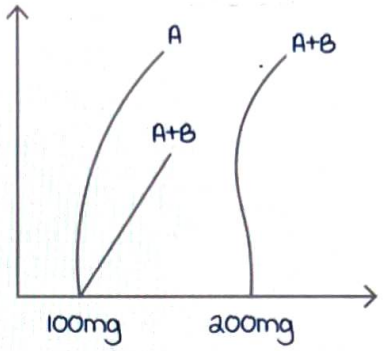
β_2 agonists are DOC in bronchial asthma but not in COPD (no role of histamine).

Competitive & Non-Competitive antagonism 00:14:25

Competitive antagonism : also known as pharmacological antagonism.

Reversible (mc)	Irreversible
E.g. 100mg drug A → causes an effect on 100 enzymatic sites (effect : 100%). 100mg drug B (Competitive antagonist)→ takes enzymatic 50 sites. ↓ Drug A left with 50 enzymatic sites (effect down by 50 %). ↓ Drug A dose increased to 200mg in presence of drug B. ↓ 200mg Drug A now operates at 100 enzymatic sites (effect : 100%). ↓ Right shift of the dose-response curve. Efficacy : no change. Vmax no change. Potency : decreases. Km increases.	E.g. Organophosphate. Proton pump inhibitors (PPI). Clopidogrel. Aspirin.

Active space



Dose response curve

Non-Competitive antagonism : Similar to irreversible competitive antagonism but acts at different sites.

E.g.

100mg drug C → causes an effect on 100 enzymes at the enzymatic site (effect : 100%).

100mg drug D (Non-Competitive antagonist) → takes 30 enzymes (allosteric sites).

↓

Conformational change in the enzymatic sites of these 30 enzymes.

Drug C left with 70 enzymes (effect down by 30 %).

↓

Drug C dose increased to 200mg in presence of drug D.

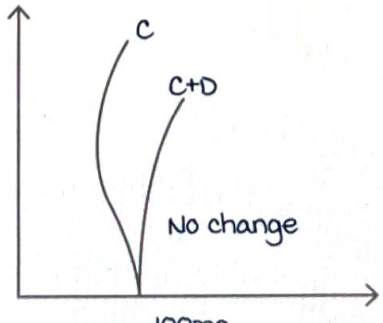
↓

No effect was seen.

- Decrease in the height/slope of the dose-response curve (no shift).

Efficacy : decreases, V_{max} decreases.

- Potency : no change, K_m no change.



Dose response curve

Michaelis Menten Equation

00:23:26

$$V = \frac{V_{max} \times [D]}{K_m + [D]}$$

V : Velocity/speed of reaction.

Vmax : Maximum speed of reaction.

[D] : Drug concentration.

Km : menten's constant.

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To find out Km, suppose Km = [D].

Then $V = \frac{V_{max} \times [D]}{[D]+[D]} = \frac{V_{max} \times [D]}{2[D]}$ = 1/2 of Vmax.

menten's constant (K_m) is drug concentration at which the speed of reaction (V) is half of the max speed (V_{max}).

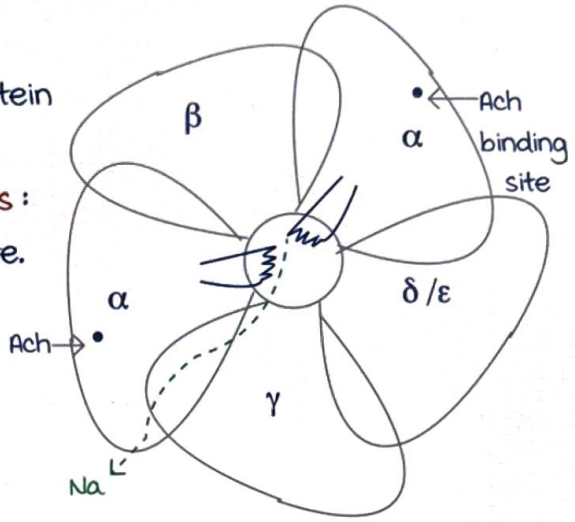
- K_m is inversely proportional to potency.
- V_{max} is directly proportional to efficacy.

Active space

PHARMACODYNAMICS : RECEPTORS

Ligand gated ion channel receptors 00:00:30

Examples :
$GABA_A$ ($GABA_B$: G protein coupled receptor).
Glutamate receptors : NMDA, AMPA, Kainate.
Only 1 receptor of Serotonergic system is $5HT_3$ (Others GPCR)

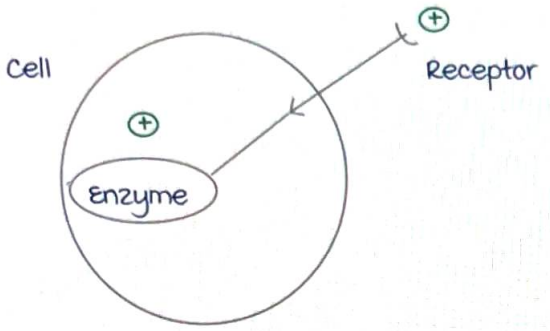


Nicotinic receptors :
The receptor is a pentameric structure.
It is an acetyl choline gated Na ion channel receptor.
Ligand gated ion channel receptors are the fastest acting receptors.
Muscarinic receptors are GPCR.

Enzymatic receptors and nuclear receptors 00:05:45

Enzymatic receptors : Ligand binds to receptor → Activates enzyme inside the cell.

Tyrosine Kinase receptors	VasculoEndothelial growth factor receptor (VEGFR), Epithelial growth factor receptor (EGFR), Her-2 receptor, Insulin receptor, IGF-1 receptor.
JAK (Janus Kinase) receptor	Growth hormone receptor, prolactin receptor, cytokine receptors.
Guanylate cyclase receptors	Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP).
Serine/threonine Kinase receptor	Transforming Growth Factor Receptor (TGFR).



Nuclear receptors :

Slowest acting receptors.

Located in Nucleus	Located in Cytoplasm
T3/T4 receptors. Vitamin A receptors : RAR : Retinoic acid receptor. RXR : Retinoid X receptor. PPAR : Peroxisome Proliferator Activated Receptor. Estrogen receptor. Progesterone receptor.	Vitamin D receptors. Androgen receptors. Mineralocorticoid receptors. Glucocorticoid receptors.

G protein coupled receptors (GPCR) 00:13:01

It is the most common target for drugs.

a.k.a 7 transmembrane receptor, heptahelical receptor, serpentine receptor or metabotropic receptor.

Receptor stimulated (in inactive state: GDP binds α subunit)

↓

GDP phosphorylated to GTP.

↓

α subunit carrying GTP dissociates from β and γ

↓

GTPase activity of α subunit

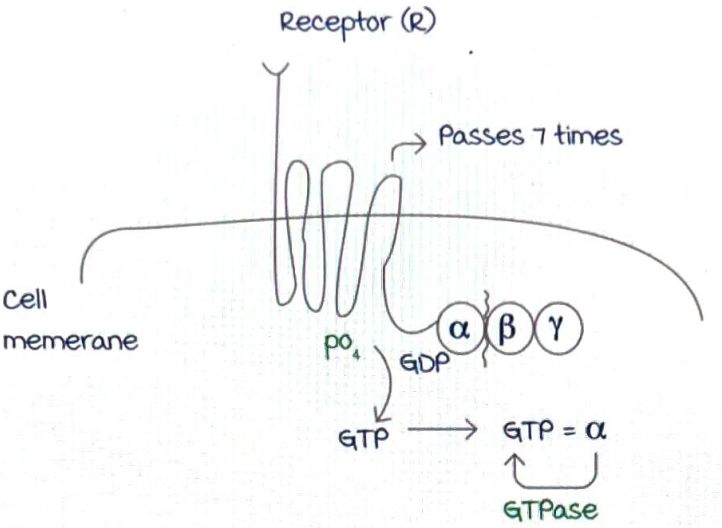
↓

GTP → GDP

↓

α subunit and GDP return to β and γ subunits.

Hence, α is the most important subunit.



Classification of G protein coupled receptors 00:19:16

Based on α subunit :

G_s	G_q	G_i / G_o
↑ α_s = GTP ↓ Stimulates Adenylate cyclase. ↓ ↑ cAMP ↓ Stimulates protein Kinase : ↓ In smooth muscles : • ⊕ MLCP • ⊖ MLCK Relaxation	↑ α_q = GTP ↓ Stimulates Phospholipase C. ↓ ↑PIP2 : Breaks down into IP_3 and DAG. IP_3 : ↑ Ca^{2+} α_1 receptor (G_q subtype) ↓ Contraction	G_i : ↓cAMP Open K^+ channels G_o : ↓ Ca^{2+} Open K^+ channels Relaxation G_i/ G_o subtype in heart → relaxation of muscle (m_2 receptors).

		$G_{12/13}$
In cardiac and skeletal muscles: ⊕Ca^{2+} channels : ↑ Ca^{2+} in muscles ↓ Contraction Salbutamol acting on β2 receptors : Lung : Bronchodilation. Cardiac and skeletal muscles : Palpitations and tremors. Theophylline blocks phosphodiesterase. ↓ Increases cAMP. ↓ Bronchodilation.	DAG : ⊕membrane Protein Kinase. α_1 receptor in blood vessels : Vasoconstriction. Oxytocin causes smooth muscle contraction of uterus.	↑Rho GTP ↓ Stimulates Rho Kinase ↓ Smooth muscle contraction. Rho Kinase inhibitors : Fasudil : Causes vasodilatation. Used in stable angina, cerebral vasospasm & pulmonary hypertension. Netarsudil : Used in glaucoma.

Cyclic AMP is metabolized by Phosphodiesterase 3/4.

MLCP : myosin light chain phosphatase.

MLCK : myosin light chain kinase.

PIP_2 : Phosphoinositol bisphosphonates.

IP_3 : Inositol triphosphate.

DAG : Diacyl glycerol.

DRUG DEVELOPMENT

Pre-clinical trials 00:00:33

A protocol is made.
Submitted to animal ethical committee.
Permission has to be given to conduct pre-clinical trials under CPCSEA Guidelines (Committee for Purpose of Control and Supervision of Experiments on Animals).

Clinical trials 00:03:11

Done on humans.
A protocol is made.
Submitted to human ethical committee.
The permission has to be given to conduct clinical trials under GCP guidelines (Good Clinical Practice).

To conduct trial in India:

- Human ethical committee's permission.
- Registration of trial with ICMR.
- Permission to be taken from Drug controller General of India (DCGI).

Phase 1 clinical trials 00:06:13

Following aspects of the drug are assessed:
Toxicity.
Safety.
Maximum tolerable dose is determined.
Pharmacokinetics
Pharmacodynamics
} Always phase I
Phase I is a.k.a human pharmacology and toxicity study.

Open label trials.
Control - placebo.
Duration: 1-2 years.
Participants: Normal healthy volunteers (20-100).
Exception: Patients in anticancer drugs, anti HIV drugs trials.

Phase II of clinical trials 00:14:08

Following aspects of the drug are assessed :
Dose range is determined.
Safety, Efficacy ← Open/blinded randomised controlled trials.

Safety and efficacy are determined in comparison to standard drug or placebo (Standard drug > placebo).
Patients : 100–500.
Duration : 2 – 3 yrs.
Maximum drug failure : 75%
Phase II is a.k.a therapeutic exploratory trial.

Phase III of clinical trials 00:20:13

Replica of phase II with an increased number of patients.
It leads to decreased errors.
Following aspects of drug are assessed :
Safety, Efficacy ← Open/blinded randomised controlled/ uncontrolled trails.
Safety and efficacy are confirmed as compared to control.
Patients : 500 – 3000. (Standard drug > placebo)
Duration : 3 – 5 years.
Phase III is a.k.a therapeutic confirmatory trial.

After phase III, new drug application is submitted by company to Food and Drug Administration (FDA in USA, CDSCO in India).
Headquarters of CDSCO : New Delhi.
CDSCO : Central Drug Standard Control Organisation.
FDA or CDSCO gives permission for marketing.

Phase IV of clinical trials 00:29:14

A.K.a post marketing surveillance.
Open label trials on many thousand patients.
Has no specific duration.

To find out adverse drug reactions (both rare and long term).
Drug – drug interaction can be found.
Can find new aspects of drugs : E.g. use of sildenafil in

erectile dysfunction (It was 1st used for treatment of pulmonary hypertension).
New routes of administration.
New dose range.
New age group.
Effectiveness of the drug.

Company needs to submit PSUR (Periodic Safety Update Report) to CDSCO once a year.

Recent advances in clinical trials

00:34:35

Non-mandatory trials.

Phase 0 :

Also known as microdosing.

Before phase-1.

Dose of the drugs → 100 mcg.
Dose of the drugs → 1/100th of normal dose.

Drugs are attached to a radioligand : helps to figure out the pharmacodynamics and kinetics of the drug.

Drugs are given to normal healthy volunteers.

↓

Sampling

↓ Pharmacokinetics

↓ Pharmacodynamics

If any aberration is found, it helps to abort the clinical trial even before beginning it.

Phase V :

Also known as Pharmacoepidemiology.

Involves case control and cohort studies.

Done in case of inconclusive reports in phase IV.

PHARMACOGENETICS AND PHARMACOGENOMICS

Pharmacogenetics and pharmacogenomics 00:00:24

Pharmacogenetics	Pharmacogenomics
Effect of genes on drugs. Genes code for enzymes and receptors : Target for drugs. If genes are more powerful : Drug failure with normal dose. If genes are less powerful : Drug toxicity with normal dose.	Individualization of drug therapy in a patient based on pharmacogenetics. To avoid drug failure : ↑ Dose. To avoid drug toxicity : ↓ Dose.

Variable effect of drug based on genes is A/K/A idiosyncratic reaction.

Examples of pharmacogenetic conditions 00:05:52

Target polymorphism:

1. VKORC 1 gene polymorphism (Vitamin K Oxide reductase).

Normally,

Warfarin
Inhibits
Vitamin K —VKOR→ Active vitamin K → γ-carboxylase
↓
Activates II, VII, IX, X coagulation factors
+
Protein C & S (anticoagulants)

If VKORC 1 gene more or less powerful : ↑ or ↓ VKOR - more or less activation of coagulation factors and warfarin will have variable effects (monitor PT/INR).

2. RYR gene polymorphism

Halothane/ Lignocaine/ Succinylcholine ↑ RYR → Ca^{2+} efflux → reuptake by Ca^{2+} ATPase with the use of ATP.

If RYR gene is more powerful → ↑ RYR on sarcoplasmic reticulum.

↓

Halothane/lignocaine/succinylcholine acts on all receptors.

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↑↑Ca^{a+} reuptake by Ca^{a+} ATPase

↓

Utilization of ATP produces heat

↓

malignant hyperthermia

3. Angiotensin converting enzyme (ACE) polymorphism :
   Decreased effect of ACE inhibitors.

4. β_a receptor polymorphism :
   Decreased effect of β_a agonist.

5. HMG- CoA reductase polymorphism :
   Decreased effect of statins.

Enzyme polymorphism

00:14:20

1. CYP2D6 polymorphism :
   CYP2D6 metabolises psychiatry drugs like antipsychotics & anti depressants.
   mayo clinic guidelines before prescribing : mandatory CYP2D6 genotyping.

↓ CYP2D6

↓metabolism → ↑toxicity of drugs

↓Activation of tamoxifen → ↓endoxifen → ↓Inhibition of estrogen receptor in breast. → Tamoxifen failure

2. CYP2C9 polymorphism :

CYP2C9 gene : metabolises warfarin.

If CYP2C9 gene more or less powerful,
metabolism of warfarin : Variable effect.

CYP2C9 polymorphism and VKORC 1 gene polymorphism are responsible for variant effect in atleast 25% of population.

3. CYP2C19 polymorphism :

CYP2C19 enzyme activates clopidogrel.

Gene less powerful → CYP2C19 enzyme → ↓activation of clopidogrel ↓ ↑ Risk of myocardial infarction.

4. Butyryl cholinesterase polymorphism :

Butyryl cholinesterase (in plasma) metabolises succinylcholine.

↓ metabolism of succinylcholine → ↑effect & prolonged apnoea.

5. G6PD polymorphism :

G6PD deficiency causes free radical injury to erythrocytes : Hemolysis.

Menadione
Anti malarials (primaquine, tafenoquine > chloroquine)
Nalidixic acid, Nitrofurantoin.
Isoniazid
Sulfonamide, Dapsone

6. N-acetyl transferase polymorphism :

NAT 1 gene (fast acetylators) — NAT 2 gene (slow acetylators)

Fast acetylators causes drug failure.

Active space

Slow acetylators causes drug toxicity.

Eg : Isoniazid's parent compound is responsible for peripheral neuropathy. Its metabolites cause hepatotoxicity.

Fast acetylators : Hepatotoxicity (Increased metabolites).
Slow acetylators : Peripheral neuropathy (High level of parent compounds).

THERAPEUTIC DRUG MONITORING

TDM 00:00:12

Principle : The plasma concentration of a drug should have a good correlation with either effects or side-effects of the drug.

Timing : TDM is done after 4–5 $T_{1/2}$; i.e. after achieving the steady state concentration.

Indications :

- If the clinical effect of a drug cannot be easily measured, e.g., antiepileptic effect.
- Low therapeutic index, e.g. theophylline, lithium, digoxin, antiepileptics, antipsychotics, aminoglycosides, methotrexate, cyclosporine/tacrolimus, antidepressants.
- To check compliance, e.g. antipsychotics.
- To prevent organ/fetal damage, e.g. aminoglycosides are nephrotoxic, but are used in case of renal failure.
- Female on Valproate,
  Pregnant → Continue Valproate and do TDM.
  Planning for pregnancy → Drug free interval → Seizure → DOC in pregnancy Levetiracetam (Alternative is Lamotrigine/Clonazepam).
- For drugs with variable effect, e.g. drugs metabolised by acetylation.

TDM is not needed in drugs such as,
Beta blockers : BP can be monitored.
Oral hypoglycaemic agents: Blood glucose level monitored.
Warfarin: PT/INR monitored.

ADR AND PHARMACOVIGILANCE

Adverse drug reactions (ADR) 00:00:16

It is a potentially harmful/ unpleasant reaction associated with the use of a drug, which warrants :

- Avoidance of future use of a drug.
- Decrease the dose/stop the drug.
- Treat the ADR.

Types of ADR :

1. Type A (Augmented) :
   - Example : CCBs → Headache.
     α_1 blocker → Postural hypotension.
   - Dose-dependent.
2. Type B (Bizarre) :
   - Not related to MOA of the drug.
   - Example : β-lactam → Hypersensitivity.
   - Dose independent.

3. Type C (Chronic) :
   - Example : HPA suppression with steroids.
   - Dose & time-dependent.
4. Type D (Delayed) :
   - Example : Teratogenicity.
     Carcinogenicity.
     Tardive dyskinesia.
5. Type E (End of use) :
   - Example : Opioid → withdrawal symptoms.
     Clonidine → withdrawal HTN.
6. Type F (Failure) :
   - Example : Rifampicin causing OCP failure.

Pharmacovigilance 00:10:18

- Done to detect ADR.
- Pharmacovigilance program of India (PVPI).
- National co-ordinating center (NCC) :
  Indian Pharmacopoeia commission (IPC) → Ghaziabad (UP).

Procedure :

The patient presents with ADR
↓
Hospitals & medical colleges (Government & private)
↓
Treat & report ADR through software Vigiflow
↓
NCC
↓
Conclusive ADR report
↓
Forwarded to CDSCO
(Central Drug Standard Control Organization)
↓

1. Inform company → Drug is banned → Drug withdrawn.
2. Inform Doctors.
3. Inform patients.
4. Inform International Pharmacovigilance Centre in Sweden : Uppsala monitoring centre → Inform other countries to continue pharmacovigilance.
   Sweden has the largest ADR database : Vigibase.
   mcc for banning a drug : hepatotoxicity.

Aim of pharmacovigilance : To maintain drug safety in the society.

ADR is a two way process.

INTRODUCTION TO AUTONOMIC NERVOUS SYSTEM

Autonomic nervous system 00:01:33

The term autonomous means on its own (involuntary).
Autonomic nervous system (ANS) can broadly be classified into :

- Parasympathetic nervous system (PNS) :
  Cranial part : III, VII, IX and X cranial nerve nuclei.
  Sacral part : S2 – S4 segments of the spinal cord.
  PNS is of craniosacral origin.
- Sympathetic nervous system (SNS) : It derives its origin from T1 – L2 segments of the spinal cord. SNS is thoracolumbar in origin.

For example,
III[rd] cranial nerve nuclei supplies the pupils. Pupils contract when stimulated.
The action potential (AP) propagated from the nuclei is intercepted by ganglion (collection of neuronal bodies) which then transmits it to the pupils causing it to contract.

The neurotransmitter (Acetylcholine) in the presynaptic neurons stimulates the receptors (Nicotinic) present in the postsynaptic neuronal membrane.
Nicotinic receptors are sodium ion channel receptors.
The AP depolarizes the presynaptic membrane causing the voltage gated Ca^{a+} channels to open which will pump calcium into the neuron.
The Ca^{a+} ions will lead to the fusion of vesical and neuronal membrane thus releasing the neurotransmitter.
The neurotransmitter released into the synaptic cleft stimulates the nicotinic receptors which causes the sodium channels to open.
The sodium influx leads to depolarization of the postsynaptic neuron and the AP is regenerated.

The AP originates from the thoracolumbar segments in the SNS which is received by the ganglions (pre & paravertebral). The ganglion regenerates the AP and propagates it towards the organ of interest.

The receptors in the ganglion are always nicotinic neuronal (N_N) subtype.
The receptors in the postganglionic segment is either muscarinic or nicotinic in PNS.
Acetylcholine is the neurotransmitter of postganglionic segments of PNS.
The postganglionic receptors in SNS are either α or β.
Norepinephrine is the neurotransmitter of the postganglionic segments of SNS.

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Exceptions in SNS :

- Acetylcholine (Ach) : Adrenal and sweat glands. Sweating is a feature of sympathetic overdrive mediated by Ach and thus cannot be controlled with β blockers.
- Dopamine : In renal blood vessels, dopamine causes vasodilatation & more plasma moves into the kidney raising (GFR) causing diuresis.

Parasympathetic nervous system 00:18:56

Acetylcholine is the universal neurotransmitter of PNS.

- It is synthesized from Acetyl CoA (from mitochondria of neurons) and Choline (from systemic circulation) by Choline acetyl transferase. Ach enters the vesicle and is stored there.
- AP opens the Ca^{a+} channels leading to calcium influx. Th Ca^{a+} ions cause the vesicles to contract until it fuses with the presynaptic membrane.
- Ach is released into the synaptic cleft & binds to the muscarinic or nicotinic receptors.
- Ach is immediately metabolized by Acetylcholine esterase (true choline esterase) present in the synapse.

Plasma choline esterase is present in the blood. It is also known as Pseudocholine esterase or Butyrylcholine esterase.

Acetyl choline esterase (ACHE) has two sites :

1. Esteratic : Has enzymatic activity that breaks down ester bond.
2. Anionic : Negatively charged

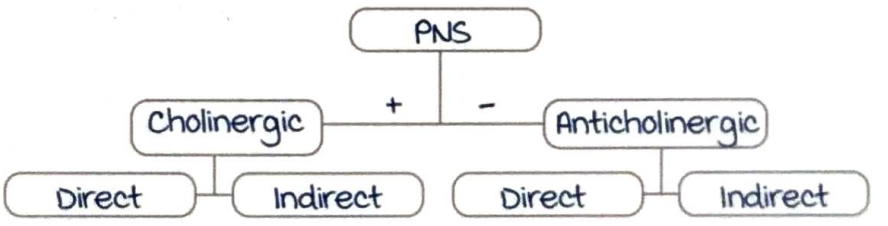
Choline is positively charged, and it immediately binds to the anionic site. The esteratic site breaks the ester bond releasing acetate and choline.

The choline is taken back into the presynaptic neuron and is called choline reuptake. It is the rate limiting step in the synthesis of Ach.

Drugs acting on synthesis of acetylcholine 00:28:43

- Hemicholinum : Choline reuptake inhibitor.
- Vesamicol : Prevents entry of Ach into the vesicle.
- Aminoglycosides : Blocks the voltage gates Ca^{a+} channels on the presynaptic neuron preventing Ach release.
  It causes neuromuscular toxicity and worsen diseases like myasthenia gravis (antibodies against N_m receptor leading to fatigue). Ca^{a+} can be used as treatment.
- β-Bungarotoxin and Botulinum toxin : Directly blocks the release of Ach.
  Botulinum toxin causes botulism. Blockade of Ach release prevents stimulation of N_m receptor blocking muscle contraction. The cause of death in botulism is respiratory paralysis. Infant botulism or floppy infant occurs due to the paralysis of muscles.

Classification of PNS drugs 00:36:39



Direct cholinergic drugs bind directly to the receptors and are agonists of N_N or N_m receptors.
Indirect cholinergic drugs act by inhibiting AChE.
Direct anticholinergic drugs directly block the N_N or N_m receptors.
Indirect anticholinergics decreases the level of Ach.
Example : Aminoglycosides, β-Bungarotoxin & Botulinum toxin.

Botulinum toxin/botox

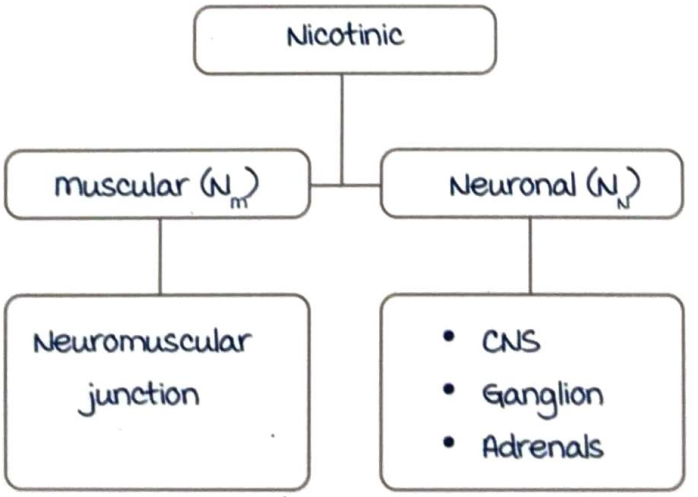
00:40:34

Botox causes relaxation of the muscle when injected. It can be used in treatment of :

- Dystonia.
- Dyskinesia.
- Migraine prophylaxis : It decreases the calcitonin gene related peptide (CGRP) release.
- Achalasia cardia.
- Cosmetology

Receptors in PNS :

- Muscarinic (m) : These are G-protein coupled receptors.
- Nicotinic (N) : These are sodium ion channel receptors.



When the N_N receptors in the CNS are stimulated, it causes a sodium influx leading to depolarization (excitation).
Seizure is a presentation of nicotinic poisoning as there is excessive excitation.

N_N receptors in the ganglion is involved in the regeneration of AP propagated along the neuronal axis.
Stimulation of N_N receptors by Ach in the adrenal medulla leads to synthesis of norepinephrine.
It is then converted into epinephrine by cortisol. Epinephrine is then released into the plasma.

Stimulation of N_m receptors leads to contraction of muscles.
In myasthenia gravis, antibodies are produced against the N_m receptor. Blockage of N_m receptor leads to decreased muscle contraction causing fatigue.

Muscarinic receptors 00:49:36

M_1, M_3 and M_5 subtypes are G_q subtype of GPCRs. Their stimulation cause an increase in Ca^{a+} levels.
M_2 and M_4 are $G_{i/o}$ subtype of GPCRs. Their stimulation causes relaxation by decreasing Ca^{a+}, Cyclic AMP and by opening K^+ channels.
M_5 and M_4 are mostly present in CNS and has no clinical significance.

M_1 receptors are present in CNS and its stimulation causes increased cognition.
Retrograde amnesia in Alzheimer's disease is due to death of cholinergic neurons or due to decrease in Ach.

Taclifensin is a new M_1 receptor agonist which can be used in the treatment of Alzheimer's disease.
M_1 receptors in GIT are responsible for increased secretion of HCl.

M_3 receptors :

- GIT : Contraction.
- Salivary glands : Salivation
- Bronchi : Bronchoconstriction.
- Bladder: Detrusor Contraction.
- Circular muscle of iris : Contraction and miosis.

- Blood vessels : Present in the endothelium and smooth muscles.

  Increased Ca^{a+} stimulates Ca^{a+} dependent endothelial nitric oxide synthase (ENOS) to produce NO leading to vasodilatation.

  Increased Ca^{a+} in smooth muscle leads to contraction.

  The vasodilatory effect is more prominent than vasocontrictory effect. The net effect is vasodilation.

M_2 receptors

00:57:34

It is present in the heart. PNS primarily supplies the nodes (Sinoatrial and Atrioventricular).

Stimulation of m_a receptor leads to inhibition of SA node leading to decreased heart rate and AV node leading to conduction block.

Location	Cholinergic	Anticholinergic
CNS (Cognition)	Inc	Dec
GIT secretion	Inc	Dec
GIT contraction	Inc	Dec
Gland secretion	Inc	Dec
Bronchi (Bronchoconstriction)	Inc	Dec
Bladder (contraction)	Inc	Dec
Detrusor	Inc	Dec
Circular muscle of iris	Inc (miosis)	Dec (mydriasis)
Heart (rate & conduction)	Dec	Inc

Inc : Increase.

Dec : Decrease.

Uses of anticholinergics :

- Peptic ulcer disease.
- Anti-spasmodic.
- Pre-anesthetic medication to decrease secretion.

- Bronchial asthma and COPD.
- Overactive bladder.
- Mydriatic.
- Bradycardia and conduction block.

Uses of cholinergics :

- Gastroparesis.
- Paralytic ileus.
- Xerostomia.
- Bladder atony.
- Miotic.

Symptoms of cholinergic poisoning :

- Diarrhea.
- Excessive salivation and lacrimation.
- Bronchoconstriction leading to breathlessness.
- Urination.
- Pinpoint pupil.
- Bradycardia and conduction block.

Symptoms of anticholinergic poisoning :

- Delirium.

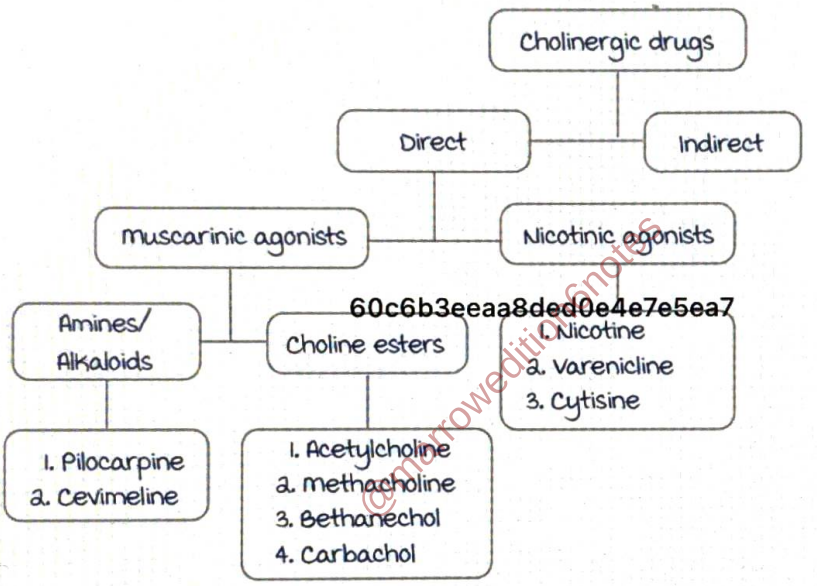
- Constipation.
- Dry mouth.
- Urinary retention.
- Mydriasis.
- Tachycardia.

CHOLINERGIC DRUGS

Cholinergic drugs 00:00:18

Stimulates the parasympathetic nervous system (PNS).
Cholinergic drugs can be broadly classified into :

- Direct acting : Directly binds to the nicotinic or muscarinic receptor.
- Indirect acting : Blocks AcetylCholine Esterase (AChE) increasing the level of acetylcholine (Ach).



Nicotinic agonists are used to treat smoking dependance.
Amides can cross Blood Brain Barrier (BBB) as they are lipid soluble. Hence, they can be used in CNS diseases.
Central side effects are common.
Choline esters cannot cross BBB as they are lipid insoluble.
No central side effects and are used to treat peripheral diseases.
Amides :

- Pilocarpine :

Used in the treatment of xerostomia (dry mouth) seen in sicca or sjogren's syndrome.
Drug of choice (DOC) in closed angle glaucoma as it is a miotic agent.
It increases trabecular outflow by miosis.

Other miotic agents include :

- Physostigmine
- Echothiophate
- Fluostigmine

} AChE inhibitors

Cataract is the common side effect of AChE inhibitors. Hence they are not preferred over pilocarpine.

Common side effects of miotic agents 00:10:06

Accommodation spasm : M_3 receptors are present in the muscles involved in accommodation as well as the circular muscle of the iris.

Brow ache (headache at the level of brow) can be seen due to accommodation spasms.

Retinal detachment may occur due to the muscle spasm as well.

All side effects are due to M_3 receptor induced calicum increase in the muscles of accomodation.

- Cevimeline is an amide used only in the treatment of xerostomia and is more effective compared to pilocarpine.

In an acute attack of closed angle glaucoma/acute congestive glaucoma, IV mannitol is the first line drug as it normalizes IOP.

Pilocarpine is used only to maintain normal IOP because iris muscles would not be able to relax because of increased pressure.

Choline esters 00:14:55

This class of drugs include acetylcholine and its derivatives. When used as a drug, acetylcholine is metabolized by pseudocholine esterase in the plasma.

Drugs metabolized in the plasma are very short acting and do not have any systemic use.

Hence, acetylcholine is used as a topical miotic agent in ocular surgery.

Other drugs metabolized by pseudocholine esterase are

- Esmolol : Shortest acting beta blocker.
- Clevidipine : Shortest acting CCB.
- Succinyl choline : Shortest acting muscle relaxant.
- Remifentanil : Shortest acting opioid.

Beta methylation of Ach makes it resistant to pseudocholine esterase. It is called methacholine and is longer acting than Ach.

methacholine : $m_a > m_1/m_3$ and has moderate nicotinic effect.

Ach derivatives resistant to both true and pseudocholine esterase :

- Bethanechol : $m_1/m_3 > m_a$.
  No nicotinic effect.
- Carbachol : $m_1/m_3 > m_a$.
  Maximum nicotinic effect.

Longer half life ($t_{1/2}$)

Carbachol has maximum nicotinic side effect. Hence, does not have any systemic use. It is used topically as :

- Miotic agent for ocular surgery.
- Closed angle glaucoma.

methacholine is used in bronchial challenge test to diagnose bronchial asthma as it is short acting.

It acts on m_3 receptor in the bronchi (m_a is present in the heart).

Peripheral effects of cholinergic drugs are seen in

- muscle.
- GIT.
- Bladder.

Bethanechol increases contraction of the bladder and can be used in bladder atony.

It can also be used in gastroparesis and postoperative paralytic ileus.

Indirect acting cholinergics

00:33:42

They are inhibitors of AChE and are broadly classified as

- Irreversible : Organophosphates.
- Reversible : Carbamates.

Organophosphate Compounds (OPC) :

AChE has esteratic and anionic sites.
OPC binds to the esteratic site with PO_4 bond.
PO_4-enzyme bond is extremely stable. One of the bonds between phospohorus and oxygen in PO_4, breaks with time. This process is called ageing.
Now, OPC binding becomes irreversible. Also, they competitvely inhibit ACh.
Oximes are positively charged molecules which binds to the anionic site.
They break PO_4-enzyme bond and liberates OPC.
They are called AChE reactivators. They are effective only if the anionic site is free and in the absence of ageing.

OPC drugs :

- Warfare agents : Nerve gas. E.g., sarin, cyclosarin, tabun, Vx and soman.
- Clinical use : Echothiophate (can cause cataract and iris cysts) and fluostigmine.

- Insecticides and pesticides : Easily available and commonly used in cholinergic poisoning.

Symptoms of cholinergic poisoning :

- Agitation.
- Increased salivation and lacrimation.
- Bronchospasm.
- Increased urination.
- Pinpoint pupil (miosis). Also seen in opioid poisoning.
- Bradycardia.

DOC is atropine (lifesaving drug).
Monitoring a patient for adequate atropinization :

- Commonly monitored is pupil size (dilation).
- Most specific : Respiratory secretion.

Atropine has only anti-muscarinic action. Oximes are given to reverse nicotinic symptoms and are the most specific drugs in OPC poisoning.

Examples of oximes include

- Pralidoxime : Most commonly used in India.
- Obidoxime.
- Diacetyl mono oxime.

Carbamates

00:52:26

Carbamates bind to both sites of AChE. Hence, oximes cannot be used to reverse carbamate poisoning.
But the binding can be broken after some time. So, carbamates are called pseudo irreversible inhibitors.

They can be broadly classified into :

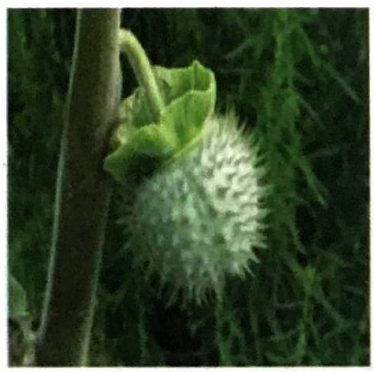
- Tertiary amines : Can cross BBB. Examples include
  1. Physostigmine.
  2. Rivastigmine.
  3. Galantamine.
  4. Tacrine.
  5. Donepezil.

  } Non-carbamates
- Quaternary amines : Cannot cross BBB.

Physostigmine is derived from calabar beans of the plant (natural source) called Physostigma venenosum.
It is used in the treatment of closed angle glaucoma and is the DOC for anticholinergic poisoning like :

- Atropine toxicity.
- Belladonna poisoning.
- Datura poisoning : The thorny fruit contains atropine like compounds.

Physostigma venenosum



Datura

Symptoms of anticholinergic poisoning :

- Delirium.
- Dilated pupils (mydriasis).
- Dry mouth.
- Decreased urine output or urinary retention.
- Constipation.
- Tachycardia.

Tertiary amines like rivastigmine, galantamine, tacrine and donepezil are used to treat Alzheimer's disease.
Donepezil is the DOC.

Quaternary amines

01:03:09

Only peripheral uses including :

Myasthenia Gravis (MG) : Antibodies competitively inhibit Ach in the NM receptor decreasing muscle contraction.
Quaternary amines block AChE. Increases Ach and helps in driving out the antibodies.

- Edrophonium (non-carbamate) : Binds only to the anionic site and is very short acting. It is the DOC in the diagnosis of MG (Tensilon test).
  It is also the DOC to differentiate MG from myasthenic crisis.
  Myasthenic crisis is caused by AChE inhibitors.
  Edrophonium worsens it.
  Edrophonium is also used in paroxysmal supraventricular tachycardia (PSVT) as it blocks the AV node.
- Neostigmine :
  Used in the diagnosis and treatment of MG when pyridostigmine is not available.
  Premedication with atropine before using edrophonium or neostigmine is mandatory to block the muscarinic side effects.
  Used in non-depolarizing muscle relaxant (NDMR) reversal seen with atracurium, pancuronium.
  Used in cobra bites as Cobra toxin damages the neuromuscular junction (NMJ) leading to respiratory paralysis.

Other uses include :

- Bladder atony.
- Post-operative urine retention.
- Paralytic ileus.
- Gastroparesis.

- Pyridostigmine :

It is a longer acting oral drug and is the DOC for treatment of generalised MG.

Steroids are given in pyridostigmine resistant patients.

Immunosuppressants like

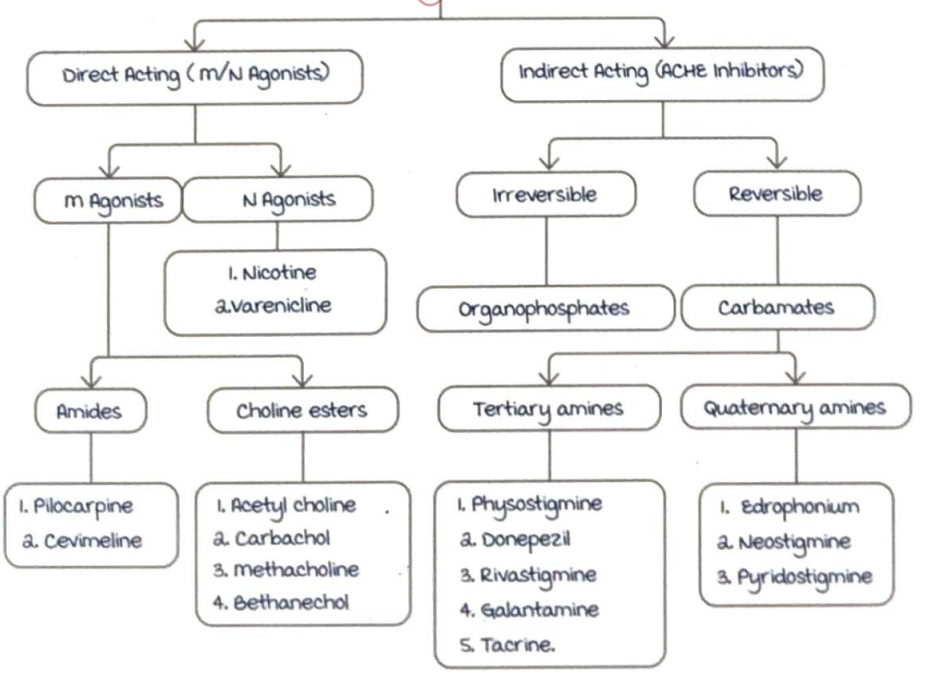
- mycophenolate mofetil.
- Cyclosporine.
- Rituximab.
- Azathioprine.

are used in both pyridostigmine and steroids resistant patients.

The DOC for treatment of myasthenic crisis is Intravenous immunoglobulin (IVIG).

Plasmapheresis is an alternate treatment modality.

Cholinergic drugs summary



ANTICHOLINERGIC DRUGS

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Direct acting anticholinergics :

Muscarinic receptor blockers.

Nicotinic receptor blockers.

- N_m Blockers (muscle relaxants)
  NDMRs : Atracurium, Mivacurium.
- N_N Blockers (ganglionic blockers).

Ganglionic blockers

00:02:43

Mechanism of action :

Ganglionic block

↓

↓ NE (norepinephrine) release in post ganglionic segment

↓

↓ BP (used in treatment of HTN).

Drugs :

1. Mecamylamine (oral route)
   Used in mild to moderate HTN (2nd line).
   Used to treat Tourette Syndrome.
   Adjunct to nicotine in smoking dependance
   (↓ peripheral side effects of nicotine).
2. Trimethaphan :
   Used in hypertensive emergency intravenously.
3. Hexamethonium : Clinically not used.
4. Tetraethylammonium : Used only in experiments as a potassium channel blocker.

Side effect :

Postural Hypotension : Advise the patient to rise slowly from sitting/lying position after taking the drug.

Active space

Muscarinic receptor blockers/ anti-muscarinic drugs

00:09:08

- CNS :

Effect : Decreases cognition.

Use : Narcoanalysis.

Drug : Scopolamine (hyoscine) a.k.a truth Serum.

DOC for Narcoanalysis : Thiopentone (less toxic).

- Pupils :

MOA : Blocks M_3 receptors in muscles of iris & accommodation.

Effects	Uses
mydriasis	Ocular fundus examination. Prevent synechiae formation in uveitis, corneal ulcers.
Cycloplegia	Refractive error tests in children, as they have powerful muscles of accommodation. ↓ Pain in iridocyclitis.

Drugs :

- Tropicamide (shortest acting) : Preferred cycloplegic in adults.
- Atropine (most potent cycloplegic) : Preferred cycloplegic in children. As an add on drug in fungal corneal ulcer (to prevent synechiae).
- Cyclopentolate.
- Homatropine.

Effect on oropharyngeal secretions & lungs

00:17:48

- Oropharyngeal secretions :

Reduce secretions and used as preanesthetic medication (anesthesia inhibits cough reflex).

Drugs :

Atropine.

Glycopyrrolate : Preferred as it is quaternary amine and does not cross BBB.

- Lungs :

  Effect : Bronchodilation.

  Used as add on drugs in bronchial asthma.

  DOC in COPD (only reversible component of bronchoconstriction in COPD is the parasympathomimetic effect).

Class	Drugs	Dosing frequency
SAMA (Short acting muscarinic antagonists)	Ipratropium	QID
IAMA (Intermediate acting muscarinic antagonists)	Oxitropium Aclidinium Glycopyrrolate	BD
LAMA (Long acting muscarinic antagonists)	Umeclidinium Revefenacin Tiotropium	OD

All drugs inhaled using PMDI (Pressurized metered Dose Inhaler).

PMDI

Nebulization with ipratropium is given in acute exacerbation of bronchial asthma /COPD.

DOC for COPD : LAMA (Tiotropium).

Nebulizer

Side effects : Dry mouth (most common).

Abnormal taste.

Lesser systemic effects like urine retention (to be avoided in patients of BPH).

Effect on heart & GIT

00:29:31

Heart :

Stimulates SA Node : Increases heart rate.

AV Node : Increases conduction.

Uses of Atropine :

- Treatment of conduction blocks. eg : Digoxin toxicity.
- DOC for bradycardia. Dose : 0.5 – 1 mg IV.
  At low doses (< 0.5mg) atropine blocks presynaptic M_1 (Gi) receptors → Increases Ach which stimulates M_a receptor causing further bradycardia.
- Bradyarrhythmia due to inferior wall MI (vagal irritation).

GIT :

1. Reduces HCl Secretion : Used in peptic ulcer disease.
   Drugs are M_1 blockers :
   - Pirenzepine.
   - Telenzepine.

2. Reduces contraction : Used as antispasmodic drugs.
   - Dicyclomine.
   - Glycopyrrolate.
   - Scopolamine : DOC in motion sickness.
     Used as a transdermal patch (applied 4–5 hrs before travel/night before travel and reapplied every 2–3 days).

Effect on bladder

00:42:23

Reduces detrusor contraction.

Use : Overactive bladder or detrusor instability.

Non selective drugs :

Flavoxate

Oxybutynin.

Fesoterodine.

Trospium : Quaternary amine, does not cross BBB.

Selective M_3 Blockers :

Darifenacin.

Solifenacin.

Tolterodine.

SYMPATHETIC NERVOUS SYSTEM – NEUROTRANSMITTERS AND RECEPTORS

Neurotransmitters 00:00:31

Norepinephrine (NE) :
Its synthesis in the pre-synaptic neuron begins with the precursor tyrosine → DOPA → Dopamine.
Dopamine enters the vesicle through vesicular monoamine transporter (VMAT$_2$).
It gets converted into NE within the vesicle.
NE is released when the depolarizing action potential reaches the neuron. The released NE binds and reacts with the α and β receptors.
After its effect NE can either return to the pre-synaptic neuron by reuptake or can get metabolized by enzymes such as :

- mono amine oxidase (MAO).
- Carboxy-O-methyl transferase (COMT).

Different regions have different neurotransmitters. In brain it is Dopamine in some regions it is NE.
Enzymes involved in the synthesis of Dopamine and NE include :

- Tyrosine hydroxylase (rate limiting enzyme) :
  Tyrosine → DOPA.
- DOPA decarboxylase : DOPA → Dopamine.
- Dopamine β hydroxylase : Dopamine → NE.

Conversion of tyrosine to DOPA catalyzed by tyrosine hydroxylase is the rate limiting step in the synthesis of NE.

Drugs acting on synthesis of NE and dopamine 00:04:53

metyrosine (methylated tyrosine) is a competitive inhibitor

(similar structure) of tyrosine hydroxylase thereby decreasing the conversion of tyrosine to DOPA.
Thus decreasing the production of both NE and Dopamine.

VMAT2 receptor blockers : Prevents the entry of dopamine into the vesicle.
The drugs included are :

- Reserpine.
- Tetrabenazine.
- Deutetrabenazine
- Valbenazine

] Derivatives of tetrabenazine and longer acting.

Metyrosine is used in pheochromocytoma to decrease the NE levels in conditions like :

- Pre-operative hypertension. It is used if α blocker followed by β blocker therapy is contraindicated (heart failure).
- Malignant pheochromocytoma where surgery is contraindicated e.g : malignant cases.

Reserpine decreases NE and dopamine levels. It is used in :

- Mild to moderate hypertension (decrease NE).
- Agitated psychotic state (decrease dopamine).

Tetrabenazine and its derivatives decrease the Dopamine levels.
Tetrabenazine and Deutetrabenazine are the DOC for Huntington's chorea.
Also used in treatment of tics associated with Tourette syndrome.
Deutetrabenazine and Valbenazine are DOC for treatment of tardive dyskinesia.

Drugs blocking the reuptake of NE and Dopamine :

- Tricyclic antidepressants : Primarily block reuptake of NE.
- SNRIs : Seretonin Norepinephrine reuptake inhibitors.
- Cocaine : Substance of abuse

Cocaine dependence

Cocaine increases both Dopamine and NE.
Increase in NE : Causes side effects such as HTN and MI.
Increase in Dopamine : It stimulates D_a receptors and gives the user KICK/high. Causes dependence.
The DOC for dependence is Bromocriptine.
It also causes D_a receptor stimulation (D_a agonist) and limits the effect of cocaine.

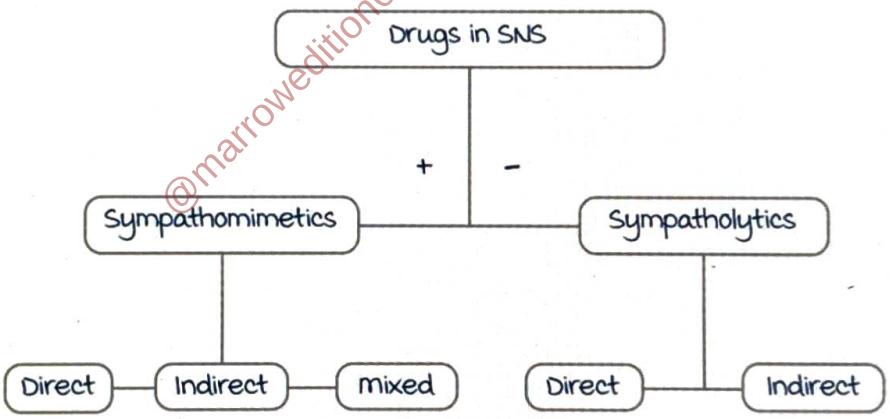
The patient is started on the drug and the dose is gradually tapered down.

Common side effects of drugs decreasing NE and dopamine levels :

- Hypotension
- Depression

Decreased NE levels.

- Parkinsonism due to decreased dopamine levels.



Direct sympathomimetics directly stimulate the α and β receptors.
Indirect sympathomimetics increase release of NE which leads to stimulation of α and β receptors.
Mixed acting sympathomimetics have both direct and indirect sympathomimetic action.

Direct sympatholytics directly block the α and β receptors.
Indirect sympatholytics decrease the NE levels.
Examples of indirect acting sympatholytics : metyrosine, Reserpine.

Receptors

00:19:15

Receptors in sympathetic nervous system (SNS) are either α or β. They are G-protein coupled receptors (GPCR). At the synapse α_1, α_2 and β_2 receptors are prsent.

α receptors : NE > epinephrine (potency of stimulation).
It can be broadly sub-classified into :
α_1 (Gq type of GPCR) : Located at the center of post-synaptic membrane. Its stimulation by NE results in increased Ca^{2+} levels. It is present in

- Blood vessels : Vasoconstriction.
- Prostatic urethra : Contraction.
- Bladder sphincter : Contraction.
- Radial muscles of iris : Contraction leading to mydriasis.
- GIT : The increase in Ca^{2+} stimulates the calcium dependent K^+ channels. Opening of K^+ channels leads to hyperpolarization of smooth muscles as the potassium moves out. This causes muscle relaxation.
- Liver and skeletal muscle : Induces glycogenolysis and gluconeogenesis leading to hyperglycemia. The increased calcium acts as a cofactor for the enzyme involved in these processes.

α_2 (Gi type of GPCR) : Located at the periphery of pre-synaptic membrane.
β_2 receptor (Gs type of GPCR) : Present in the periphery of pre-synaptic membrane.

Selectivity of catecholamines to α_1, α_2, and β_2 depends on the concentration :

- At low concentration : Stimulates the β receptors.
- At high concentration : Stimulates the α receptors.

At the synapse, as soon as NE is released even though the concentration is low it binds with α_1 receptor weakly and produces some effects.
Since the concentration of NE is low, the affinity towards β_2 is high. Thus, β_2 receptors get stimulated which leads to further increase in NE levels.

When the NE level is high enough to breach the threshold it stimulates the α_a receptor which leads to inhibition of release of NE.

α_a are called auto receptors (Gi subtype of GPCR) as they automatically control the release of NE. Other examples of auto receptors include :

- m_1/m_a receptors in parasympathetic nervous system.
- α_a in SNS.
- H_3 in histaminergic system.
- $5HT_1$ in serotonergic system.

α_a receptor decreases release of NE.

Exceptions include :

Post-synaptic α_a in blood vessels (G_q subtype) :

- Stimulation causes vasoconstriction.
- Clonidine is an α_a agonist which is given as slow or fast intravenous infusions.
- Slow infusion acts on the presynaptic α_a causing a decrease in NE levels and thus decrease blood pressure.
- Fast infusion acts on the postsynaptic α_a causing vasoconstriction and thus worsening the hypertension.

Post-synaptic α_a receptors (Gi subtype) :

- Present in the β_a islet cells of pancreas.
- stimulation decreases insulin release causing hyperglycemia.

Effect of β_a receptor on glucose levels :

- β_a receptor (Gs subtype) has a similar effect as α_1.
- Its stimulation increases the glycogenolysis and gluconeogenesis leading to hyperglycemia.
- β_a receptors are also present on the β islet cells in the pancreas. Here unlike α_a, they are Gs subtype.
- Its stimulation increases the insulin release and decrease the glucose levels (hypoglycemia).

The hyperglycemic effect predominates over the hypoglycemic effect.

Catecholamines act on the β_1 and β_a receptors on the heart

causing palpitations and β_2 receptors on the skeletal muscles causing tremors and sweating. This is known as hypoglycemic awareness.

β receptors

00:37:23

They are Gs subtype of GPCR and its stimulation increases the level of cyclic AMP (cAMP). There are three subtypes of β receptors :

- β_1 receptors : Potency – Epinephrine > NE
  In heart : Increased cAMP increases the Ca^{2+} levels leading to increased contraction, heart rate & conduction.
  In Kidney (juxtaglomerular cells) : Its stimulation increases the release of renin which activates the renin-angiotensin system (RAS) thus increasing blood pressure.
- β_2 receptors : Potency – Epinephrine > NE
  In smooth muscle : Increases cAMP levels blocks the myosin light chain kinase (MLCK), stimulates myosin light chain phosphorylase (MLCP) and opens the K^+ channels.
  There is resultant relaxation of smooth muscles in :
  1. Bronchi : Bronchodilation. β_2 agonists like salbutamol can be used in bronchial asthma.
  2. Blood vessels : Vasodilation.
  3. Uterus : Ritodrine is used as a uterine relaxant.

  In cardiac and skeletal muscle : Increase Ca^{2+} levels leading to increased contraction.
  Use of β_2 agonists like Salbutamol and Ritodrine can lead to side effects like palpitations and tremor.
- β_3 receptor : Potency – NE > Epinephrine
  In detrusor (bladder) : causes muscle relaxation.
  In adipocytes : Activates hormone sensitive lipase which leads to increased lipolysis.

SYMPATHOMIMETICS : PART - 1

Classification 00:00:20

3 types :

- Direct acting : Drugs that stimulate alpha or beta receptors.
- Indirect acting : Drugs that increase release of norepinephrine which in turn stimulate alpha or beta receptors.
- Mixed acting : Drugs that have both direct and indirect actions.

Direct acting sympathomimetics :

Subclassified into catecholamines and non-catecholamines.

1. Catecholamines are further subclassified into endogenous and exogenous catecholamines.
2. Non-catecholamines are synthetic chemicals that stimulate alpha or beta receptors.

Endogenous catecholamines :

Dopamine, norepinephrine and epinephrine.

- Epinephrine is an agonist at alpha 1, beta 1 and beta 2 receptors.
- Norepinephrine is an agonist at alpha 1 and beta 1 receptors.

Norepinephrine :

It is a more potent vasoconstrictor.

- Drug of choice in cardiogenic and vasodilatory shock (sepsis).
- Given intravenuously as IM injection causes muscle necrosis .

Epinephrine :

It is a more potent cardiac stimulator.

- Drug of choice in cardiac arrest. IV epinephrine in 1 : 10,000 dilution.
- Drug of choice in anaphylactic shock. 0.3–0.5 ml IM epinephrine in 1 : 1000 dilution.
  In case of no response despite multiple doses, 0.25 ml IV in 1 : 10,000 dilution is given.
- Used as a local vasoconstrictor to decrease bleeding. Combined with a local anaesthetic to increase the duration of action and decrease the toxicity of local anaesthetic.
- Epinephrine or its prodrug dipivefrine can be used in open angle glaucoma as they decrease aqueous humor production (similar to apraclonidine and beta blockers). They also increase uveoscleral outflow.

Dilutions of epinephrine 00:15:00

1. 1 : 1000 : IM or subcutaneous or endotracheal route.
2. 1 : 10,000 : IV or intraosseous or intracardiac route.
3. 1 : 1,00,000 : Local vasoconstrictor to decrease bleeding.
4. 1 : 1,00,000/2,00,000 : Along with local anaesthetic.

Dale's phenomenon :
Whenever given to a living system, epinephrine at higher concentration increases BP (alpha 1 stimulation) and at lower concentration decreases BP (beta 2 stimulation). This is known as biphasic pattern of blood pressure.

Vasomotor reversal of Dale 00:20:52

If epinephrine is given with an alpha blocker in a living system, there will be a decrease in BP due to unopposed beta 2 action.

Vasomotor re-reversal of Dale :
If epinephrine is given with a beta blocker in a living system, there will be a significant rise in BP due to unopposed alpha 1 action.

Dopamine 00:24:30

Has dose dependent action & is given as continuous IV infusion

Dose 0-2 mcg/kg/min : D_1 receptor stimulation leads to diuresis because of renal blood vessel dilatation.
Used in oliguria.
Dose >2-10 mcg/kg/min : Beta 1 receptor stimulation.
Increases cardiac contraction. Used in acute congestive heart failure (CHF).
Dose >10 mcg/kg/min : Alpha 1 receptor stimulation. Produces vasoconstriction. Used in cardiogenic shock.

In acute congestive heart failure with oliguria, dopamine is no longer the drug of choice. Dobutamine with a diuretic such as furosemide is used.

Exogenous catecholamines 00:29:48

Dobutamine :

- Mechanism of action : Agonist at beta 1 receptor >>>> beta 2 receptor. Net effect on alpha receptors is zero.
- Increases cardiac contractility by acting on beta 1 receptor on myocardial cells.
  No effect on heart rate/conduction.
  There is no significant increase in myocardial oxygen demand. Hence it is the inotrope of choice in acute congestive heart failure.
- Given as continuous IV infusion. Dose is 2-8 mcg/kg/min.
- Used in stress echocardiography in patients who are unable to exercise.

Isoprenaline (Isoproterenol) 00:34:15

Agonist at beta 1 and beta 2 receptors.
Beta 1 agonism causes increase in contraction, heart rate and AV conduction. Can be used in acute CHF, cardiogenic shock, bradycardia, torsades & conduction block.

Beta 2 agonism causes bronchodilation.
Can be used for bronchospasm during anaesthesia.

Droxidopa :
Prodrug of norepinephrine.
Used to treat neurogenic hypotension in Diabetic neuropathy.

Fenoldopam and dopexamine :
Both are D_1 receptor agonists : Cause diuresis and decreases BP.
Fenoldopam is also an alpha 2 agonist : Decreases BP. Used in hypertensive emergency intravenously.
Dopexamine is a beta 2 agonist : Decreases BP. Used in acute congestive heart failure.

Differences between epinephrine, norepinephrine and isoprenaline

00:40:22

	Epinephrine	Norepinephrine	Isoprenaline
Receptor selectivity	Alpha 1, beta 1, beta 2	Alpha 1, beta 1	Beta 1, beta 2
Systolic blood pressure (SBP)	Increase in SBP (more cardiac contractility)	Increase in SBP (more vasoconstriction)	SBP normal/ decreased
Diastolic blood pressure (DBP)	Increase in DBP is not very significant	Significant increase in DBP	Decrease in DBP
mean blood pressure (MBP)	Increase in MBP	Significant increase in MBP	Decrease in MBP
Heart rate (HR)	Direct effect : Significant increase in HR Reflex effect : Decrease in HR. Net effect is increase in HR.	Direct effect : Increase in HR Reflex effect : Significant decrease in HR. Net effect is decrease in HR	Significant increase in HR

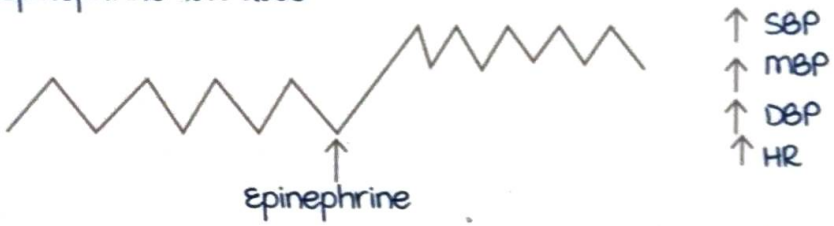
Norepinephrine increases heart rate if given with atropine or in patients with transplanted heart due to absence of vagal reflex.

Active space

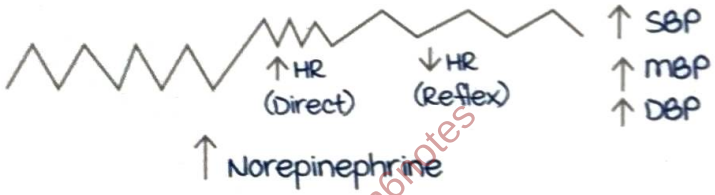
Tracing

00:50:28

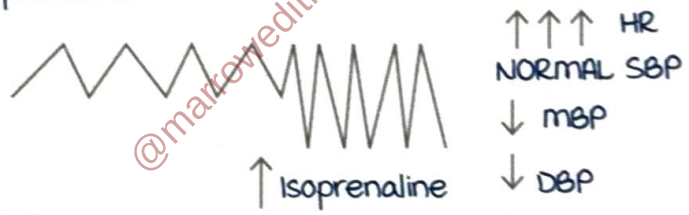
Epinephrine: low dose



Norepinephrine (also seen with high dose epinephrine)



Isoprenaline :



Non-catecholamines

00:56:08

Chemicals that stimulate either alpha or beta receptors.
Broadly classified into alpha and beta receptor agonists.

Alpha receptor agonists :
Subclassified into alpha 1 & alpha 2 agonists.
Alpha 1 agonists are used in hypotension.

Phenylephrine :

- Drug of choice for priapism, spinal anaesthesia induced hypotension (without associated bradycardia).
  In presence of bradycardia, use ephedrine.
- Used as a mydriatic & nasal decongestant.

Side effect is bradycardia.

Xylometazoline :
Used only as nasal decongestant (topical).

Midodrine :
Drug of choice for postural hypotension.

Mephentermine, metaraminol, methoxamine : Used to treat hypotension.

Alpha 2 agonists 01:01:30

Stimulates alpha 2 receptor, causes central sympatholysis & decreases norepinephrine and BP.
Alpha 2 receptor stimulation in brain causes sedation.

Clonidine :

- Used in mild-moderate hypertension.
- Drug of choice in hypertensive urgency.
- Can be used to treat ADHD, postmenopausal hot flashes, diarrhea in diabetes mellitus, opioids/smoking/alcohol dependance and as a pre-anaesthetic medication.

Side effect : Withdrawal hypertension due to alpha 2 receptor down regulation.

Dexmedetomidine 01:07:25

Potent central alpha 2 agonist.
Used as a pre-anaesthetic medication & causes sedation, analgesia and decrease secretions.
Not used for induction of anaesthesia due to requirement of high dose (High risk of hypotension).

Tizanidine :
Used as a muscle relaxant.

Lofexidine :
Approved for treatment of opioid dependance.

Alpha methyl dopa :

It is pro drug which is converted to alpha methyl norepinephrine.
Stimulates alpha 2 but depletes norepinephrine in vesicles.
Used in the treatment of pregnancy induced hypertension (current drug of choice is oral labetalol).
Side effect is haemolysis.

Guanabenz, guanfacine : Used to treat ADHD.

- Guanfacine and clonidine are drugs of choice for mild tics associated with Tourette syndrome. Guanfacine is preferred as sedation is less.
- If tics are severe, atypical antipsychotics (drugs of choice) or tetrabenazine are used.

Apraclonidine and Brimonidine :

- Used to treat open angle glaucoma as they decrease aqueous humor production and increase uveoscleral outflow.

Side effects of apraclonidine (alpha 1 agonism = alpha 2 agonism) : mydriasis, lid retraction, conjunctival blanching.

Side effects of brimonidine : Crosses blood brain barrier causing sedation/drowsiness and apnea in neonates.

SYMPATHOMIMETICS PART - 2

Imidazoline receptor agonist 00:00:32

They also have alpha 2 agonism as well.
Drugs : Moxonidine, Rilmonidine.
Uses : Resistant HTN, neuropathic pain.

Beta receptor agonists :
Beta 3 agonists : mirabegron, Vibegron.
Use : Urge incontinence.
Side effects : HTN, headache, UTI, nasopharyngitis.

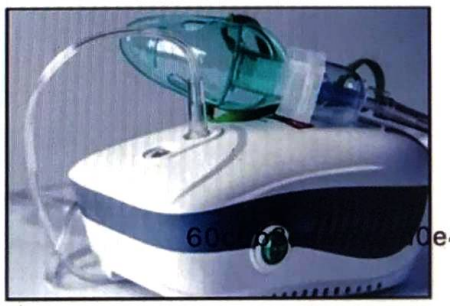
Beta 2 agonists : Broadly sub-classified into,

- SABA : Duration of action is 2-4 hours.
  Salbutamol, Terbutaline, Pirbuterol.
- LABA : Duration of action is 12 hours.
  Salmeterol, Formoterol.
- VLABA : Duration of action is 24 hours.
  Olodaterol, Vilanterol, Carmoterol, Indacaterol.

Fast acting drugs : All SABA + Formoterol.
Used in acute attack of bronchial asthma. Preferred route is inhalational (PMDI).
Used in acute exacerbation of asthma/COPD (nebulizer).

PMDI

Nebulizer



LABA : It is used as BD dosing by a PMDI (inhalational).

Uses :

In persistent BA : Add on drug to ICS.

Prophylaxis of asthma.

COPD : Add on drug to anticholinergics.

VLABA : OD dosing via PMDI.

FDA approved only for COPD treatment (long-term management).

Side effects of beta 2 agonist : Palpitations, tremors (m/c), hyperglycemia, hypokalemia.

Indirect acting sympathomimetics 00:17:08

Mechanism of action : Increasing release of norepinephrine.

Drug enters inside the vesicle containing NE in the presynaptic terminal and displace NE into the synaptic cleft.

Overall effect is sympathomimetic.

When the drug is given in continuous dose : Sympatholytic effect due to depletion of NE.

Intermittent dosing will produce sympathomimetic effect.

Tyramine :

Dietary amine which is present in cheese and red wine.

Metabolised by monoamine oxidase (MAO).

When taken along with MAOI ⟶ Acute surge of tyramine ⟶ Release huge amount of NE ⟶ Stimulate alpha 1 receptor (vasoconstriction) ⟶ HTN emergency/crisis.

This is called as cheese reaction.

DOC : IV Phentolamine. (alpha blocker)

Methylphenidate :

Stimulant.

DOC for ADHD.

Drawbacks : Worsen ticks, abuse potential.

Not used with ADHD with Tourette syndrome and ADHD with family history of drug abuse potential.

Atomoxetine/Viloxazine (selective NE reuptake inhibitor) can be used in this scenario.

Other uses of methylphenidate : Narcolepsy (DOC : modafinil, acts by increasing levels of Dopamine).
modafinil is also DOC in excessive sleepiness/OSA, shift worker disease.
Drugs used in narcolepsy :

- Stimulants : methylphenidate, amphetamine.
- DOC : modafinil.
- Pitolisant (H3 receptor blocker).
- Solriamfetol (DNRI).

Amphetamine 00:31:52

Stimulant.
Uses : ADHD, narcolepsy, obesity.

Derivatives of amphetamine : Dextroamphetamine, Lisdexamphetamine (prodrug of amphetamine).

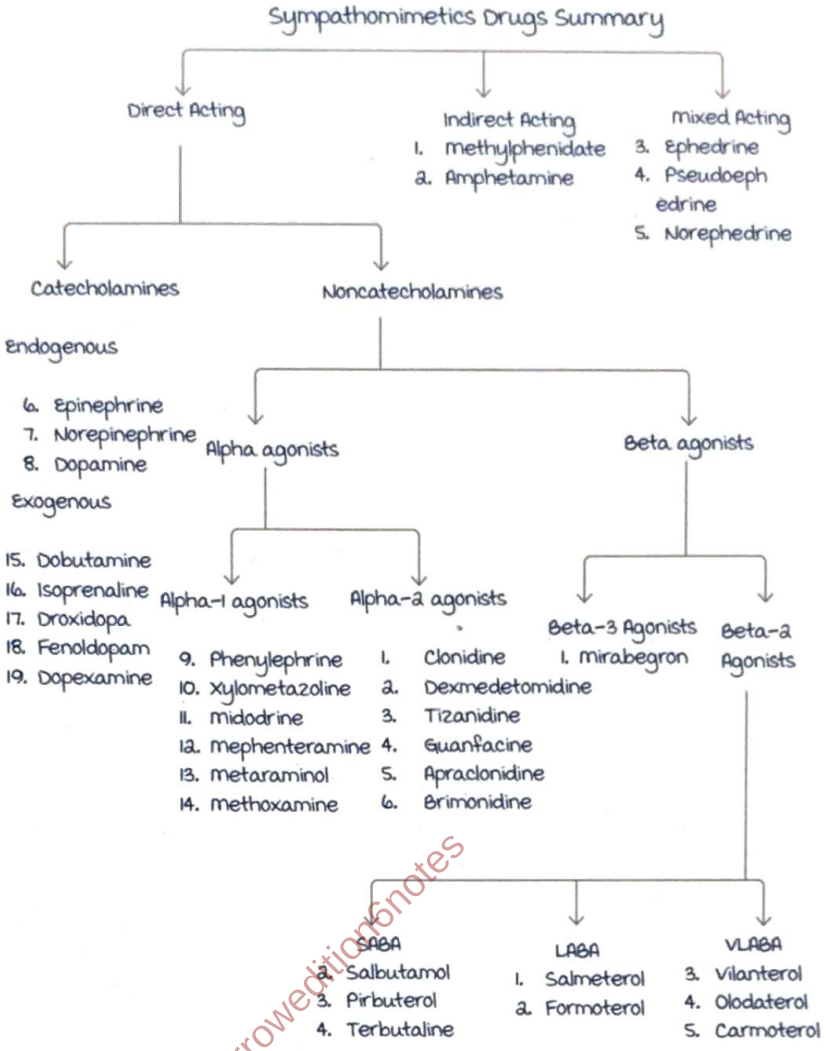
methamphetamine/crystal meth/designer drug : Drug of abuse.
Guanethidine & Guanadrel :
Used for treatment of HTN (continuous dose).
Contraindicated in pheochromocytoma : Precipitate HTN crisis.

Mixed acting sympathomimetics 00:36:41

Mechanism of action: Both direct and indirect action.
Direct : Stimulate alpha and beta receptors.
Indirect : Increase release of NE.

Ephedrine :
Used in treatment of spinal anaesthesia induced hypotension
Preferred if there is associated bradycardia.
(phenylephrine is preferred overall because of less fetal effects).
Ephedrine is also used as mydriatic and nasal decongestant (topical route).

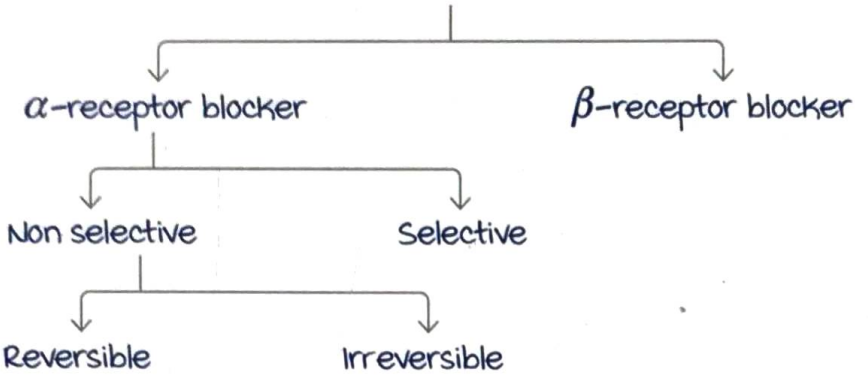
Derivatives of Ephedrine :
Pseudoephedrine: Oral nasal decongestant.
Norephedrine or Phenylpropanolamine : Earlier was used for treatment of obesity (banned because of high risk of stroke).



SYMPATHOLYTICS

Classification

00:04:38



Non selective α-receptor blockers

00:01:26

Tolazoline (peripheral vasodilator) :

Uses :

Raynaud's disease.

Angiography.

Phentolamine (IV) :

DOC :

Clonidine withdrawal HTN.

Cheese reaction.

Intraoperative hypertension in pheochromocytoma (to decrease spike of BP while handling tumour during surgery).

Used for erectile dysfunction.

(DOC in erectile dysfunction : Sildenafil).

Phenoxybenzamine.

DOC : Preoperative HTN in pheochromocytoma.

Treatment of choice :

α blocker

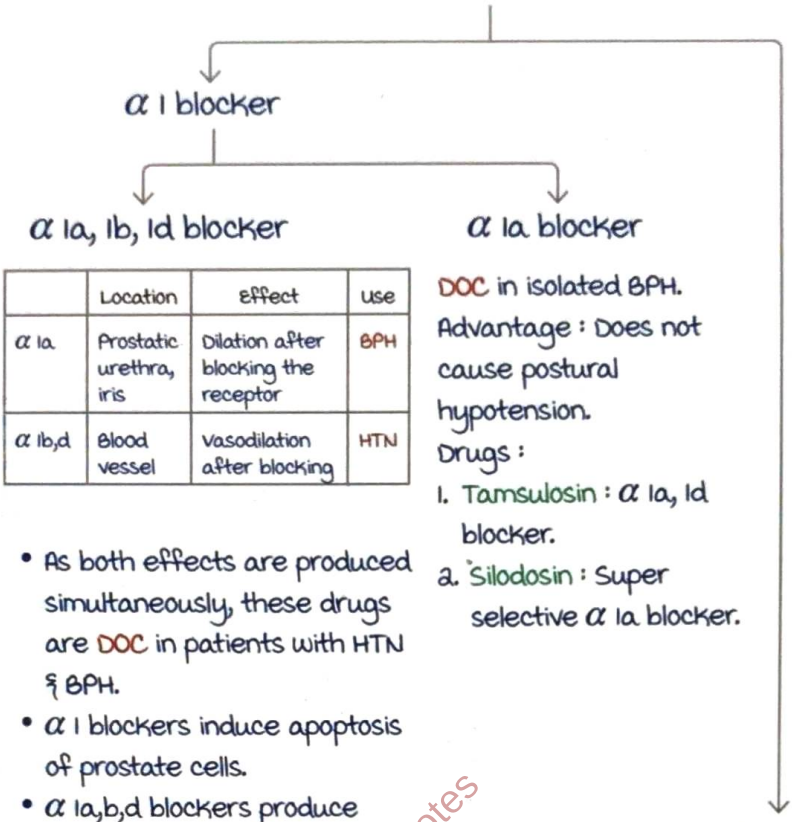
↓ followed by

β blocker

If β blocker is given first, β_a mediated vasodilation will be blocked worsening hypertensive crisis.

Selective α–receptor blockers

00:07:55



	Location	Effect	Use
α 1a	Prostatic urethra, iris	Dilation after blocking the receptor	BPH
α 1b,d	Blood vessel	Vasodilation after blocking	HTN

- As both effects are produced simultaneously, these drugs are DOC in patients with HTN & BPH.
- α 1 blockers induce apoptosis of prostate cells.
- α 1a,b,d blockers produce non selective vasodilation.
  Side effect : Postural hypotension or 1st dose effect.
  Dose to be taken at night time to prevent dizziness or LOC.
  Ask patient to stand up gradually from sitting or lying position.

DOC in isolated BPH.
Advantage : Does not cause postural hypotension.
Drugs :
1. Tamsulosin : α 1a, 1d blocker.
2. Silodosin : Super selective α 1a blocker.

1. Yohimbine : Found in food supplements for postural hypotension, peripheral neuropathy, erectile dysfunction.
2. Idazoxan.

Drugs :

1. Terazosin
2. Doxazosin
3. Prazosin

— DOC for HTN with BPH

4. Alfuzosin : BPH.
5. Bunazosin
6. Indoramin
7. Urapidil

— HTN

Prazosin : DOC in scorpion bite induced pulmonary edema and hypertension.

Other drugs used for symptomatic treatment of scorpion bite are :

In seizures – DOC : Diazepam.

In bradycardia – DOC : Atropine.

Common side effects of selective α 1a blockers :

Location	Side effect
Prostatic urethra	• Ejaculation failure • Retrograde ejaculation
Iris (α 1a increases Ca^{2+} and maintains tone of iris)	Floppy iris : Discontinue α 1a blocker before ocular surgery

The side effects are maximum in Silodosin.

β–blockers

00:22:55

Effects :

- Heart : Decreases contraction, heart rate & conduction.
- Kidney : Decreases renin → Decreases blood pressure.
- Skeletal muscle : Decreases contraction.
  Decreases glucose.
  Therefore, decreases exercise tolerance and is contraindicated in atheletes.
- Glucose : Long term use increases insulin resistance and causes hyperglycemia.
- Eye : Decreases aqueous production.
- Brain : Depression, insomnia, nightmares (crosses BBB).
- Bronchi : Precipitates bronchospasm hence contraindicated in bronchial asthma, COPD.
- Block symptoms of hypoglycemia except sweating. Hence, they are contraindicated in diabetes.

Uses of β-blockers :

- Hypertension : 2nd line drugs in hyperreninemic hypertension.
- DOC :
  1. Migraine prophylaxis.
  2. Essential tremor.

Active space

3. Stable angina for long term management.
   Contraindicated in variant angina as β blockers can cause vasospasm abruptly by blocking β2 mediated vasodilation.
4. Hypertrophic obstructive cardiomyopathy : They decrease the force of contraction.
5. Hyperthyroidism : Symptomatic relief.
6. Aortic dissection.
   β blockers are DOC if patients have any of these conditions along with hypertension.
7. Chronic congestive heart failure
8. History of myocardial infarction

   } decreases mortality

9. Glaucoma :
   Timolol – S/E : Nasolacrimal duct obstruction.
   Betaxolol (Cardioselective) : preferred in bronchial asthma/COPD.

Classification of β-blockers

00:33:53

Beta blockers : 1st gen (non selective)	Cardioselective	3rd generation
Propranolol Pindolol Penbutolol Timolol Oxprenolol Nadolol	Mr : Metoprolol B : Bisoprolol, Betaxolol (3rd gen) E : Esmolol A : Atenolol, Acebutolol N : Nebivolol (3rd gen) Cardiologist : Celiprolol	Alpha blockers : Labetalol, Carvedilol, Bevantolol, Bucindolol Beta 2 agonism : Bopindolol CCB : Carvedilol NO release : Nipradilol, Nebivolol K channel opener : Tilisolol

Betaxolol, Nebivolol are 3rd generation drugs.

Cardioselective drugs : β1 blockade >>> β2 blockade.

Most cardioselective : Nebivolol.

2nd most cardioselective : Bisoprolol.

3rd gen drugs : Can be cardioselective or non selective.
They also are vasodilators (diverse MOA).

β blockers with anti-oxidant effect : Nebivolol, Carvedilol.

Beta blocker with partial agonism/intrinsic sympathomimetic effect	Beta blocker with Na channel block/LA activity/membrane stabilizing effect	Water soluble beta blockers
C : Celiprolol L : Labetalol A : Acebutolol P : Penbutolol, Pindolol (max) C/I in MI & Migraine	Can : Carvedilol (max) Blow : Betaxolol (min) L : Labetalol A : Acebutolol M : Metoprolol P : Propranolol (max), Pindolol C/I in glaucoma except Betaxolol.	B : Betaxolol, Bisoprolol A : Atenolol N : Nebivolol A : Acebutolol N : Nadolol A S : Sotalol Chips : Celiprolol

Carvedilol : α 1 blocking action.
Calcium channel blocker.
Anti-inflammatory.
Anti-oxidant.

Water soluble β blockers :
They do not cross blood brain barrier : No central side effects like insomnia, depression, nightmares.
Excreted by Kidney : Contraindicated in renal failure.

Pharmacokinetics 00:41:36

Half life ($t_{1/2}$) :
- Maximum $t_{1/2}$: Nadolol.
- Minimum $t_{1/2}$: Esmolol.

Plasma protein binding (PPB) :
- Maximum : Carvedilol.
- Minimum : Celiprolol.

Bioavailabilty :
- Maximum (100%) : Penbutolol, Pindolol.
- Minimum (30%) : Carvedilol, Propanolol.

Metabolic effects of β-blockers

00:43:06

	Insulin resistance	Lipid
1st Generation : Negative	Increases (hyperglycemia)	Decreases HDL, Increases LDL
2nd Generation : Neutral	-	-
3rd Generation : Positive	Decreases (hypoglycemia)	Increases HDL, Decreases LDL

DRUGS ACTING ON PUPIL AND BLADDER

Drugs acting on pupil 00:00:40

Structure of pupil :

Types of muscles	Circular muscles	Radial muscles
Receptors	M_3 receptors (Gq subtype)	Alpha 1a receptors (Gq subtype)
Contraction	Miosis	Mydriasis

Gq subtype increases calcium ions.

Mydriasis :

	Active mydriasis	Passive mydriasis
	Stimulation of alpha 1a receptors	M_3 receptors blockade
Example	Phenylephrine, Ephedrine	Tropicamide, Atropine, Cyclopentolate, Homatropine
Uses	Ocular fundal examination, decreasing synechiae formation in uveitis/corneal ulcer	Ocular fundal examination, decreasing synechiae formation in uveitis/corneal ulcer

M_3 receptor blockade also causes cycloplegia. Therefore, anticholinergics are useful in refractive error test and decreasing pain in iridocyclitis.

Phenylephrine is a mydriatic but not a cycloplegic.
Atropine is a mydriatic and also a cycloplegic.

Miosis :

	Active miosis	Passive miosis
Mechanism	Stimulation of M_3 receptors	Blockade of alpha 1a receptors
Example	Pilocarpine, Physostigmine, Echothiopate, Fluostigmine, Carbachol.	Prazosin, Phenoxybenzamine

Uses	Useful in closed angle glaucoma (preferred drug : Pilocarpine).	No clinical use

Drugs acting on bladder

00:10:40

Receptors on detrusor muscle	M3 receptors (Gq subtype)	Beta 3 receptors (Gs subtype)
Stimulation	Increase calcium	Increase cAMP
Action on detrusor	Contraction	Relaxation

- cAMP contracts cardiac & skeletal muscle, relaxes smooth muscle.
- Alpha 1 receptors (Gq subtype) are present on sphincter. Stimulation causes contraction of sphincter.
- On voiding, parasympathetic system is stimulated. While not voiding, sympathetic overfiring occurs leading to relaxation of detrusor & sphincter contraction causing retention of urine.

Drugs acting on parasympathetic nervous system :

	Cholinergics	Anticholinergics
Parasympathetic nervous system	Stimulators	Blockers
Action on detrusor muscle	Increases contraction	Decreases contraction
Indications	Bladder atony (overflow incontinence)	Overactive bladder : Detrusor instability (urge incontinence).
Example	Bethanechol Neostigmine	Non-selective M_3 blockers : Flavoxate Fesoterodine Oxybutynin Trospium Selective M_3 blockers : Darifenacin Solifenacin Tolterodine

Drugs acting on sympathetic nervous system :

	Beta 3 agonists	Alpha 1 stimulators
Action	Decreases detrusor contraction	Increases sphincter contraction
Indication	Urge incontinence	Stress incontinence
Example	Mirabegron Vibegron	Duloxetine (SNRI) : Increases norepinephrine which stimulates alpha 1 receptors

ANTIARRHYTHMIC : PART - 1

Normal action potential generation in heart 00:00:58

Action potential that depolarizes myocardial cells is generated in the SA node.

Resting membrane potential (RMP) :

SA node & AV node : −60 mv.

Myocardial cell : −90 mv.

Action potential in a myocardial cell :

Sodium channels open

↓

Shift of positive ions into cell

↓

Decrease in intracellular negativity

↓

K^+ channels open (Early rectifiers)

↓

Loss of K^+ ions causes transient increase in negativity

↓

Calcium channels open causing inflow of calcium

↓

K^+ outflow & Ca^{a+} inflow maintains action potential in plateau phase

↓

Calcium channels begin to close

↓

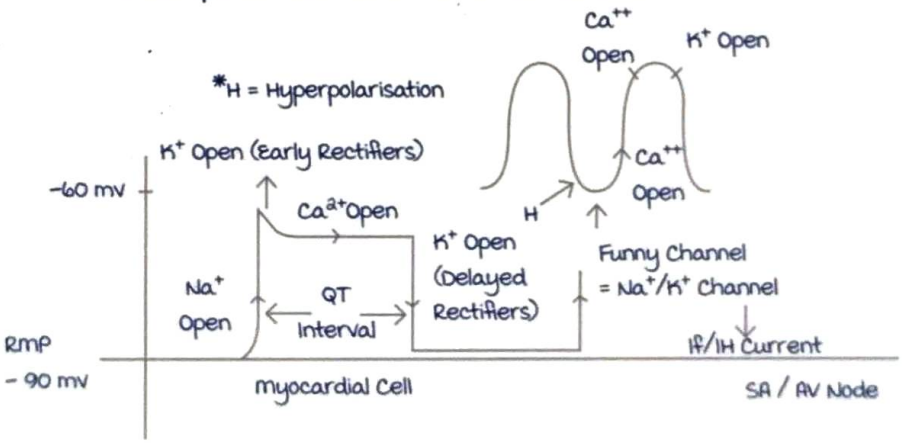
more K^+ channels open (Delayed rectifiers)

↓

Loss of K^+ ions increases intracellular negativity

↓

Action potential reaches towards RMP.



In myocardial cells, there is a gap between two depolarizations.

Action potential in SA node differs from that of myocardial cells in two ways :

1. Depolarization occurs due to opening of calcium channels.
2. Depolarization is initiated immediately after hyperpolarization due to opening of Na^+/K^+ channels (funny channels).

- In a myocardial cell, duration between depolarization & repolarization coincides with the QT interval of ECG.
- Ivabradine is a funny Na^+/K^+ channel blocker used in angina, congestive heart failure. It decreases only heart rate by blocking SA node.

Classification of antiarrhythmic drugs 00:11:08

Vaughan-Williams classification :

5 Classes

Class 1 : Sodium channel blockers.

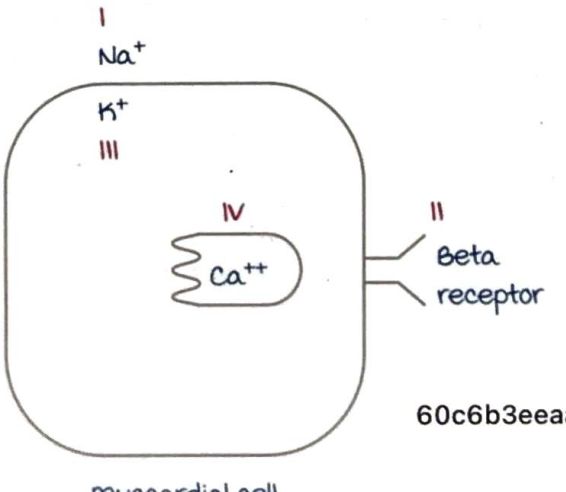
Class 2 : Beta blockers.

Class 3 : Potassium channel blockers.

Class 4 : Calcium channel blockers.

Class 5 : Miscellaneous. Example : Adenosine, Magnesium sulfate, Atropine, Digoxin.

Arrhythmia can arise from both atrium and ventricle.



Myocardial cell

Atrial arrhythmias

00:16:48

Supraventricular tachycardia (SVT) and Paroxysmal supraventricular tachycardia (PSVT) :

- Main aim of treatment is to block AV node.
- Drugs that block AV node are Adenosine, Beta blockers, Calcium channel blockers, and Digoxin (Mnemonic : ABCD)
- In an acute attack of SVT and PSVT, Adenosine is the drug of choice ($T_{1/2}$ 1 to 5 seconds). If Adenosine is contraindicated, IV Esmolol or IV Verapamil can be used.
- For long term management, oral calcium channel blockers or Beta blockers or Digoxin is used.

Atrial fibrillation & Atrial flutter :

- Adenosine cannot be used.
- Treatment of choice in acute attack is cardioversion.
- Long term management is by rate and rhythm control.
- Main aim in rate control is to maintain ventricular rate < 100 beats/min. AV nodal blocking agents such as Beta blockers (drug of choice), Calcium channel blockers and Digoxin can be used.
- Rhythm control is done to restablish SA node as the sole pacemaker. This can be achieved by blocking action potential in myocardial cells using potassium channel blockers (preferred DOC : Amiodarone) and sodium channel blockers.

Ventricular arrhythmias :

Ventricular tachycardia and Ventricular fibrillation

- Potassium channel blockers and sodium channel blockers can be used to suppress myocardium.
- Drug of choice is potassium channel blockers (Amiodarone).

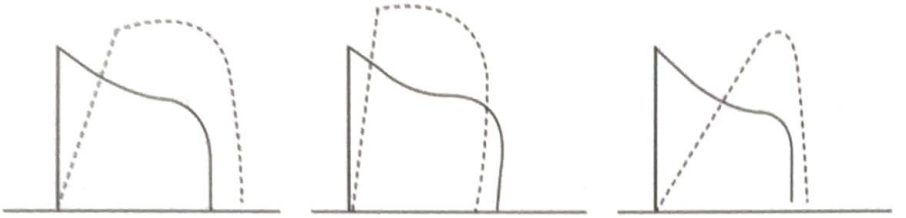
Class 1 antiarrhythmics

00:31:20

Sodium channel blockers.

Can be broadly subclassified into :

- Class Ia : Blocks Na^+ channels for 1 – 10 sec in open state
  Also block K^+ channels for long time.
- Class Ib : Blocks Na^+ channels for < 1 sec in closed state.
  Open K^+ channels.
- Class Ic : Blocks Na^+ channels for >10 sec in open state.
  Also block K^+ channels for short time.



Ia
QT prolongation/ Torsades

Ib
QT shortening

Ic
Normal QT

—— Normal action potential in myocardial cell
---- Effect of class I antiarrhythmics on action potential

Maximum delay in depolarization is caused by
Class Ic > Class Ia > Class Ib drugs.
Maximum delay in repolarization is caused by Class Ia.
Slight delay in repolarization is caused by Class Ic.
Early repolarization is caused by Class Ib.

QT prolongation (risk of Torsades) is seen with Class Ia.
QT shortening is seen with Class Ib.
Class Ic drugs have no clinically significant effect on QT interval.

Class Ia and Class Ic can significantly increase refractoriness in normal cells of myocardium, accessory pathways and AV node.
60c6b3eeaa8ded0e4e7e5ea7
Increased refractoriness in AV node can cause AV nodal block and PR prolongation.
Quinidine and Disopyramide are Class Ia drugs that have anticholinergic side effects (Disopyramide > Quinidine) & can increase AV conduction in some patients.

Class Ib has normal PR interval as it does not affect AV node.

Uses of Class 1 drugs

00:43:00

Class Ia & Class Ic :

Ventricular tachycardia, ventricular fibrillation, rhythm control in atrial flutter/atrial fibrillation.

Class Ic is most arrhythmogenic. Hence, Class Ic drugs are used only in resistant cases or life threatening cases.

Class Ia drugs :

- Quinidine : Oral drug used for long term management.
  Side effects : QT prolongation.
  Diarrhoea (most common)
  Hypotension (alpha blocker).
  Cinchonism (tinnitus, vertigo).
  Drug interaction : Digoxin toxicity (Blocks P glycoprotein).
- Procainamide : Preferred route is IV.
  Used in acute attacks.
  Side effects :
  Hypotension by ganglion blockade.
  Drug induced SLE.
  QT prolongation.
  Agranulocytosis (monitor CBC and ask patients to report symptoms like sore throat, fever).
- Disopyramide : Oral drug used for long term management.
  Anticholinergic side effects :
  Dry mouth, urine retention, constipation.
  Contraindications : Glaucoma, Benign prostatic hyperplasia, congestive heart failure.

Class Ic drugs :

Flecainide : Oral drug. Can be used for long term management.

Encainide, Propafenone (derived from beta blocker Propranolol), Moricizine are other Class Ic drugs.

They are most arrhythmogenic.

Class Ia and Class Ic drugs are used to treat Wolff-Parkinson-White (WPW) syndrome, arrhythmia caused

by an accessory pathway. WPW syndrome is an atrioventricular re-entry tachycardia and can cause atrial fibrillation in some patients.

Drug of choice for atrial fibrillation with WPW syndrome is IV Procainamide.
For long term management of WPW syndrome, drug of choice is oral Flecainide.
Treatment of choice for WPW syndrome is radiofrequency ablation.

Class 1b drugs 00:56:13

- Blocks Na^+ channels in closed state (depolarised cells).
- Can be used in myocardial infarction and Digoxin toxicity induced Ventricular tachycardia/ventricular fibrillation as ca^{a+} ions are depolarising the cells.
- Not effective in atrial arrhythmias as Na^+ channels are in closed state for a short time in the atria as compared to that in the ventricles.

Lidocaine :

- Not useful in oral route due to high first pass metabolism. IV route is used.
- Loading dose should be given due to high volume of distribution.
- Drug of choice for myocardial infarction and digoxin toxicity induced ventricular tachycardia/ventricular fibrillation.

Side effetcs :
Lidocaine can cause malignant hyperthermia. Drug of choice is Dantrolene.
It can cause neurological side effects such as nystagmus
(earliest sign of toxicity), paresthesia, delirium, seizures

(Benzodiazepines like Diazepam is used to treat seizures & not phenytoin because it is also a Na^+ channel blocker).

mexiletine : Oral derivative of Lidocaine. Can be used in ventricular tachycardia, diabetic neuropathy (blocks propogation of action potential) and myotonia.

Phenytoin : Can be used in Digoxin induced ventricular tachycardia.

ANTIARRHYTHMICS : PART - 2

Class 2 drugs

00:00:25

Beta blockers :

MOA : Block AV node.

Oral drugs : For long term management. Example : Metoprolol.

IV drugs : Acute arrhythmia. Example : Esmolol.

Drug of choice for :

- Rate control in atrial fibrillation/flutter.
- Idiopathic ventricular tachycardia.
- Ventricular premature beats.
- Long term management of congenital long QT syndrome.
- Catecholamine induced arrhythmia.
  Example : Pheochromocytoma, exercise/emotion induced arrhythmia, Cyclopropane/Halothane induced arrhythmia.

Esmolol can be used in the acute attack of supraventricular tachycardia (SVT) and paroxysmal supraventricular tachycardia (PSVT).

Class 3 drugs :

- K^+ channel blockers.
- Causes delay in repolarization → QT prolongation and risk of Torsades.

QT prolongation causing antiarrhythmics : class Ia & III

- Risk of Torsades – maximum with Ibutilide
  minimum in Amiodarone.
- Used in the treatment of ventricular tachycardia, ventricular fibrillation and rhythm control in atrial fibrillation/flutter.

Drugs : Mnemonic – DIVAS

Dofetilide.

Ibutilide.

Vernakalant.

Amiodarone.

Sotalol.

- Ibutilide is the shortest acting K^+ channel blocker.
  IV Ibutilide can be used in acute attack of atrial fibrillation/flutter, when there is no response to cardioversion.
- Vernakalant acts only on atrium. Used only in atrial fibrillation. No QT prolongation.
- Sotalol belongs to both class 2 and class 3.

Amiodarone 00:09:35

- Longest acting antiarrhythmic : 53 days.
- Loading dose is required.
- Inhibitor of P glycoprotein → Can cause digoxin toxicity.
- Mechanism of action : Blocker of potassium, sodium, calcium channels and beta receptors.
- Least risk of Torsades due to calcium channel blockade.
- most wide spectrum antiarrhythmic.
- Drug of choice for :
  Ventricular tachycardia/ventricular fibrillation (not due to myocardial infarction or digoxin toxicity).
  Rhythm control in atrial fibrillation/flutter.

Side effects :

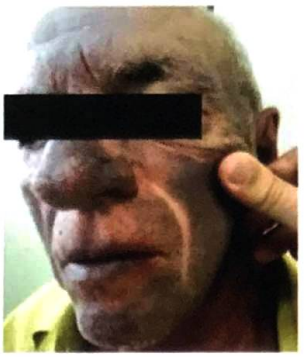
Mnemonic : Potassium Channel Blockers Make Liver And Skin Toxic.

Pulmonary fibrosis due to damage to type 2 pneumocytes.

Drug of choice for treatment is Steroids.

Corneal micro-deposits : "Whorl like"

Blue gray skin in sun exposed area : Ceruloderma.



Myocarditis.
Liver granulomas.
Alpha 1 blockade causes hypotension.
Photosensitivity in sun exposed area : Brown color pigmentation (more common than ceruloderma).
Patient is advised to apply sunscreen and cover up.
Hypo/hyperthyroidism. Hypothyroidism is more common.

"Whorl like" corneal deposits are seen with Amiodarone (more common), Phenothiazines - Chlorpromazine, Chloroquine, Indomethacin (least common).

Dronedarone - derivative of Amiodarone obtained by removing iodine from amiodarone. It is less toxic & less efficacious.

Class 4 & Class 5 drugs

00:21:20

Class 4 drugs
Non-dihydropyridines : Verapamil (preferred), Diltiazem.
Block AV node.
Used in SVT and PSVT.

Class 5 drugs/Miscellaneous drugs :
Adenosine :

- Mechanism of action :
  Stimulates Adenosine-1 receptor (Gi subtype) in AV node causing AV nodal block.

Stimulates Adenosine-2 receptor (2 types):
Gq subtype – in bronchi causing bronchoconstriction (by increasing ca^{2+})
Gs subtype – in blood vessel causing vasodilatation.

- Given by rapid IV push → Adenosine is rapidly taken up by cellular adenosine uptake proteins.
- Has a half-life of 1 to 5 seconds : Shortest acting anti-arrhythmic.

Uses :

1. IV Adenosine is the drug of choice for acute attack of SVT and PSVT. Dose : 6mg IV is given initially, if no response, 12 mg IV is given.
2. Used to maintain controlled hypotension during surgery.
3. Used in the diagnosis of coronary artery disease.

Side effects :
Hypotension (Adenosine is a vasodilator).
Flushing, dyspnea : most common.
Increases risk of atrial fibrillation due to opening of K^+ channels.

Contraindications :
Bronchial asthma/COPD (In such patients with acute attack of SVT/ PSVT : Drug of choice is IV Verapamil).
Transplanted heart because of denervation hypersensitivity.

Magnesium sulphate 00:32:10

mechanism of action : Blocks calcium channels.
Used for treatment of long QT syndrome.
Acute attack (Torsades) – congenital or acquired :
Drug of choice is $MgSO_4$ (causes early repolarization & QT shortening).
Isoprenaline is an alternative (causes significant tachycardia).

Long term management :

Aim is to prevent the attack of Torsades.

Congenital : Drug of choice is beta blockers as Torsades attack is preceded by adrenergic crisis. Treatment of choice is pacing.

Acquired : Avoid drugs causing QT prolongation.

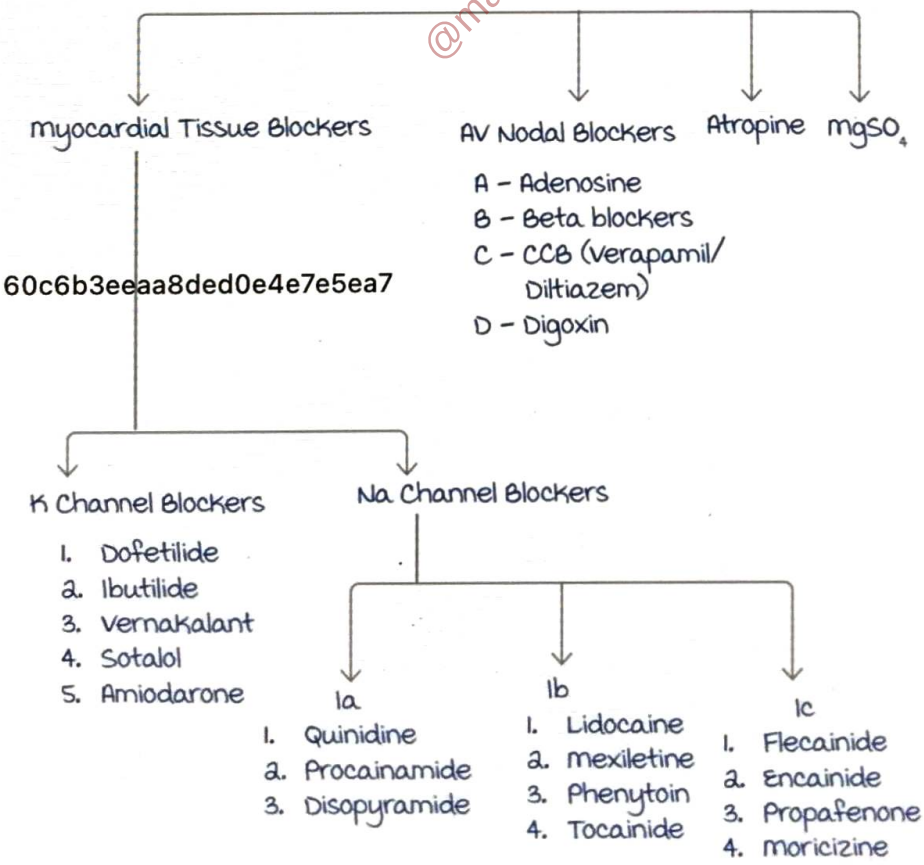
Atropine 00:32:30

- Increases heart rate and AV nodal conduction.
- Drug of choice in bradycardia. Dose : 0.5-1mg.
- Used in conduction block (drug of choice) and inferior wall MI (for bradycardia caused by vagal irritation).

Digoxin :

- Blocks AV node.
- Used in long term management of SVT and PSVT in patients with chronic congestive heart failure.

Antiarrhythmic drugs summary



DRUGS USED IN CHF

Classification of heart failure 00:00:59

Broadly sub-classified into acute and chronic CHF.

Acute CHF :
m/c cause is myocardial infarction.
There is an acute decrease in contraction of left ventricle due to an acute insult.
Leads to stasis of blood in the left ventricle and atrium which gives a back-pressure to the lungs (engorgement of capillaries).
Patient ends up in pulmonary edema.

Aim of pharmacotherapy :
First : Treatment of pulmonary edema : DOC : Furosemide,
if no response : Add IV Nitroglycerine (NTG :
Venodilator, decreases preload)
if no response : Add BNP analogue (Nesiritide).

Second : To increase contraction of heart :
DOC : Dobutamine. It increases contraction without altering heart rate or conduction
Others : Dopamine.
Even in acute CHF with oliguria : DOC is Dobutamine.
If no response : PDE-3 inhibitors like Milrinone.

Chronic CHF 00:07:22

There is gradual decrease in cardiac output.
There will be decreased oxygen supply to different organs.
This will lead to activation of compensatory mechanisms.

If compensatory mechanisms fail to maintain cardiac output :
Decompensated CHF. Clinical presentation is similar to acute CHF.

So decompensated CHF was merged with acute CHF : Acute heart failure syndrome.
If compensatory mechanisms maintains cardiac output : Compensated Chronic CHF or Chronic CHF.

There is compensatory increase in release of catecholamines.
Effect on heart : Increase contraction and heart rate.
Effect on blood vessels : Vasoconstriction.

RAAS activation : Vasoconstriction, sodium and water retention.
The aim is to achieve increased contraction and optimum cardiac output.
Because of increased load on heart : Myocardium undergoes hypertrophy (cardiac remodelling).
There will be an increase in metabolic and oxygen demand.
Reason for mortality : Decrease in myocardial oxygen supply and increase in oxygen demand.

Aim of pharmacotherapy : Delay the mortality.

Drugs which decrease mortality :
Beta blockers (negative inotropes) : They block contraction of the heart.
Funny channel blcoker (Ivabradine) : They decrease heart rate without altering contraction or conduction.
Vasodilators : Isosorbide dinitrate (venodilator) + hydralazine (arterial dilator)
Vericiguat : Guanylase cyclase stimulator (venodilator)
RAAS activity blockers : ACEIs, ARBs, spironolactone.

If patient is symptomatic (congestive symptoms like edema, dyspnoea) : Digoxin (does not decrease mortality).

Drugs used in acute CHF 00:19:54

Brain Natriuretic Peptide analogue :

mechanism of action :

Increase in blood volume : Increases stretch of renal blood vessels (release urodilatin), atrium (release ANP), ventricles (release BNP).

Effects of these peptides :

Kidney : Sodium loss and water loss. Decrease blood volume.

Blood vessels : Vasodilatation.

Overall there will be reduced risk of developing pulmonary oedema.

Only FDA approved BNP analogue is Nesiritide.

ANP analogue : Carperitide.

Urodilatin analogue : Ularitide.

Nesiritide :

tide (peptides)/ase (enzymes)/mab (proteins) : Never given orally.

Route : IV.

It is reserved for the treatment of drug resistant pulmonary oedema in acute CHF.

metabolized by Neutral endopeptidase.

Sacubitril : Neutral endopeptidase inhibitor (increase BNP).

Used in chronic CHF along with Valsartan.

Side effects of Sacubitril : Angioedema (contraindicated with ACEIs or within 36 hours of use of ACEIs).

Phosphodiesterase 3 inhibitors 00:26:50

Function of PD-3 : metabolises cAMP in heart and blood vessels.

mechanism of action: Increases cAMP in heart (increased contraction) and blood vessels (vasodilation).

This class of drugs are called as inodilators.

Uses : Resistant acute CHF, Acute CHF on beta blockers.

Drugs :

Amrinone (Inamrinone) : Side effects - Significant thrombocytopenia.

Milrinone is more preferred.

Levosimendan :

Mechanism of action : PD-3 blocker, sensitizes myocardium to calcium ions (more inotropic effect), potassium channel opener (vasodilatation).

Drugs used in chronic CHF 00:30:48

Drugs decreasing mortality :
Sacubitril, Spironolactone.
Hydralazine + IDN.
Ivabradine.
Vericiguat.
ACEIs/ARBs.
Beta blockers.

How to use in a clinical setting :
Note : Renin levels are very high in chronic CHF.
Start ACEIs/ARBs at low doses (to prevent postural hypotension) and then gradually increase [illegible] the dose till maximum recommended dose.
If maximum recommended dose is well tolerated, then switch to Sacubitril + valsartan.

When 50% of the maximal dose of ACEIs/ARBs are reached :
Beta blockers like metoprolol, Carvedilol, Bisoprolol, Nebivolol are to be started.
Maximum decrease in mortality is by beta blockers.
Even beta blockers are started at low doses. Dose is increased gradually (2 weeks once).

If no response : Spironolactone.
If no response : Ivabradine.
If no response : IDN + hydralazine or vericiguat.

In case of symptomatic patients : Digoxin.

Digoxin

00:40:12

Source : Derived from a plant known as Digitalis Lanata (white foxglove plant).

Pharmacokinetics :

Good oral absorption (oral route).

High volume of distribution (loading dose).

Half-life : 36-48 hours.

Time taken for digitalization : 7-10 days (4-5 half lives).

It is a substrate for P-glycoprotein pumps.

Elimination : Renal.

Mechanism of action :

1. Cellular mechanism (myocardial cell) :
   Blocks Na^+-K^+-ATPase pump.
   Function of Na^+-K^+-ATPase pump : Reverse depolarization.
   They throw Na^+ out of the cell and take K^+ in.
   Digoxin blocks this pump leading to accumulation of K^+ outside the cell (hyperkalemia) and Na^+ inside the cell.

2. K^+ limits binding of digoxin to the Na^+- K^+- ATPase pumps.
   If the levels of K^+ are depleted due to diuretics : Extra binding of digoxin to these pumps results in digoxin toxicity.
   Hypokalemia causes digoxin toxicity and digoxin toxicity causes hyperkalemia.
3. Increased Na^+ inside the cell : Dysfunctioning of Na^+/Ca^{2+} exchanger.
   The function of this pump is to throw ca^{2+} out and take Na^+ in whenever the cell needs Na^+.
   As there is increased in Na^+ inside the cell, no calcium

moves out. Intrcellular ca^{a+} increases which increases contraction of myocardium (inotropic effect).

4. Gradual increase in intracellular calcium : Causes delayed after depolarization.
   If further increase in intracellular calcium : It casuses extra abnormal contractions known as Extrasystoles.
   If extrasystoles are repetitive in nature :
   Ventricular bigeminy >> trigeminy (benign arrhythmia).
   If further increase in intracellular calcium : Ventricular tachycardia (self-sustained, bidirectional).
   If further increase in intracellular calcium : Ventricular fibrillation.

Treatment of benign arrhythmia : Potassium.
K^+ binds to Na^+/K^+ ATPase pump and prevents binding of Digoxin to it. Prevents worsening of benign arrhythmia
Potassium is contraindicated in VT and VF.
DOC for VT and VF is Lidocaine.
Alternatives : Amiodarone, Digibind (antidote for Digoxin).

2. Organ mechanism 00:58:27

Effect on heart : Dose dependant.
At normal dose : Parasympathomimetic effect -
Blocks both SA node and AV node.

Combining this with the cellular effects :
There is increased level of Ca^{2+} in the atrial cells and the SA node is blocked which leads to Atrial tachycardia. But, this is resisted by AV nodal block.

most characteristic digoxin induced arrhythmia : Atrial tachycardia with AV nodal block.
Use : To convert atrial flutter to fibrillation (easier to control).

At high dose : Sympathomimetic effect - Tachyarrhythmia.

Side effects :
m/c common as well as earliest is nausea and vomiting (it can be sign of impending toxicity).
Xanthopsia (yellow vision).
Gynaecomastia.
Hyperkalemia.

Contraindications :

- WPW syndrome (because it blocks AV nodal block but not accessory pathway).
- HOCM (because it increases force of contraction and causes LVOT obstruction).
- Conditions which increase the risk of digoxin toxicity (increase intra cellular calcium) : Hypercalcemia, hypomagnesemia, MI, hypokalemia, renal failure.

Digoxin is a drug of low Therapeutic Index.
Therapeutic drug monitoring is to be done.
Safe range : 0.5 to 2.0 ng/ml.
Therapeutic range is 0.5 to 0.9 ng/ml.
Toxicity is seen with range more than 2.0 ng/ml.

Increased mortality from atrial fibrillation: If the range is more than 1.2 ng/ml.

Drug interactions :
increased risk of toxicity of digoxin
Diuretics : Hypokalemia
P-glycoprotien pump inhibitors (Clarithromycin, Amiodarone, Verapamil, Quinidine)

CHF drugs summary

Acute CHF

Increase cardiac contraction
1. Dobutamine
2. Dopamine
3. PDE-3 blockers (milrinone)

Treat pulmonary edema
Furosemide
IV NTG
BNP analogue (Nesiritide)

Chronic CHF

1. Drugs decreasing mortality
A - ACEI/ARB → Sacubitril + Valsartan
+
B - Beta blockers

Spironolactone
Ivabradine
IDN + Hydralazine
Vericiguat

2. Symptomatic treatment of congestion : Digoxin

VASODILATORS

Classification 00:00:51

3 classes :

- Arterial dilators : Decrease afterload.
- Venodilators : Decrease preload.
- Mixed dilators : Decrease both afterload and preload.

Postural hypotension as a side effect will be seen with veno and mixed dilators.

Arterial dilators 00:04:28

Calcium channel blockers/CCBs : Calcium channel blockade will produce vasodilatation.

They are broadly subclassified into :

- Dihydropyridines (DHPs) : Potent vasodilators. Produces significant reflex tachycardia.
  Drugs : Amlodipine (longest acting DHP, least reflex tachycardia, maximum oral bioavailability),
  Nifedipine, Isradipine, Nimodipine,
  Clevidipine (IV shortest acting : metabolized by plasma esterase),
  Nicardipine (IV : most potent parenteral DHP).

  60c6b3eeaa8ded0e4e7e5ea7
- Non-DHPs :
  Less potent vasodilators.
  They also delay the recovery of calcium channels.
  Hence, they block SA (reduce HR) and AV node. So, the net effect is normal/near normal HR.
  They are the only class of CCBs used in arrhythmia.
  Drugs : Verapamil more potent than Diltiazem. They can be given either by oral (long term management) or parenteral route (emergency).

Uses of CCBs

00:12:24

- Treatment of hypertension :
  One of the first line drugs in mild to moderate HTN.
  Severe HTN :
  HTN urgency : Oral Nifedipine.
  HTN emergency : IV Nicardipine (DOC) > Clevidipine.
- DOC in Raynaud's disease.
- Used in stable angina (non DHPs as monotherapy, DHPs must always be used with beta blockers because of significant reflex tachycardia) and variant angina (DHP/non DHPs).
- They are used in cerebral vasospasm secondary to subarachnoid hemorrhage (Nimodipine is preferred because of high lipid solubility and affinity to cerebral blood vessels).
- Non DHPs like Verapamil > Diltiazem (AV node blockade) In supraventricular tachycardia and paroxysmal supraventricular tachycardia.

Side effects

- m/c : Headache (meningeal artery dilatation).
- Ankle edema due to precapillary dilatation.
  Prevented by drugs causing post capillary dilatation (ACEIs/ARBs).
- Constipation : By Verapamil (high water intake, high fiber diet can prevent it).
- Conduction block : AV nodal block (Verapamil >Diltiazem).

Contraindication :
Verapamil and Diltiazem are contraindicated with beta blockers because of conduction block.

Drug interaction : CCBs are blockers of p glycoprotein pumps. Can cause digoxin toxicity. It can be prevented by reducing the dose of digoxin.

Hydralazine

00:24:26

mechanism of action :

- Blocks IP_3 induced calcium release in the smooth muscles of blood vessels.
- Opens K^+ channels.
- Releases NO from endothelium of blood vessels (Also released by Nitrates and Sodium nitroprusside).

Use : Given IV in HTN emergency in pregnancy .
(Present DOC : Labetalol).
Side effects : SLE (metabolized by acetylation), sweet syndrome (Neutrophilic dermatoses).

Minoxidil :
mechanism of action : K^+ channel opener (very potent vasodilator).
Uses : Resistant HTN (rarely), androgenic alopecia (topical).
DOC for androgenic alopecia is Finasteride (S/E : Reversible impotence).
Side effects : Hirsutism, sodium and water retention (weight gain and edema).

Diazoxide

00:32:02

mechanism of action : K^+ channel opener (very potent vasodilator).
Use : Intravenously in HTN emergency (not used nowadays because of side effect like severe hypotension).
DOC for treatment of insulinoma (Opens potassium channels in the pancreatic beta cells causing hyperpolarization and decreasing insulin release).

Fenoldopam :
mechanism of action : D1 and $\alpha 2$ agonist.
Causes significant fall in blood pressure.
Use : Given IV in HTN emergency.

Venodilators

00:35:14

Nitroglycerine :

Mechanism of action :

NTG

↓ aldehyde dehydrogenase.

Nitric Oxide (NO)

↓

Stimulates guanylate cyclase

↓

Increasing cGMP

↓

Smooth muscle relaxation.

Net effect is vasodilatation and GIT relaxation.

Uses : Angina, Esophageal spasm.

Long term/continuous use:

Downregulates the production of aldehyde dehydrogenase.

Nitroglycerine cannot be converted to NO.

This is called as Nitrate tolerance.

Prevented by 8 hours of Nitrate free period (night time).

Drug interactions :

cGMP is metabolized by PDE 5.

PDE 5 is blocked by drugs like Sildenafil and Tadalafil (long acting).

Uses of Sildenafil and Tadalafil :

Pulmonary HTN and erectile dysfunction.

NTG and sildenafil/Tadalafil interaction leads to severe hypotension and shock.

Riociguat and Vericiguat are stimulators of Guanylate cyclase.

Riociguat used in pulmonary HTN.

Vericiguat used in chronic CCF.

Active space

Uses of nitroglycerine

00:44:26

DOC for acute attack of any type of angina (sublingual route).

Long-acting formulations as long term prophylaxis of angina:

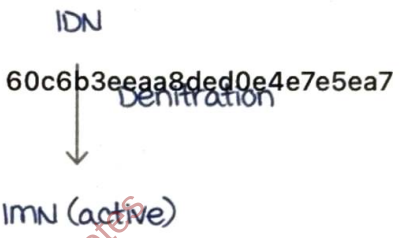
Oral sustained release tablets are used because of high first pass metabolism.

Transdermal patch, gel.

IV route : HTN emergency, pulmonary edema (decreases preload).

Isosorbide Dinitrate (IDN) :

Pharmacokinetics :



Uses : By oral route :

Long term prophylaxis of angina.

Chronic CCF (combined with hydralazine : Decrease mortality)

Sub lingually : Acute attack of angina.

Isosorbide mononitrate (IMN) :

Pharmacokinetics : It does not undergo first pass metabolism.

Use : Long term prophylaxis of angina (oral route).

Side effects : Postural hypotension, headache (improves with tolerance development).

Contraindications : PDE-5 inhibitors (Sildenafil and Tadalafil).

Mixed dilators

00:52:54

Sodium nitroprusside :

Pharmacokinetics :

It is activated to NO in the endothelium (vasodilatation).

metabolized into cyanide (primary metabolite).

Cyanide is further metabolized by Rhodonase (liver) into thiocyanate.

Thiocyanate : Sodium iodide symporter inhibitor, earlier used for the treatment of hyperthyroidism.
Discontinued because of hypothyroidism, neuropsychiatric side effects & cyanide toxicity.

Uses : In HTN emergency (2nd line), earlier it was used as DOC in malignant HTN. Malignant HTN has now been merged with HTN emergency.
Always used with beta blockers in aortic dissection to prevent reflex tachycardia.

RAAS inhibitors :
Pharmacokinetics :
Liver is the source of angiotensinogen.
Renin (in kidney) is required for conversion of angiotensinogen to Angiotensin (AT)-I.
ACE (in lungs) converts AT-I into AT-II. ACE is similar to Kininase.
Aminopeptidase converts AT-II to AT-III and AT-III to AT-IV.
AT-IV acts on CNS and increases cognition.
AT-IV analogues might be the future of treatment of Alzheimer's disease.

Both AT-II and AT-III have similar effects like,

- Binds to AT-I receptor in blood vessels : Vasoconstriction.
- In the adrenals : Increases aldosterone thus facilitating sodium and water retention and potassium loss.
- In the glomerulus : AT-II acts both on afferent and efferent arterioles. Causes vasoconstriction.
  Prostaglandins acts on afferent arteriole causing Vasodilatation.
  Net effect in afferent arteriole is Vasodilatation.
  This increases the plasma accumulation in glomerular capillaries : GFR generation.

Direct renin inhibitors block renin, blocking conversion of angiotensinogen to AT-I.
ACEIs block ACE, inhibiting conversion of AT-I into AT-II.

ACEIs increase renin by competitive inhibition.

Kininase metabolizes substance P, bradykinin, prostaglandins
ACEIs block kininase and stimulates medullary cough centre leading to dry cough, angioedema.

ARBs : Blocks AT I receptor leading to vasodilatation (decreases BP, postural hypotension).
One of the first line drugs for treatment of hyper reninemic HTN.
Hyperkalemia and postural hypotension are the common side effect of all RAAS inhibitors.

RAAS inhibitors effect on kidney :
~~Normal GFR with decreased~~ filtration fraction (loss of AT 2 effect on arterioles causing vasodilatation).
Decreases proteinuria. (DM, CKD, nephrotic syndrome).
DOC for treatment of HTN along with DM,CKD, nephrotic syndrome & scleroderma : RAAS inhibitors.

ACEIs 01:14:31

Oral ACEIs:
Captopril (Shortest acting).
Lisinopril.
Fosinopril.
Enalapril.
Ramipril (Longest acting).
Enalaprilat : Only IV ACEI.
All ACEIs are prodrugs except Captopril and Lisinopril.
Uses :

- First line in mild to moderate HTN (hyperreninemic)
  Oral ACEIs in HTN urgency.
  IV ACEIs in HTN emergency.
  DOC for treatment of HTN along with DM, CKD, nephrotic syndrome & scleroderma.
- Used in patients with history of MI and chronic CHF (to reduce mortality).

- Captopril test : To diagnose renovascular HTN & differentiate from essential HTN.
  A multifold increase in the level of renin is suggestive of renovascular HTN.
  Positive captopril test: Do renal angiography.
  Specific side effects : Dry cough (m/c), angioedema, dysgeusia, rash with itch.

ARBs 01:21:40

Uses similar to ACEIs.
Losartan :
Extra effects (mneumonic : sart PUT)
PPAR γ agonism : Reduces insulin resistance and portal pressure.
Decreases uric acid by excretion : Treatment of chronic gout.
Blocks thromboxane A2 : Antiaggregant effect.

Telmisartan : Maximum PPAR γ agonism.
Olmesartan & candesartan are prodrugs.
Irbesartan : For rhythm control in atrial fibrillation.

Pharmacokinetics : Oral drugs but they have poor oral absorption.
High plasma protein binding.
Telmisartan has maximum $T_{1/2}$.
Eprosartan has minimum $T_{1/2}$.

Side effects : Alopecia, agranulocytosis, sprue like syndrome is seen with olmesartan (weight loss and abdominal pain).
Uses : Same as ACEIs.

Direct renin inhibitors 01:27:06

Aliskiren :
FDA approved use : mild to moderate HTN (2nd line).
Side effects : GERD, diarrhoea, hyperuricemia.

Common S/E of RAAS inhibitors:

Postural hypotension

Hyperkalemia (Avoid K^+ rich food or K^+ supplements.)

Common contraindications of RAAS inihibitors:

1. Pregnancy
(1st trimester: CNS defects,
2nd & 3rd trimester : Renal defects).
2. Bilateral renal artery stenosis.

Vasodilator Drugs Summary

- Arterial Dilators
  1. CCB
     - A. Non-DHPs
       - Verapamil
       - Diltiazem
     - B. DHPs
       - Oral :
         - Amlodipine
         - Nifedipine
         - Isardipine
       - IV :
         - Nicardipine
         - Clevidipine
  2. Hydralazine
  3. Minoxidil
  4. Diazoxide
  5. Fenoldopam
- Venous dilators
  - Nitrates
    1. Nitroglycerine
    2. ISDN
    3. IMN
- Mixed Dilators
  1. Na Nitroprusside
  2. RAAS inhibitors
     - ACEI
     - ARB
     - DRI

ANTI HYPERTENSIVE DRUGS

Mild-moderate hypertension 00:00:34

First line : ACE inhibitors/ARBs, calcium channel blockers, diuretics (Thiazides).

Second line : Alpha blockers, beta blockers, direct renin inhibitors, Spironolactone, alpha 2 agonists etc.

Age criteria for choosing antihypertensive drugs :

- Calcification/atherosclerosis causes vascular stiffness in old age. Renin levels are low (by RAAS inactivation) in old patients with hypertension → Hyporeninemic hypertension.
- Renin levels are high in young hypertensive patients. (Hyperreninemic hypertension)

Young age (< 55 years) : ACE inhibitors/ARBs (DOC), beta blockers.

Old age (≥ 55 years) : Calcium channel blockers (DOC), Thiazides (diuretics).

Clinical aspect of hypertension 00:08:02

Patient with hypertension : 60c6b3eeaa8ded0e4e7e5ea7

Ist step :

Check the age :

If < 55 years → Start on ACE inhibitors/ARBs.

If > 55 years → Start on calcium channel blockers.

- If patient has inadequate control of blood pressure with maximum dosage of ACE inhibitors/ARBs after 1 month → Add a calcium channel blocker.
- If patient has inadequate control of blood pressure with maximum dosage of calcium channel blocker after 1 month → Add ACE inhibitor/ARBs.
- If no response after 1 month in the above cases → Add a diuretic.

- If no response after 1 month with combination of ACE inhibitor/ARB + calcium channel blocker + diuretic : Resistant hypertension.

Resistant hypertension 00:11:38

Patient has inadequate response despite concurrent use of
- Three antihypertensive agents of different classes
- Taken at maximally tolerated doses,
- One of which should be a diuretic.

These patients have high levels of aldosterone.
So, Spironolactone (aldosterone antagonist) should be added to ACE inhibitor/ARB + calcium channel blocker + diuretic.

Hypertension with comorbidities 00:13:53

Mild to moderate hypertension with comorbidities :
- Patient with diabetes/chronic kidney disease/nephrotic syndrome/scleroderma : DOC is ACE inhibitor/ARB.
- Patient with migraine/hyperthyroidism/stable angina/anxiety/essential tremors : Drug of choice is Beta blockers.
- Patient with benign prostatic hyperplasia : Drug of choice is Alpha blockers (Prazosin).
- Patient with osteoporosis : Drug of choice is Thiazides as they cause hypercalcemia.
- Patient with Raynaud's disease : Drug of choice is Calcium channel blockers.
- Patient with Cyclosporine induced hypertension : Drug of choice is Calcium channel blockers.

Severe hypertension 00:17:10

- Hypertensive emergency : End organ damage (retinopathy/encephalopathy/congestive heart failure/pulmonary edema/eclampsia) present irrespective of blood pressure readings.

- Hypertensive urgency : BP ≥ 220/125 mm Hg with no end organ damage.

Treatment :

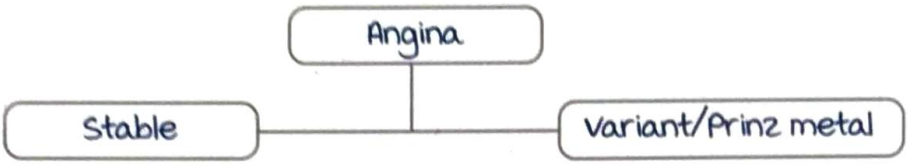
- Hypertensive emergency : DOC is intravenous Nicardipine except in pregnancy where intravenous Labetalol is used.
- Hypertensive urgency : DOC is Clonidine (orally). Captopril or Nifedipine can also be used.

Drugs used in hypertensive emergency :
(mnemonic HELEN dance.)
Hydralazine.
Esmolol.
Labetalol/Lasix (DOC : pregnancy).
Enalaprilat.
Nitroglycerine/Sodium nitroprusside.
Dihydropyridines (Nicardipine preferred over Clevidepine).

ANTI-ANGINAL DRUGS

Anti-anginal drugs 00:00:25

Angina is a common disorder mostly occurring due to atherosclerosis.



Stable angina can become unstable due to the breakdown of atherosclerotic plaque.
The treatment is same as for a non ST segment elevation myocardial infarction (NSTEMI) or STEMI (together called acute coronary syndrome).

Stable angina :

Caused by an atherosclerotic plaque

↓

Decreases the blood and oxygen supply to the coronary arteries.

↓

The decreased O_a supply is coupled with an increased O_a demand by myocardium during physical or emotional stress.

↓

This mismatch in O_a supply and demand leads to ischemia and pain.

Variant angina :

Caused by the acute contraction of the coronary artery.

↓

There is an immediate decrease in O_a supply

↓

Leading to ischemia and pain.

Sublingual nitroglycerine is the drug of choice (DOC) in an acute attack of stable or variant angina.

Mechanism of action :

- Stable angina : Venodilatation leading to a decreased preload on the heart. It decreases O_a demand of the myocardium.
- Variant angina : Coronary vasodilatation.

Long term management

00:06:52

Variant angina :

- Long acting nitrates.
- Ca^{a+} channel blockers.

The aim is to prevent coronary vasospasm.

Stable angina :

Aim : To decrease mortality due to MI.
To decrease ischemia and pain.

To decrease mortality :

- Statins.
- Aspirin.
- ACE inhibitors.

To decrease ischemia/pain :

- β blockers : Act by decreasing the contraction and heart rate thereby decreasing the O_a demand.
  It is the best drug for the long term treatment of pain and ischemia.
- Long-acting nitrates :
  1. Isosorbide mononitrate.
  2. Isosorbide dinitrate.
  3. Nitroglycerine : Oral sustained release tablet, transdermal route, or gel.

  Mechanism of action (MOA) : Decreases preload and thus decreases the O_a demand.
- Calcium channel blockers :
  MOA is coronary vasodilatation and increase O_a supply.

Non-dihydropyridines (DHP) like Diltiazem & Verapamil can be given as monotherapy.
DHPs must always be used with a cover of β blockers as they can cause reflex tachycardia.

- Ivabradine :

  Blocks the funny channels and SA node.
  It causes a decrease in heart rate.
  There is no effect on contraction or conduction.
  It is hence called a bradycardic drug. It is used in a patient who is already on a β blocker with a heart rate > 75 BPM.
  In such patients, β blockers are stopped, and they are started on Ivabradine.
  Adverse effects include :

  1. Increased risk of atrial fibrillation : SA node suppression leads to increased firing of atrial cells causing the formation of a functional circuit.
  2. Luminous phenomena : Patients see multiple-colored halos in the visual field.
  3. QT prolongation and torsades de Pointes.

Contraindications :

Can lead to severe bradycardia in a patient already on β blocker or Verapamil and Diltiazem.

- Ranolazine :

  It acts by blocking the late inward sodium channels in the myocardial cells thus indirectly activating Na^+/Ca^{a+} exchanger.
  It decreases the Ca^{a+} levels in the myocardium leading to decreased contraction and O_a demand.
  It also acts by an additional mechanism of inhibiting PFOX enzyme.
  The drug is used in resistant cases (when the patient is not responsive to any other drug).
  Adverse effects : Mild QT prolongation. Torsades de Pointes is not usually seen.
  Ranolazine decreases HbAIc thus improving glucose tolerance and decrease risk of atrial fibrillation.

The drug is contraindicated in liver failure.

- Nicorandil : It is a K^+ channel opener which causes vasodilatation leading to decreased O_a demand. It is reserved for the treatment of resistant cases. Hypotension is a side effect. The drug must not be used along with phosphodiesterase 5 inhibitors like Sildenafil or Tadalafil.

Recent drugs

00:22:34

Fasudil :

It is a Rho Kinase inhibitor.

Rho Kinase causes vasoconstriction.

Its inhibition leads to vasodilatation.

Trimetazidine :

It acts by blocking partial fatty acid oxidase (PFOX) which is required for the breakdown of fatty acids or triglycerides. Triglycerides are the source of ATP for myocardial cells. Blockage of PFOX leads to increased glycolysis in myocardium.

There is decreased ATP consumption by myocardium in glycolysis thus decreasing the O_a demand.

HYPOLIPIDEMIC DRUGS

Biochemistry of lipids 00:01:14

Lipids are absorbed in small intestine.
Cholesterol is absorbed by NPCILI (Neimann pick Cl like receptor I) into the intestinal epithelium.
It is converted into esterified cholesterol by ACAT (Acyl CO-A tranferase).
Triglycerides are also absorbed from food.
Esterified cholesterol along with triglycerides are transported in blood as chylomicrons.
Bile acid is secreted into small intestine.
It undergoes enterohepatic circulation.

Another source of lipids : Adipocytes.
HSL (hormone sensitive lipase) breaks down fat into free fatty acids (FFA).
FFA can be used for synthesis of triglycerides (Tg).

In the liver :
microsomal triglycerides transport proteins (MTP) transports Tg to the lipoprotein (which are synthesized by ribosomes) and packed as VLDL. VLDL is secreted into the blood stream.

Chylomicrons and VLDL get stuck only in the capillaries of adipose tissue, breast and heart which have an enzyme called as lipoprotein lipase (LPL).
Lipoprotein lipase breaks down chylomicrons and VLDL to IDL and provides lipid for storage and energy.
IDL again acted upon by lipoprotein lipase and hepatic lipase forming LDL.

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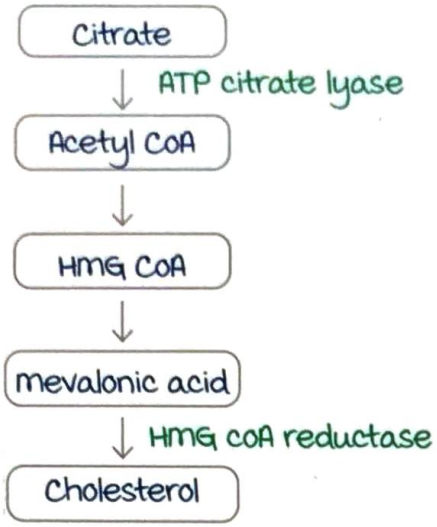
Synthesis of cholesterol :
Cholesterol can be synthesized from citrate pathway.
Rate limiting enzyme : HMG CoA reductase.



Cells can uptake LDL via LDL receptor upregulation and break it down to cholesterol.

Mechanism of action of hypolipidemic drugs :
Ezetimibe : Blocks NPC1 L1 receptor. Reduces absorption in S.I.
Avasimibe : Blocks ACAT. Decreases esterification.
Niacin : Blocks HSL. Decrease in FFA, Tg, VLDL, IDL, LDL.
Bile acid binding resins : Block enterohepatic circulation of bile acids. This will reduce the amount of bile acid in liver.

Lomitapide : Blocks MTP.
Icosapent : Block VLDL secretion.
} Approved for treatment of familial Hypertriglyceridemia

Fibrates : Increase production of lipoprotein lipase. Decrease in chylomicrons, Tg, VLDL and increase in LDL & IDL.

LDL is transported along with apo-B100
Mipomersen sodium : Blocks synthesis of apo-B100.

Statins : Increase LDL receptors and decrease plasma LDL. They are HMG CoA reductase inhibitors hence, they reduce cholesterol synthesis triggering an increase in LDL receptors to obtain more LDL from plasma.
Bempedoic acid : Block ATP citrate lyase which reduces the cholesterol synthesis and increases LDL receptors.

Active space

Drugs which increase LDL receptors : Statins, Bempedoic acid, Ezetimibe, Bile acid binding resins, PCSK-9 inhibitors like Alirocumab, Evolocumab, Inclisiran.

PCSK - 9 : Phosphoprotein which breaks LDL receptors.
Alirocumab and Evolocumab blocks PCSK-9.
Inclisiran : (Siran : Small interfering RNA) breaks mRNA for PCSK-9 and decreases its synthesis.

All these drugs reduce plasma LDL and are used in Atherosclerotic cardiovascular disease (ASCVD) like stroke, MI, unstable and stable angina.
Maximum decrease in plasma LDL : Statins.

Statins

00:25:38

Mechanism of action :
HMG CoA reductase inhibitor (peak activity is at night).
Maximum decrease in plasma LDL levels.
Blocks VLDL synthesis.
Decrease in Tg.
Increase in HDL.

Pleiotropic effects of statins :

- Anticoagulant effect.
- Antiaggregant effect.
- Increase release of nitric oxide (vasodilatation).
- Atherosclerotic plaque stabilizing effect.
- Anti-inflammatory effect.

Uses :
DOC for any condition where LDL should be decreased :
Type 2 hyperlipoproteinemia.
Primary and secondary prophylaxis for ASCVD, diabetes mellitus.

Pharmacokinetics : Oral route.
Lovastatin alone is taken along with food.

Metabolism : Phase I by CYP3A4, except Fluvastatin (CYP2C9) & Rosuvastatin (CYP2C9),
Pravastatin (excreted unchanged in urine).
No active metabolites : Fluvastatin, Pravastatin.

Pravastatin : DOC for treatment of protease inhibitors induced dyslipidemia.

Phase 2 metabolism via Glucuronidation.

First pass metabolism : In the liver by OATP$_1$B$_1$ (efflux pump).
Elimination : Renal.
In case of renal failure : safest is Atorvastatin.

Maximum $T_{1/2}$: Rosuvastatin > Atorvastatin.
Dosing of all drugs is at night time except Rosuvastatin and Atorvastatin (half life of 20 hours).

Pharmacodynamics :
Most potent : Pitavastatin > Rosuvastatin.
Maximum decrease in LDL : Rosuvastatin. Because Pitavastatin has ceiling effect beyond 4 mg.

Side effects : myopathy (do not monitor CPK because it can be delayed), hepatotoxicity (monitor LFT once in every 3-6 months), insulin resistance.

Contraindications: Pregnancy, children < 11 years (except Pravastatin < 8 years).

Bile acid binding resins 00:39:48

Cholestyramine.
Colestipol.
Colesevelam.

Mechanism of action : They bind to bile acids and interfere with enterohepatic circulation.

Decrease plasma LDL by increasing LDL receptors.

Uses :

DOC to decrease LDL in pregnancy and children.

Used as add on along with statins.

Side effects :

Increase levels of Tg and can cause hypertriglyceridemia.

GI upset : Bloating, diarrhoea (least with Colestipol).

Decreased absorption of other drugs and fat-soluble vitamins like A, D, E, K (least with Colestipol).

Atypical use : Colesevelam is approved for treatment of type 2 DM.

Niacin

00:43:27

Mechanism of action : Stimulates Gi subtype in adipocytes

↓

Decrease cAMP

↓

Decreases HSL

Decrease in FFA : Decrease in Tg, VLDL, IDL, LDL.

Maximum increase in HDL.

Uses : Dyslipidemia with decreased HDL.

Side effects :

Increases synthesis of prostaglandins which cause flushing (DOC : Aspirin).

Hepatoxicity.

Insulin resistance.

Fibrates :

Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil.

Mechanism of action : Stimulates PPAR alpha ↑

increase LPL

↓

decrease in chylomicrons, VLDL, Tg.

Uses :

DOC for chylomicronemia syndrome, type 3 hyperlipoproteinemia and hypertriglyceridemia.

Fenofibrate decreases uric acid levels so used in the treatment of chronic gout.

Side effects : Cholelithiasis (max : Clofibrate), myopathy (not seen with Bezafibrate).

Clinical implications :

- Clinical signs of atherosclerotic cardiovascular disease (ASCVD) or Plasma LDL >/= 190 mg/dl : Start statins.
  If no response at maximum dose and deficit decrease in LDL levels >/= 25% : PCSK-9 inhibitors.
  If deficit decrease in LDL levels < 25% : Ezetimibe.
  If no response/intolerant to Ezetimibe : Bile acid binding resins.

- No clinical signs of atherosclerotic cardiovascular disease (ASCVD) & LDL < 190 mg/dl : Start statins.
  If no response at maximum dose : Add Ezetimibe.
  If intolerant to Ezetimibe : Bile acid binding resins.

DIURETICS : PART - 1

Diuretics 00:00:18

These are a class of drugs which increases urine output thereby decreasing plasma volume. It is used to treat edema and hypertension.

Diuretics acting on proximal convoluted tubules (PCT) :
The class of diuretics acting on PCT are carbonic anhydrase inhibitors (CAI).

Physiology link :
The H^+ combines with HCO_3^- to produce carbonic acid (H_aCO_3) in the lumen of PCT.
H_aCO_3 splits into H_aO and CO_a with the help of an enzyme called carbonic anhydrase within the lumen.
H_aO and CO_a diffuses back into the epithelial cell and combine to form carbonic acid.
This is mediated by cytoplasmic carbonic anhydrase in the epithelial cell.
H_aCO_3 breaks down to form HCO_3^- and H^+. The HCO_3^- is retained by systemic circulation.
Na^+/H^+ exchanger moves H^+ from cytoplasm for Na^+ from the lumen (antiporter system).
H_aO is absorbed along with the Na^+. Maximum reabsorption of Na^+ occurs in the PCT.

This physiological process is blocked by CAIs.
If luminal carbonic anhydrase is blocked, there is an increased level of carbonic acid or HCO_3^- in the urine.
When the cytoplasmic carbonic anhydrase is blocked, proton production is halted. This leads to increased Na^+ and H_aO in the urine.
Majority of luminal Na^+ is reabsorbed by the $Na^+/K^+/2Cl^-$ pump present in the thick ascending limb of loop of Henle.
CAIs are hence weak diuretics.

The rest of Na^+ reaches the collecting duct. The epithelial sodium channel (ENaC) reabsorbs sodium.

Depolarization caused due to the reabsorption of Na^+ activating :

- Proton ATPase : Loses H^+ into the lumen.
- ROMK channel : Loses K^+ into the lumen.

Any diuretic leading to loss of Na^+ into the collecting duct invariably causes loss of K^+ and H^+. Loss of H^+ may lead to metabolic alkalosis.

CAIs predominantly cause the loss of HCO_3^- rather than H^+ leading to metabolic acidosis.

Loop diuretics and thiazides cause metabolic alkalosis.

Diuretics causing hypokalemia :

- Carbonic anhydrase inhibitors (maximum hypokalemia at equal natriuretic doses).
- Loop diuretics.
- Thiazides.

Excretion of NH_4^+ is inhibited by CAI and can lead to hyperammonemia.

Effects, uses and side effects of CAIs 00:12:35

They cause minimal loss of Na^+ and H_2O.

1. Used in the treatment of metabolic and respiratory alkalosis as they cause loss of HCO_3^-.
2. Used to treat obstructive sleep apnea (OSA). They make the CSF pH acidic stimulating the medullary ventilatory center leading to hyperventilation.
   Hyperventilation causes compensatory respiratory alkalosis.
3. Increased HCO_3^- in the urine causes precipitation of Ca^+ leading to formation of calcium stones (nephrolithiasis).

Any drug blocking carbonic anhydrase can lead to nephrolithiasis :

- Zonisamide
- Topiramate

} Antiepileptics

Paradoxical use of CAIs : To prevent cysteine stones in cystinuria as they become water soluble in alkaline urine.

4. CAIs increases CO_2 in the CNS neurons leading to the release of inhibitory neurotransmitters like glycine and GABA. This can lead to somnolence.

5. CAIs can be used in catamenial epilepsy.
   It cannot be used as a long-term therapy due to the development of tolerance.

CAIs are contraindicated in liver cirrhosis as hyperammonemia caused by the drug can increase the risk of hepatic encephalopathy.

Hypokalemia is seen due to increased excretion of K^+.
It is still used in the treatment of hypokalemic periodic paralysis. Mechanism of action is unknown.
Postulated to be due to the direct action on the muscles.
Methanamide is the drug of choice. Acetazolamide may be used.

6. CAIs decrease aqueous and cerebrospinal fluid production.
   H_2O released from the breakdown of H_2CO_3 is required for the synthesis of aqueous humor and CSF.
   It can be used to treat :
   - Glaucoma : Acetazolamide (oral) for acute congestive glaucoma.
     Brinzolamide and Dorzolamide are used as eye drops for open angle glaucoma.
   - Acute mountain sickness : Oral acetazolamide is the DOC.
   - Idiopathic intracranial hypertension (pseudotumor cerebri).
   - To prevent CSF leak.
   - Dural ectasia seen in congenital disorders like marfan's syndrome.
   - Raised CSF pressure headache.

7. CAIs are sulfonamide derivatives, hence can cause hypersensitivity. It can be seen in the form of rash or bone marrow suppression.

Other diuretics with weak carbonic anhydrase inhibitory effect :

- All loop diuretics except Bumetanide.
- All thiazides except Indapamide.

Loop diuretics 00:29:31

They act on the thick ascending limb (TAL) of loop of Henle.

Physiology link :
The TAL is not permeable to H_2O.
The $Na^+/K^+/2Cl^-$ pump mediates the reabsorption of sodium, potassium, and chloride.
Na^+ and Cl^- are extracellular ions and ~25% of filtered sodium is reabsorbed here and retained by the systemic circulation.
It can cause medullary hyperosmolarity.
Sodium and chloride are accommodated in the epithelial cell because of low intracellular concentrations.
The K^+ moving in is immediately pushed out as the intracelluar concentration of K^+ is high.

This makes the membrane negatively charged leading to absorption of Ca^{2+} and Mg^{2+}.

- Loop diuretics blocks the $Na^+/K^+/2Cl^-$ pump which leads to loss of Na^+ and Cl^- dragging water along with it.
  There is maximum loss of water and Na^+/Cl^- with loop diuretics. They are the most potent or high ceiling diuretics.
- Osmotic pressure is decreased and there is resultant decrease in plasma volume and blood pressure.
- Hyperuricemia is seen due to compensatory reabsorption of uric acid and water. This effect is also seen with thiazides.
- There is stimulation of sympathetic nervous system which leads to release of catecholamines. It binds to the β_3 receptors in the adipocytes inducing lipolysis leading to dyslipidemia. Seen with thiazides as well.
- Loss of calcium and magnesium leads to hypocalcemia and hypomagnesemia. An increased loss of K^+ and H^+ occurs in the collecting duct.

Effects, uses and side effects of loop diuretics 00:38:30

Maximum loss of sodium and water is seen with loop diuretics. These are the only class of diuretics which are effective when the glomerular filtration rate (GFR) is < 40 and are hence effective in renal failure or insufficiency.

Loop diuretics are the DOC for treatment of pulmonary edema. They can also be used in :

- Cerebral edema : Mannitol is the DOC.
- Nephrotic syndrome.
- Chronic Kidney disease.
- Cirrhosis.

These drugs can be used in the treatment of hypertensive emergencies (Furosemide is the preferred drug).

1. Loop diuretics increase prostaglandin release leading to indirect vasodilation. It is the first effect that occurs in treatment of pulmonary edema. It decreases preload. This effect can be blocked by non-steroidal anti inflammatory drugs (NSAIDs) and decrease the overall effect.
2. Leads to hyperuricemia thus worsening gout.
3. They cause dyslipidemia.
4. Used in the treatment of hypercalcemia of malignancy as they cause ca_a^+ loss in urine.
5. Magnesium loss can lead to hypomagnesemia.
6. Increased potassium loss can lead to hypokalemia. Decreases insulin release causing hyperglycemia.

Normally, the ATP sensitive K^+ channels in the β islet cells are blocked by ATP derived from glycolysis.
There is retention of K^+ within the cell leading to a constant state of depolarization and prevents hyperpolarization.
In hypokalemia, the intracellular K^+ levels are depleted preventing the release of insulin.
Insulin resistance is also seen with the use of loop diuretics.

7. Proton loss can lead to metabolic alkalosis.
8. Loop diuretics can cause reversible ototoxicity. Contraindicated with ototoxic drugs like aminoglycosides or cisplatin.

Examples of loop diuretics include :

- Furosemide (Lasix) : most commonly used loop diuretic.
- Bumetanide : most potent (low dose is required).
- Torsemide : Longest acting.
- Ethacrynic acid : most ototoxic and currently not used.

DIURETICS : PART - 2

Thiazides 00:00:17

They act on the distal convoluted tubule (DCT).

Physiology link :
Na^+/Cl^- co-transporter reabsorbs sodium and chloride. ~ 10% of filtered sodium is reabsorbed here and water is not reabsorbed.
The reabsorbed sodium is moved to the systemic circulation.

Thiazides block the Na^+/Cl^- co-transporter.
There is resultant loss of sodium, chloride, and water.
This leads to decreased osmotic pressure due to the loss of Na^+, Cl^- and water leading to compensatory reabsorption of uric acid (hyperuricemia) and water.
Sympathetic overactivation leads to lipolysis and dyslipidemia (also seen with loop diuretics).

The intracytoplasmic Na^+ concentration also decreases due to the blockade of co-transporter.
To compensate, Na^+/Ca^{2+} exchanger pumps sodium from the systemic circulation into the epithelial cells in exchange for calcium.

The declining calcium levels inside the cell will draw more calcium from the lumen into the systemic circulation.
This results in hypercalcemia (unlike loop diuretics which cause hypocalcemia).
There is also increased loss of Mg^{2+}, K^+ and H^+.

Effects,uses and side effects of thiazides 00:05:28

These drugs cause moderate loss of solute and water (moderate diuretics).

1. Thiazides are not effective if the glomerular filtration rate (GFR) is less than 40 except metolazone.

metolazone is used as an add on drug along with Furosemide to produce diuresis in patients with low GFR.

2. Thiazides can be used in cases of edema such as :
   - Chronic Kidney disease.
   - Nephrotic syndrome.
   - Cirrhotic edema.

Thiazides are preferred in a hypertensive patient with CKD.

3. Thiazides can cause direct vasodilation as it opens K^+ channels in the smooth muscles of blood vessels.
   Can be used in hypertension as one of the first line drugs.
4. Thiazides increase Ca^{a+} absorption leading to hypercalcemia. DOC in hypertensive patients with osteoporosis.

5. Used in treatment of hypercalciuric renal stones.
   Thiazides increase Ca^{a+} absorption and decreases the risk of stone formation.
6. Thiazides can precipitate gout as they increase uric acid absorption.
7. Thiazides trigger sympathetic overdrive which causes dyslipidemia.
8. Increased K^+ loss leads to hypokalemia which decreases insulin release (like in loop diuretics) leading to hyperglycemia.

Dyslipidemia and hyperglycemia are more prominent in thiazides as compared to loop diuretics.

9. Thiazides cause increased magnesium loss leading to hypomagnesemia.
10. Proton loss can lead to metabolic alkalosis.

Thiazide drugs :

- Chlorothiazide : Shortest acting and least preferred.
- Chlorthalidone : Longest acting and thiazide of choice in hypertension (24 hour BP control).
- Indapamide : Primarily hepatic excretion. Poor diuretic effect. It is effective in treating hypertension but not in edema.

- Metolazone : Primarily renal excretion. Good diuretic effect and is effective in patients with GFR <40. Used primarily in edema and secondarily in hypertension.
- Bendroflumethiazide
- Polythiazide

} 100% oral bioavailability

Diuretics acting on collecting duct 00:16:13

Physiological link :
Collecting duct is primarily under the control of Aldosterone (mineralocorticoid) for which the receptor is present in the cytoplasm of the epithelial cell.
Aldosterone binds to the mineralocorticoid receptor (MCR) in the cytoplasm.
Aldosterone bound to MCR translocates into the nucleus and increases transcription factors for the synthesis of Epithelial sodium channels (ENaC).
ENaC in the collecting duct reabsorbs ~2% of sodium and water.

Aldosterone antagonists :

- Spironolactone.
- Eplerenone.
- Finrenone.

ENaC channel blockers :

- Amiloride.
- Triamterene.

These drugs cause loss of sodium and water but are poorly effective diuretics.

Normally, the sodium reabsorbed in the collecting duct depolarizes the cell. It activates H^+ ATPase and ROMK channels. Potassium and proton loss occurs through these channels.
Diuretics acting on collecting duct cause proton retention leading to metabolic acidosis.
Retention of potassium leads to hyperkalemia.
These drugs are also called potassium sparing diuretics and are given along with other diuretics to prevent hypokalemia.

Aldosterone antagonists 00:22:31

Spironolactone :

It is a prodrug that is activated into Canrenone which blocks the receptor. It is the DOC in conditions where the aldosterone levels are high like in :

- Cirrhotic edema.
- Resistant hypertension.
- Drug resistant edema.

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It is also used in patients with :

- History of myocardial infarction
- Chronic congestive heart failure

} To reduce mortality

Eplerenone may also be used in the above-mentioned conditions.

Side effects of spironolactone :

- Gynaecomastia
- Impotence

} due to androgen receptor. blockage.

- Menstrual irregularities : due to blocking of progesterone receptor.

Spironolactone can be used in polycystic ovarian syndrome (PCOS) to treat hirsutism when oral contraceptive pills (OCPs) are not effective.

Finrenone :

Recently approved in treatment of CKD associated with type II diabetes mellitus (DM). It can be given to prevent :

- Progression to end stage renal disease (ESRD).
- MI.
- Congestive heart failure.

ENaC inhibitors 00:28:05

Amiloride is the DOC for :

- Liddle syndrome (over expression of ENaC).
- Lithium induced diabetes insipidus : Lithium has a similar structure as sodium and is hence absorbed by ENaC. Thiazides can also be used to treat the condition but is not the DOC. It induces solute and water loss which

triggers the proximal convoluted tubule to reabsorb more solute and water.

- Inhalational Amiloride is used to treat cystic fibrosis as the secretions become liquified.

Triamterene :

It is used in treatment of edema.

Causes folic acid deficiency and is contraindicated in liver cirrhosis (folic acid deficient state).

Carbonic anhydrase inhibitors are also contraindicated in liver disease as it causes hyperammonemia.

Common side effects of potassium sparing diuretics :

- Hyperkalemia : Patients on these drugs are advised not to have potassium rich food to prevent hyperkalemia.
- Metabolic acidosis.

Osmotic diuretics

00:32:53

Mannitol :

It is given intravenously for diuretic effect. When given orally it acts as a laxative.

It has two mechanisms of action :

- Cellular : Extract water from the cells. It is hence the DOC for cerebral edema and acute congestive glaucoma to decrease intraocular pressure (IOP).
  Once IOP is normalized, treatment is shifted to Pilocarpine.

- Renal : It induces solute free water loss and is hence used in :
  1. Diuretic breaking (diuretic resistance).
  2. Impending renal failure in shock/trauma.
  3. Dialysis disequilibrium.

Side effects of mannitol due to cellular mechanism :

- Hyponatremia : They pull water from the cells causing relative hyponatremia.
- Hypokalemia (relative).

Active space

Due to renal mechanism :

- Hypernatremia.
- Hyperkalemia.

Other side effects include :

- Pulmonary edema (paradoxical) : mannitol can move out of pulmonary capillaries (unlike cerebral capillaries) dragging water along with it.

Contraindications of mannitol :

- Pulmonary edema.
- Renal failure.
- Hemorrhagic stroke.

Antidiuretics

00:39:30

Physiological link to medullary collecting duct (MCD) :
A large amount of water and some amount of solute reaches the MCD.
The medulla is hyperosmolar (high amount of sodium absorbed in thick ascending limb).
Hypothalamus releases vasopressin which binds to vasopressin 2 receptor (V_2R) which is of G_s subtype.
It increases the cyclic AMP levels which activates aquaporins (water channels) which leads to reabsorption of water.

Vasopressin analogues (anti-diuretics) : increase water absorption. Used in central diabetes insipidus.

Examples include :

- Synthetic vasopressin : Acts by stimulating vasopressin 1 and 2 receptor. V_2R is present in the kidney and is used in treatment of central diabetes insipidus.
  V_1R is a Gq subtype of GPCR which is present in blood vessels and GIT. Its stimulation causes vasoconstriction and contraction in GIT.
  1. Acute variceal bleeding.
  2. Norepinephrine resistant shock.
  3. Abdominal distension.
  4. Paralytic ileus.

Vasoconstriction causes facial pallor.
GI side effects include nausea and vomiting due to increased contraction.

- Terlipressin :
  DOC for acute variceal bleeding. It maintains a more stable portal pressure compared to octreotide.
  DOC for prophylaxis of variceal bleeding is Propranolol.
  Treatment of choice is endoscopic band ligation.
- Desmopressin :
  Given subcutaneously for central diabetes insipidus (not for nephrogenic).
  DOC for nocturnal enuresis.
  DOC for Von Willebrand's disease (vWD) and hemophilia A.
  It increases release of vW factor and factor VIII by acting on the endothelium.
  Side effects include headache (water intoxication)

Vasopressin antagonists :
Used in Syndrome of Inappropriate AntiDiuretic Hormone secretion (SIADH).

Parenteral vasopressin antagonists :

- Conivaptan : Preferred in emergency treatment of SIADH.

Oral antagonists :

- Mozavaptan
- Tolvaptan

} Long term treatment

Long term treatment of choice is free water restriction. V_2R receptor blockers are given in resistant cases.
Side effects :

- Hyperglycemia.
- Hypokalemia.
- Hepatotoxicity : Specific to tolvaptan.

It can only be used up to one month.

Free water clearance 00:52:00

Proximal convoluted tubule (PCT) : Na^+ and H_2O absorbed.
Descending thin limb (DTL) : Only permeable to H_2O.
Ascending thin limb (ATL) : Only permeable to H_2O.

Thick ascending limb (TAL) : Permeable to Na^+ and Cl^- but not to water.
Distal convoluted tubule (DCT) : Permeable to Na^+ and Cl^- but not to H_2O.

Any water that remains in the lumen without solute is termed free water.
Positive free water is generated in the TAL and DCT as sodium and chloride are absorbed and water remains in the lumen
TAL maintains medullary hyperosmolarity which drives H_2O from the medullary collecting duct into the tissue.
Only free water is moving from the lumen into the tissue and is hence called as negative free water clearance.

Carbonic anhydrase inhibitors increase the positive free water clearance. They block absorption of sodium and water in PCT. The sodium drags the water to the TAL and there only sodium is reabsorbed.

Loop diuretics block the $Na^+/K^+/2Cl^-$ pump thus blocking the reabsorption of sodium. This decreases the positive free water clearance.
If the $Na^+/K^+/2Cl^-$ co-transporter is blocked, the sodium level decreases in the medulla. The free water does not move from the collecting duct's lumen and thus decrease negative free water clearance.

Loop diuretics decreases both positive and negative free water clearance. Thiazides blocks the reabsorption of sodium and decreases the positive free water clearance.

Carbonic anhydrase inhibitors	Loop diuretics	Thiazides	Potassium sparing diuretics	Osmotic diuretics
Block carbonic anhydrase in PCT	Block Na/K/2Cl pump in TAL (Indirect vasodilators : increase prostaglandin)	Block Na/Cl co-transporter in DCT (Direct vasodilators : Open K channels)	Spironolactone : Blocks aldosterone. Amiloride : Blocks ENaC in CD.	Promotes solute free water loss.
Acetazolamide : DOC in acute mountain sickness	Furosemide : DOC in pulmonary edema Torsemide Bumetanide Ethacrynic acid Loop diuretics : Effective in GFR < 40	Chlorthalidone : mild to moderate hypertension. Metolazone : Effective in GFR < 40	Spironolactone : DOC in nephrotic edema and resistant hypertension Amiloride : DOC in lithium induced diabetes insipidus	Mannitol : DOC in cerebral edema and acute congestive glaucoma.

Side effects of diuretics				
Carbonic anhydrase inhibitors	Loop diuretics	Thiazides	Potassium sparing diuretics	Osmotic diuretics
• Metabolic acidosis. • Hypokalemia. • Hypersensitivity (Rash/bone marrow suppression). • Renal stones (nephrolithiasis). • Hyper ammonemia.	• Metabolic alkalosis. • Hypo Kalemia. • Hypomagnesemia. • Hyper uricemia. • Hypo calcemia. • Hyper glycemia. • Ototoxicity	• Metabolic alkalosis. • Hypo-Kalemia. • Hypomagnesemia. • Hyper uricemia. • Hyper calcemia. • Hyper glycemia.	• Metabolic acidosis. • Hyper Kalemia. • Spirono lactone : Gynecomastia. • Triamterene – Folic acid deficiency.	• Hyperkalemia. • Hypokalemia. • Hypernatremia. • Hyponatremia. • Dehydration • Pulmonary edema

ANTIEPILEPTIC DRUGS

Pathophysiology of epilepsy 00:01:19

Generalized seizures :

Seen in Generalized tonic clonic seizures (GTCS) and myoclonic seizure (m/c Juvenile myoclonic epilepsy).

Mechanism :

Thalamus

↓

Spontaneous firing of T- type calcium channel

↓

Action potential

↓

Retrograde propagation of action potential to cortex :

Thalamocortical reciprocal firing

↓

Cortical neuron depolarization

↓

Sodium channel opens

↓

Depolarization of spinal cord segments

↓

Spontaneous contraction and relaxation of muscles

Clinical presentation :

- Clenching of teeth.
- Spontaneous urination and defecation.

Absence seizure :

Clinical presentation : Brief staring episodes for < 10 seconds.

Cause : Ca^{2+} channel alone (Na^{+} channel has no role).

Thalamus

↓

Spontaneous firing of T- type Ca^{a+} channel

↓

Action potential within sub cortex.

Partial seizure :

Cause : Na^+ channel alone (Ca^{a+} has no role).

Pathophysiology :

Space occupying lesions irritate neurons in the vicinity

↓

Generates action potential via Na^+ channels

↓

Specific segment of spinal cord gets stimulated

↓

Contraction of a specific muscle (area representing the muscle that is occupied by lesion in cortex)

Treatment of seizures in general 00:09:40

Generalized seizure :

Both Ca^{a+} and Na^+ channel blockers can be used.

DOC : Ca^{a+} channel blockers → Valproate.

Myoclonic seizure is worsened by two Na^+ channel blockers :

Phenytoin and Carbamazepine.

Partial seizure : DOC : Na^+ channel blocker → Carbamazepine.

Add on drugs (to inhibit propagation of action potential) :

Most commonly used in partial seizure.

- K^+ channel opener.
- Drugs increasing GABA effect.
- Drugs decreasing glutamate effect.

Duration of therapy : Continue atleast till 2 years of seizure free period.

Exception : myoclonic seizure/JME or stroke induced seizure
→ They require lifelong therapy.

Calcium channel blockers 00:18:08

Valproate :

mechanism of action :

- Calcium channel blocker.
- Sodium channel blocker → Second line drug in partial seizure.
- Increases GABA by inhibiting its metabolism.
- Blocks Histone deacetylase that causes neuronal proliferation.

Uses :

Drug of choice in

- GTCS.
- Myoclonic seizure (JME).
- Atypical absence seizure (absence seizure with change in muscle tone and lasts for > 20s).
- Lennox-Gastaut Syndrome (LGS) : Mixed seizure syndrome, different types of seizures seen in the same patient. Difficult to treat.
- Dravet syndrome.
- Rapid cyclers : patients with bipolar disorder who have > 4 episodes of mania/depression in 1 year.
- Rheumatic chorea (in antibiotic resistant chorea).

Other uses :

- Acute mania, bipolar disorder.
- Prophylaxis of migraine (2nd line).

Side effects :

- Vomiting and nausea (most common).
- Alopecia.
- Liver toxicity → Hyperammonemia.
- DOC for liver toxicity : Carnitine (as valproate can cause Carnitine deficiency).

- Pancreatitis.
- Rash.
- Obesity.
- Tremor.
- Teratogenicity (most teratogenic antiepileptic).
  Neural tube defects are commonly seen.

Drug interactions :

Valproate is an enzyme inhibitor. It can cause toxicity of other drugs which are metabolized by microsomal enzymes.

Calcium channel blocker : Ethosuximide 00:29:42

Mechanism of action : Mostly limited to Ca^{a+} channel blockade.

Use : DOC in typical absence seizure (no change in muscle tone and duration < 10 secs).

Side effects : mnemonic : ETHOS

Emesis.

Toxic to CNS.

Hematological toxicity.

Systemic lupus erythematosus.

Sodium channel blockers 00:32:24

Phenytoin/Diphenyl hydantoin :

Uses :

- GTCS.
- Partial seizures.
- Treatment of neuropathic pain.
- Antiarrhythmic drug (class Ib).

Purple glove syndrome with phenytoin

Routes :

- Oral.
- IV.

Drawbacks of IV phenytoin :

- Precipitates with glucose (use NS).
- Purple glove syndrome due to thrombosis of veins causing edema, pain, discoloration.

Active space

- Tissue necrosis with extravasation.

  Hence, we prefer IV Fosphenytoin which is water soluble.

Side effects : mnemonic : HYDANTOIN

Hyperplasia of gums (most common) : oral hygiene is essential.

Hirsutism with acne in young females (2nd most common).

Hyperglycemia.

LYmphadenopathy (resembles Hodgkin's disease).

Decreased vitamin D due to abnormal metabolism causing hypocalcemia.

Diplopia

Ataxia
Nystagmus
} Signs of acute toxicity indicating high plasma levels. Requires TDM & Dose adjustment.

Teratogenic → Fetal hydantoin syndrome : Cleft lip and palate.

Osteomalacia (hypocalcemia + reduced bone matrix)

Inducer of enzymes.

Induces vitamin K metabolism, thereby leading to :

- Decreased bone matrix.
- Deficiency of clotting factors 2, 7, 9, 10.

Effect in Pregnancy : Hemorrhagic disease of newborn.

Prevent by giving Inj. Vitamin K to mother.

Neutropenia, megaloblastic anemia because folic acid absorption is reduced.

Sodium channel blocker : Carbamazepine 00:45:21

Carbamazepine (old drug) : causes hypersensitivity, hyponatremia.

New drug : Oxcarbazepine is a prodrug of Eslicarbazepine.

Eslicarbazepine :

Dereased hypersensitivity.

Increased risk of hyponatremia.

Uses of Carbamazepines :

- Partial seizures (DOC).
- GTCS.
- Trigeminal neuralgia (carbamazepine : DOC > Phenytoin)
- Acute mania/bipolar disorder.
- Rheumatic chorea.

Side effects : Mnemonic: HEADS

Dilutional Hyponatremia (due to SIADH).

Delayed side effects are more common in elderly.

Hypersensitivity.

Eosinophilia.

Agranulocytosis : Report symptoms like sore throat/fever.

Aplastic anemia.

Ataxia.

Diplopia/Blurring of vision.

Splenomegaly.

Stevens-Johnson syndrome (SJS)

SJS is associated with HLA-B 1502 gene (Seen with Carbamazepine and Phenytoin).

Abacavir induced SJS : Associated with HLA-B 5701 gene.

Allopurinol induced SJS : Associated with HLA-B 5801 gene.

Contraindication : Not to be used with Clozapine as both causes agranulocytosis.

Lamotrigine 00:55:20

Mechanisms of action : wide spectrum of action.

- Na^+ channel blocker.
- Ca^{2+} channel blocker (2^{nd} line drug in absence seizure).
- Decreases glutamate levels.

Uses :

First line in

- GTCS
- Myoclonic seizure

} Safer in pregnancy.

- Partial seizure (also in partial seizure during pregnancy)
- Lennox-Gastaut syndrome
- Bipolar disorder (not in acute mania)

Lamotrigine cannot be given in emergency as bolus dose can cause SJS.

Side effects :

- Ataxia.
- Diplopia.
- Nausea and vomiting.
- SJS.

Topiramate

00:58:38

Mechanisms of action :

- Na^+ channel blocker.
- K^+ channel opener.
- Carbonic anhydrase inhibitor.
- Blocks glutamate receptors like AMPA and Kainate subtype.

Uses :

- GTCS.
- Partial seizure.
- LGS.
- Bipolar disorder.
- Prophylaxis of migraine (most preferred antiepileptic for migraine prophylaxis).
- Alcohol dependence (non-FDA approved).
- Obesity in combination with Phentermine.

Side effects : Carbonic anhydrase inhibitors cause :

- metabolic acidosis.
- Nephrolithiasis.
- Hypohidrosis.

Other side effects :

- Weight loss.
- Secondary angle closure glaucoma :

Due to choroidal edema

↓

Lens pushed forward

↓

Blocks the angle and impairs aqueous outflow in patients with small anterior chamber

↓

Secondary angle closure glaucoma

Hence, prior Ophthalmological examination is a must.

Zonisamide, Rufinamide, Lacosamide 01:05:00

Zonisamide :

Mechanisms of action :

- Blocks Na^+ channel.
- Ca^{2+} channel blocker.
- Free radical scavenger.

Used in Partial seizure.

Side effects :

Carbonic anhydrase inhibition causes

- metabolic acidosis.
- Hypohidrosis.
- Nephrolithiasis.

Rufinamide :

Mechanism : Blocks Na^+ channel.

Use : LGS.

Pharmacokinetics : Metabolized by non-microsomal enzymes.

Thus, lesser drug interactions.

Lacosamide :

Source : L-serine

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Na^+ channel blocker.

Used only in Partial seizure.

Side effects :

- PR prolongation.
- Suicidal tendency (FDA gives black box warning).

Active space

Potassium channel opener 01:09:35

Ezogabine/Retigabine :
Used in resistant partial seizure.

Never used as first line drugs because of

- QT Prolongation : Torsades de Pointes (Blocks K^+ channel in the heart but acts as K^+ opener in the brain).
- Retinal deposits.
- Blue pigmentation of nails and lips.

Drugs that decrease the effects of glutamate 01:12:10

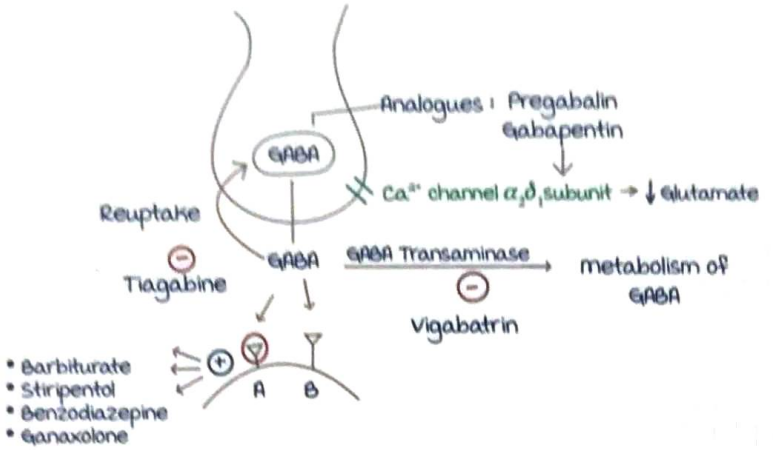
NMDA blocker :
Felbamate : used for GTCS and partial seizure.
Not used widely because of bone marrow suppression and hepatotoxicity.

AMPA receptor blockers :
Perampanel, Talampanel : used in partial seizure.
Side effect : Somnolence, mood abnormality.

Drugs that increase effect of GABA 01:14:06

GABA acts on 2 receptors on the post synaptic membrane : GABA-A and GABA-B receptors.

	GABA-A receptor	GABA-B Receptor
Location	Brain	Spinal cord
Receptor	Chloride ion channel	Gi subtype of GPCR : Opens K^+ channel
Effect	Anti-epileptic.	Muscle relaxant (e.g., Baclofen)



GABA A receptor agonist :

Stiripentol :

- Approved for treatment of Dravet syndrome as add on to Valproate and Clobazam.
- Side effect : Decreased appetite causing weight loss.

Ganaxolone : Used in resistant partial seizure and infantile spasm.

Drugs increasing GABA at the synapse :

Tiagabine : Used in resistant partial seizure.

Side effect :

- Paradoxical seizure in non-epileptics.
- Psychosis.

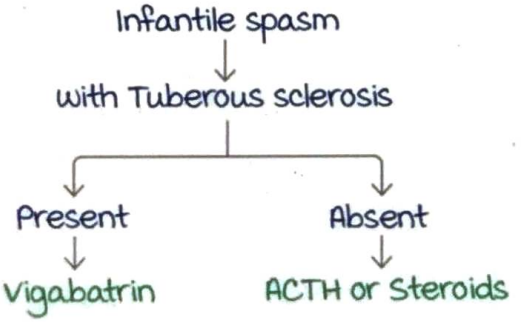
Vigabatrin :

Mechanism of action : Inhibits GABA transaminase.

Side effects : Irreversible visual field defect.

Uses :

- Resistant partial seizure.
- Infantile spasm.



GABA analogues/GABA pentinoids :

Pregabalin and Gabapentin.

Mechanism : Inhibits $\alpha_2\delta_1$ subunit of presynaptic Ca^{2+} channels → decrease glutamate.

Uses of both the drugs :

- Partial seizure.
- Peripheral neuropathy.

Uses of Gabapentin :

- DOC in Postherpetic neuralgia.
- Prophylaxis of migraine.
- Bipolar disorder.
- Generalized anxiety disorder.
- Phobia.

Pharmacokinetics : Not metabolized.

Excreted unchanged by Kidneys.

Hence, no drug interactions.

Side effects : Somnolence, weight gain.

Miscellaneous drugs

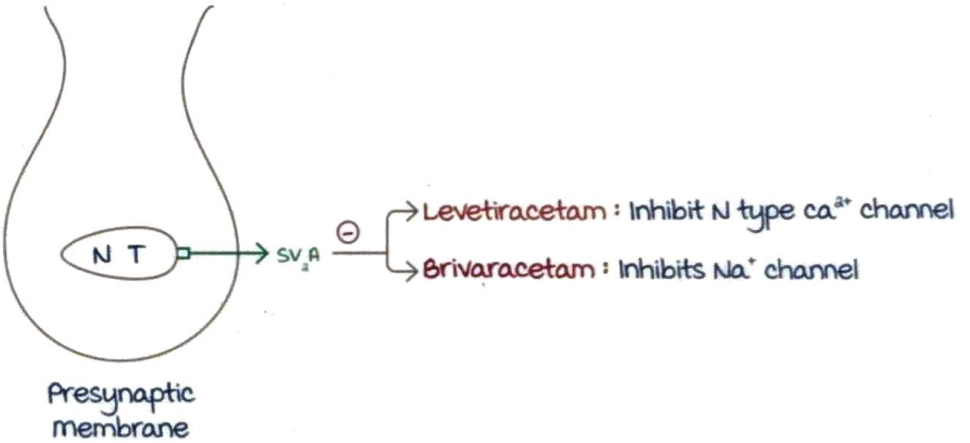
01:30:02

SV_2A blocker :

By blocking of SV_2A

↓

Modulates release of glutamate (decrease) and GABA (increase)



Levetiracetam :

Mechanism :

- SV_2A inhibitor.
- N-type Ca^{2+} channel blocker.

Uses :

- GTCS.
- Myoclonic seizure.
- Partial seizure.
- Status epilepticus.
- Levodopa induced dyskinesia.

Side effect : Mood disorder.

Safest antiepileptic in pregnancy.

Epilepsy in pregnancy :

- Already pregnant & on anti epileptic :
  Seizures are well controlled : Continue the same drug along with folic acid.
  Therapeutic drug monitoring to be done.

- Planning pregnancy & on anti epileptic drug :

Give drug free interval

Seizure⊕	Seizure⊖
DOC : Levetiracetam Lamotrigine Clonazepam	Continue pregnancy without drug.

Cannabidiol :

- Source of the drug is cannabis.
- Mechanism : unknown.
- Approved for Dravet syndrome and LGS.
- Side effect : Hepatotoxicity.
- Contraindicated in children less than 2 years.

Active space

SEDATIVE HYPNOTICS

Sedative hypnotics 00:00:23

Sedation means anxiolysis or to produce calmness and hypnosis means sleep. This class of drugs relieves anxiety and insomnia.

GABA-A receptor agonists (stimulators of GABA-A) : GABA-A receptor is a chloride ion channel receptor and is pentameric in structure.
The lumen of the ion channel is formed by 5 protein subunits around it. The 2 α subunits are always common.
One or two of the subunits are β or γ. Projections from the α subunits keep the lumen closed preventing chloride ions from moving in.
The binding site for GABA is present at the junction of α and β subunits.
The projections in the lumen disappear when GABA binds to the binding site. The lumen becomes patent and conducts chloride ions.

The site of action of benzodiazepine (benzodiazepine site) lies between α and γ subunits. Three types of drugs act here :

- Full agonist : Benzodiazepines (BZD).
  When BZD binds at the binding site, GABA increases the frequency of chloride ion channel opening. When chloride ions move into the neuron, it relaxes the neurons causing effects like sedation, hypnosis, antiepileptic effect, muscle relaxation etc.

  Barbiturates : Binds to the β subunit and GABA increases the duration of chloride ion channel opening.
- Inverse agonist : β carboline.
  They produce inverse effects like seizure and anxiety. It is not used clinically.

- Antagonist : Flumazenil.
  It is given intravenously for benzodiazepine toxicity.
  There is a risk of seizure as the effect of benzodiazepine is antagonized.
  Flumazenil cannot be used for barbiturate poisoning and is only an antidote for benzodiazepine poisoning.

Antagonist of GABA is a toxin called bicuculine which binds to the GABA binding site. Can cause seizures as well.

Z-compounds : α subunit is further made up of $\alpha 1$ and $\alpha 2$ subunits. $\alpha 2$ is responsible for antiepileptic and muscle relaxant effects. $\alpha 1$ is responsible for sedation and hypnosis. Z-compounds selectively stimulate $\alpha 1$ subunit. They are primarily used in treatment of insomnia.

Benzodiazepines 00:14:55

They are classified into three types based on the metabolism.

1. metabolized both in phase I (CYP3A4) and II (Glucuronidation). They are the longest acting class of BZDs. Least chance of dependance and withdrawal. Maximum sedation.
   E.g. Diazepam, Clorazepate, Chlordiazepoxide, Quazepam and Flurazepam (maximum $T_{1/2}$).
2. metabolized in phase I by CYP3A4 and in phase II by faster glucuronidation. Shortest acting class of BZDs.
   E.g. Triazolam and Midazolam.
3. metabolized by phase II or by direct glucuronidation. Short acting BZDs. No active metabolites. Safer to use in the elderly and in liver failure.
   E.g. Lorazepam, Temazepam, Oxazepam and Estazolam.

Longer the action of BZDs, lesser the chance of dependence and craving. Hence, Class I drugs have the least chance of dependence and withdrawal.
Active metabolites are formed in phase I reaction thus, class 3 BZDs do not have any active metabolites.

Uses of benzodiazepine

00:26:05

Uses include :

- Antiepileptics : Intravenous lorazepam > diazepam. These are preferred in treatment of status epilepticus.
  Single best drug of choice (DOC) in status epilepticus is lorazepam.

  Clonazepam (oral) is used in
  1. Juvenile myoclonic seizure.
  2. Absence seizure.
  3. Infantile spasm.

  Clorazepate (oral) is used to treat partial seizure.

  Clobazam (oral) is used to treat :
  1. Lennox Gastaut syndrome and Dravet syndrome. Clobazam is mostly used as an add on drug.
  2. Febrile seizures.

  BZDs used intranasally :
  1. Clonazepam
  2. Midazolam

  } To treat acute repetitive seizure/crescendo seizure.

  Rectal diazepam is the DOC for treatment and prophylaxis of febrile seizures at home.

- Insomnia : (Mnemonic - QIET). Benzodiazepines are less preferred than the Z-compounds in treating insomnia.
  1. Quazepam.
  2. Flurazepam. (S/E: can cause nightmares).
  3. Estazolam.
  4. Temazepam and Triazolam.
- Anxiety treatment :
  1. Diazepam.
  2. Clorazepate.
  3. Chlordiazepoxide.
  4. Alprazolam : Mostly used to treat anxiety. Can be given the night before surgery to relieve pre-operative anxiety.
- Muscle relaxation : only Diazepam is used.
- Analgesia : Intrathecal midazolam to produce analgesia.

- Alcohol dependence or withdrawal symptoms.
    1. Diazepam.
    2. Clorazepate.
    3. Chlordiazepoxide: Preferred except in patients with seizures. Diazepam is preferred in that case.
- BZD of abuse : Flunitrazepam is a tasteless drug used commonly as date rape drug. It is also mixed with beer and consumed by drug abusers (also known as roofie). Alcohol and BZDs have a synergistic effect.

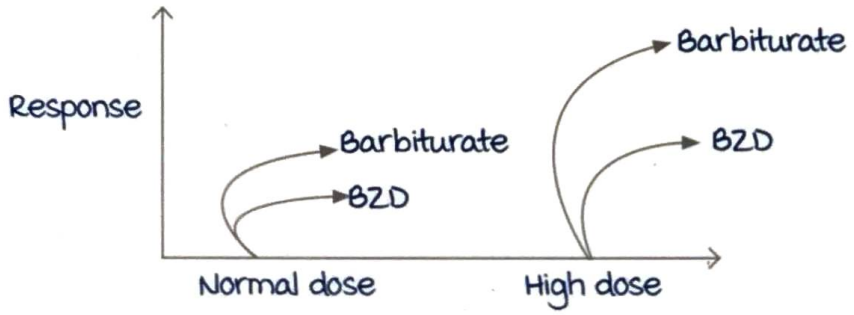
CNS side effects of benzodiazepines :

- Drowsiness.
- Confusion.
- Paradoxical disinhibition or stimulation characterized by anxiety, seizure and euphoria.
- Anterograde amnesia.

Barbiturates

00:39:08

Mechanism of action by GABA-A agonism (like BZDs) and this effect is called GABA facilitatory effect.
They decrease the levels of excitatory neurotransmitter glutamate.
Barbiturates have GABA mimetic action when used in high doses.
These drugs have a steep dose response curve (DRC) and are highly unsafe to use.



Classification of barbiturates 00:43:10

Barbiturates are classified into :

- Ultrashort acting : They have very high lipid solubility and undergo redistribution.
  1. Thiopentone (Preferred).
  2. Methohexital (used in patients during electroconvulsive therapy).

  These drugs are used as intravenous anesthetic agents for induction or maintenance.
- Short acting :
  1. Butobarbital.
  2. Secobarbital.
  3. Pentobarbital.

  These drugs are used as pre-anesthetic medication.
- Long acting :
  1. Mephobarbital.
  2. Phenobarbital : It is the DOC for treatment of seizures in neonates as phenobarbital decreases cerebral metabolism and thus cerebral oxygen demand.
     Most common cause of seizures in neonates is hypoxic ischemic encephalopathy (HIE).
     It is the DOC for treating Crigler-Najjar syndrome type II as it induces glucoronosyl transferase.
     Phenobarbital is the third line drug in treating status epilepticus.

Side effects of barbiturates :

- CNS :
  1. Confusion.
  2. Drowsiness.
  3. Paradoxical disinhibition causing seizures.
- Hyperalgesia.

Acute intermittent porphyria : Barbiturates are enzyme inducers and can induce δ aminolevulinic acid synthase leading to increased porphyrin synthesis.

Z-compounds 00:50:35

These drugs are preferred to BZDs in :

- Insomnia : For sleep induction and maintenance.
- Jet lag.

Examples of Z-compounds include :

- Zolpidem.
- Zaleplon.
- Eszopiclone (S isomer of zopiclone).

Melatonin agonists 00:52:30

Physiology link:
Darkness stimulates pineal gland to release melatonin which in turn stimulates melatonin 1 and 2 receptors in the hypothalamus. It is responsible for the physiological sleep induction.

Ramelteon is a drug which stimulates melatonin 1 and 2 which can be used only for sleep induction (not for maintenance).
It has good oral absorption but undergoes a very high first pass metabolism leading to low oral bioavailability (~2%).
Half-life is ~2 hours.
Ramelteon is used for :

- Sleep induction.
- Jet lag.

It is less efficacious as compared to BZDs or Z-compounds.
Ramelteon has lesser chance of addiction or dependence.
They do not cause drowsiness or confusion.

Other melatonin agonists include :

- Agomelatine is used in treatment of resistant depression.
- Tasimelton is used to treat sleep awake disorder in blind people.

- Chloral hydrate :
  It is metabolized into trichloro ethanol which stimulates the GABA-A receptor. It is used in the treatment of paradoxical seizures (caused by BZDs or barbiturates).
  Chloral hydrate is a drug of abuse and is used to make mickey Finn cocktail where it known as knock out drops.

- Carisopodol : 60c6b3eeaa8ded0e4e7e5ea7
  It is a prodrug of meprobamate. The drug is used as a muscle relaxant and meprobamate is used as an anxiolytic.

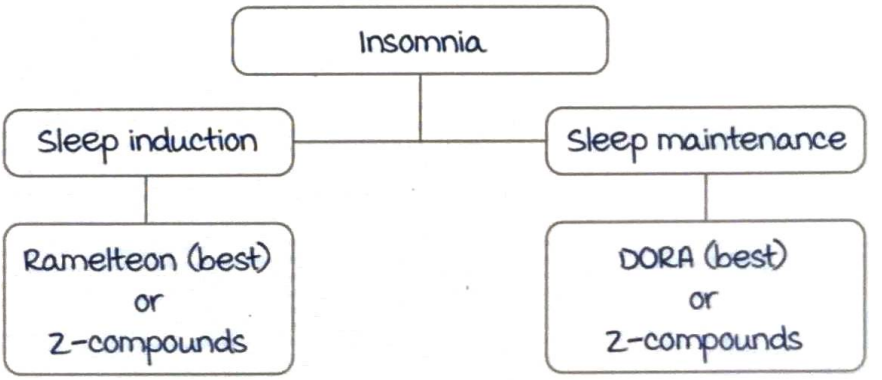
Recent advances in treatment of insomnia 01:02:18

Dual orexin receptor antagonist (DORA) :
Lateral hypothalamus releases Orexin A and B. Orexin A stimulates orexin 1 and 2 receptors. Orexin B stimulates orexin 2 receptors.
Together it increases wakefulness, appetite and produce an anti-stress effect.
The drugs include :

- Suvorexant.
- Daridorexant (released in 2021).

These drugs are used orally for sleep maintenance.
Side effects include worsening of depression and suicidal tendency.

Summary of treatment of insomnia 01:06:14



Sedative Hypnotic Drugs Summary

- GABA-A Agonists
  - Benzodiazepines
    1. Long acting :
       - Diazepam
       - Clorazepate
       - Quazepam
       - Flurazepam
    2. Shortest acting :
       - Triazolam
       - Midazolam
    3. Short acting :
       - Lorazepam
       - Temazepam
       - Oxazepam
       - Estazolam
  - Barbiturates
    1. Long acting :
       - Phenobarbital
    2. Shortest acting :
       - Thiopentone
       - methohexital
    3. Short acting:
       - Butobarbital
       - Secobarbital
       - Pentobarbital
  - Z compounds
    1. Zolpidem
    2. Zaleplon
    3. Eszopiclone
- Melatonin Agonists

OPIOIDS

Receptors 00:00:33

3 types of receptors :

- μ receptor effects (mnemonic : MUSCARINE)
  Miosis.
  Urine retention.
  Sedation.
  Constipation.
  Analgesia.
  Respiratory depression.
  Increased muscle rigidity.
  Negate bile flow by contraction of sphincter of Oddi (still can be used in biliary colic).
  Euphoria : Elevated mood.
  Causes contraction of circular smooth muscles & relaxation of longitudinal smooth muscles.
- κ receptor effects (mnemonic : CAP)
  Constipation.
  Analgesia.
  Antipruritic effect.
  Psychomimetic effect (dysphoria).
  K receptor agonist (Difelikefalin): Recently approved for treatment of pruritis associated with chronic kidney disease patients on dialysis.
- δ receptor effects :
  Analgesia.
  Modulate release of neurotransmitters and hormones.
  Common effect of all 3 receptors is Analgesia.

Endogenous opioids :
Enkephalin : more potent on δ receptors.
Endorphin : more potent on μ receptors.
Dynorphin : more potent on κ receptors.

Exogenous opioids :

Classification based on their source :

Natural/opiates	Semisynthetic	Synthetic
Derived from plant Papaver somniferum (poppy plant).  60c6b3eeaa8ded0e4e7e5ea7 Opioid derivatives : Codeine. Morphine (maximum amount can be derived). Non opioid derivatives : Thebaine. Noscapine is a non opioid antitussive. Papaverine : Blocks PDE –> Increases Cyclic AMP –> smooth muscle relaxation. Used in treatment of GIT, urethra, biliary spasm.	Derived from natural opioids. Morphine derivatives : Heroin (opioid derivative) : more potent, crosses blood brain barrier more. Thus producing more Rush. Apomorphine (non opioid derivative of morphine) : D2 receptor agonist. Used in Parkinson's disease. Hydromorphone : Used as an analgesic. Ethylmorphine & Pholcodine are used as antitussives. Codeine derivatives : Hydrocodone as analgesic. Thebaine derivatives : Buprenorphine. Oxycodone & Oxymorphone are used as opioid analgesic/ antitussive.	Fentanyl : 100 times more potent than morphine. Used along with Pentazocine in sequential opioid analgesia/anesthesia. Side effect : wooden/rigid chest syndrome. Alfentanil : 20 times more potent. Used along with Propofol for TIVA (Total intravenous anesthesia). Sufentanil : 1000 times more potent. most potent opioid. Max PPB (Plasma protein binding) Use : Blocks stress response in procedures like bronchoscopy, intubation. Remifentanil : metabolized by Plasmaesterase. shortest and fastest acting opioid. Given by continuous IV infusion. Mostly used for daycare procedures. Pethidine. Methadone. Tramadol/Tapentodol.

Opioid-receptor interaction

Full agonists :

Morphine :

Pharmacokinetics :

metabolized in the liver to form active compounds and excreted by kidneys. Half-life is 2 hours but is long acting as the active compounds have a half-life of 24 hours.

Contraindicated in liver and kidney failure (morphine toxicity).

Uses :

- Analgesic in severelabour pain, cancer, myocardial Infarction (MI).
- Pulmonary edema : Decreases preload.
- Antitussive in severe intractable cough (bronchogenic cancer).

Contraindications :

- Head trauma (absolute C/I) : Can increase ICP.
- Bronchial asthma/COPD (relative C/I) : Can increase histamine and cause bronchoconstriction.

Codeine :

In the liver, 90% of codeine is inactivated by glucuronidation, 10% is activated by CYP2D6 to morphine.

Uses :

- Antitussive in mild/moderate cough.
- Analgesic in mild/moderate pain.

Pharmacogenetic condition : If there is decreased CYP2D6, effect of codeine is decreased.

Side effect : Constipation.

Pethidine or Meperidine :

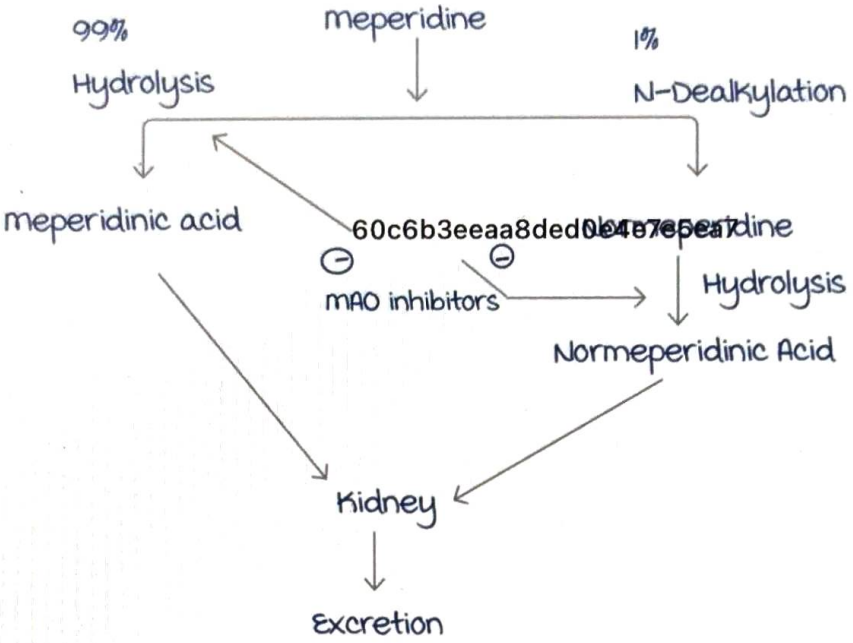
Used as an analgesic in labour pain, postoperative pain.

DOC for post-op/post-anesthetic chills by α_a agonism. (used for maximum 48 hours because of toxicity).

DOC for chills caused by monoclonal antibodies, drugs like Amphotericin B.

Active space

Pharmacokinetics :



Contraindications :

- MAO inhibitors block hydrolysis leading to accumulation of normeperidine, which is neurotoxic and causes seizures.
  Normeperidine itself is a MAO inhibitor leading to surge of 5HT and causes Serotonin syndrome.
- In renal failure.

Side effects : Hypotension. Used judiciously in hypovolemic and MI patients.

Methadone :

Pharmacokinetics :

- IV route : Analgesic effect is seen in 10–20 mins.
- Oral route : Analgesic effect is seen in 1 hour.

Because of extensive sequestration in tissues, withdrawal symptoms are not seen.

Uses :

- In opioid dependance as there are no withdrawal symptoms.
- In chronic pain.
- As antitussive in bronchogenic cancer.

Side effects :

- QT prolongation.
- Anticholinergic side effects.

Loperamide (DOC)	Uses : Non secretory diarrhea in IBS & due to Irinotecan. Reduces motility of intestine.	Does not cross BBB (no dependance).
Diphenoxylate Difenoxin		Crosses BBB (abuse potential). combined with atropine to prevent abuse.

Tramadol/Tapentadol :

Inhibits reuptake of 5HT/NE, thus contraindicated with MAO inhibitors.

Uses :

- Analgesic in Mild to moderate pain.
- Post-operative or post-anaesthetic chills.

Oliceridine (approved in 2020) : used as an analgesic through IV route for acute severe pain.

Mixed agonist/antagonist

00:55:26

Mnemonic: Do Not Mix Pani with Bodka.

Dezocine	All drugs act as antagonists at mu receptor except Pentazocine. side effects of mu are not seen. All drugs act as full agonists at Kappa receptor : Produces analgesia.		All the drugs are analgesics with better side effect profile. Common Side effect : dysphoria.
Nalbuphine			
Nalorphine		Previously used in opioid toxicity.	
Pentazocine Partial agonist at mu receptor but behaves as an antagonist.		Contraindicated in MI (as it increases HR and worsens ischemia).	
Butorphanol			

Buprenorphine	Partial agonist at mu and antagonist at Kappa. Binds to mu with high affinity. No withdrawal symptoms are seen. Used in opioid dependence. Used in chronic pain. Limited use because of ceiling effect. Contraindicated in labour pain as naloxone cannot reverse neonatal respiratory depression caused by buprenorphine.

Pure antagonist 01:06:10

60c6b3eeaa8ded0e4e7e5ea7

Central : Can cross BBB.

- Naloxone : Short acting. Given via IV. DOC in opiod toxicity. Side effects due to increased catecholamines (HTN, arrhythmia, pulmonary edema).
- Nalmefene : Long acting. Given via IV and oral route. Oral drug is used in alcohol dependence.
- Noltrexone : Longest acting. Given via oral route. Used to treat alcohol and opioid dependence (prevents relapse). Used along with morphine to prevent abuse/dependence. Used along with Bupropion to treat obesity. Side effects : Hepatoxicity (do LFT), dysphoria (C/I in depression).

Peripheral : Cannot cross BBB.

Uses are because of effects on GIT.

- Alvimopan : Post-op ileus.
- methyl naltrexone
- Naloxegol
- Naldemedine

Used in treatment of opioid induced constipation.

Opioid addiction 01:13:38

Mainly occurs due to euphoria.

Tolerance: Continuous increase in dosage to get a response.

Tolerance develops to all effects of opioids except :

- Constipation.
- Convulsion.
- Miosis.

Withdrawal symptoms :

Severity is directly proportional to dose and potency.

Mnemonic : WITHDRAWAL/Opposite effects of mu receptor.

W – (m) Mydriasis.

I – Increased yawning.

T – Hyperthermia.

H – Hyperventilation.

D – Diarrhoea.

R – Rhinorrhoea.

A – Anxiety.

W – (m) Myalgia.

L – Lacrimation.

Deaddiction

01:21:18

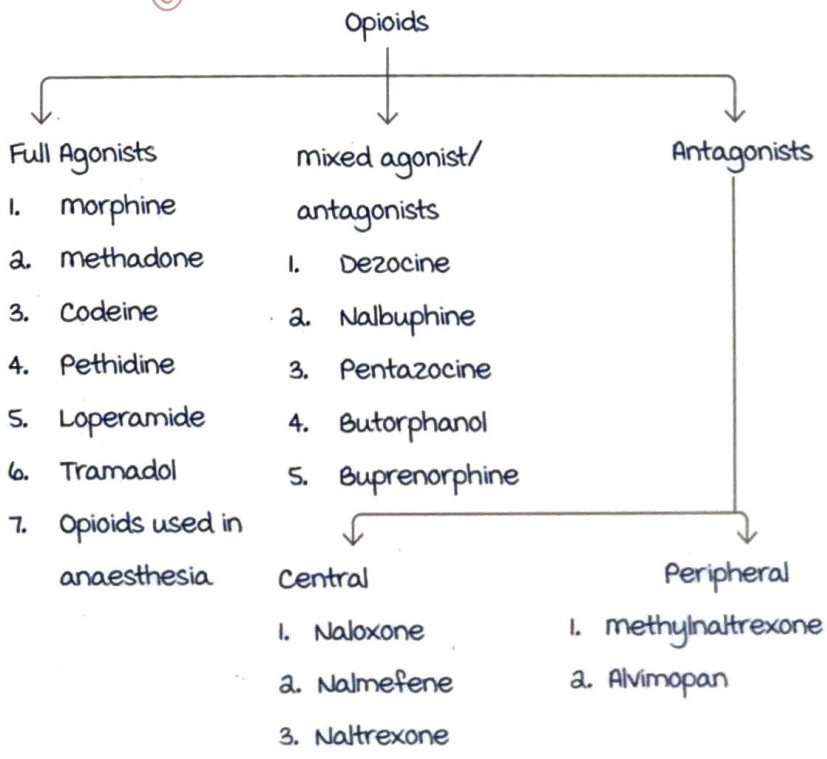
Aim :

To reduce withdrawal symptoms.

Start on Methadone/Buprenorphine.

Upon tapering the dose, if there are any mild withdrawal symptoms treat with β-blockers, Clonidine.

To prevent relapse, block opioid receptors with Naltrexone.

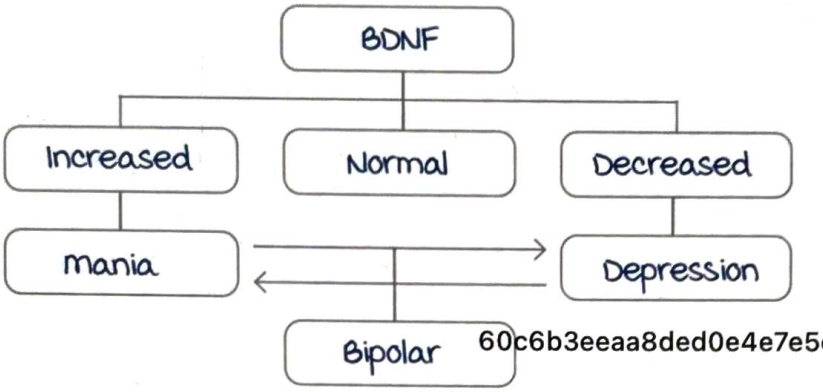


AFFECT DISORDER - 1

Affect disorder

00:00:46

All affect disorders depend on the Brain derived neurotropic factor (BDNF). In a diseased state the BDNF can either be increased or decreased.



If the levels of BDNF fluctuates from one pole to the other, there could be fluctuating episodes of mania and depression termed as bipolar disorder.
If there are more than 4 fluctuations in a year, it is termed as rapid cycler.

Anti-mania and bipolar disorder drugs

00:04:08

Lithium :
Pathways for BDNF synthesis include :

β catenin pathway : β catenin is a cytoplasmic factor which enters the nucleus and increases the production of BDNF.

Stimulation of F_2 or Frizzle receptor on the neuron
↓
Increases production of glycogen synthase kinase 3 (GSK3)
↓
Breaks β catenin
↓
Decreasing the production of BDNF

If there is excess BDNF in the brain, there is stimulation of the F_2 receptor resulting in decreased levels of BDNF.

G-protein coupled receptor (GPCR) pathway :

When the Gq receptor in the neuron is stimulated

↓

Phosphatidyl inositol bisphosphonate (PIP2) increases

↓

Breaks down into inositol triphosphate (IP3).

↓

BDNF is produced.

BDNF is responsible for neuroplasticity and neuroprotection.

GPCR pathway is initiated when the levels of BDNF drops in the brain.

IP3 breaks down into inositol monophosphate → Inositol → recycled for PIP2 synthesis.

Inositol monophosphatase converts inositol monophosphate into inositol.

Lithium blocks G_q subtype receptor and inositol monophosphatase enzyme

↓

Decrease in BDNF levels

↓

Decrease neuroplasticity and neuroprotection.

Mania is controlled by this mechanism.

A minimum treatment duration of 2 weeks with lithium is required for this effect.

Lithium is not the drug of choice (DOC) for acute mania as it is not immediately effective.

Lithium is the DOC for prophylaxis of mania.

DOC for acute mania : Atypical antipsychotics as they are the fastest acting anti-mania drugs.

These may be combined with benzodiazepines.

Alternative drugs for acute mania include valproate and carbamazepine.

Lithium is also started during an acute attack. It is given for almost 2 months and then is continued as monotherapy.

It is the DOC for bipolar disorder. Given for prevention of mania or depression.

Lithium also inhibits GSK3 leading to an increased level of β-catenin causing an increased synthesis of BDNF. Hence can be used in treatment of resistant unipolar depression.
Lithium or lithium like drugs are called mood stabilizers.

Treatments which decrease suicidal tendency :

- Lithium.
- Clozapine.
- Electro convulsive therapy (ECT).

Other uses of lithium :

- DOC for hypnic headache (headache during sleeping) as long term prophylaxis.
- Leucopenia.

Side effects of lithium

00:22:24

Lithium blocks GPCR in the brain and two other GPCRs like :

1. Vasopressin$_a$ receptor :
   Lithium induced diabetes insipidus. DOC for treatment is amiloride. Thiazides can also be used.
2. Thyroid stimulating hormone receptor : causing hypothyroidism.

Other side effects include :

- Fine tremors even at normal plasma concentration.
- Increased parathyroid hormone causing hypercalcemia.
- Acne.
- Obesity.
- Worsening of psoriasis.
- Lithium is a teratogenic drug causing Ebstein's anomaly (cardiac defect). The right atrium expands (atrialization of the ventricles) leading to ventricular outflow tract obstruction. Hence, contraindicated in first trimester of pregnancy.

The DOC for mania during pregnancy is atypical antipsychotics.
Aripiprazole is the preferred atypical antipsychotic.

Lithium can cause floppy infant (also seen with botulism). It

blocks transmission at the neuromuscular junction thus causing hypotonia.

Lithium toxicity 00:28:21

Earliest presentation of lithium toxicity :

- Nausea and vomiting.
- Profuse diarrhoea.

If not treated, it progresses to :

- Ataxia.
- Dysarthria.
- Coarse tremors.
- Arrhythmia or seizure.
- Coma.

Dialysis is the treatment for lithium toxicity.

Lithium is a drug with low therapeutic index and therapeutic drug monitoring (TDM) must be done by measuring the plasma concentration.

The first sampling is done 5 days after starting the drug.
The half-life of lithium is 24 hours and steady state concentration is achieved after 4 to 5 half-lives.
The blood sample is taken 12 hours after the last dose.

Normal plasma concentration of lithium (old standard) :

- 0.6 – 1.0 mEq/L for mania prophylaxis.
- 1.0 – 1.5 mEq/L for acute mania.

Therapeutic range = 0.6 – 1.5 mEq/L.

Currently, the concentration is maintained at 1 mEq/L.
Signs and symptoms of toxicity appear when the concentration exceeds 1.5 mEq/L.
Concentration > 4.0 mEq/L is an indication for dialysis.

Drug interactions of lithium 00:37:04

The structure of lithium is like sodium. Conditions causing sodium loss or deficiency can lead to lithium retention causing lithium toxicity. Such conditions include :

- Diuretics use :

Thiazides > K^+ sparing/ loop diuretics → Lithium retention.
Osmotic diuretics and carbonic anhydrase inhibitors can increase lithium clearance.

- Severe nausea/vomiting or diarrhea
- Prolonged fasting

} measure serum electrolytes and lithium.

Other drug interactions :

- Renin-angiotensin-aldosterone system (RAAS) inhibitors/ non-steroidal anti-inflammatory drugs (NSAIDs) decrease lithium clearance as they alter glomerular filtration rate.
- Muscle relaxants : Lithium can increase the effect of muscle relaxants and is hence stopped 24 – 48 hours before surgery (24 hours > 48 hours).

Other drugs in mania and bipolar disorders 00:43:33

These drugs include (mnemonic : VOLTAGE)

- Valproate : DOC in rapid cyclers.
- Oxcarbazepine/Carbamazepine.
- Lamotrigine : Antiepileptic used to treat bipolar disorder.
- Topiramate.
- Antipsychotics (atypical > typical).
- Gabapentin.

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AFFECT DISORDER - 2

Antidepressants 00:00:23

monoamine hypothesis :
Depression is a result of decrease in monoamines like serotonin and norepinephrine in the synapse. Leading to decrease in BDNF.
Serotonin is most important amine involved in depression.

Serotonin and norepinephrine are metabolised by MAO (inhibited by MAOIs).
They also undergo reuptake (inhibited by tricyclic antidepressants, SNRIs, SSRIs).

TCA blocks a range of receptors like H, muscarinic, 5HT, α 1 causing more side effects.

SNRI (serotonin norepinephrine reuptake inhibitors) : Only block Serotonin and norepinephrine reuptake.
SSRI (Selective serotonin reuptake inhibitors) : DOC for depression

Selective norepinephrine reuptake inhibitor:
Atomoxetine, Viloxazine.
Not used for treatment of depression.
Used in ADHD.

Classification of antidepressants :
Typical antidepressants :
Increase 5HT, NE → Increase in BDNF.
(Lag period : Antidepressant effect takes minimum of 2 weeks).
MAOIs, TCA, SNRI, SSRI.

Atypical antidepressants :

- 5HT2 receptor inhibitors.
- Bupropion (increases dopamine and NE)

Active space

Drugs used in the treatment of depression

00:13:27

MAO Inhibitors :

Broadly subclassified into

- Non selective MAOIs (A & B) : Irreversible (hit and run drugs).
  Phenelzine, Isocarboxazid, Tranylcipromine.
- Selective MAO A inhibitors : Reversible.
  moclebemide, Eprobemide.

Use : They are second line drugs for treatment of depression.
They are more effective in atypical depression.

Adverse effects : Hepatoxicity.

Cheese reaction

MAOIs when consumed with cheese block metabolism of tyramine → thereby increasing NE causing HTN crisis.
DOC for cheese reaction is IV phentolamine.

Serotonin syndrome

MAOI are contraindicated with SSRI, SNRI, TCA, Amphetamine, methylphenidate, Opioids, Pethidine, Tramadol.
It causes severe muscle rigidity, hyperthermia, tremors, tachycardia, elevated BP, akathisia (restlessness).

Treatment :
Mild cases : Benzodiazepines.
Moderate to severe : Cyproheptadine/Chlorpromazine.

Tricyclic Antidepressants

00:21:02

Used as second line in treatment of depression (typical).
Drugs :
Clomipramine : Maximum SHT reuptake inhibitor.
Used for resistant OCD (DOC for OCD is SSRIs).
Desipramine : Causes maximum NE and Dopamine reuptake inhibition. Used in cocaine dependence.
It is the most lethal TCA on overdosing.
Imipramine : Used for nocturnal enuresis.
Amitriptyline : most effective TCA for neuropathic pain.

m/c cause of lethality due to overdosing.
Maximum antimuscarinic action.

Nortriptyline : Used in smoking dependence.
Doxepin : H_1 blocker used as TCA.
Amoxapine : D_a blocker used in psychotic depression.
Loxapine : Antipsychotic. Developed from Amoxapine.

Side effects due to blockage of other receptors (Caused by TCA, antipsychotics) :
Muscarinic blockade : mydriasis, constipation, urine retention (Contraindicated in closed angle glaucoma).
H_1 blockade : Obesity, sedation.
5HT blockade : Obesity.
α 1 blockade : Postural hypotension.

Toxicity : High risk of suicidal deaths.
Death is usually due to arrythmia (quinidine like effect : Na channel blocker).
DOC for TCA toxicity : Sodium bicarbonate.

SNRI

00:34:45

Better than TCA.
Uses :
First line drugs for depression (typical).
Anxiety disorders.
Hot flushes.

Drugs :
Venlafaxine : Very short acting. It is associated with withdrawal symptoms. Also used in PTSD, HTN, panic disorder.

Desvelnafaxine : Longer acting. Less association with withdrawal symptoms.
Milnacipran/Levomilnacipran : Used in fibromyalgia.
Duloxetine : Used in fibromyalgia, neuropathic pain, PMS, stress incontinence. It is longest acting. Minimum risk of withdrawal symptoms.
Side effects : Same as SSRI (because of high serotonin levels).
Milnacipran and Duloxetine can cause anticholinergic side

effects. (Contraindicated in closed angle glaucoma).
Duloxetine can cause mild sedation.

SSRI

00:39:40

They are the DOC for depression (both typical and atypical), premenstrual syndrome (PMS).
They can be used in postmenopausal hot flashes (DOC : HRT).
DOC for neurosis.
Used in OCD, phobia, PTSD, GAD, anorexia, bulimia.

Drugs :
Fluoxetine : Half life of 50 hours.
Prodrug activated into norfluoxetine.
Norfluoxetine has half-life of 200 Hours.
It is the longest acting (no withdrawal symptoms).
Only SSRI with once a week formulation.

Fluvoxamine : Preferred in OCD, anxiety.
Citalopram : Preferred in PMS.
Escitalopram : Most specific SSRI.

Paroxetine : Risk of maximum erectile dysfunction.
Maximum enzyme inhibition of CYP_2D_6.
Teratogenic. C/I in pregnancy.
It is also H_1 blocker (sedation) : Only SSRI with night time dosing.
Used in depression associated with insomnia.
Short half life. Shortest acting SSRI (risk of withdrawal symptoms).
Only SSRI without any active metabolite.

Withdrawal symptoms : Anxiety, insomnia and irritability.
Maximum with Venlafaxine, Paroxetine.
Minimum with Fluoxetine, Duloxetine.
Novel drugs :

- Vilazodone : SSRI plus $5HT_{1A}$ agonist.
- Vortioxetine : SSRI with partial agonism at $5HT_{1A/1B}$, antagonist at $5HT_D/5HT_3/5HT_7$.

Used in resistant depression.
Both drugs do not cause erectile dysfunction.

Side effects of SSRIs :
Increases serotonin all over in the body.
Stimulate receptors like SHT_2/SHT_3/SHT_4.
Side effects from Brain :
Anxiety (transient), insomnia and vivid dreams.
Side effects from Spinal cord side :
Erectile dysfunction, anorgasmia, delayed ejaculation (Secondary used in premature ejaculation).

Mechanism of anxiolysis and anxiety with SSRI :
When serotonin stimulate SHT_2 receptors : Anxiety (persists for 2-6 weeks).
After that SHT_2 receptors downregulates : Anxiolysis.
BZD are given for 1 month to counter the transient anxiety.
Dosing of SSRI in insomnia : morning.

SHT_3 : Nausea and vomiting (m/c)
SHT_4 : Loose stools.
m/c delayed side effect is erectile dysfunction.
Others : Akathisia, increase risk of bleeding (decrease 5HT in platelets).

Drugs used in Atypical depression 00:57:12

SHT_2 blockers

Older drugs :

- Trazadone

  Uses :

  Used with other antidepressants like SSRIs, SNRIs to treat insomnia.

  Treatment of erectile dysfunction.

  Side effects : Priapism, sedation.

- Nefazodone (not preferred because of hepatoxicity).

Newer drugs :
Mirtazapine.
Mianserin.

Mechanism of action :

- $5HT_3$ blockade : Anti emetic effect.
- α2 blockade : Increases release of serotonin and NE (antidepressant effect).
- 5HT2 blockade : Antidepressant effect.
  5HT2 and α2 blockers are also called as NASSA (noradrenergic specific serotonergic antidepressant drugs).
- H_1-blockade : Sedation.

Lesser risk of erectile dysfunction.

Use : DOC for depression with insomnia/ED.

Side effects : Mirtazapine can cause agranulocytosis.

Bupropion

01:02:05

Structurally similar to Amphetamine.

Mechanism of action : Increase dopamine and NE (increase release and inhibit reuptake).

Use : ADHD.
Obesity.
Depression (2nd line).
Smoking dependence.
Used for treatment of peripheral neuropathy.

Side effects : most anxiogenic anti-depressant.
Stimulant side effects like agitation, insomnia, seizure
Decreased appetite causes weight loss.

Recent antidepressants :

Brexalonone : Approved for postpartum depression. IV route for 60 hours.

Esketamine : Given in the form of nasal spray.
Used as add-on to other anti depressants.

Antidepressants and Antimanic and BPD Drugs summary

Antidepressants

Typical

1. MAOI
2. TCA
3. SNRI
4. SSRI

Atypical

1. SHT-2 blockers
   Trazadone
   Nefazodone
   mirtazapine
2. Vilazodone
3. Bupropion

Antimanic and BPD Drugs

1. Lithium
2. Valproate
3. Carbamazepine
4. Lamotrigine
5. Topiramate
6. Antipsychotics

ANTIPSYCHOTICS

Dopamine hypothesis

00:00:36

Increased level of dopamine in limbic system

↓

Stimulates D_a (Gi) receptor

↓

Blocks function of limbic system

↓

Blocks thought and affect.

Thus, drugs blocking D_a receptor were developed and termed as typical antipsychotics.

Drawback : Causes many side effects together referred to as EPS (Extrapyramidal side effects).

Serotonin (5HT) hypothesis :

A group of scientists accidentally found increased levels of 5HT in the urine of LSD abusers.

LSD is a hallucinogen and hallucinations are cardinal symptom of psychosis.

They hypothesized that increased stimulation of $5HT_a$ receptors in brain may lead to psychosis.

Drugs blocking $5HT_a$ were developed and termed as atypical antipsychotics.

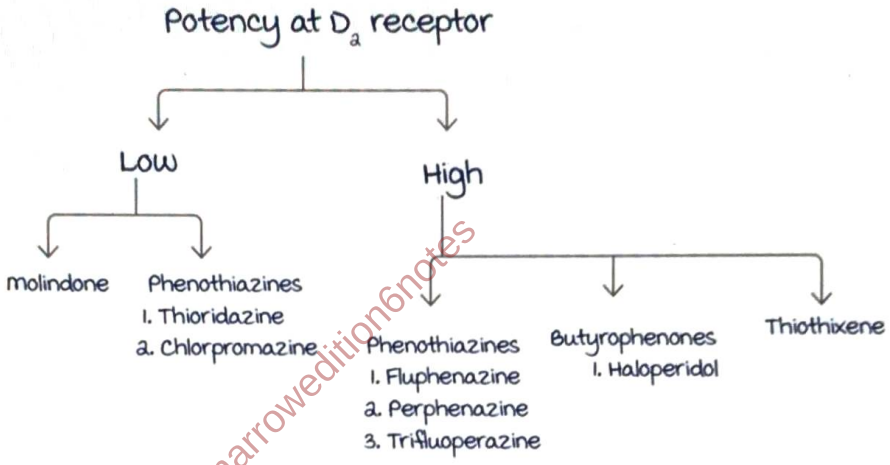
Typical antipsychotics	Atypical antipsychotics
Block D_a receptors. Causes significant EPS. Uses : Schizophrenia : 2nd line drugs. Rheumatic chorea. (DOC is Valproate or carbamazepine).	Block $5HT_a$ and mildly D_a receptors. Causes mild EPS. Uses : Schizophrenia : 1st line drugs except clozapine and olanzapine. Antidepressants : As add on drugs.

Atypical antipsychotics are preferred over typical antipsychotics in the treatment of :

- mania/bipolar disorder.
- Huntington's chorea.
- Tics associated with tourette syndrome.
- Antiemetics (Olanzapine in chemo induced vomiting).

Antipsychotic drugs 00:10:58

Typical antipsychotics :



Atypical antipsychotics :

Clozapine :

Minimum D_a blockade among all atypical antipsychotics.

most toxic antipsychotic. It causes :

Seizures (denovo seizures),

myocarditis.

Agranulocytosis.

- It has poor correlation with plasma concentration.
- Contraindicated with carbamazepine as it also causes agranulocytosis.
- Associated with HLA DQB1 gene.

most effective antipsychotic.

Uses :

Drug of choice for resistant schizophrenia (mechanism of action : Blocks D_4 receptor).

Drug of choice for suicidal tendency.

Other treatments for decreasing suicidal tendency :
Lithium.
ECT (Electro convulsive therapy).

Quetiapine :
Uses :
- Depression : Can be given as monotherapy.
- Insomnia.

Side effects :
Cataract.
QT Prolongation : Maximum with Ziprasidone. Minimum with Sertindole. Overall QT prolongation is more common with typical > atypical AP.

Risperidone/Iloperidone :
Causes maximum D_2 block.

Aripiprazole/Brexpiprazole :
Mechanism of action : $5HT_{1A}$ blocker and partial agonist at D_2 and $5HT_{1A}$.

Cariprazine :
Mechanism of action : $5HT_{1A}$ blocker and partial agonist at D_2 and D_3.

Drugs with partial agonism at D_2 cause hypoprolactinemia.
Drugs blocking D_2 receptors cause hyperprolactinemia.

Pimavanserin :
Mechanism of action : Only blocks 5HT2. No action on D_2.
Thus, no Extra pyramidal symptoms and no worsening of parkinson's disease.
Drug of choice for levodopa induced psychosis.

Side effects of antipsychotics

00:26:24

mechanism of action and side effects of antipsychotics.	Blocking D_2 receptor causes : EPS. Hyperprolactinemia.	Blocking muscarinic receptors cause mydriasis (contraindicated in closed angle glaucoma). Constipation . Urine retention. Blocking H_1 receptor causes sedation. Blocking 5HT and H_1 receptors cause obesity. Blocking α_1 receptors cause postural hypotension. metabolic side effects : Dyslipidemia. Insulin resistance causing hyperglycemia and diabetes mellitus.
Typical antipsychotics	Maximum with high potency drugs like haloperidol. Minimum in low potency drugs like thioridazine.	Maximum in low potency drugs. Minimum in high potency drugs.
Atypical antipsychotics	Maximum with high potency drugs like Risperidone. Minimum in low potency drugs like Clozapine.	Maximum in Clozapine > Olanzapine. Minimum with Risperidone. These side effects are not seen in : Aripiprazole, Cariprazine, Ziprasidone — Weight neutral

EPS (Extrapyramidal side effects)

00:35:41

Akathisia :

Most common EPS.

Cause : Unknown.

Patient becomes restless.

Drug of choice : β-blockers.

Acute Dystonia

Acute dystonia :
Earliest EPS.
Abnormal posturing.
(Antiemetic that cause acute dystonia : metoclopramide)
It is more common in young patients

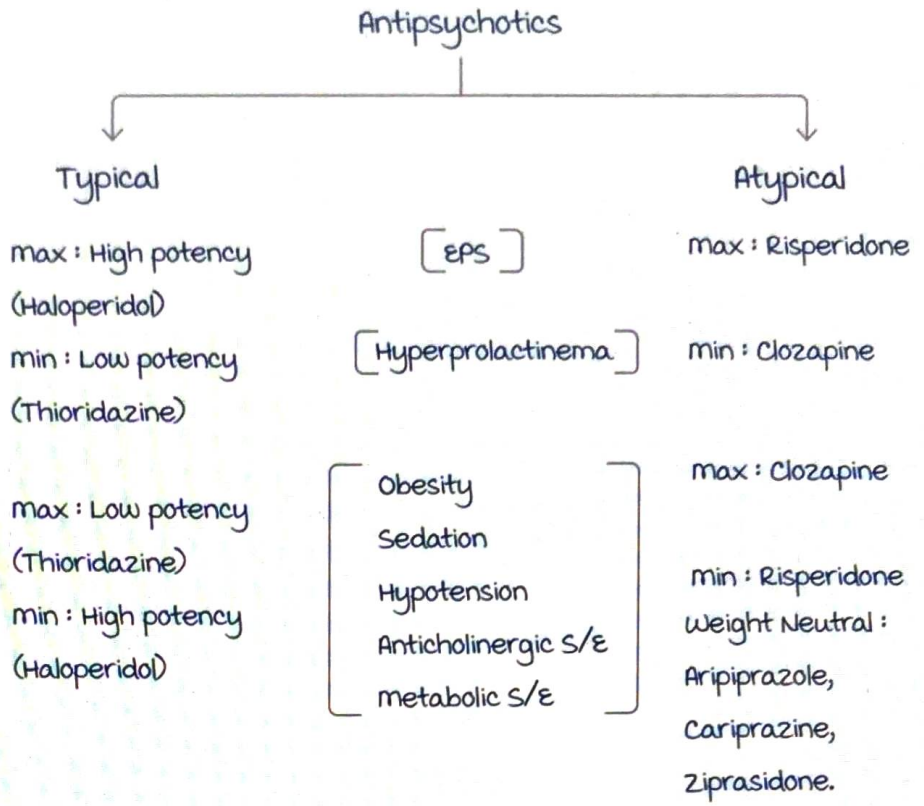
Parkinsonism is an EPS causing tremors, bradykinesia.
To treat parkinsonism, it is better to block cholinergic effect than to increase dopamine (worsens psychosis).

Drugs of choice :

- Anticholinergics : Benzhexol (trihexyphenidyl), Benztropine, Biperiden.
- Antihistamines having maximum anticholinergic effects : Promethazine, Diphenhydramine, Dimenhydrinate.

Tardive dyskinesia :
Abnormal slow movements that develop over the years.
most late EPS.
Cause : Upregulation of D_2 receptors due to blockade for a long time.
Drug of choice : VMAT2 inhibitors like Valbenazine, Deutetrabenazine.

Neuroleptic Malignant Syndrome (NMS) :
most severe/lethal form of EPS.
Cause : D_2 receptor blockade.
Presents with severe muscle rigidity, hyperthermia and hypotension.
Drug of choice is dantrolene (mechanism of action : blocks RYR receptor).
Dantrolene is also the drug of choice for malignant hyperthermia.
Bromocriptine : D_2 agonist (most specific drug).



NEURODEGENERATIVE DISORDERS

Alzheimer's disease : Death of cholinergic neurons.
Amyotrophic lateral sclerosis : Death of motor neurons.
Parkinson's disease : Death of dopaminergic neurons in the corpus striatum.

Alzheimer's disease 00:03:40

Cholinergic drugs (only for symptomatic relief) :

- Blocks the enzyme acetylcholinesterase and increase the level of acetylcholine.
- Example : Tacrine, Rivastigmine, Galantamine, Donepezil.
- Tacrine is hepatotoxic. Less preferred.
- Donepezil is the drug of choice for the treatment of Alzheimer's disease. It is most active.

NMDA antagonists :

- Can be used as an add on drug.
- Example : Memantine.

Nootropic drugs :

- Add on drugs for memory enhancement.
- Not FDA approved.
- Example : Citicoline, Cerebrolysin, Piribedil, Piracetam.

Amyotrophic lateral sclerosis 00:08:00

Riluzole :

- Blocks glutamate receptors like NMDA and AMPA, decreases glutamate & also blocks sodium channels
  → Blocks neurodegeneration.
  Delays disease progression.
- Side effects : Nausea, vomiting, hepatotoxicity.

Edaravone :

- Approved by FDA in 2014.
- MOA : free radical scavenger.
- Blocks neurodegeneration.
- S/E : hypersensitivity.

Baclofen :

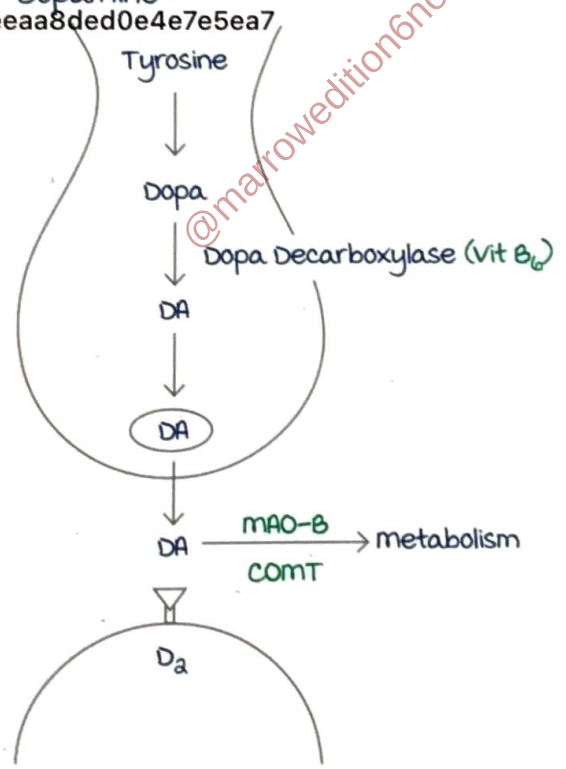
- GABA-B receptor agonist.
- Used as a muscle relaxant.
- Only used for symptomatic treatment.

Parkinson's disease

00:11:38

Cause : Progressive depletion of dopaminergic neurons in the corpus striatum.

Dopamine :



D_2 agonists and drugs that increase dopamine are used in the treatment of Parkinson's disease.

Dopamine can be increased by :

- Blocking metabolism : Inhibition of MAO B and COMT.
- Prodrug : Levodopa.

Levodopa is metabolized into dopamine by dopa

Active space

decarboxylase. As dopa decarboxylase is present throughout the body, 90% of Levodopa gets metabolized into dopamine in the periphery and only a small percentage reaches the brain.

Carbidopa is an analogue of dopa and it is lipid insoluble. It does not cross the blood brain barrier.
If carbidopa is given with Levodopa, Carbidopa competitively blocks dopa decarboxylase in the periphery and inhibits peripheral metabolism of Levodopa.

However, Carbidopa increases dopamine in the brain and increases the risk of central side effects.

- Levodopa + Carbidopa undergoes metabolism in the periphery by COMT. COMT inhibitors inhibit peripheral metabolism of Levodopa and increases bioavailability.
- Vitamin B_6 is contraindicated with Levodopa as it increases the activity of dopa decarboxylase.

Levodopa

00:20:48

- Prodrug of Dopamine.
- Drug of choice for the treatment of Parkinson's disease in patients ≥ 65 years.
- Always combined with Carbidopa to inhibit peripheral metabolism by dopa decarboxylase.

Side effects :

1. Increases dopamine :
   - D_1 receptor stimulation → Hypotension.
   - D_2 receptor stimulation in CTZ area → Nausea, vomiting.
   - D_2 receptor stimulation in limbic system → Psychosis (Drug of choice is Pimavanserin : 5HT2 receptor blocker).
   - D_2 receptor stimulation in corpus striatum → Levodopa induced dyskinesia (Treated with Amantadine > Levetiracetam).
2. Can worsen peptic ulcer disease and melanoma (more melanin synthesis from tyrosine).

On-off phenomenon (Weaning/wearing off effect) :
Levodopa is given in TDS dosing to cover for the deficit of dopamine.
Parkinson's disease is a progressive disease and levels of dopamine decreases with time. Dose of levodopa may be insufficient after few months → Patient becomes symptomatic in between the doses → Fluctuation in the symptoms is known as on-off phenomenon.
Treatment : COMT inhibitors (Preferred), MAO-B inhibitors, D_a receptor agonists.

C/I in psychosis and closed angle glaucoma (S/E : mydriasis).

MAO-B inhibitors

00:31:42

Irreversible : Rasagiline, Selegiline.
Reversible : Safinamide.

Rasagiline is more potent compared to other drugs.
Selegiline can block neurodegeneration (experimental finding). It is metabolized into Amphetamine and can cause agitation, insomnia. Dosing should be given in morning (better) and afternoon.

Uses of irreversible MAO-B inhibitors :
Reserved for the treatment of mild Parkinson's disease and on-off phenomenon.
Safinamide : Approved only for on-off phenomenon.

Side effects of MAO-B inhibitors :

- Side effects are similar to Levodopa but less severe. If combined, MAO-B inhibitors increase side effects of Levodopa.
- MAO-B inhibitors are contraindicated with Tramadol, Tapentadol, Pethidine, Amphetamine due to risk of serotonin syndrome.

Reversible COMT inhibitors 00:36:48

Used as a supplement to Levodopa as they increase the oral bioavailability of Levodopa.
Drugs that block both peripheral and central COMT : Tolcapone.
Drugs that block only peripheral COMT : Entacapone, Opicapone.

Tolcapone :
more potent and has longer duration of action. It is hepatotoxic and hence is reserved for resistant cases.

Entacapone, Opicapone :
Drugs of choice for treatment of on-off phenomenon seen with Levodopa.

Side effects :
Dopaminergic side effects due to increase in dopamine.

D_2 receptor agonists 00:39:58

Ergot alkaloids :

- Bromocriptine, Pergolide, Cabergoline.
- Not used in Parkinson's disease.
- Bromocriptine is the drug of choice for hyperprolactinemia in a female who is planning for pregnancy.
- Cabergoline is the overall drug of choice for hyperprolactinemia.

Side effects :

- Bromocriptine causes peripheral vasoconstriction.
- Pergolide, Cabergoline can cause cardiac valve defects.

Non-ergot alkaloids :

- Pramipexole, Ropinirole, Rotigotine.
- Oral drugs.
- Drug of choice for the treatment of Parkinson's disease in patients <65 years and restless leg syndrome.

- Can be used in the treatment of on-off phenomenon.
- Rotigotine can be used as a transcranial patch.

Side effects : Fatigue, somnolence, compulsive gambling, compulsive sexual activity.

Apomorphine :

- Subcutaneous route.
- Can be used as a rescue therapy in on-off phenomenon.
- Side effects : Severe nausea/vomiting.
  Prevention : Start Trimethobenzamide at least 3 days before using Apomorphine and continued for minimum 2 months. Ondansetron has no role as it increases the risk of hypotension.

Amantadine 00:48:35

Mechanisms of action :

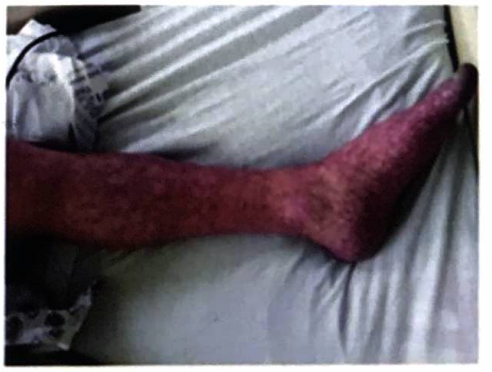
- NMDA receptor antagonism (main mechanism).
- Increases dopamine.
- Anticholinergic effect.

Uses :

- Mild Parkinson's disease.
- Levodopa induced dyskinesia.

Side effects :

Ankle edema, livedo reticularis (purple colored pigmentation).



Clinical correlation :

Patient of Parkinson's disease → Ask about interference of symptoms on quality of life.

If nil or mild interference → No drugs. Can start MAO-B inhibitors or Amantadine.

If severe interference : <65 years : D_a agonists like pramipexole etc.

≥65 years : Levodopa.

Neurodegenerative Disorders Summary

Alzheimer's disease

1. Cholinergics :
   - Donepezil
   - Rivastigmine
   - Galantamine
   - Tacrine
2. NMDA antagonist :
   - Memantine

ALS

1. Riluzole
2. Edaravone

Parkinson's Disease

- Levodopa
- D_a agonist
  - Pramipexole
  - Ropinirole
  - Rotigotine
  - Apomorphine
- MAO-B inhibitor
  - Rasagiline
  - Selegiline
  - Safinamide
- COMT inhibitor
  - Tolcapone
  - Entacapone
  - Opicapone
- Amantadine

ALCOHOL AND SMOKING DEPENDANCE

Alcohol dependence 00:00:20

FDA approved drugs :

1. Disulfiram (Aversive agent) :

Mechanism Of Action :

Alcohol
↓ Alcohol dehydrogenase
↑↑ Acetaldehyde
↓ Aldehyde dehydrogenase (–) Disulfiram
Acetic acid
↓
Excreted

Increased Acetaldehyde in body causes toxicity which leads to nausea and vomiting, hypotension, flushing and dyspnea, thereby creating aversion to alcohol.

- Should be given after at least 12 hours of abstinence.
- Should be given to strongly motivated patients.
- Does not decrease craving.

2. Naltrexone :

Side effects : Hepatotoxic, dysphoria.

CAT- Alcohol dependence concomitant with depression.

3. Acamprosate :

Side effect : Mild diarrhoea.

Non-FDA approved drugs :

- Benzodiazepine.
- Clonidine.
- Topiramate.
- Nalmefene.
- Baclofen.

All these drugs except Disulfiram decrease craving.

Smoking dependence 00:09:47

First line drugs :

Bupropion : Anti depressant drug.

Varenicline : Nicotinic receptor agonist.
most effective drug overall.

Nicotine replacement as :

Gums : Avoid liquids 15 mins before and after consumption, as it washes away the alkaline saliva. Place the gum between 2 molars and slightly chew it, then shift it between teeth and cheek and let it get absorbed. As nicotine levels decline, slightly chew again and let it get absorbed through the buccal mucosa.

Lozenges : Keep it between teeth and cheek to let it get absorbed by buccal mucosa.

Nasal sprays : most effective form of nicotine replacement.

Patch : Expensive.

Second line drugs :

Cytisine : Nicotinic receptor agonist.

Nortriptyline : TCA.

Clonidine : Alpha agonist.

Active space

ANTI-MICROBIAL DRUGS

Introduction :

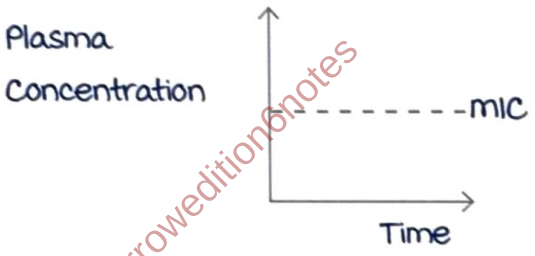
MIC (Minimum Inhibitory concentration) : Minimum plasma concentration of a drug which is required to inhibit visible growth of a microbe in a media.

$$MIC \propto \frac{1}{Potency}$$

Optimal Dose : The dose that is required to inhibit growth of 90% of organisms at the site of infection.

$$\text{Optimal Dose} \propto \frac{1}{Potency}$$

Concentration Time Curve 00:05:12

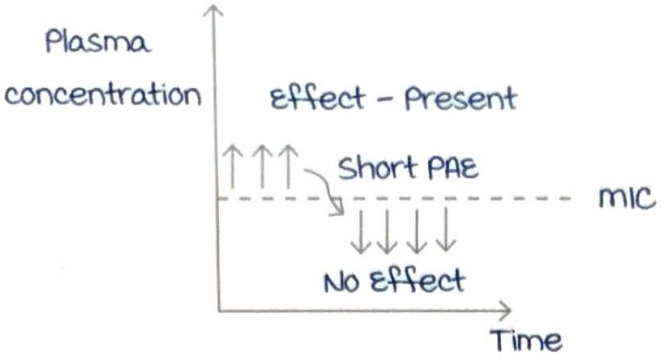


For an antibiotic to be effective, plasma concentration should be more than MIC.

Post antibiotic effect (PAE) : Effect is seen even if plasma concentration comes below MIC.

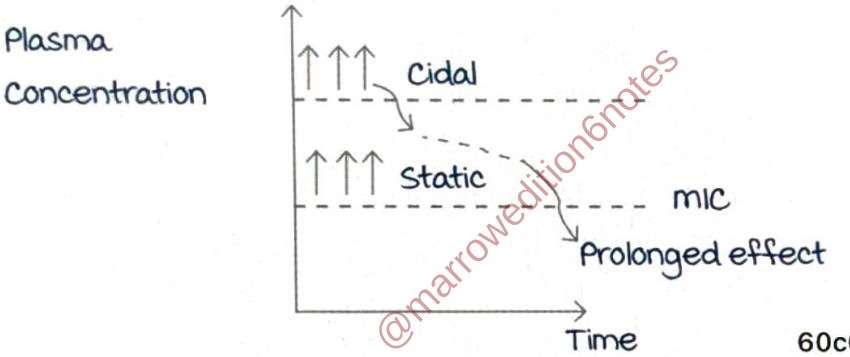
Time dependent Killing (TDK) with short PAE :

- Effect is seen when plasma concentration is above MIC.
- No effect below MIC.
- Effect seen only in particular time. After that no effect (time dependent).
- Short PAE : Because when the concentration comes below MIC, effect will be lost only after sometime.



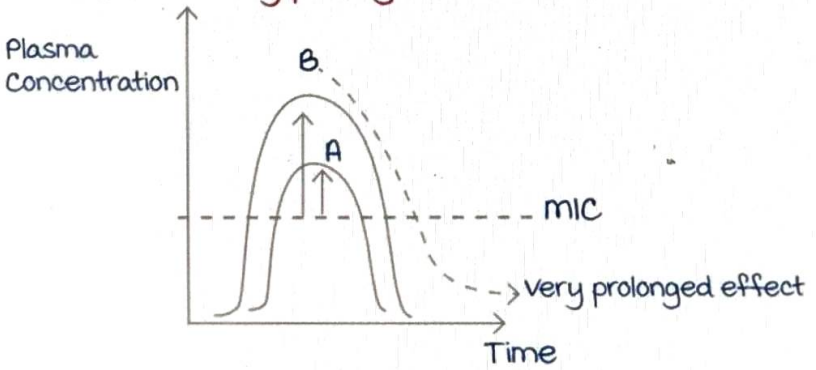
TDK with prolonged PAE :

- They are usually static drugs at lower concentration above MIC.
- At very high concentration : Cidal effect is seen.
- Cidal effect present only until plasma concentration is above certain range. As it comes below, cidal effect is gone (time dependent) but it still has static effect for some time (prolonged PAE).



Concentration Dependent Killing (CDK) with very prolonged PAE :

- Effect of the drug depends on how much the plasma concentration goes up above MIC.
- Here, effect of drug B > A.
- Time Independent.
- Even once in 24 hours, if the plasma concentration touches the maximum level, maximum effect is seen throughout the day (Concentration dependent).
- Hence, it has very prolonged PAE.



Active space

	TDK with short PAE	TDK with prolonged PAE	CDK with very prolonged PAE
Dosing	Continuous i.v. infusion (or) multiple dosing	Does not matter.	OD dosing is preferred. Hence are less toxic.
Examples	β- Lactams : Penicillins, Cephalosporins Monobactams Carbapenems Vancomycin Flucytosine	1. Protein synthesis inhibitors (except Aminoglycosides & Azithromycin) • Tetracycline • Clindamycin • Erythromycin • Clarithromycin • Linezolid etc. 2. Azoles	Aminoglycosides Azithromycin Fluoroquinolones Daptomycin Metronidazole Rifampicin Amphotericin B Echinocandins

Mechanisms of drug resistance 00:20:40

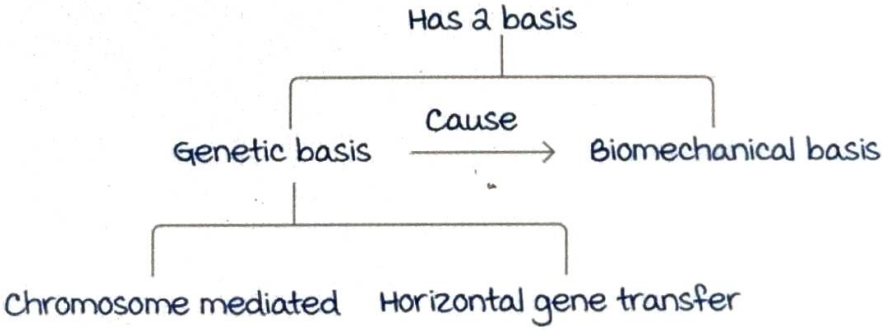
2 types :

- Intrinsic resistance.
- Acquired resistance.

Examples of intrinsic resistance :

Drugs	Not active against
Aminoglycosides	Anaerobes
Aztreonam	Gram positive
Vancomycin	Gram negative
Colistin/Aminoglycosides/ Fluoroquinolones	Burkholderia cepacia & Stenotrophomonas

Acquired resistance :

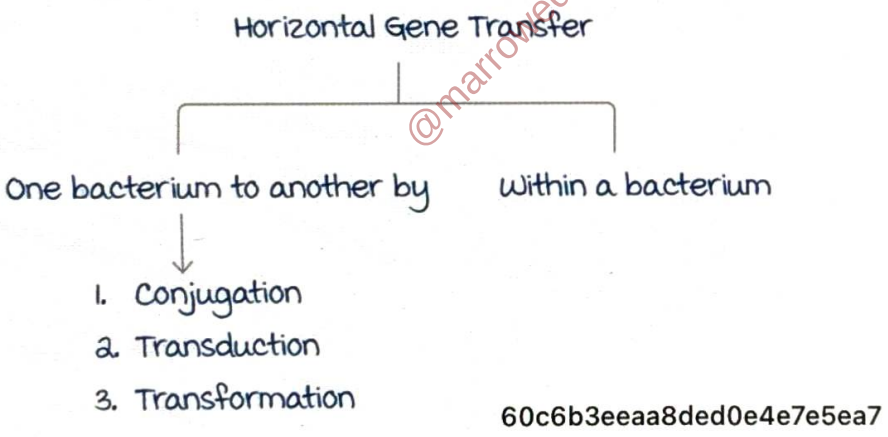


Chromosome mediated can be because of :

1. Spontaneous mutation (due to faulty DNA repair) :
   - Change target for antibiotic :
     Example : rpo-B gene mutation changes RNA polymerase that leads to Rifampicin resistance.
   - Decreased/absent porin production in gram negatives. Example : resistance of Pseudomonas to most of the antibiotics.
   - Activate drug degrading enzymes : Example : β-Lactams, Aminoglycosides, Tetracyclines.
   - Activate efflux pumps : Examples : Tetracyclines, β-Lactams, Fluoroquinolones.
2. Hypermutation : Example : MDR-TB of Beijing subtype.
3. Adaptive mutation : Example : Fluoroquinolones (once active) blocks DNA gyrase which leads to mutation of DNA gyrase in E. Coli (resistance developed).

Horizontal Gene Transfer

00:32:45



Conjugation :

- Most common mechanism.
- Transfer of resistance through plasmid transfer.
- Overall most common carrier for gene transfer : Plasmid.

Transduction :

- Mediated by Bacteriophage.
- Bacteriophage replicates inside bacteria.
- All the replicated ones acquire information about resistance.

- These phages now infect other bacteria and pass on the information about resistance.

Transformation :

- Transfer of free DNA released (with resistance information) from donor to the recipient bacteria.

Gene Transfer within a bacterium :

- Transfer of resistance is mediated by transposomes (don't have information of resistance).
- Transposomes are mobile DNA sequences that can move around to different positions within genome of the cell.
- Integron has the information of resistance and are found in transposomes.
- Gene cassettes are mobile genetic elements with information of resistance to multiple drugs. They pass on information of resistance to chromosome or plasmid.

Drug Synergism

One drug can increase the effect of another drug.

1. Sequential enzyme block :
   - Example : Cotrimoxazole
     (Trimethoprim + Sulfamethoxazole)
     ↓ Block DHFR ↓ Block DHPS
   - DHFR & DHPS : Needed for folic acid synthesis and activation.
   - Trimethoprim & Sulfamethoxazole individually static, together they are cidal.
2. Block drug inactivating enzyme :
   - Example : Ampicillin + sulbactam.
   - β-lactamase can inhibit Ampicillin while Sulbactam is an inhibitor of β-lactamase.
3. Increase entry of drug into microbes :
   - Cell wall synthesis inhibitor increases the entry of Aminoglycoside (cidal).
   - Example : Ceftazidime (DOC) + Gentamicin (for treatment of pseudomonas).

Vancomycin (DOC) + Gentamicin (for treatment of Enterococcus).

- Here Ceftazidime & Vancomycin are cell wall synthesis inhibitors.
- They inhibit cell wall synthesis and increase the entry of Gentamicin.

Drug Antagonism

00:49:33

One drug can inhibit or decrease the effect of another drug.

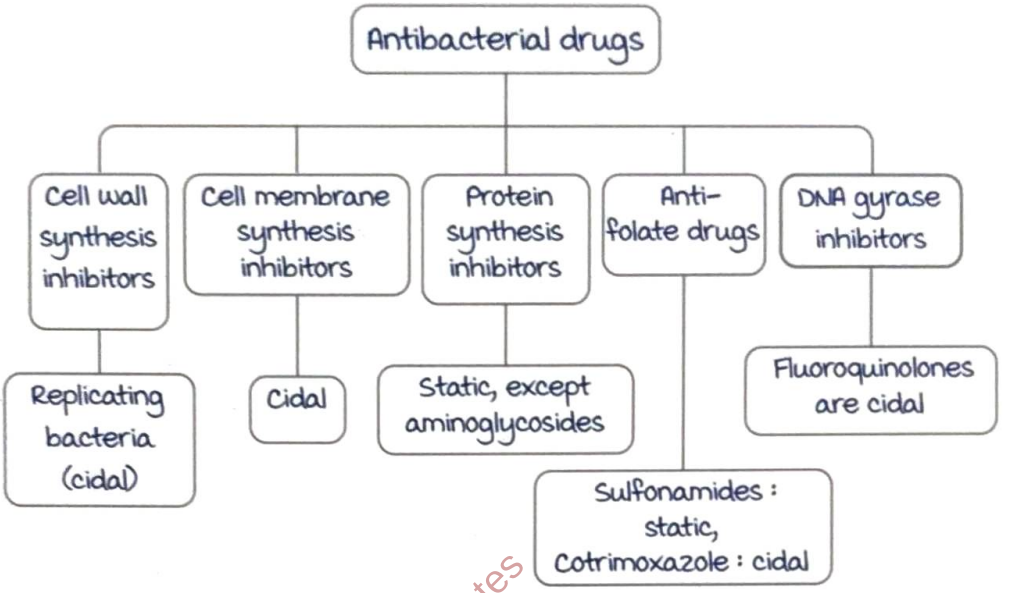
Examples :

- Cell wall synthesis inhibitor : On combining with protein synthesis inhibitor (static), it decreases the effect of cell wall synthesis inhibitor (antagonistic).
- Penicillin inactivates Aminoglycoside in a solution.
- One β-lactam can induce β-lactamase production which can break down other β-lactams.

CELL WALL SYNTHESIS INHIBITORS PART - I

Classification

00:00:32



The class of drugs which are least toxic and most effective are cell wall synthesis inhibitors (DOC is Beta lactams).
If patient is not responding to cell wall synthesis inhibitors, aminoglycosides are added (synergistic effect : Both are cidal drugs).
Cell membrane synthesis inhibitor drugs are only used in resistant cases.
Drugs for chlamydia, mycoplasma, and legionella : Protein synthesis inhibitors.
Anti-folate drugs are preferred in protozoal infections.

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Cell wall synthesis inhibitors

00:08:40

Cell wall is a peptidoglycan.
Cell wall synthesis occurs in Cytoplasm.

L-alanine
↓ Alanine racemase
D-alanine
Glycine ↓ Alanine ligase
Peptide chain

Active space

N-acetyl glucosamine (NAG)

Enol pyruvate transferase | Phosphoenol pyruvate

↓

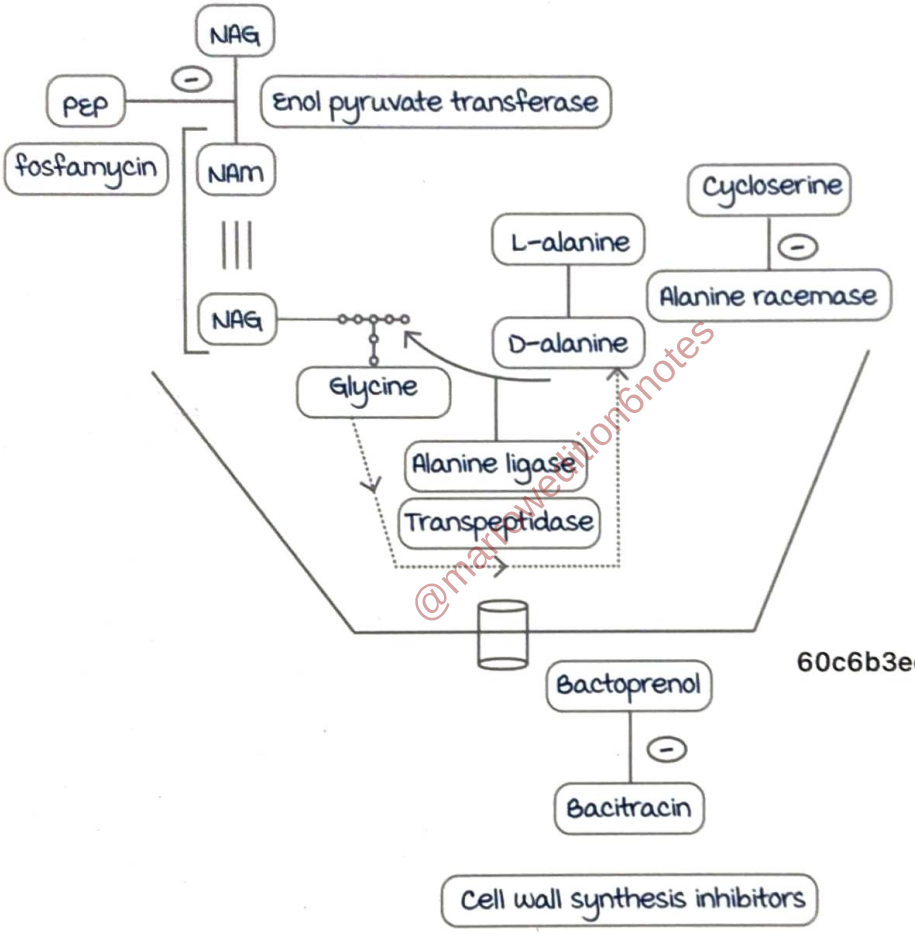
N-acetyl muramic acid (NAM)

↓

Incorporation of NAG to NAM

↓

Glycosaminoglycan complex (GAG)



Unit of cell wall : GAG plus peptide chain.

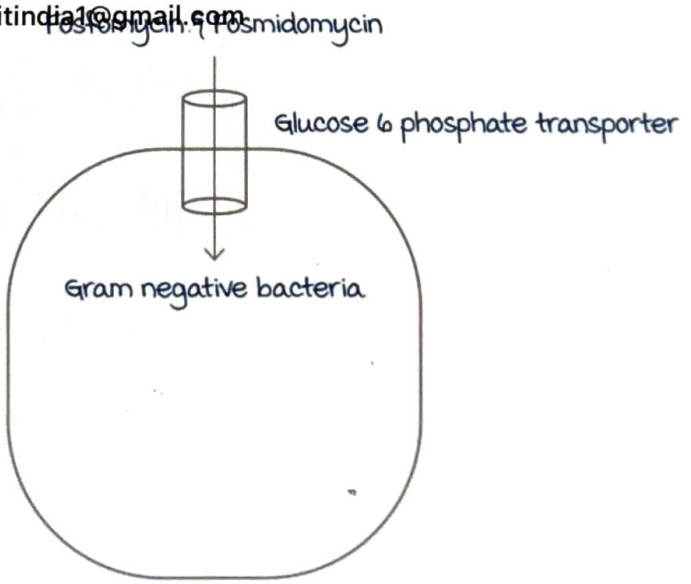
They are transported outside cell membrane by a lipid transporter : Bactoprenol.

Crosslinking of D-alanine of one unit with glycine of another unit : Transpeptidase.

Class of antibacterial drugs	Mechanism of action
Fosfomycin, Fosmidomycin	Phosphoenol pyruvate analogues. Competitively inhibit Enol pyruvate transferase. Blocks synthesis of GAG.
Cycloserine	D-alanine analogue. Blocks Alanine racemase and ligase (peptide synthesis).
Bacitracin	Blocks Bactoprenol, inhibits transport of cell wall unit outside cell membrane
Glycopeptides : Vancomycin	Blocks D-alanine
Beta lactams (penicillins, cephalosporins, monobactams, carbapenems)	Blocks Transpeptidase (penicillin binding protein) and prevents cross linking.

Fosfomycin and Fosmidomycin 00:20:46

They are Phosphoenol pyruvate analogues.
Mechanism of action : Blocks Enol pyruvate transferase.
These drugs need glucose-6-phosphate transporter (Present only in gram negative) for entry into the bacteria.
Well concentrated in urine.
Used for treatment of UTI.
Dose in UTI : 3 g single dose.
They are safe in pregnancy.



Cycloserine :
It is an analogue of D-alanine.
Competitively blocks Alanine racemase and ligase.
Blocks peptide chain synthesis.
Used as 2nd line TB drug.
Side effects : Neuropsychiatric (psychosis, seizures, peripheral neuropathy).

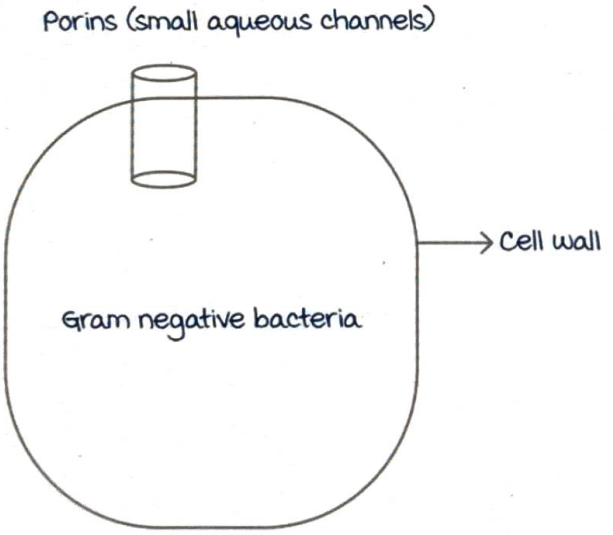
Bacitracin 00:25:42

↓

Inhibits Bactoprenol.

Blocks the transport of cell wall units outside cell membrane.

Side effects : Nephrotoxicity and bone marrow suppression.
It can be used topically in bacterial skin infection, Staphylococcal nasal carriers (even with MRSA, DOC is topical mupirocin).
It can also be given by oral route for local effect on GIT (not absorbed) : Pseudomembranous enterocolitis, Enterococcal infection.



Glycopeptides :
They are proteins (large size) : Poor oral absorption.
Spectrum : Gram positive.
Gram negative cell wall contains aqueous channels called as porins (small in size).

Antibacterial drug should be water soluble and have small size to enter the gram negative cell wall.

Vancomycin :
Mechanism of action : Blocks D-alanine.
Use: Intravenously, DOC for MRSA and E. faecium.
Oral route : Treatment of Pseudomembranous enterocolitis.

Treatment of pseudomembranous enterocolitis :

	Drug of choice
First episode	Fidaxomicin (DOC)
Recurrence : • Before 6 months • After 6 months	 Fidaxomicin + Bezlotoxumab Fidaxomicin
Fulminant cases	Oral Vancomycin + IV metronidazole

Bezlotoxumab is anti C. difficile toxin B monoclonal antibodies.

Common antibiotics causing Pseudomembranous enterocolitis :
3rd generation cephalosporins > Aminopenicillins > FQ > Clindamycin.

Side effects of Vancomycin

Due to release of histamine which can cause flushing (red man syndrome). Mild nephrotoxicity and ototoxicity.

Resistance :
D-alanine is changed to D-lactate (not a target for vancomycin).

Other glycopeptides :
Teicoplanin.
Dalbavancin : Longest acting.
Telavancin : Disrupt cell membrane (more cidal).
Oritavancin : Used in MRSA skin and soft tissue infection.

ANTIBACTERIAL PART II

Penicillins

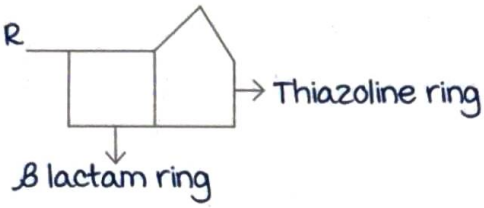
00:00:38

Penicillin G :

Low water solubility (cannot enter into a gram negative).

Narrow Spectrum : Limited to most gram positives and few gram negatives.

Structure :



Amidase enzyme

↓

Breaks side chain R

↓

Functional group is placed instead of R → Broad spectrum penicillins which are water soluble

Aminopenicillins (+ve charged)	Carboxypenicillins (−ve charged)	Ureidopenicillins (+ve and −ve charged)
Spectrum : • Gram positive similar to penicillin G and Enterococcus faecalis. • Gram negative : Against E. coli, Proteus, Shigella, Salmonella, H. influenza, H. pylori. • Drugs : Amoxicillin. Ampicillin.	Parenteral route • Carbenicillin. • Ticarcillin.	Parenteral route Piperacillin : used against severe gram negative infection

Active against Pseudomonas

Addition of charged functional groups makes the molecule ionized and water soluble thus increasing its spectrum.

Active space

	Amoxicillin	Ampicillin
Oral absorption	Absorbed more	Relatively less absorbed
Peak plasma concentration	more (oral route)	Less (oral route)
Dosing	TDS dosing of Amoxicillin is equivalent to QID of Ampicillin	
Diarrhoea	Relatively less	Remains more in the gut so side effect of diarrhoea is more
Route	Oral route is more preferred	Parenteral route is preferred by IM or IV infusion or IV push IV push : Slow IV over 10–15 minutes. Rapid IV push can cause seizure.

Uses :

Infections of mild to moderate severity.

(oral amoxicillin > ampicillin).

- GIT infection :
  - → Salmonella : Ceftriaxone (DOC).
  - → Shigella : Ciprofloxacin (DOC).
  - → E. faecalis : DOC : Ampicillin (because Ampicillin remains more in the gut).
- Respiratory : H. influenza, Pneumococcus.
- UTI : E. coli, Proteus.

Severe infections : IV or IM Ampicillin. 60c6b3eeaa8ded0e4e7e5ea7

- Bacteremia.
- Endocarditis (with Gentamicin).
- In entercoccal endocarditis :
  E.faecalis : Ampicillin + Gentamicin
  E. faecium : Vancomycin (DOC) + Gentamicin.
- Meningitis : H. influenza, Meningococcus : DOC is Ceftriaxone.
- Listeria : DOC is Ampicillin (with Gentamicin).

Penicillin G

00:18:56

- Aqueous Penicillin G given IV.
- Narrow spectrum.
- Poor oral absorption as penicillin G is broken down by gastric HCl.
- Oral penicillin V is resistant to gastric HCl and similar to penicillin G except not active against Meningococcus.
- Penicillin G is very short acting as rapid tubular secretion occurs. It is excreted by P-glycoprotein pumps.

Long acting penicllins :

1. Probenecid Penicillin G : Tubular secretion blocked.
2. Procaine penicillin G
3. Benzathine penicillin G

} make a depot in muscles and are slowly released

These drugs are given IM, as they are toxic by IV route.

Benzathine penicillin G : Longest acting penicillin.

One dose can be effective for 28 days.

Uses :

Benzathine penicillin G : DOC in

- Rheumatic fever prophylaxis (once a month).
- Streptococcus.
- Yaws.
- Leptospirosis.
- Gas gangrene.
- Rat bite fever.
- Syphilis :
  1. Primary, secondary and early latent : 2.4 million IU once.
  2. Tertiary syphilis (except CNS syphilis), CVS syphilis, late latent : 2.4 million IU, 3 doses, once a week.
  3. Neurosyphilis : 18–24 million IU by continuous intravenous infusion for 10–14 days.

Jarisch Herxheimer reaction :

Associated with the use of Penicillin in syphilis (usually secondary syphilis). Occurs due to release of Spirochaetal proteins (hypersensitivity).

It is characterized by fever, rash, lymphadenopathy, worsening of the cutaneous lesions.

Syphilis in pregnancy + penicillin allergy :
Desensitization with lower doses of penicillin (use benzathine Penicillin G).

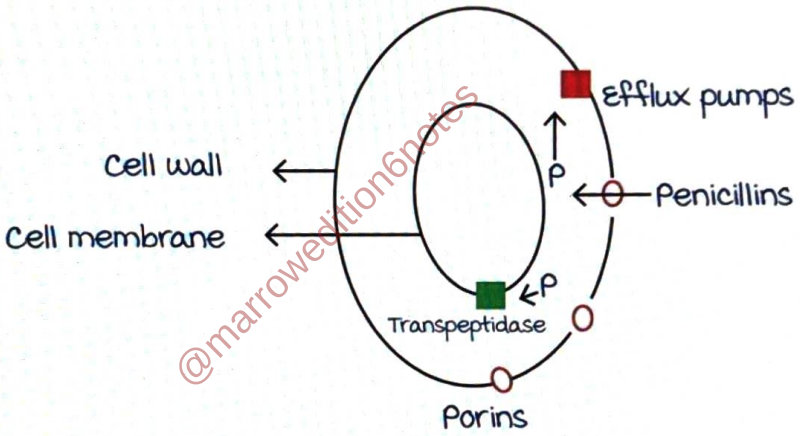
Mechanism of resistance to Penicillin 00:30:48

Gram negative bacteria :

Normally, penicillin enters cell through porins

↓

Blocks Transpeptidase enzyme



1. Decreased porin production : Pseudomonas.
2. Drug efflux : Pseudomonas, E. coli, Gonococcus.

Gram negative and positive bacteria :

1. Altered Transpeptidase (penicillin binding protein) :
   Structure of transpeptidase is changed and penicillin cannot bind to it.
   E.g. Staphylococcus aureus (MRSA).
   The gene responsible for transfer of resistance : mec A gene.
2. β lactamase production :
   Bacteria produces β lactamase which breaks down base of β lactam ring, rendering the drug ineffective.

Types of β lactamase : Ambler's classification.

Type A : ESBL enzymes (Extended spectrum β lactamase)

- Penicillinase
- Cephalosporinase
- Monobactamase

} DOC : Carbapenems

Type B : All enzymes except Monobactamase.

Type C : Cephalosporinase.

Type D : Cloxacillinase.

NDM1 β lactamase (New Delhi metallo-1 β lactamase) :

Breaks most antibiotics like all β lactams, Aminoglycosides, Tetracyclines, Fluoroquinolones.

Treatment : Colistin, Tigecycline.

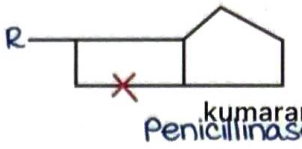
β lactamase inhibitors

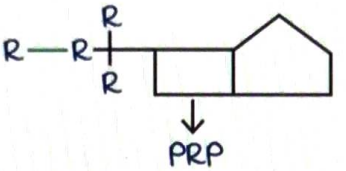
00:42:49

Drug with lactam rings :

- Sulbactam : used with ampicillin.
  Used in the treatment of Acinetobacter.
- Clavulanic acid : Combined with Amoxicillin.
- Tazobactam : Combined with Piperacillin and is preferred for ESBL producing organisms (DOC : Carbapenems).
- Avibactam : Used with Ceftazidime.
- Vaborbactam : Used with Meropenem.
- Relebactam : Combined with Imipenem + Cilastatin.

Penicillinase resistant penicillin 00:48:19





Staphylococcus
↓
Penicillinase enzyme
↓
Breaks beta lactam ring
↓
Change structure of side chain R
↓
Penicillinase resistant penicillins (PRPs)
↓
Anti-Staphylococcal Penicillins

Oral drugs : Preferred for mild to moderate infections like mastitis, cellulitis.
Eg : Oxacillin, Dicloxacillin, Cloxacillin.
Dicloxacillin is most active against staphylococcus.

IV drugs : Severe infections like endocarditis.
E.g. : Oxacillin, Nafcillin, methicillin.
Nafcillin : most active against non-staphylococcal organisms.
methicillin is not used anymore because it can cause interstitial nephritis.

Methicillin resistant and Vancomycin resistant Staphylococcus (MRSA/ VRSA) 00:53:50

Altered penicillin binding protein
↓
Resistance to methicillin
↓
MRSA : No beta lactams are effective

DOC : Vancomycin (acts on D-Alanine).
Bacteria → D-alanine → D lactate → VRSA (vancomycin resistance).
DOC for VRSA : Daptomycin.

Other drugs against MRSA causing skin/ soft tissue infections :

- Cotrimoxazole : Targeting folic acid synthesis.
- Doxycycline/ Minocycline : Targeting protein synthesis.
- Clindamycin.
- Other glycopeptides.
- 5th generation cephalosporins like Ceftaroline : Only β lactam effective against MRSA. It can bind to normal and altered transpeptidase.

Other drugs against MRSA/VRSA systemic infections :

- Tigecycline.
- Linezolid.
- Streptogramins.

CEPHALOSPORINS

Generations of cephalosporins 00:00:43

	First	Second	Third	Fourth	Fifth
Gram positive bacteria	↑ Active against most	↑	↑	same as Ceftriaxone ↑	Better than Ceftriaxone ↑ and cover Staphylococcus (MRSA) and Streptococcus
Gram negative bacteria	↑ Active against very few	↑	↑	↑ Better than Ceftriaxone and cover Pseudomonas and Enterobacter	↑ Similar to Ceftriaxone
	They are active against aerobes, anaerobes except gram negative anaerobes like Bacteroides	They are active against aerobes, anaerobes including gram negative anaerobes like Bacteroides	They are active only against gram negative aerobes (reference drug: Ceftriaxone).		

First generation cephalosporins 00:06:39

Mnemonic : Dr Reddy's X in Zoo

Cefadroxil
Cefradine
Cephalexin
} Oral route : Mild to moderate UTI, cellulitis, mastitis.

CefazoLin : IV route : Used for severe infections like endocarditis. DOC for surgical prophylaxis (2 doses : Before incision, 24 hours before surgery)

They are active against most gram positive and some gram negative bacteria.

Active space

Second generation cephalosporins :

They are active against both gram positive and negative aerobes and anaerobes.

Fa : Cefaclor.

Lo : Loracarbef.

ma : Cefomandole. Mnemonic : FaLo maUr TaXi PaR

Ur : Cefuroxime.

Ta : Cefotetan.

Xi : Cefoxitin.

Par : Cefprozil.

Cefotetan > Cefoxitin : Most effective against gram positive anaerobes.

Cefuroxime : Effective only against gram positive aerobes.

Cefuroxime : For gram positive aerobes.

Route of administration : Oral/IV/IM.

Active against Pneumococcus, H. influenza, moraxella.

Uses : Otitis media, sinusitis, pneumonia.

Cefotetan & Cefoxitin : For gram positive anaerobes.

IV route.

Use : Surgical prophylaxis of colorectal surgery.

PID.

Diverticulitis.

Peritonitis.

Lung abscess.

Third generation cephalosporins 00:17:10

Delhi : Cefdinir, Cefditoxin, Cefpodoxime (oral).

P : Cefoperazone.

m : Moxalactam.

T : Ceftriaxone, Ceftizoxime, Cefotaxime, Ceftazidime.

] Parenteral

Exam : Cefixime (oral).

Ceftriaxone :

DOC for most gram negative aerobes except Pseudomonas, Enterobacter, Serratia and Acinetobactor.

DOC for Gonorrhoea (monotherapy).

Resistant Gonorrhoea : Spectinomycin.

DOC for E.coli, Klebsiella, Providencia, typhoid, meningitis (except Listeria).

DOC for empirical treatment of meningitis.

Alternative in meningitis : Cefotaxime.

Cefoperazone and Ceftazidime : Only 3rd generation drugs active against Pseudomonas.

DOC for Pseudomonas, Melioidosis and febrile neutropenia is Ceftazidime.

If resistant to Ceftazidime : Add Aminoglycosides.

Ceftalozone : Derived from Ceftazidime.

Also be used for treatment of Pseudomonas.

Ceftalozone/ Ceftazidime + Avibactam combination : For complicated abdominal infection.

Cefixime : Oral route.

Oral DOC for typhoid.

Fourth & fifth generation cephalosporins

They are only given by IV route.

4th : Cefepime, Cefpirome.

5th : Ceftobiprole, Ceftaroline.

Uses are similar to the uses of Ceftriaxone.

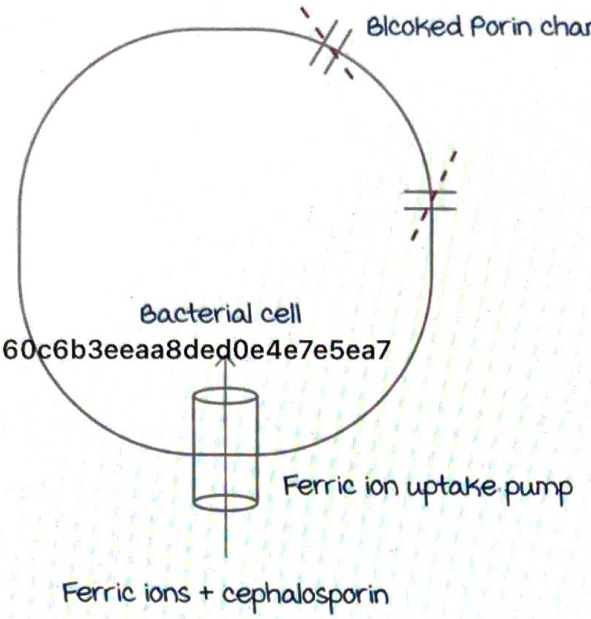
4th generation is also active against a few gram negatives like Pseudomonas and Enterobacter.

5th generation is also active against a few gram positives like Streptococcus, Staphylococcus (MRSA).

Sixth generation Cephalosporins :

Cefiderocol : Siderophore Cephalosporin (attached to a ferric ion).
Helps in entry via ferric uptake pumps in the cell wall and bypasses porins.

Uses : Approved for complicated UTI including pyelonephritis (resistant cases of Pseudomonas).



Carbapenems

00:31:40

These are the most wide spectrum drugs.
Including gram positive and negative aerobes and anaerobes.
So, they are the drugs of reserve.

Imipenem :
metabolised by renal dihydropeptidase - 1.
Very short acting.
Always combined with Cilastatin (inhibitor of renal dihydropeptidase - 1). To make it longer acting.
Use : DOC for ESBL producing organism.
DOC for Serratia, Enterobacter, Acinetobacter.
Also used for Pseudomonas.

Doripenem > Meropenem : Most active against gram negatives like Pseudomonas, Enterobacter.
Less active against gram positive bacteria as compared to Imipenem.

Ertapenem : Longest acting.
Least active against gram negative like Pseudomonas, Enterobacter, Acinetobacter.
Effective against anaerobes : Used in PID, lung abscess, diverticulitis.

Monobactams

Aztreonam :

Spectrum is limited to gram negative organism only.

They cannot bind to Transpeptidase of gram positive organism.

They cover Pseudomonas, Enterobacter.

Uses are similar to Ceftriaxone.

It has no cross sensitivity to other beta lactams, except Ceftazidime.

It is used in gram negative infections in Penicillin allergic patients.

Side effects of beta lactams :

Hypersensitivity like rash, anaphylaxis.

Pseudomembranous enterocolitis.

Few cephalosporins have MTT group attached to the normal compound. This MTT group causes side effects like Disulfiram like reaction, hypoprothrombinemia (increase risk of bleeding).

Contraindicated with alcohol.

Cephalosporins with MTT groups are,

2nd generation : Cefamandole, Cefotetan.

3rd generation : Cefoperazone, Moxalactam.

Other side effects :

Seizures (Imipenem).

Hepatotoxicity : Oxacillin, Aztreonam (children).

Nephrotoxicity (renal tubular necrosis) : Cephaloridine > Cephalothin.

Thrombocytopenia, pseudolithiasis, Kernicterus in new born (high plasma protein binding) : Ceftriaxone.

Dose reduction with all beta lactams is required in renal failure except :

- Cefoperazone and Cefpiramide (100% liver excretion) (never used in UTI).
- Ceftriaxone (50% liver and 50% Kidney).

DRUGS ACTING ON CELL MEMBRANE

Drugs acting on bacterial cell membrane are bactericidal.

Polymyxins

00:00:32

Mechanism of action :

- Cationic detergents bind to phospholipids in the cell membrane and create pseudopores → Increased entry of water and solute → bacterial cell lysis.
- They can increase entry of other drugs into the bacteria.
- They also bind to endotoxin causing inactivation.

Spectrum : Mostly Gram negative aerobes.

Polymyxin B (Neosporin) :
Used as a topical antibiotic for bacterial skin infections.

Polymyxin E (Colistin) :

- Used topically for bacterial skin infections.
- Used intravenously for multi-drug resistant gram negative bacteria like Pseudomonas, Enterobacter, Klebsiella.
- Side effects : Nephrotoxicity, neuromuscular toxicity.
- Contraindicated with aminoglycosides. They share the same side effects.

Lipopeptide

00:06:04

Poor oral absorption. Given intravenously.
Spectrum : Gram positive organisms such as Staphylococci, Enterococci.

Daptomycin :

- Mechanism of action : Depolarizes cell membrane → K^+ efflux → bacterial death.
- Given by IV route.
- Drug of choice for VRSA (Vancomycin resistant Staphylococcus aureus), empirical treatment of MRSA.

- Can be used for the treatment of VRE (Vancomycin resistant Enterococci).
- Contraindicated in the treatment of pneumonia as Daptomycin is inactivated by surfactant.
  For VRSA pneumonia, drug of choice is Linezolid.

Side effects : myopathy, neuropathy, allergic pneumonitis.

PROTEIN SYNTHESIS INHIBITORS PART - 1

Protein synthesis inhibitors 00:00:16

Protein synthesis in the bacteria occurs in the ribosomes (30S and 50S subunits).

most of the protein synthesis inhibitors are bacteriostatic except Aminoglycosides (bactericidal).

There are 3 sites in the ribosomes for the synthesis of proteins :

- A (acceptor site) : It accepts a new tRNA which brings in a new amino acid.
- P (peptidyl site) : The peptide chain is primarily present at the P site.
- E (ejection site) : The tRNA which is no longer of use is ejected out.

When a new amino acid arrives at the A site, older amino acids break away from the P site and are transferred to the A site.

The enzyme which transfers the peptides is called Transpeptidase.

The tRNA at the P site is transferred to the E site which is then ejected out.

Peptide with the newly added amino acid is then transferred to the P site. This process is called translocation.

The A site is now free and a new tRNA with an amino acid attaches to the site.

This cycle repeats until a desired length for synthesis of protein is achieved.

The process of protein formation is blocked by protein synthesis inhibitors to exert their antibacterial effect.

Antibiotics blocking interactions of a new tRNA at A site :

- Tetracycline : Directly binds to the A site and blocks it.
- Aminoglycoside : Binds to the A site and causes misreading of the RNA. It induces synthesis of proteins that are toxic to bacteria.

Antibiotics blocking transpeptidase :

- Chloramphenicol.
- Pleuromutilin.

Antibiotics blocking translocation :

- Macrolides.
- Linezolid.
- Streptogramins.
- Lincosamide (Clindamycin).

Drugs acting on A site : Target 30S subunit.

Antibiotics blocking transpeptidase and translocation : Target 50S subunit.

Wide spectrum protein synthesis inhibitors :

- Tetracyclines.
- Chloramphenicol.
- Pleuromutilin.

Moderate spectrum protein synthesis inhibitors :

- Aminoglycosides.
- Macrolides.

Narrow spectrum protein synthesis inhibitors :

- Linezolid.
- Streptogramins.
- Lincosamide.

Tetracyclines 00:12:04

The drugs include :

- Tetracycline.
- Oxytetracycline.
- Chlortetracycline.
- Minocycline : A new class is designed based on its structure called Glycylcycline. Tigecycline is a glycylcycline similar in structure to Minocycline.
- Doxycycline : Most used tetracycline.
- Demeclocycline.

Mechanism of action : Blocks the A site.

Mechanism of resistance : Drug efflux (most common mechanism).

Other mechanisms include increased production of drug inactivating enzymes and ribosomal protective proteins.

Route of administration : Oral.

Oral bioavailability is maximum with Minocycline (~100%) > Doxycycline.

These drugs can be given intravenously but never by intramuscular (IM) route. It causes severe pain and inflammation when given IM.

Uses of Tetracyclines : Doxycycline is the most used currently. Other drugs like Tetracycline or Chlortetracycline are not preferred due to resistance.

Spectrum of action : Tetracyclines are active against gram positive bacteria and many gram negative bacteria except :

- Pseudomonas.
- Proteus. Mnemonic : PPP
- Providencia.
- Enterobacter.
- Acinetobacter.

Doxycycline is the drug of choice (DOC) for :

Mnemonic : My Pink RBC.

- Mycoplasma hominis (STD). Azithromycin is the DOC for M. pneumoniae causing pneumonia.
- Plague prophylaxis, Pleurodesis and Pericardiodesis. It is injected in cases of recurrent Pneumothorax and cardiac tamponade.
  It is an irritant which causes inflammation and fibrosis leading to obliteration of the space when injected into the pleural or pericardial space.
- Rickettsia (DOC for scrub typhus).
- Borrelia and Brucella.
- Chlamydia (STD) and Cholera. Azithromycin is the DOC in Chlamydia pneumoniae.

Doxycycline can also be used to treat malaria, filaria and syphilis in case of Penicillin allergy.

It can also be used to treat anthrax but is not the DOC.

Minocycline 00:21:15

It is used in treatment of :

- Acne.
- Leprosy (only Tetracycline used in resistant leprosy).

Demeclocycline is used in the treatment of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH). It is the most potent V_2 receptor blocker of all tetracyclines.

Newer tetracyclines :

- Sarecycline : Used in acne.
- Omadacycline : Used in pneumonia and skin infection.
- Eravacycline : Approved for treatment of complicated abdominal infections.

Glycylcycline : Tigecycline
It acts by blocking A site (same as Tetracycline).
Mechanism of resistance is by drug efflux. Resistance is rare.
This drug can only be given intravenously.
It has poor concentration in both urine and in blood. It is hence not used in the treatment of :

- Urinary tract infection.
- Bacteremia.
- Meningitis.

The use of this drug is associated with increased risk of mortality and is hence reserved for resistant infections like :

- Gram positive : Methicillin or Vancomycin resistant Staphylococcus aureus.
- Gram negative : E. coli, Klebsiella, Enterobacter and Acinetobacter.

Side effects of tetracyclines 00:27:10

GIT side effects :

- Nausea and vomiting (most common).
- Esophagitis : The patient must be asked to take the drug with a full glass of water and not to lie down for 30 minutes.

Note : The same advice is given to patients taking Bisphosphonates to prevent esophagitis.

Liver : Hepatotoxicity which is most evident during pregnancy.

Renal side effects :

- Direct nephrotoxicity is seen except with Doxycycline and Tigecycline.
- Fanconi syndrome : Damage to the proximal convoluted tubule (PCT) leading to salt wasting nephropathy as PCT cannot reabsorb solute.
  This syndrome is typically seen with expired drugs.
- Blocks V_a receptors leading to Diabetes insipidus.

Skin : Photosensitivity (pigmentation in sun exposed areas).
The patient must be asked to cover up the skin or use an umbrella and use sunscreen while stepping out.

Vestibulotoxicity : Seen only with Minocycline and streptomycin.

Tetracyclines have high affinity for Ca^{a+} binding leading to :

- Yellow discoloration of teeth or enamel.
- Bone growth abnormality.

Contraindications of tetracyclines :

- Pregnancy.
- Contraindicated along with milk as it chelates Ca^{a+} and will not be absorbed.

Aminoglycosides

00:34:40

Classification of aminoglycosides based on the source :

- Derived from Streptomyces (suffix mycin) :
  1. Streptomycin.
  2. Tobramycin.
  3. Paromomycin.
  4. Capreomycin.
- Derived from Micromonospora (suffix micin) :
  1. Amikacin.
  2. Gentamicin.
  3. Plazomicin.
  4. Netilmicin.

Mechanism of action : Misreading of RNA leading to production of toxic proteins.

Mechanism of resistance :

- Enzymatic inactivation (most common). Amikacin and Netilmicin are not inactivated by enzymatic inactivation.
- Altered ribosomal structure. It is specific to Streptomycin.

Spectrum of activity :
It is only active against aerobic gram negative organisms.
A molecule of Aminoglycoside enters the cytoplasm of the bacteria through a porin.
It requires a transmembrane potential (TMP) generated in the cell membrane of gram negative organisms.
TMP generation requires ATP and O_2. TMP pulls the Aminoglycoside into the cytoplasm.

It then produces toxic proteins which are bactericidal.
Aminoglycosides are not active against anaerobic organisms.
These drugs are either given intravenously or intramuscularly but never orally.

Uses of Aminoglycosides 00:42:06

Gentamicin and streptomycin are currently used.

- DOC for plague and tularemia.
- Used as an add on drug with cell wall synthesis inhibitors :
  1. With Ceftriaxone to treat gram negative aerobes like E. coli, Klebsiella, gonorrhoea and providencia.
  2. Pseudomonas infection.
  3. Enterobacter.
  4. Acinetobacter.
- It can be used as an add on drug to treat aerobic gram positive infection like Enterococcus.
  For example, Gentamicin or Streptomycin can be combined with Ampicillin or Vancomycin to treat Enterococcal endocarditis.

Amikacin, Capreomycin and Kanamycin are used as 2nd line drugs in treatment of tuberculosis (gram positive organism).

Neomycin is used orally for gut sterilization in hepatic encephalopathy.

Bacteria in the gut produce ammonia leading to encephalopathy.
DOC for gut sterilization is Rifaximin.

Tobramycin can be used by inhalational route to treat pseudomonas infection in cystic fibrosis.
Systemic antibiotics may not be able to adequately penetrate through the thick secretions seen in cystic fibrosis.
Tobramycin is more effective against pseudomonas compared to Gentamycin or streptomycin.

Plazomicin is approved in treatment of urinary tract infections including pyelonephritis.
Paromomycin is mostly used against protozoans like Amoeba, Leishmania etc.

Side effects of Aminoglycosides 00:50:30

Nephrotoxicity (reversible) : Maximum toxicity is seen with Neomycin and minimum with Streptomycin.

Ototoxicity is irreversible and is due to direct hair cell damage.

It can be of two types :

- Auditory toxicity is maximum with :
  1. Kanamycin.
  2. Amikacin.
  3. Neomycin.

  Minimum auditory toxicity is seen with Netilmicin.
- Vestibular toxicity is maximum with streptomycin.

Neuromuscular toxicity due to blockage of :

- N_m receptors.
- Decrease in release of Ach by blocking voltage gated presynaptic calcium channels.

It is maximum with Neomycin and minimal with Tobramycin.
Neuromuscular toxicity can be reversed by calcium.
There is no role for Neostigmine in treating the toxicity.
Most toxic Aminoglycoside is Neomycin.
Aminoglycosides are absolutely contraindicated in pregnancy.

PROTEIN SYNTHESIS INHIBITORS PART - 2

Macrolides

00:00:22

They act by blocking translocation.
Mechanisms of resistance :

- Enzymatic inactivation.
- Drug efflux.
- Altered ribosomal structure.
- Methylation of ribosomes : The bacteria produce an enzyme called methylase. It is coded by erythromycin ribosomal methylase (ERM) gene.

	Macrolides			Ketolides
Feature	Erythromycin	Azithromycin	Clarithromycin	Telithromycin
Oral bioavailability	Least			Highest
Route	Oral/ Parenteral	Oral/ Parenteral	Oral	Oral
Half life	1.5 hours (shortest)	68 hours (longest)	6 hours	10 hours
Dosing	QID	OD	BD	OD

Oral bioavailability : Telithromycin (T) > Clarithromycin (C) > Azithromycin (A) > Erythromycin (E).

Ketolides has a very high affinity for 50S subunit.
These can be effective in treating community acquired pneumonia (even in erythromycin/azithromycin resistance).
Telithromycin is a potent hepatotoxic drug.
Solithromycin is another Ketolide, but is not hepatotoxic.
It is used in treatment of CAP.

Spectrum of activity of erythromycin is mostly against gram positive organisms (like Penicillin G) and some gram negative organisms.

Erythromycin is the drug of choice (DOC) for :

- Pertussis.

- Diphtheria.
- Prophylaxis of rheumatic fever in case of penicillin allergy.

Side effects of Erythromycin :

- Cholestatic jaundice seen with estolate salts.
- Hypertrophic pyloric stenosis in infants.
- Stimulates motilin receptors causing diarrhea. It can hence be used in gastroparesis (secondary use).
- QT prolongation : Erythromycin > Clarithromycin > Azithromycin.

Drug interactions : Macrolides are enzyme inhibitors.

- Theophylline toxicity and is contraindicated with macrolides.
- Digoxin toxicity : Macrolides are p glycoprotein pump inhibitors.
  Digoxin dosage must be reduced to prevent toxicity.

All macrolides are safe in pregnancy.

Clarithromycin 00:10:08

It is mostly used against mycobacterium :

- Tuberculosis.
- Leprosy.
- Mycobacterium avium complex.

It is also used against Helicobacter pylori infection.

Azithromycin :

It is the longest acting macrolide. DOC for :

- Atypical pneumonia caused by Chlamydia, Mycoplasma, and Legionella.
- Campylobacter.
- Chlamydia (sexually transmitted disease) and cholera in pregnancy.
- Cholera in children.

Oxazolidinones :

These drugs act by blocking translocation.

Mechanism of resistance is due to mutation of ribosomal site in the 50S subunit.

The drugs include :

- Linezolid : Good oral absorption and the oral bioavailability is ~100%. It can be given either orally (BD dosing) or intravenously (IV).

  Side effects include :

  1. Bone marrow suppression leading to thrombocytopenia, anemia, or leukopenia. Platelet count must be monitored.
  2. Serotonin syndrome as it is a mono amine oxidase inhibitor activity.
  3. Mitochondrial toxicity.
     Blocks aerobic glycolysis and the resultant anaerobic glycolysis will precipitate lactic acidosis, optic neuritis and peripheral neuropathy.

  It is used mostly for resistant infections by gram positive organisms.
  It is used in treatment of methicillin resistant (MRSA) and Vancomycin resistant (VRSA) staphylococcus aureus.
  It is the DOC for VRSA pneumonia and Vancomycin resistant enterococcus (VRE) infection.
  It can also be used as a second line drug for tuberculosis.

- Tedizolid : It can be given orally (OD dosing as it is longer acting than linezolid) or IV.
  It is less toxic compared to Linezolid.

Streptogramins

They block translocation by acting on 50S subunit of ribosomes.
It is a combination of two drugs :

- Quinupristin (30%).
- Dalfopristin (70%).

The combination is used as it is more effective (synergistic) than either one given alone.

MOA :

Dalfopristin binds to its binding site near the Erythromycin

binding site on 50S ribosome.

↓

Structural changes in the Erythromycin binding site

↓

makes Quinupristin to bind to erythromycin binding site.

Drugs binding to erythromycin binding site on 50S ribosome :

- Erythromycin.
- Quinupristin (also called streptogramin B).
- Lincosamide (Clindamycin).

Mechanism of resistance :

Methylation of Erythromycin binding site by an enzyme called methylase. It is coded by the ERM gene.
Methylation makes the bacteria resistant to Erythromycin (macrolide), Lincosamide and Streptogramin B.
It is called MLSB resistance.

These drugs can be given intravenously but cause injection site reactions like pain, edema, and inflammation. Hence preferred to be given via central line.
Spectrum of activity include gram positive organisms and atypical organisms.

They are used as reserved drugs in the treatment of :

- MRSA.
- VRSA.
- VRE.

Lincosamide 00:25:15

Clindamycin blocks translocation by acting on the 50S ribosome.

Mechanism of resistance :

- Enzymatic inactivation.
- Altered ribosomal structure.
- MLSB type resistance.

Spectrum of activity :

- Gram positive organisms :

1. Aerobes : Staphylococcus, streptococcus and Nocardia
2. Anaerobes : Gas gangrene (Clostridium perfringens) and Actinomycosis.

- Gram negative organisms :
  1. Aerobes : Not active against gram negative aerobes (E. coli, typhoid, Klebsiella and providencia).
  2. Anaerobes : Bacteroides and Prevotella.

It is the DOC in treatment of toxic shock syndrome (TSS).
Clindamycin blocks Staphylococcal toxin synthesis.
Clindamycin is given in treatment of osteomyelitis.
It has good bone penetration.

It is the DOC for supradiaphragmatic anaerobes like oral cavity infections.
DOC for infradiaphragmatic infection is metronidazole. Eg. Diverticulitis due to Bacteroides.

Side effects :

- Pseudomembranous enterocolitis.
- Neuromuscular toxicity.

Chloramphenicol

00:31:48

It acts by blocking transpeptidase.
It is currently not used due to side effects like bone marrow suppression and grey baby syndrome.

Grey baby syndrome in neonates is postulated to be due to cardiotoxicity leading to decreased cardiac output. It leads to decreased oxygenation of the skin.
Currently the drug is used in severe resistant infections like rickettsial disease.

Pleuromutilins :
They act by blocking transpeptidase in 50S ribosome.

The drugs include :

- Lefamulin (latest) :
  It is given IV due to poor oral absorption.
  Spectrum of activity includes gram positive (Pneumococcus), gram negative (Klebsiella/H. influenza) and atypical organisms.

It is used in treatment of resistant cases community acquired pneumonia. The drug is expensive.
Side effects include QT prolongation and hepatotoxicity.
It is absolutely contraindicated in pregnancy.

- Retapamulin :
  It is active against gram positive and some gram negative organisms.
  The drug is used topically for bacterial skin infections.

Fidaxomicin 00:36:16

It acts by blocking RNA polymerase and has poor oral absorption.
It is the current DOC for pseudomembranous enterocolitis.

Rifaximin :
It acts by blocking RNA polymerase and has poor oral absorption.
It is used orally and is the DOC for gut sterilization in hepatic encephalopathy.
The drug can also be given in traveller's diarrhea (DOC is Ciprofloxacin) and in pseudomembranous enterocolitis.

Mupirocin :
It is a protein synthesis inhibitor which acts by inhibiting tRNA synthase.
The spectrum of activity is mostly against gram positive organisms.
It is the DOC (given topically) for staphylococcal nasal carriers.
It is used topically in skin infection and impetigo.

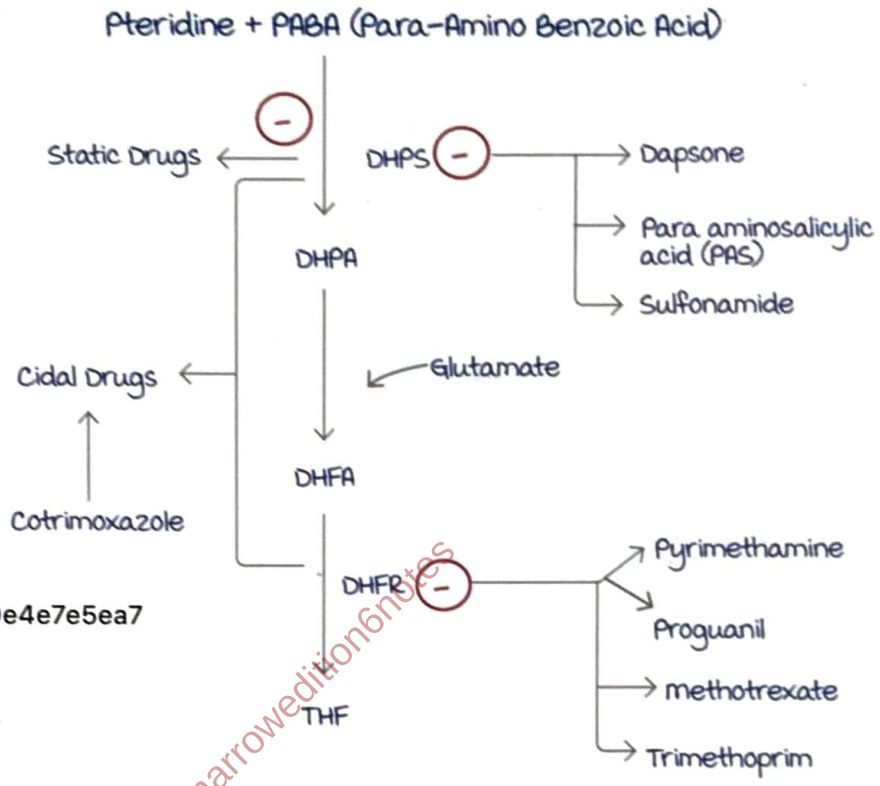
Fusidic acid 00:40:15

It acts by blocking peptide elongation which occurs at the P site.
It is used topically in bacterial skin infections.

All protein synthesis inhibitors are bacteriostatic drugs except aminoglycosides.

ANTI-FOLATE ANTIBIOTICS

Two substrates : Pteridine and PABA (Para-Amino Benzoic Acid).



DHPS : Dihydropteroate synthase.
DHPA : Dihydropteroic acid.
DHFA : Dihydrofolic acid.
DHFR : Dihydrofolate reductase.
THF : Tetrahydrofolate.

Sulfonamides

00:04:22

mechanism of action : Competitive inhibitors of DHPS (PABA analogues).

Spectrum :

- Active against aerobic gram positive except enterococcus.
- Active against aerobic gram negative except Pseudomonas & Rickettsia (cause paradoxical growth).
- No activity against anaerobes.

Drugs :

1. Sulfadoxine :

   Longest acting.

Used along with Pyrimethamine and Artesunate for treatment of malaria.

2. Sulfamethoxazole (SMX) : Used along with Trimethoprim (TMP).
   This combination is known as cotrimoxazole.
   (produces cidal effect).
   Ratio in tablet of TMP : SMX is 1 : 5.
   Ratio in plasma is 1 : 20 (because of high volume of distribution of TMP).

Uses of cotrimoxazole :

- DOC for pneumocystosis.
- DOC for nocardiosis.
- DOC for cystitis.
- DOC for prostatitis.
- DOC for cyclosporiasis.
- DOC for sarcocystosis.
- DOC for isosporiasis.

3. Sulfisoxazole : most water soluble sulfonamide → Causes least crystalluria. Used in treatment of otitis and urinary tract infection.
4. Sulfadiazine : Used along with Pyrimethamine.
   Treatment of choice for toxoplasmosis.

   Drugs that blocks DHFR are contraindicated in pregnancy.

Spiramycin is the DOC for toxoplasmosis in pregnancy.

Topical Sulfonamides 00:12:02

1. Sulfacetamide : Used for treatment of trachoma and conjunctivitis.
2. Sulfadiazine : DOC in burn patients. Also used in fungal Keratomycosis.
3. Mafenide : Can also be used in burn patients.
   Adverse reaction (it is a carbonic anhydrase blocker) : Causes metabolic acidosis & Severe pain on application.

Side effects of Sulfonamides

00:14:37

- Hypersensitivity : Seen as rash or bone marrow suppression.
- Crystalluria. Advice : Drink as much water as possible.
- Acute intermittent porphyria.
- Methemoglobinemia.
- Kernicterus in newborns (high plasma protein binding).

DNA GYRASE INHIBITORS

DNA gyrase/Topoisomerase II inhibitors 00:00:16

Blocking DNA gyrase exerts a bactericidal effect.
These drugs are active against gram negative organisms.

Nalidixic acid (Quinolone) :
Spectrum of activity is only against gram negative organisms.
The drug has poor tissue concentration.
It is used in :

- Urinary tract infection/UTI (Good concentration in urine).
- Infectious diarrhoea like traveller's diarrhoea.

Fluorine was added to Quinolone to form a class of drugs called Fluoroquinolones.
These drugs block :

- DNA gyrase or Topoisomerase II.
- Topoisomerase IV.

Since they block II and IV, they have wider spectrum of activity against gram negative and gram positive organisms.
Mechanisms of resistance :

- Mutation of Topoisomerase II or IV.
- Drug efflux.

Feature	Maximum	Minimum
Oral bioavailability	Levofloxacin	Norfloxacin
Plasma protein binding	Gemifloxacin	Norfloxacin
Half-life ($t_{1/2}$)	moxifloxacin	Ciprofloxacin < Norfloxacin

moxifloxacin has the highest risk of seizure and maximum QT prolongation.

Fluoroquinolones

00:05:12

Norfloxacin :

Poor tissue concentration and is the least active fluoroquinolone.

It is used in UTI and traveller's diarrhoea.

Ciprofloxacin :

most active fluoroquinolone.

It can be given orally, intravenously and topically according to the severity.

It is the drug of choice (DOC) in :

- Traveller's diarrhoea.
- Typhoid carrier. Ceftriaxone is the DOC in a case of typhoid.
- Meningococcal meningitis prophylaxis in a contact and also in mass chemoprophylaxis.
  Ceftriaxone (best drug) is preferred in a case of meningococcal meningitis.
- Pyelonephritis.
- Anthrax. Penicillin G is also active against anthrax but is not the DOC.

Other uses include :

- Pseudomonas infection : Ciprofloxacin and Levofloxacin.
- Tuberculosis : 2nd line drug.

Ofloxacin and moxifloxacin are used as second line drugs in treating tuberculosis and leprosy.

moxifloxacin is the most active fluoroquinolone against leprosy.

Moxifloxacin, Gemifloxacin and Levofloxacin have good activity against :

- Gram positive organisms like Pneumococcus.
- Gram negative organisms like Klebsiella and H. influenza.
- Atypical organisms like mycoplasma, chlamydia and legionella.

These drugs are hence called respiratory fluoroquinolones.

These are one of the first line drugs for treatment of pneumonia.

Recent Fluoroquinolones (FQ) :

- Ozenoxacin.
- Delafloxacin.

They are used in treatment of bacterial skin infections.

Side effects :

- Tendinitis (most common side effect). Tendon rupture may be seen and the risk is more if the patient is :
  1. Elderly.
  2. On steroids.
  3. Organ transplant patient.
- Decrease GABA and precipitate seizure. Maximum risk with Moxifloxacin.
- QT prolongation.
- Photosensitivity.

Contraindications :

- Pregnancy.
- Children.
  They can cause cartilage growth defects and are absolutely contraindicated in children and pregnancy.
- Renal failure as they are excreted exclusively via kidney.
  Moxifloxacin is the only fluoroquinolone which can be given in renal failure as it is excreted by liver.
  Hence, Moxifloxacin cannot be used in UTI.

Active space

URINARY ANTISEPTIC AGENTS

Poor tissue concentration : Not used for systemic conditions.
Well concentrated in urine and have good activity against gram negative infections.
Used for treatment of urinary tract infections (UTI).

Methenamine 00:00:52

- Drug formulated with hippuric acid and mandelic acid.
- These acids make urine pH acidic.
- Acidic pH converts methenamine into ammonia and formaldehyde.
  Formaldehyde has antibacterial effect.
- Vitamin C or ammonium chloride can be used to increase acidic pH and further increase the effect of methenamine.
- Use : Prophylaxis of UTI.
- Side effects : GIT upset.
- Contraindications :
  Renal failure (hippuric and mandelic acids are excreted unchanged by kidney).
  Liver failure (ammonia can cause toxicity and lead to hepatic encephalopathy).
  Contraindicated with sulphonamides as they inactivate formaldehyde.

Nitrofurantoin 00:04:10

Mechanism of action :
Activated by bacterial reductase → Produces free radicals that block synthesis of proteins and nucleic acids.
Uses : Treatment of UTI and asymptomatic bacteriuria.
Side effects : Hemolysis in G6PD deficient individuals, peripheral neuropathy.

Trimethoprim :

- Inhibitor of dihydrofolate reductase (DHFR).
- Used in the treatment of UTI.
- Side effects : Megaloblastic anemia due to inhibition of DHFR.
  Hyperkalemia due to blockage of ENac.

Other urinary antiseptic agents :

Fosfomycin

Fosmidomycin.

Nalidixic acid.

Norfloxacin.

ANTI TUBERCULAR DRUGS

First line drugs

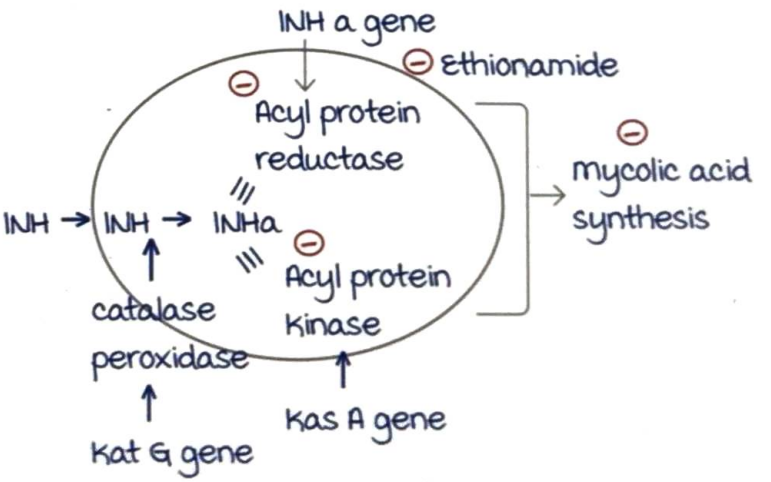
00:00:30

	Isoniazid (H)	Rifampicin (R)	Pyrazinamide (Z)	Ethambutol (E)
Mechanism of action	Bactericidal (First drug to make the patient non infective)	Bactericidal (Maximum action)	Bactericidal	Bacteriostatic
Effective against :	Rapidly dividing M. TB	Slow growers (persisters) : Found in caseous lesions (Rifampicin > Pyrazinamide)		Rapidly dividing M. TB
Cellularity	Intracellular and extracellular	Intracellular and extracellular	Intracellular	Extracellular
Organ of excretion	Liver	Liver (maximum metabolism)	Liver	Kidney
Safest drug in renal failure : Rifampicin most unsafe drug in renal failure : Ethambutol most hepatotoxic drug : Z > H > R				

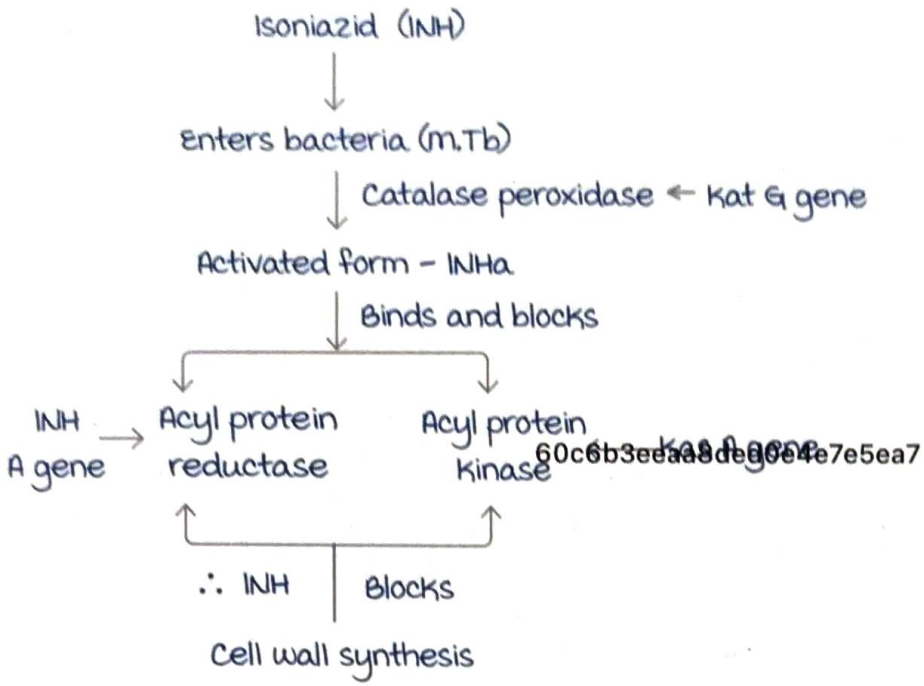
Isoniazid (INH)

00:05:52

Mechanism of action : Blocks mycolic acid synthesis



Active space



Mechanism of resistance :

- Kat G gene mutation : most severe form of resistance.
- Kas A gene mutation.
- INH A gene overexpression :
  Causes cross resistance to Ethionamide.
  INH can be used by doubling the dose.

Uses of Isoniazid :

Treatment of TB.

DOC for prophylaxis of TB (latent TB infection).

Isoniazid : Side effects and toxicity 00:12:06

Side effects :

Gynecomastia.

INH blocks activation of pyridoxine into pyridoxal phosphate.

Pyridoxal phosphate is required for synthesis of

GABA

Decrease in GABA causes :

- Hallucination
- Psychosis
- Euphoria
- Peripheral neuropathy

Heme

Decrease in heme causes anemia.

To prevent these side effects, Vitamin B_6 10 mg/day to be given prophylactically.

Toxicity :

- metabolic acidosis.
- Seizure : Does not respond to phenytoin.
  Treatment : 1 gm of Pyridoxine IV given for 1 gm of INH.
  Maximum dose is 5 gm.
  If dose of INH is unknown, give 5gm IV Pyridoxine.
  Benzodiazepines like Diazepam/Lorazepam can be given.

Rifampicin

00:15:50

Uses :

Treatment of :

- TB.
- Leprosy.
- Nontuberculous mycobacterium : M. Avium Complex, M. Kansasii.

Treatment of Gram positive and negative bacteria :

- Contacts of meningococcal meningitis (current DOC : Ciprofloxacin).
- Used as add on :

To Penicillin /Vancomycin against Staphylococcus.

To Doxycycline for Brucellosis.

Side effects (mnemonic : RIFAMPICIN) :

mechanism of action : RNA polymerase inhibitor → Bactericidal.

mechanism of resistance : rpob gene mutation.

Interstitial nephritis.

Flu like symptoms (seen with intermittent dosing only).

Anaemia.

Makes secretions and urine reddish orange colour, e.g., orange staining of contact lens.

Decreases Platelet count, Pulmonary syndrome :

Stop Rifampicin and never restart as these are hypersensitivity reactions.

Rifampicin is an enzyme Inducer causing :

- Contraceptive failure.
- INR deranged (with warfarin), change rifampicin to Rifabutin (less potent inducer).
- Nevirapine failure (metabolized by microsomal enzymes).

Other Rifamycins :

	Rifabutin	Rifapentine	Rifampicin
Half-life ($t_{1/2}$)	↑↑↑ (Longest acting)	↑↑	↑ (Shortest acting)
Enzyme inducing activity	↑ (Preferred for TB with HIV)	↑↑ Prophylaxis of TB (once a week)	↑↑↑ (Preferred for TB without HIV)
Effect of food on absorption	No effect	Increased (taken with fatty food)	Decreased (taken on empty stomach)
Effect on M. Avium Complex	↑↑	↑	↑
Effect on M. TB	↑	↑↑	↑↑

Pyrazinamide

00:25:17

Prodrug
↓ Pyrazinamidase coded by Pnc A gene
Pyrazinoic acid
↓
Blocks fatty acid synthase
↓
Blocks mycolic acid synthesis

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Pyrazinoic acid accumulates :

- Intracellularly.
- At site of active inflammation due to acidic pH.

Hence pyrazinamide is used in intensive phase (first two months) as it is most effective when inflammation is most active.

Mechanism of resistance : Pnc A gene mutation.

Side effects :

- Most hepatotoxic drug.
- Hyperuricemia, gout.
- Peripheral neuropathy.
- Arthralgia.

Ethambutol

00:28:36

Mechanism of action : Blocks arabinosyl transferase which decreases synthesis of arabinogalactan, which can be a component of cell wall of mycobacterium.
The enzyme arabinosyl transferase is coded by emb A/B gene.

Mechanism of resistance : emb B gene mutation.
Uses :

- Treatment of TB.
- Treatment of M. Avium Complex and M. Kansasii.

Side effect :
Eye toxicity : Retrobulbar optic neuritis.
Red green color blindness (green > red).
Ethambutol can be used in children with regular monitoring.

MDR TB : Resistance to INH + Rifampicin.
Pre XDR TB : Resistance to INH + Rifampicin + Fluoroquinolones or second line injectables (SLI).
Extremely drug resistant TB (XDR TB) : Resistance to INH + Rifampicin + Fluoroquinolones + second line injectables (SLI).

Older second line drugs for TB

00:32:55

Ethionamide : Bactericidal drug.

Prodrug
↓ mono-oxygenase (Eth A gene)
Activated
↓
Inhibits acyl carrier protein reductase
↓
Blocks mycolic acid synthesis

mechanism of resistance : Mutation of Eth A gene.

Contraindication : Not to be given with Isoniazid or Thioacetazone due to cross resistance.

Side effects (Mnemonic : ETHI)
Eye toxicity.
Toxic to liver.
Hypothyroidism.
Impotence.

Thioacetazone : Bactericidal drug.

Prodrug
↓ mono-oxygenase (Eth A gene)
Activated

mechanism of resistance : Mutation of Eth A gene.
Side effects : (Mnemonic : HBS)
Hemolysis.
Bone marrow suppression.
Steven Johnson syndrome.

Para aminosalicylic acid (PAS) :
mechanism of action : Blocks DHPS (Dihydropteroate synthase).
Bacteriostatic drug.
Contraindicated with Rifampicin as PAS decreases absorption of Rifampicin.

Other drugs :

Clofazimine : Anti leprosy drug.

Antibiotics : Clarithromycin, Linezolid, Fluoroquinolones, Aminoglycosides.

Newer second line drugs for TB

00:39:27

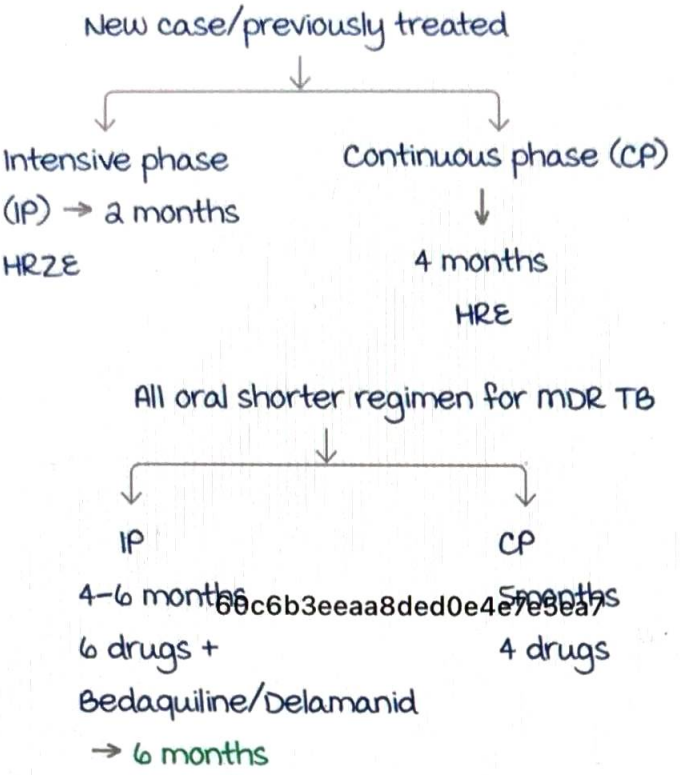
	Bedaquiline	Delamanid	Pretomanid
Mechanism of action	Blocks mycobacterial ATP synthase	These are nitroimidazoles. Blocks mycolic acid synthesis in replicating bacteria. Free anion radical in static bacteria.	
Use	Resistant TB (MDR, XDR, Pre XDR TB)		
Effect of food	Food increases absorption (taken with food).		
Contraindication	Pregnancy and lactation		
	Arrhythmia (QT prolongation) (Not present with Pretomanid)		
Contraindicated in age group	< 18 years	< 6 years	<18 years and > 65 years
Pharmacokinetics	Sequestered in tissues except CNS Extensive $t_{1/2}$: 165 days but plasma $t_{1/2}$: 24 hours	High plasma protein binding (99%) metabolized by plasma albumin Contraindicated if serum albumin < 2.8 g/dl	High plasma protein binding (86%) metabolized in liver by microsomal enzymes Excreted by kidney
Dosing	Intermittent dosing 0 to 2weeks : 400 mg OD 2 to 24 weeks : 200 mg thrice a week, with gap of 48 hrs between doses	100 mg BD	200 mg OD

TB regimens

00:47:00

Intensive phase : more number of drugs are given for a lesser time period. Initial high intense attack on the bacteria.

Continuous phase : Fewer drugs are given for longer time. Gradually acts on the remaining bacteria.



All oral longer MDR regimen :
4 drugs given for 18–20 months + BDQ/DLM given for 6 months.

Pre XDR and XDR :
Treatment based drug sensitivity testing (DST)
Or BPAL regimen.

BDQ
Pretomanid
Linezolid
} 26 weeks, can be increased if required

ANTI-LEPROSY DRUGS

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First line drugs

00:00:32

Rifampicin :

- most Cidal drug.
- Contraindications :
  ENL (Erythema Nodosum Leprosum).
  Reversal reaction.
  These are hypersensitivity reactions to Lepra antigen.
- In mild to moderate ENL/Reversal reaction :
  Clofazimine is preferred.
- In severe cases : Steroids > Thalidomide.
  (Thalidomide is more toxic).

Dapsone :

Blocks DHPS (Dihydropteroate synthase). It is a Static drug.

- Uses :
  1. To treat Leprosy, Malaria.
  2. For prophylaxis of Pneumocystosis, Toxoplasmosis.
  3. It's anti-inflammatory effect is used to treat pemphigoid, relapsing chondritis, dermatitis herpetiformis.

- Side effects :
  1. Hemolysis in G6PD deficiency.
  2. Peripheral neuropathy.
  3. Methemoglobinemia.
  4. Neuropsychiatric side effects.

Clofazimine :

Mechanism of Action : Free radical production (Bacteriostatic).

- Uses :
  1. TB (second line drug) : Cidal drug.
  2. Leprosy (first line drug) : Static drug.
  3. ENL/reversal reaction.

- Side effects :
  1. Crystals are deposited in tissues.
     Example : In intestinal mucosa causing nausea, vomiting, diarrhoea, anorexia (leading to weight loss).
  2. Ichthyosis.
  3. Skin/secretions discoloration : Reddish black or orange brown (Not malignant).

Second line drugs

00:09:24

Fluoroquinolones (Cidal) :

- Ofloxacin.
- moxifloxacin.
- Levofloxacin.

Clarithromycin (Static).
Minocycline (Static).

WHO regimen for treatment of leprosy :
Multibacillary : 12 months.
Paucibacillary : 6 months.

In a Rifampicin sensitive patient, 2 drugs are given under supervision.

	>14 years	10 – 14 years	< 10 years
Rifampicin	600mg/month	450mg/month	10mg/Kg/ month
Clofazimine	300mg/month	150mg/month	6mg/Kg/ month

Without supervision (once/day)

	>14 years	10 – 14 years	< 10 years
Dapsone	100mg	50mg	2mg/kg
Clofazimine	50mg	50mg on alternate days	1mg/kg

Rifampicin resistant cases :

(Two from second line & One from first line which is always Clofazimine).

Intensive phase : 6 months			Continuous phase : 18 months		
Ofloxacin Minocycline Clofazimine	(or)	Ofloxacin Clarithromycin Clofazimine	Ofloxacin Minocycline Clofazimine	(or)	Ofloxacin Clofazimine

Rifampicin & Ofloxacin resistant cases :

Intensive phase : 6 months	Continuous phase : 18 months
Clarithromycin Minocycline Clofazimine	Clarithromycin/Minocycline Clofazimine

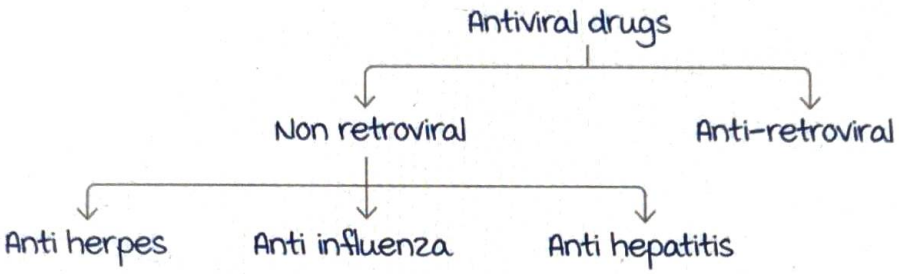
Post exposure prophylaxis

00:15:14

Drug of choice : Rifampicin

- > 15 years : 600mg
- 2 – 14 years : 450mg
- 6 – 9 years or weight ≥ 20kg : 300mg
- ≥ 2years or weight <20kg : 10 – 15mg/kg

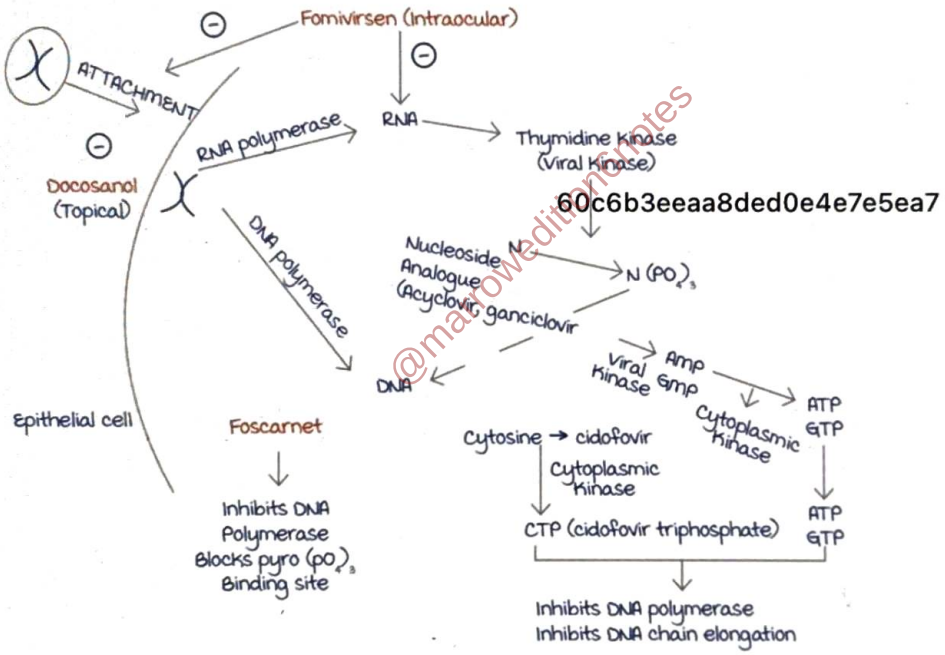
ANTIVIRAL DRUGS : NON-RETROVIRAL DRUGS



Anti-herpes drugs :

00:03:08

Replication of herpes virus (DNA virus) :



Nucleoside analogues : After phosphorylation, forms abnormal substrates that

- Gets incorporated into DNA and stops DNA chain elongation.
- Competitively inhibit DNA polymerase enzyme.

Guanosine nucleoside analogues : Acyclovir, ganciclovir.
Cytosine nucleoside analogue : Cidofovir.
Thymidine nucleoside analogues : Idoxuridine.
Pyrimidine nucleoside analogue : Trifluridine.

} Topical
MOA : Inhibits DNA chain elongation

Active space

Mechanism of resistance :

Acyclovir, ganciclovir : Decreased production/absence of thymidine kinase (viral kinase).

Without viral kinase, these drugs cannot be phosphorylated and hence cannot be active.

DOC for resistance : Foscarnet.

Anti-herpes drugs

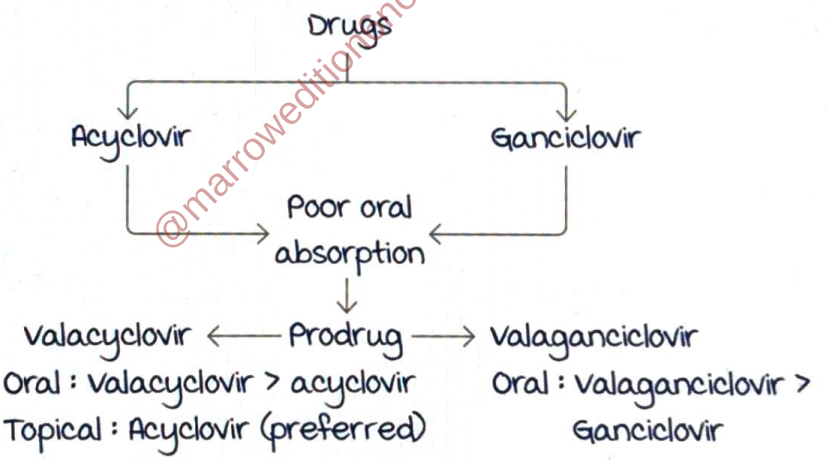
00:19:48

Guanosine nucleoside analogues :

MOA : Blocks DNA polymerase and DNA chain elongation.

Mechanism of resistance :

- DNA polymerase mutation.
- Change in the function of viral kinase (does not phosphorylate Acyclovir).
- Impaired viral kinase production : most common mechanism of resistance.



	Acyclovir	Ganciclovir
Prodrug	Valacyclovir	Valaganciclovir
Uses	DOC is oral Valacyclovir > topical Acyclovir for mild to moderate infections like mucocutaneous infections caused by HSV and VZV. For severe infections like HSV encephalitis : DOC is IV Acyclovir.	Oral Valaganciclovir is DOC for treatment and prophylaxis (immunocompromised patients) for CMV retinitis. IV Ganciclovir is used only when there is high risk of vision loss.

Side effects of IV Acyclovir :

Neurotoxicity : Cause seizures.

Crystalluria : Leads to obstructive renal failure (advise patients to consume lots of water/IV fluids).

Side effect of Ganciclovir/Valaganciclovir :

Bone marrow suppression (dose limiting toxicity)

Other drugs causing bone marrow suppression are :

- Zidovudine.
- Linezolid.
- Other anticancer drugs.

Other drugs :

Famiciclovir : Better oral absorption

↓

Pro drug of Penciclovir

Long acting
Less potent
Uses : Alternatives for HSV, VZV

Cytosine nucleoside analogue 00:31:13

Cidofovir : Does not require viral kinase.

MOA : Blocks DNA polymerase and DNA chain elongation.

Poor oral absorption. So, route is IV or topical.

IV Cidofovir uses :

Resistant herpes (HSV, CMV).

BK virus/adenovirus : Organ transplant patients.

Topical cidofovir uses :

- Molluscum contagiosum.
- Anogenital warts.

Intralesional drug : DOC for recurrent laryngeal papillomatosis.

Side effect : Nephrotoxicity.

Foscarnet :

MOA : Binds to pyrophosphate binding site & blocks DNA polymerase.

Route : IV.

IV Foscarnet is DOC for resistant HSV/CMV infection.

Side effects :

- Nephrotoxicity.
- Hyper/hypocalcemia (symptomatic).
- Hypo/hyperphosphatemia.
- Hypomagnesemia.
- Hypokalemia.

Fomivirsen :

MOA : Blocks viral attachment and viral RNA.

Route : Intraocular.

Use : CMV retinitis (alternative to Ganciclovir).

Side effect : Cataract, iritis, vitreitis.

Other topical drugs :

Docosanol : Oral labial herpes.

Idoxuridine :

- Oro labial herpes.
- Genital herpes.
- HSV Keratitis.
- VZV skin lesions.

Trifluridine : HSV Keratitis.

Side effect : Punctate keratopathy.

Recent advances :

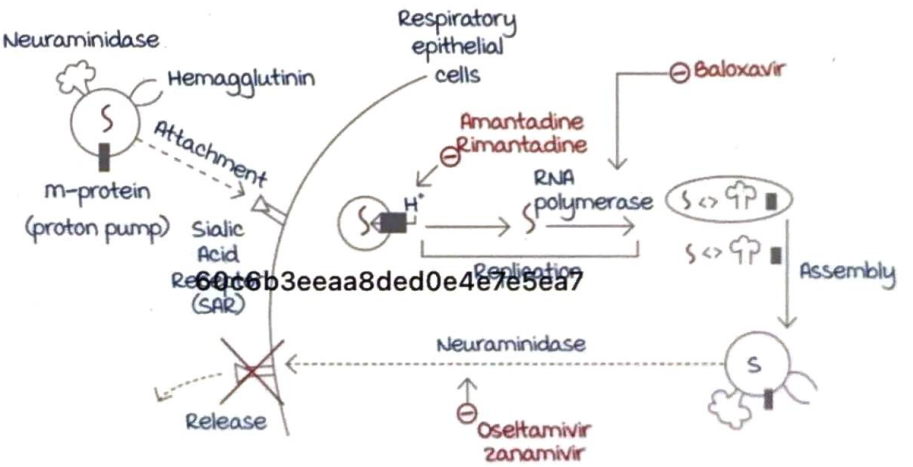
Letermovir :

MOA : Blocks CMV DNA terminase.

Use : Prophylaxis of CMV infections in stem cell transplantation.

Anti-influenza drugs

00:43:46



RNA virus attachment :

Hemagglutinin + SAR binds → RNA influenza virus enters.

Replication :

m protein proton pump → makes Intraviral pH acidic → Corrodes nucleocapsid → RNA exposed → RNA polymerase → Copies viral components.

Assembly → Formation of progeny RNA virus.

Release → Neuraminidase → Breaks down SAR → Breach in cell membrane → Move out of the cell.

m protein inhibitors :

MOA : Blocks viral uncoating/RNA release from virus.

Drugs : Amantadine, Rimantadine.

Uses : Not used for treatment of influenza currently because of high resistance.

Side effects : Ankle edema, livedo reticularis (purple pigmentation).

Baloxavir :

MOA : Blocks RNA polymerase → inhibits viral replication.

Uses : Treatment of Influenza A and B.

Drugs used in treatment of influenza are most effective when used within 48 hours of symptom onset (primary replication period).

Neuraminidase inhibitors :

MOA : Blocks viral release.

Oseltamivir (Tamiflu) :

Route : Oral.

DOC for Influenza A, B and Bird flu.

Treatment : 75 mg BD for 5 days.

Prophylaxis : 75 mg OD for 7 days.

Side effect : Nausea and vomiting (to be taken with food).

Active space

Zanamivir :

Poor oral absorption. So, route is inhalational > IV.

Inhalational zanamivir is DOC in oseltamivir resistant Influenza A, B and bird flu.

Treatment : 10mg BD for 5 days.

Prophylaxis : 10 mg OD for 7 days.

Side effect : Bronchospasm.

Contraindicated in Bronchial asthma, COPD.

Recent drugs :

Peramivir : IV route, 600 mg once for treatment of oseltamivir sensitive case.

Laninamivir : Inhalational route, 40 mg once for oseltamivir resistant case.

Anti-Hepatitis drugs

00:59:40

Hepatitis B :

Treat only chronic active state. (Raised ALT/AST or histological signs of ongoing hepatic inflammation.

Hepatitis C :

Treat both acute and chronic cases. Treat acute cases to prevent chronicity.

Drugs used in hepatitis B

Specific drugs :

Used only for Hep B.

MOA : Blocks DNA polymerase

E.g. Entecavir, Adefovir.

Non-specific drugs :

Used as both anti-HIV and anti-Hep B.

E.g. Tenofovir, Lamivudine.

Entecavir :

Oral drug, taken on empty stomach.

most potent first line drug.

Not DOC as it develops resistance in patients with Lamivudine resistance.

Tenofovir :

1st line for Hep B (DOC).

Effective in Lamivudine resistance.

Other drugs :

Lamivudine.

Emtricitabine.

Adefovir :
Poor oral absorption.
Prodrug :
Adefovir dipivoxil : Can be given orally.
Least potent drug but effective in cases of Lamivudine resistance.

Clevudine.
Telbivudine.

Emtricitabine is a derivative of Lamivudine. Hence both drugs are never used together.

Anti-Hepatitis C drugs 01:07:54

Interferon α :
(Two other interferons,
β : Used in multiple sclerosis.
γ : Used in chronic granulomatosus disease.)
MOA : Increases production of viral RNA degrading enzymes, which decreases protein synthesis.
Route : Subcutaneous or Intramuscular : 3 times a week.
Subcutaneous pegylated interferon α once a week.
Uses :

- Hep C, Hep B, Hep D (only drug active against Hepatitis D).
- DOC for Hep B + Hep D coinfection.
- Kaposi sarcoma.
- CML.
- HIV induced thrombocytopenia.
- Hairy cell leukemia.

Side effects :

- Bone marrow suppression.
- Hypo/hyperthyroidism.
- Flu like syndrome.

Therefore it is not recommended.

Ribavirin :
MOA : Inhibits RNA dependent RNA polymerase (RDRP).
Uses :

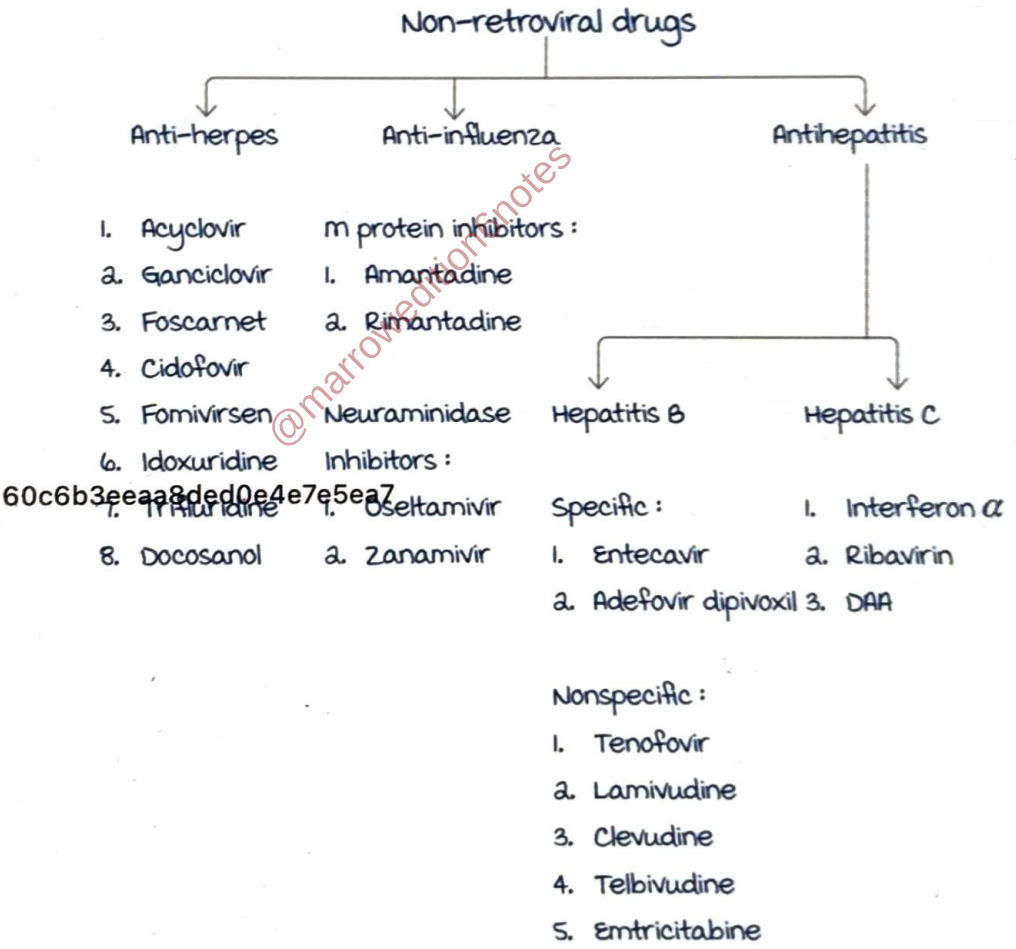
- Oral : Used with interferon α or direct acting antivirals (DAA).
- Inhalational : DOC for treatment of respiratory syncytial

virus (RSV) (m/c cause of bronchiolitis in infants).
DOC for RSV prophylaxis is Palivizumab.

- IV : Severe influenza.

Direct acting antivirals (DAA) :
Oral drugs :
Never used as monotherapy because of resistance.
Used as regimens. Current treatment of choice for Hep C.
Three classes of drugs :

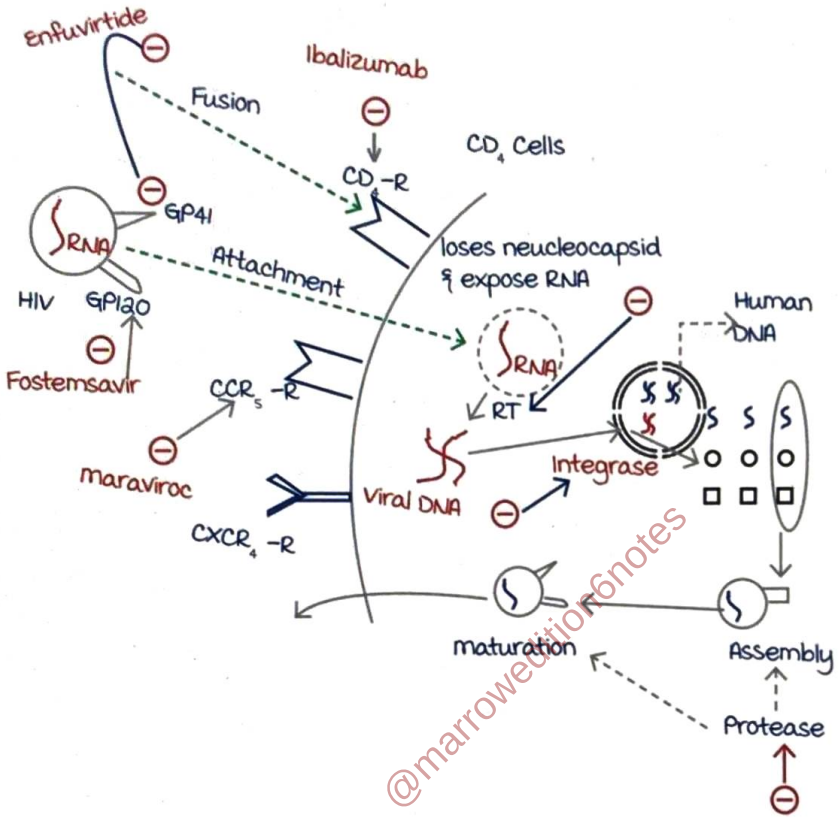
- NS5B blocker (RNA polymerase inhibitor). E.g. Sofosbuvir.
- NS5A blocker : Velpatasvir.
- Protease inhibitor (NS 3/4 blocker) : Paritieprevir.



ANTIVIRAL DRUGS- ANTIRETROVIRAL DRUGS

Replication of HIV virus

00:00:36



Attachment :

- Gp41 → CD4 receptor (fusion).
- Gp120→ CCR5 receptor (only in early course of disease).
- Gp120 → CXCR4 receptor (late course of disease).

Entry :

- HIV-1 = CD4/CCR5.
- HIV-2 = CCR5 + CD4.

Conversion of RNA → DNA by Reverse transcriptase.

Transcription : Integration of viral DNA + Human DNA by Integrase.

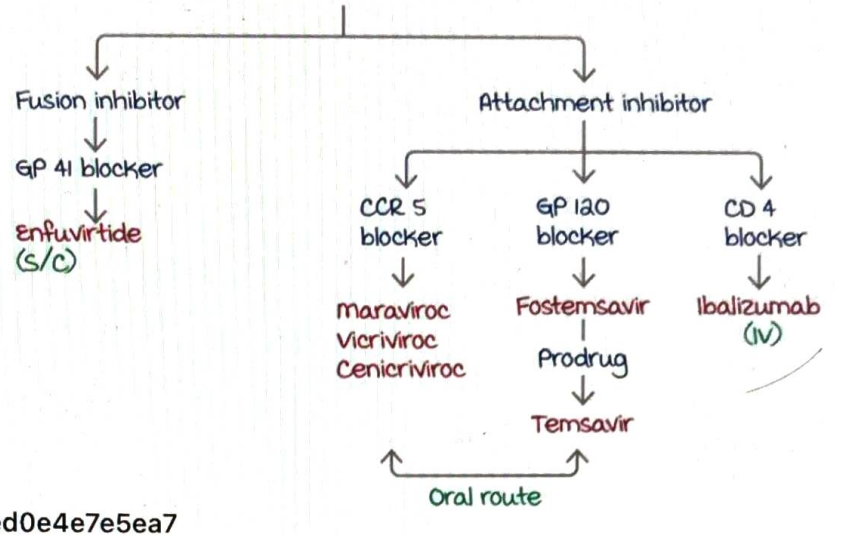
Replication : Formation of viral protein & RNA.

Assembly : Aggregation of viral components together by Protease.

Maturation : Break down protein to appropriate size & shape to ensure survival. Done by Protease.

Entry inhibitors

00:08:34



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Only CCR5 inhibitors are used in both HIV 1 and 2.
All other drugs are used in HIV 1 only.
All these drugs are used only in case of resistant HIV.

Reverse transcriptase inhibitors

00:12:29

Mechanism of resistance : mutation of Reverse transcriptase enzyme.

Nucleoside RTI	Non-nucleoside RTI
Used in both HIV 1 and 2	Only HIV 1
Nucleoside analogue	Not an analogue
Blocks enzymatic site of Reverse transcriptase	Blocks allosteric site of Reverse transcriptase
Mitochondrial toxicity seen.	Mitochondiral toxicity is not seen.

NRTI :

Target : Reverse transcriptase (RNA dependent DNA polymerase) enzymatic site.
Viral enzymatic site is similar in structure to Human DNA polymerase γ enzymatic site in mitochondria.
Hence, NRTI also blocks mitochondrial enzymatic site in humans.

This leads to mitochondrial toxicity causing lactic acidosis, peripheral neuropathy, myopathy, pancreatitis.

Pharmacokinetics : All NRTIs are excreted by Kidney except Zidovudine and Abacavir (excreted by liver).
All NRTIs are metabolized by non-microsomal enzymes. Hence can be used along with Rifampicin.

Zidovudine :

Uses :

- Treatment of HIV → Adults = 2nd line drug.
  in Children <10 years = 1st line drug.
- As 2nd line drug prevent perinatal transmission of HIV .
  (DOC is Nevirapine).
  Zidovudine is DOC to prevent perinatal transmission in :
  1. HIV-2.
  2. History of Nevirapine intake in previous pregnancy.

Side effects :

- Bone marrow suppression : Anemia, leucopenia.
  (contraindicated if Hb < 9 mg/dl).
- Myopathy.
- Hepatotoxicity.
- Insomnia.

Stavudine : Shows maximum peripheral neuropathy hence not commonly used.

Didanosine : Not used now as it causes Pancreatitis.

Abacavir :

- Effective only in HIV 1.
- Use : treatment of HIV in adults and children < 10 years (2nd line).
- It is the DOC in children < 10 years with anemia.

Side effects :

- MI.
- SJS- Associated with HLA-B 5701 gene.

Other drugs :

Lamivudine (India)
Emtricitabine (USA)
Tenofovir (Nucleotide RTI)

→ Least potent inhibitors of Human polymerase γ
→ Least toxic NRTIs.

Side effects of Tenofovir :

- Nephrotoxic.
- Fanconi syndrome.

Contraindications of Tenofovir :

- Renal failure
- Child < 10 years
- Weight < 30 Kg

→ Safety is not established.

Regimens for HIV treatment and post exposure prophylaxis

2NRTI + Any other
- 1st line– Dolutegravir
- 2nd line : Lopinavir/Ritonavir
- 3rd line : Efavirenz

Tenofovir+ Lamivudine+ Dolutegravir : Current regimen used in adults and adolescents >10 years.

Exceptions :

- Renal failure
- Weight < 30 Kg

→ Abacavir + Lamivudine + Dolutegravir.

- Children <10 years : Zidovudine + Lamivudine + Dolutegravir.
- Children <10 years with anemia : Abacavir + Lamivudine + Dolutegravir.

Non nucleoside reverse transcriptase inhibitors NNRTI

00:33:47

Acts only against HIV 1.
All NNRTIs are excreted by liver.
Drugs : mnemonic : NEED RTI
Nevirapine.
Efavirenz. } metabolized by non-microsomal enzymes.
Etravirine. } Hence, can be used with Rifampicin.
Delavirdine.
Doravirine.
Rilpivirine.

All other drugs are metabolised by microsomal enzymes.
All are enzyme inducers except Delavirdine (enzyme inhibitor) and Doravirine (no effect on enzymes).

Uses :
Treatment of HIV : Efavirenz – 3rd line drugs.
Nevirapine : DOC for prevention of perinatal transmission of HIV.

Side effects :

- most common is rash.
- Nevirapine can cause fatal hepatoxicity. Never used for treatment of HIV.
- Efavirenz is teratogenic.

Integrase inhibitors

00:39:40

Consists of drugs like
Raltegravir.
Bictegravir.
Elvitegravir (used in combination with Cobicistat).
Dolutegravir

Uses : Treatment and post-Exposure prophylaxis (PEP) of HIV.
PEP is most effective if taken within 2 hours and can be taken up to 72 hours after exposure.

Side effects :

Raltegravir : Rhabdomyolysis as a presentation of myopathy.

Raltegravir and Bictegravir : hepatoxicity.

Protease inhibitors

00:42:46

Uses :

HIV treatment and as 2nd line PEP drugs in India.

Common features :

- Metabolized by CYP3A4 (except Nelfinavir → CYP2C19).
- Enzyme inhibitors of CYP3A4.
- Can cause metabolic side effects :
  1. Dyslipidemia (DOC is Pravastatin which is metabolized by non-microsomal enzymes).
  2. Insulin resistance resulting in hyperglycemia.
  3. Lipodystrophy : central obesity, thin limbs, buffalo hump.

Oral bioavailability and $T_{1/a}$: Maximum with Darunavir.
Minimum with Saquinavir.

Protease inhibitors causing auto-induction of metabolism :

mnemonic : Not Like Reverse Transcriptase

Nelfinavir.

Lopinavir.

Ritonavir.

Tipranavir.

Drugs :

Lopinavir : Always used with Ritonavir.

Ritonavir :

Most potent enzyme inhibitor.

Used as a booster : prevents metabolism and boosts $T_{1/a}$ of other protease inhibitors except Nelfinavir.

Cobicistat : Booster drug.

Analogue of Ritonavir but has no antiviral effect.
Used along with Elvitegravir, Darunavir, Atazanavir.

Darunavir :
Taken with food as food increases its absorption.

Atazanavir :
Only Protease inhibitor that does not cause dyslipidemia.
Causes hyperbilirubinemia as it unconjugates bilirubin.

Indinavir :
Causes nephrolithiasis and hyperbilirubinemia.

Tipranavir :
Only non-peptide protease inhibitor.
Side effect : anticoagulant effect → increased risk of bleeding.

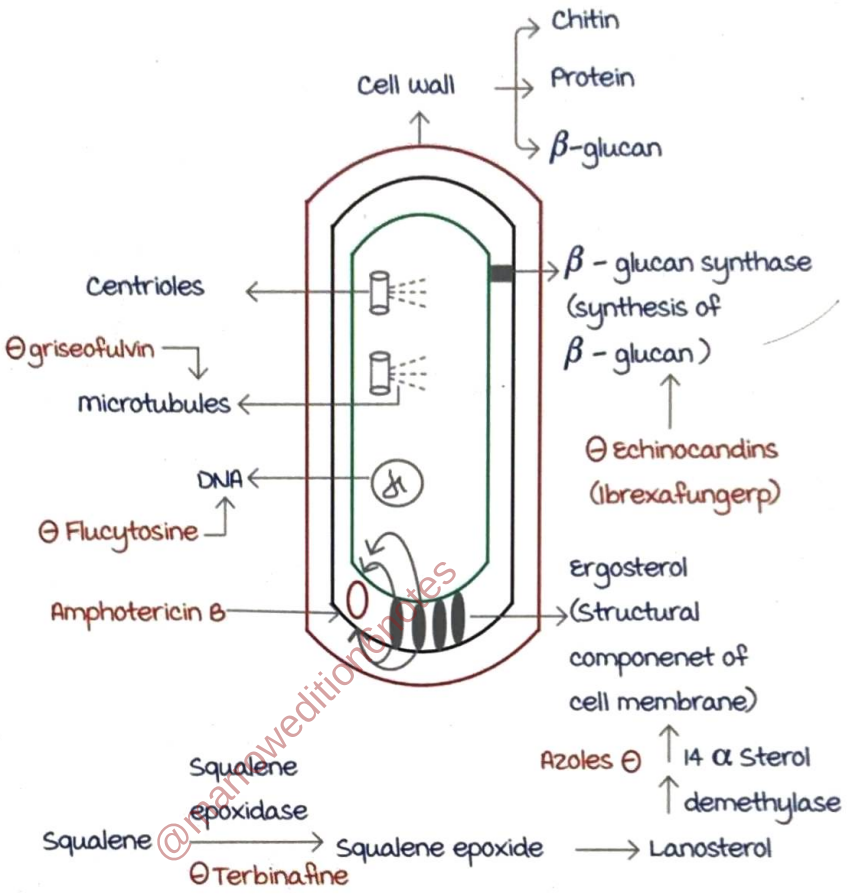
Antiretroviral Drugs Summary

Reverse Transcriptase Inhibitors	Protease Inhibitors	Integrase Inhibitors	Entry Inhibitors
NRTI Zidovudine Lamivudine Emtricitabine Tenofovir	Ritonavir = Cobicistat Saquinavir Atazanavir Darunavir Indinavir	Raltegravir Dolutegravir Bictegravir Elvitegravir	CD-4 Inhibitors: Ibalizumab GP-41 Inhibitor: Enfuvirtide CCR-5 Inhibitor: Maraviroc GP-120 Inhibitor: Fostemsavir
NNRTI Nevirapine Efavirenz Etravirine Delavirdine/Doravirine Rilpivirine			

ANTIFUNGAL DRUGS

Structure of fungus

00:01:09



Amphotericin-B

00:08:46

Mechanism of action :

Old : makes pores in the fungus.

New : Sequesters ergosterol in cell membrane like a sponge.

Route : IV along with a carrier (5% Dextrose).

Uses : DOC for

- Systemic fungal infections like candida meningitis.
- Kala azar.
- Mucormycosis.
- Cryptococcal meningitis. Treatment : IV Amphotericin B + IV Flucytosine. Discharge on Oral Fluconazole.

Side effects :

- Hypokalemia : For prevention KCl is given.
- Anemia.
- Hypomagnesemia.
- Hypotension.
- Infusion reaction : Characterised by chills. Pethidine is used treat.
- Nephrotoxicity : For prevention :
  1. Preload the patient with 1-2 L of Normal saline (also with Cisplatin).
  2. Combine Amphotericin B with liposomes (most common but costly), lipids, colloids.

Azoles

00:17:15

Mechanism of action : Blocks 14 α sterol demethylase causing block of ergosterol synthesis.

Classification

Imidazoles	Triazoles
Ketoconazole	Fluconazoles
Clotrimazole	Itraconazoles
miconazole	voriconazoles
Block fungal and human sterol synthesis.	Posaconazoles
Hence, more toxic.	Isavuconazoles
	Block fungal sterol synthesis only.

Spectrum : Azoles have wide spectrum.

- Candida.
- Dermatophytes.
- Cryptococcus.
- Endemic mycoses.

Fluconazole :

DOC : Coccidioidal meningitis.

DOC : Candida [only C. albicans] : Mucocutaneous candidiasis (vaginal, esophagitis, cystitis)

DOC for oral candidiasis : Topical Clotrimazole.

Itraconazole : DOC for

- Dermatophytes.
- Sporotrichosis.
- Endemic mycoses.

Other uses :

ABPA (Allergic bronchopulmonary aspergillosis)

DOC : Steroids (Prednisolone).

Itraconazole decreases dose of steroid required.

Voriconazole :

DOC : Invasive aspergillosis.

If patient develops intolerance to voriconazole, use Posaconazole or Isavuconazole.

Posaconazole :

DOC : Prophylaxis of invasive aspergillosis.

Other uses :

- Antifungal of choice in GVHD (Graft v/s host disease), Induction chemotherapy in leukemia.
- Mucormycosis.

Isavuconazole :

Uses : Mucormycosis, Invasive Aspergillosis.

Side effects of Azoles :

Common side effect is hepatotoxicity.

- Fluconazole → Alopecia.
- Itraconazole → Increases mineralocorticoid effect which is sodium and water retention (CHF / Edema) and potassium loss (Hypokalemia).

- Voriconazole → visual abnormalities, basal cell carcinoma of skin.
- Ketoconazole :

1. Decreased androgen in males : Gynaecomastia, impotence.
2. Decreased Estradiol in females : menstrual irregularities.
3. Decreased steroid synthesis reduce cortisol. Secondary use is treatment of Cushing's disease.

Terbinafine 00:32:10

Mechanism of action : Blocks squalene epoxidase and blocks ergosterol synthesis.

Route :

- Topical.
- Oral : maximally concentrated in skin, hair, nails → hence used in treatment of dermatophytes.
  (but DOC is Itraconazole).

Side effects : Hepatotoxicity, Stevens-Johnson syndrome.

Griseofulvin :
MOA : Inhibition of microtubules (Fungistatic).
Oral route → Maximum concentration in stratum corneum
Pharmacokinetics : Fatty food increases absorption (use ghee).
Uses :

- Dermatophytes.
- DOC : T. Capitis (Kerion/Boggy swelling).

Side effects : Hepatotoxicity, neutropenia.

Beta glucan synthase inhibitors 00:33:56

Echinocandins :
MOA : Inhibits β glucan synthase → Inhibits cell wall synthesis.
Route : IV.

Uses :

- C. albicans : 2nd line.
- Non albicans candida like C. Krusei, C. Glabrata, C. Parapsilosis (DOC is echinocandins).
- Aspergillosis : 2nd line.

Drugs :

- Caspofungin : Approved for Rx of candida and Aspergillus.
- micafungin : Treatment of candida only and to prevent fungal infection after stem cell transplant.
- Anidulafungin : Treatment of candida.

Ibrexafungerp : Recent drug.

Oral route for treatment of all types of candida causing vaginal infection.

60c6b3eeaa8ded0e4e7e5ea7

Flucytosine

Prodrug of anticancer drug : 5 fluorouracil.

Use : IV → Cryptococcal meningitis.

Side effect : Bone marrow suppression and colitis.

Hence not used for more than 2 weeks.

Topical antifungals 00:43:30

Used against Candida and Dermatophytes.

(mnemonic : BHUTAN)

Butenafine.

Halprogin.

Undecyclenic acid, Tolnaftate } Only against dermatophytes

Tavaborole

Azoles : Clotrimazole, Efinaconazole, Miconazole, Luliconazole.

Nystatin : only against candida.

Natamycin : DOC fungal corneal ulcer.

5% Taraborale, 10% Efinaconazole } Solutions to be used for fungal toenail infection.

ANTIHELMINTHIC DRUGS

Benzimidazoles

The drugs in this class include :

- Albendazole.
- Mebendazole.
- Triclabendazole.
- Thiabendazole.

Mechanism of action :

- Ovicidal and Larvicidal.
- They block microtubules in helminths which are present in the intestinal epithelial cells.
  Microtubules are required for the absorption of glucose in helminths.
  Benzimidazoles thus decrease the glucose absorption and ATP.
  Decrease in the ATP renders them immobile.

Pharmacokinetics :

These drugs have poor oral absorption and must be taken with fatty food (as it increases absorption).
High first pass metabolism inactivates these drugs except Triclabendazole and Albendazole.
Albendazole is activated into Albendazole sulfoxide. This active metabolite has a high tissue concentration.
Albendazole is hence the best drug for tissue infection.

Side effects :

- Hepatotoxicity.
- Bone marrow suppression due to inhibition of microtubules.

Uses of benzimidazoles

00:05:50

Nematodes :

Albendazole is the drug of choice (DOC) in treating :

- Round worm
- Hook worm
- Whip worm

→ Soil transmitted helminths.

60c6b3eeaa8ded0e4e7e5ea7

Only soil transmitted helminth against which Albendazole is not effetctive is Strongyloides.

- Trichinella spiralis.
- Enterobius vermicularis.

Albendazole is not effective against nematodes like :

- Strongyloides
- Onchocerca volvulus

→ Ivermectin is the DOC.

- Loa loa
- Filaria

→ Diethylcarbamazine (DEC) is the DOC.

- Dracunculiasis : Metronidazole is the DOC.

Ivermectin acts by stimulating glutamate sensitive chloride channels present in helminths. These channels are only seen in nematodes.

It is not active against cestodes and trematodes. It can be used as a second line drug for nematodes other than Strongyloides and Onchocerca.

Cestodes :

Albendazole is the DOC for :

- Neurocysticercosis (tissue form of T. solium).
- Albendazole is not active against intestinal T. solium (DOC : Praziquantel).

  The first drug given in neurocysticercosis is Prednisolone to reduce the perilesional edema.

  If Albendazole is given without Prednisolone, it can cause irritation leading to seizures.
- Echinococcus granulosus.
- Echinococcus multilocularis.

Albendazole is not effective against :

- T.saginata
- H. nana
- D. latum

— Praziquantel is the DOC.

Treatment of trematodes 00:13:40

Triclabendazole is the DOC for Fasciola hepatica.
It is not effective against :

- Liver flukes other than F. hepatica
- Lung flukes
- Schistosoma

— Praziquantel is the DOC.

Ivermectin :
It acts by stimulating glutamate sensitive chloride channels and causes tonic paralysis.
Ivermectin is effective only against nematodes.
It is the oral DOC for scabies. Treatment of choice is topical Permethrin.

Mazzotti like reaction may be seen when Ivermectin or DEC is given to treat filariasis. It is a hypersensitivity like reaction due to hyperstimulation of immune system by the dying parasite. The reaction is characterized by fever, rash and lymphadenopathy.

Praziquantel :
It stimulates Ca^{2+} channels in the helminths which causes spastic paralysis.

Praziquantel is used to treat cestode and trematode infections mentioned above.

Side effects :

- Impaired alertness.
- myalgia and arthralgia.

Contraindication : Ocular cysticercosis as it can worsen the condition due to irritation of parasite.

Metrifonate

It acts by blocking Acetyl choline esterase (ACHE).
Increased acetylcholine levels stimulate N_m receptors causing spastic paralysis.
It is approved only in the treatment of Schistosoma haematobium.

Drugs acting by stimulation of N_m receptors (causes spastic paralysis):

- Pyrantel pamoate.
- Levamisole.
- Tribendimidine.

They are used in treatment of some of soil transmitted helminths (STH).

Oxamniquine causes spastic paralysis by an unknown mechanism.

Niclosamide blocks oxidative phosphorylation thus decreasing the ATP synthesis in helminths. Used in treatment of cestodes.

Piperazine acts by stimulating GABA sensitive chloride channels causing flaccid paralysis.
It can be used to treat soil transmitted helminths.

ANTIPROTOZOAL DRUGS

Amoebiasis

00:00:27

Broadly subclassified into :

1. Intestinal :
    - Symptomatic : DOC is metronidazole. Nitazoxanide, Emetine/Dihydroemetine and Chloroquine (in hepatic amoebiasis as an add on drug to metronidazole).
    - Asymptomatic : Drug of choice is Paromomycin. Diloxanide furoate and Iodoquinol can also be given (Mnemonic : DIP).
2. Extraintestinal : DOC is metronidazole. Other drugs in treatment of symptomatic intestinal amebiasis can be given.

Metronidazole is a nitroimidazole.

It acts by producing free nitro anion radicals which is responsible for its wide range of action.

Other nitroimidazoles include :

- Satranidazole.
- Tinidazole : Commonly used in amoebiasis and giardiasis in the West.
  Metronidazole is commonly used in India for amoebiasis and giardiasis.
- Secnidazole : Used in bacterial vaginosis.
- Benznidazole : Used in Chagas disease.
- Fexinidazole : Used in treatment of West African sleeping sickness. It is the only oral drug available for treatment.

Metronidazole is the DOC in :

- Amoebiasis.

- Bacterial vaginosis.
- Trichomoniasis.
- Giardiasis.
- Bacteroides.
- Tetanus.

Side effects :

- Dysgeusia (metallic taste).
- Reddish brown urine.
- Disulfiram like reaction. Patients must be advised against consuming alcohol while taking metronidazole.

Leishmaniasis 00:09:43

Can be of 2 types :

- Visceral (Kala azar) : DOC is Liposomal Amphotericin B. It is an expensive intravenous (IV) drug.
  Miltefosine is the oral DOC in visceral leishmaniasis. It is also the DOC for post-Kala azar dermal leishmaniasis.
- Cutaneous : DOC is Sodium stibogluconate. Other drugs include IV Liposomal Amphotericin B, Paromomycin and Pentamidine.

Side effects of miltefosine is persistent nausea, vomiting and diarrhea. The drug is contraindicated in pregnancy.

Other intravenous drugs given in leishmaniasis :

- Paromomycin.
- Pentamidine.
- Sitamaquine.

Trypanosomiasis 00:13:39

Broadly subclassified into :

- African (Sleeping sickness) :

East African sleeping sickness :

1. Early : DOC is Suramin (IV).
2. Late : DOC is Melarsoprol (IV).

West African sleeping sickness :

1. Early : DOC is Pentamidine (IV).
2. Late : DOC is Eflornithine (IV).

- American (chagas disease) :DOC is Benznidazole. Nifurtimox is an alternate drug.

Fexinidazole is a new oral drug in the treatment of early and late West African sleeping sickness.

Cryptosporidiosis 00:17:12

The DOC in treatment of cryptosporidiosis is Nitazoxanide. It is also used in amoebiasis and resistant giardiasis (DOC).
Nitazoxanide is derived from Niclosamide (anti-helminthic drug).
It acts by blocking pyruvate ferredoxin oxidoreductase (PFOR) enzyme which is required for oxidative phosphorylation.
Its blockade will result in decreased levels of ATP.
The drug has a wide spectrum of activity :

- Antiprotozoal.
- Anti-helminthic.
- Antibacterial.
- Antiviral.

Greenish discoloration of urine is a side effect.

Babesiosis :
The current treatment of choice for mild/moderate/severe babesiosis is Atovaquone + Azithromycin.
Alternative is Quinine + Clindamycin (earlier TOC for mild and moderate babesiosis).

Cyclosporiasis/Isosporiasis/Sarcocystosis : Cotrimoxazole is the DOC.

Plasmodium 00:22:36

Sporozoites are the infective form of the parasite which is injected by a mosquito bite.
It moves to the liver and can lay dormant inside a hepatocyte (hypnozoite stage). This stage is seen only with P. vivax and P. ovale.
Hypnozoite stage is responsible for relapse of malaria.
The sporozoites keeps replicating inside the cell till hepatocyte ruptures. It is called a hepatic schizont and releases merozoites.
merozoites can form gametocytes which are infective for mosquitoes.
Gametocytes are responsible for transmission of malaria.

merozoites can enter RBC and replicate forming erythrocytic schizont. The rupture of RBC's coincides with rise in temperature and chills (symptoms of malaria).

Radical cure means prevention of relapse of malaria by eliminating hypnozoites. Drugs like Primaquine and Tafenoquine kills hypnozoites.

Elimination of gametocytes prevents transmission of malaria.

The drugs include :

- Primaquine/Tafenoquine.
- Artemisinin drugs.

Elimination of erythrocytic schizonts leads to symptomatic cure. The drugs used are called erythrocytic schizonticidal drugs like :

- Fast acting : Quinine, Artesunate etc.
- Slow acting : Clindamycin, Sulfadoxine, Pyrimethamine etc.

A treatment regimen is made by combining fast and slow acting drugs. The fast acting drug is usually the DOC.

Artemisinin group of drugs 00:32:00

It includes :

- Artesunate (IV).
- Artemether (oral).
- Dihydroartemisinin (oral).

IV Artesunate is preferred in severe life-threatening malaria.

These drugs act by free radical production.

It is hence contraindicated in first trimester of pregnancy.

Artemisinin group of drugs are the most potent and fastest acting schizonticidal drugs.

These are short acting and cannot be used as monotherapy or for prophylaxis.

Uses of Artemisinin drugs :

- Severe falciparum malaria : TOC is IV Artesunate as continuous infusion for 48 hours. Normal regimen is followed after 48 hours.
- Uncomplicated malaria :

P. vivax : DOC is Chloroquine for 3 days + Primaquine for 14 days for radical cure. Tafenoquine (once) is a recent alternative.

P. falciparum : Universally resistant to Chloroquine.

In case of chloroquine resistance, the treatment is same as that of P. falciparum. TOC is Artemisinin based combination therapy (ACT).

Primaquine for 14 days or Tafenoquine is given once in resistant cases of P. vivax. Only Primaquine is given once in case of P. falciparum.

Artemisinin based combination therapy (ACT) :

- Oral Artesunate + Sulfadoxine + Pyrimethamine : All states of India except northeastern states.
- Oral Artemether + Lumefantrine : Northeastern states. Lumefantrine is more active against the strains in these regions.

Quinine + Clindamycin/Tetracycline/Doxycycline is an alternative if ACT is not available.

Treatment of uncomplicated malaria in pregnancy :

- P. vivax : DOC is Chloroquine. Primaquine is given postpartum.
  In case of Chloroquine resistance, the TOC in Ist trimester is Quinine + Clindamycin.
  ACT can be given in 2nd and 3rd trimester.
- P. Falciparum : 1st trimester TOC is Quinine + Clindamycin.
  ACT is the TOC in 2nd and 3rd trimester.

Prophylaxis of malaria

00:44:05

It depends on the duration of travel :

- < 6 weeks : Doxycycline (100 mg OD) is the DOC. It is initiated 2 days before travel and continued for 4 weeks after coming back.
- >/= 6 weeks : mefloquine (250 mg/week) is the DOC. It is initiated 2 weeks before travel and continued for 4 weeks after coming back.

Chloroquine :

It binds to hemoglobin in the RBC and produces toxic heme compounds which are lethal to Plasmodium.

Mechanism of resistance : Drug efflux.

Uses of chloroquine :

- Malaria.
- Giardiasis.
- Hepatic amoebiasis.
- Infectious mononucleosis.
- Rheumatoid arthritis (Hydroxychloroquine is more commonly used).
- Systemic lupus erythematosus (SLE).
- Discoid lupus erythematosus (DLE).
- Porphyria cutanea tarda.

Side effects :

Bull's eye retinopathy or maculopathy.

Whorl like corneal deposits (also seen with Amiodarone).

Quinine :

The mechanism of action is unknown.

It is reserved for treatment of resistant malaria.

Side effects :

Hypotension due to α blocker activity.

Hypoglycemia as it increases release of insulin.

Blocks potassium channels leading to QT prolongation.

Cinchonism characterized by tinnitus and vertigo.

Quinine given at inadequate doses causes black water fever.

Mefloquine

00:52:00

It is used as prophylaxis for malaria and in treatment of resistant malaria.

Side effects :

Neuropsychiatric effects like seizure and psychosis. It must not be given to a patient with history of epilepsy or psychotic disorders.

Cardiac conduction block. It is contraindicated with other drugs like Quinine and Halofantrine which cause QT prolongation.

Atovaquone + Proguanil :

Atovaquone blocks electron transport in mitochondria and proguanil causes direct mitochondrial toxicity.

Used for synergistic activity.

It can be used in treatment of resistant malaria.

Other uses of Atovaquone :

- Babesiosis.
- Toxoplasmosis.

Proguanil prevents ovulation in mosquitoes rendering it infertile.

Primaquine/Tafenoquine :

They are used in radical cure of vivax malaria. Primaquine is given for 14 days and Tafenoquine once.

Side effects :

- Hemolysis in G6PD deficiency.
- Peripheral neuropathy.
- methemoglobinemia.

Pregnancy is an absolute contraindication. Can be given postpartum.

Clindamycin/Tetracycline/Doxycycline :

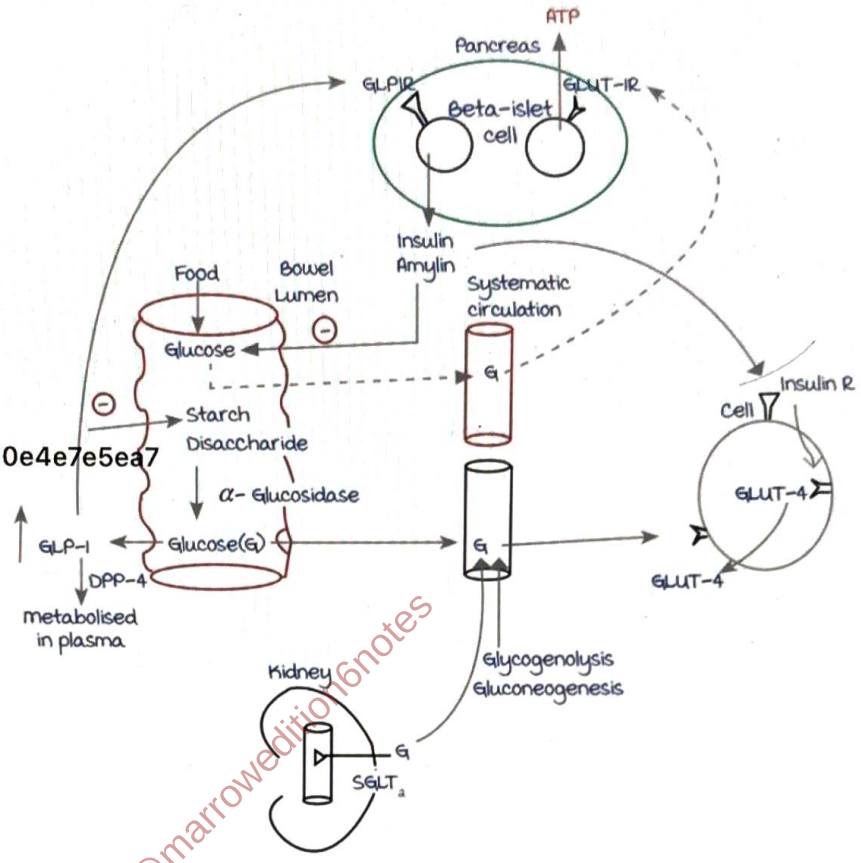
They are used in resistant malaria along with Quinine.

Clindamycin is safe in pregnancy and in children.

ANTI-DIABETIC DRUGS PART - 1

Physiology of glucose regulation

00:00:43



The pancreas has two types of receptors in beta islet cells : GLP1-R, GLUT I receptor.

Intestinal lumen : Glucose is directly absorbed. Starch and disaccharides are converted into glucose by α glucosidase before absorption into the circulation.

Glucose enters into the intestinal epithelial cells

↓

Increases release of GLP I (incretin)

↓

metabolised in plasma.

GLP 1 (short-acting)

Delays gastric emptying → Induces satiety → Blunts post prandial hyperglycemia.

Act on GLP-1 R

- Releases insulin and amylin
- Insulin acts on cells and brings GLUT- 4 receptors out of cell.
- Amylin inhibits the motility of stomach and delays gastric emptying thus blunting post prandial hyperglycaemia

Glucose level continues to increase during post prandial period

↓

Sensed by GLUT-1 R on the beta islet cells of the pancreas

↓

Facilitated glucose transport occurs into beta cells.

↓

concentration of plasma glucose decreases

↓

ATP is generated using the glucose absorbed into the beta islet cell

↓

ATP sensitive potassium channels are blocked

↓

An increase in calcium in the cell causes insulin release (beta cell depolarization leads to calcium release).

The amount of insulin released depends on glucose concentration in the blood.

Other sources of glucose are :

- Glycogenolysis.
- Gluconeogenesis.
- Glucose reabsorption by SGLT2R in the proximal convoluted tubules.

2 aims in the treatment of DM :

- To treat postprandial hyperglycemia.
- To maintain the blood glucose level throughout the day.

Drugs for treatment of Diabetes Mellitus 00:14:00

Alpha glucosidase inhibitor :

GLP I related drugs :

- GLP I agonists.
- DPP4 blockers.

Amylin analogue

Insulin

Insulin and Amylin analogues are the only drugs that are used in both type I and type 2 DM.

Oral hypoglycaemic agents (OHA) :

- Increase insulin release by inhibiting ATP sensitive potassium channels : Sulfonylureas.
- Decreases insulin resistance : Pioglitazone.
- Decreases hepatic glucose production by blocking gl coneogenesis : metformin.
- SGLT2 blockers : Canagliflozin.

Miscellaneous drugs

- Bromocriptine.
- Colesevelam.

Common side effects for GLP-I related drugs, insulin and OHA is hypoglycemia.

Pioglitazone and metformin do not cause hypoglycemia.

Alpha glucosidase inhibitors 00:25:48

- Acarbose.
- Voglibose.
- Miglitol (maximum oral absorption).

Approved only for type2 DM by FDA.

Used for treatment of postprandial hyperglycemia in type 2 DM (to be taken with the meal).

Side effects : Flatulence and osmotic diarrhoea.

Contraindicated in renal failure as they are absorbed and excreted by kidney.

GLP I related drugs :

GLP I agonist : Stimulates GLP1-R.

In the saliva of the Gila monster, Exendin-4 was found which

stimulates GLP 1 receptors and reduces glucose by releasing insulin.

Analogues of exendin-4 were developed, Exenatide (BD dose) & Lixisenatide (OD dose).

They have hypoglycemic effects.

GLP 1 analogues :

- Liraglutide (OD)
- Semaglutide
- Albiglutide
- Dulaglutide

} Once a week dosing.

Route: subcutaneous.

Used in type 2 DM for maintenance.

Side effects : They delay gastric emptying and cause

- weight loss (Liraglutide is the current DOC for obesity).
- nausea/ vomiting.

DPP4 inhibitors : increases GLP1

- Sitagliptin.
- Saxagliptin.
- Alogliptin.
- Linagliptin.
- Vildagliptin.

Route : oral. Used for maintenance in type 2 DM.

Side effects :

- Pancreatitis (maximum with Sitagliptin).
- Weight neutral as they do not delay gastric emptying.
- DPP4 structure is similar to CD 26 present in lymphocytes, decreases the activity of lymphocytes and increases the risk of infection.
  Can cause hypersensitivity reactions like steven Johnson syndrome, angioedema.

Saxagliptin : increased risk of CHF

Vildagliptin : risk of hepatitis

All gliptins are contraindicated in renal failure except Linagliptin (excreted through the liver).

Amylin analogue

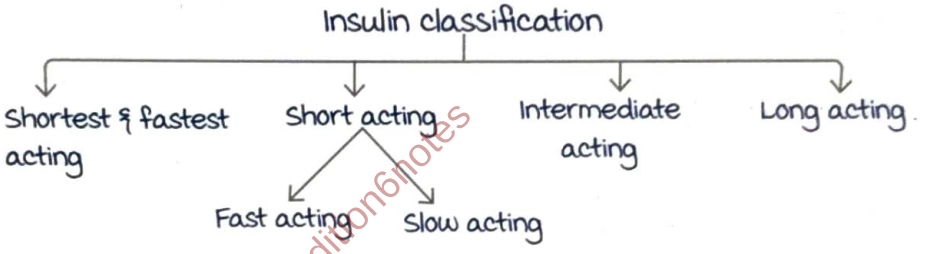
00:37:50

Drug : Pramlintide by subcatenous route.
MOA : delays gastric emptying thus slowing glucose absorption, increasing satiety and also decreases glucagon.
Used in postprandial hyperglycaemia in type 1 & 2 DM.
Can be used with insulin but in a different syringe. If mixed with insulin, dose of insulin should be reduced by 50% (increases risk of hypoglycemia by insulin).
Side effects : Weight loss/nausea/ vomiting.

Insulin

00:41:07

Can be used in both type 1 & 2 DM.



Shortest & fastest acting insulin: Afrezza (instant action).
Route of administration : Inhalational.

Short but fast acting (15 min to produce effect): Glulisine, Lispro, Aspart. They are called Monomeric insulin.
Short but slow acting (45 to 60 min to produce effect): regular insulin.
Route: subcutaneous route.
These insulins are used for postprandial hyperglycemia.

Intermediate acting insulin :
NPH (Neutral Protamine Hagedorn) a.k.a Isophane insulin.
Only insulin which is milky cloudy white colour/turbid.
All other insulin are clear colorless solution except afrezza (powder).

Lente insulin :
made by combining regular insulin and zinc.
The products are amorphous powder (semi-Lente) which is short acting and crytals (ultra-lente) which are long-acting.
Lente (30% semi-Lente + 70 % ultra-Lente).

Route: subcutaneous.
Used for maintenance. Also called basal insulin.

Long acting insulin :
Detemir : Regular insulin combined with a saturated fatty acid → increases plasma protein binding.

Glargine : Regular insulin combined with 2 arginine and 1 glycine. Only insulin with acidic pH.
Whenever injected, it crystallises in tissue → breaks down and becomes long acting.
Because of acidic pH when injected with any other insulin in a syringe → forms white crystals.

Degludec : Longest acting insulin.
Made when regular insulin is combined with hexadecanoic acid.
It forms hexamers in tissue → breaks into monomers making them long acting.

Route : subcutaneous route. used for maintenance.
Also called as basal insulin.

Insulin administration 00:54:58

Subcutaneous :
Site of injection : most common is abdomen except the periumbilical region.
most reliable and fastest absorption is from the abdomen.
Glargine is the only insulin for which rate of absorption does not depend on the site of injection because the rate of breakdown of crystals is the same everywhere.
Other sites : anterior thigh, the upper area of buttocks and upper arm.

method to mix insulin injection :
Mixed in different syringes.
In one syringe (only 2 insulin) : first load regular and then load NPH.

Continuous subcutaneous infusion for regular insulin.

- Benefit : less risk of hypoglycemia.
- Drawback : Dose cannot be adjusted based on plasma glucose.

Storage :

- Opened vial : store in fridge up to 1 month (do not store in freezer).
- New vial : store in a cool dark place till expiry.

Afrezza insulin

01:02:36

Inhalational insulin. Rapidly absorbed.
Used in the treatment of postprandial hyperglycemia.
Available in colour coded cartridges :

- Blue (4 units),
- Green (8 units)
- Yellow (12 units)

Side effects:

- cough.
- Bronchospasm (Avoid in patients with COPD and bronchial asthma).

Side effects of insulin :

1. Hypoglycemia (most common).
   Short acting : high risk of hypoglycemia.
   (afrezza > short & fast acting > short & slow acting)
   Long acting : least risk of hypoglycaemia
   (smooth peak less curve).
2. Hypokalemia.
3. Lipodystrophy.
4. Lipohypertrophy.

Advice patients to change the site of injection with minimum 1 inch distance between two sites.

Other uses of IV Regular insulin :
When given IV, aspart & regular insulin have similar efficacy.

- DOC for Diabetic Ketoacidosis (DKA).
- Hyperkalemia.

Insulin moves both glucose and potassium into the cells.

ANTI-DIABETIC DRUGS PART - 2

Oral hypoglycemic agents increasing insulin release

00:00:28

It acts by blocking ATP sensitive potassium channels.

There are 2 classes of drugs :

- Sulfonylureas :
  Causes more insulin release compared to meglitinides and are longer acting.
  Used in maintenance of type II diabetes mellitus.
- Meglitinides/Nateglinide :
  Shorter acting and lesser insulin release. They are used in postprandial hyperglycemia in type II diabetes mellitus.

Side effects :

- Hypoglycemia : more with Sulfonylureas.
- Weight gain due to fat deposition : Seen more with Sulfonylureas & are not preferred in obese patients.
  Insulin blocks hormone sensitive lipase → Inhibits lipolysis → Fat accumulation/weight gain.
- Hypersensitivity (rashes) and Disulfiram like reactions.
  Patients must be advised not to take alcohol along with Sulfonylureas.

Meglitinide drugs :

- Repaglinide.
- Mitiglinide.

Phenyl alanine derivative :

- Nateglinide.

Sulfonylureas :

- 1st generation drugs with low potency and more toxicity.
  They are less preferred.

1. Acetohexamide.
2. Tolbutamide : Hepatotoxic.
3. Chlorpropamide : causes Syndrome of Inappropriate Antidiuretic Hormone (SIADH) followed by dilutional hyponatremia.

- 2nd generation drugs are more potent and less toxic as compared to the 1st generation. They are currently used.
  - Glyburide or Glibenclamide :
    It has an active metabolite. The drug gets concentrated in the β islet cells and thus is longer acting than its half-life ($T_{1/2}$).
    OD dosing is sufficient.
  - Glimepiride :
    Sulfonylurea with least dose requirement to induce hypoglycemia.
  - Gliclazide :
    It has an additional antiaggregant effect.
  - Glipizide :
    Short acting.
    Lesser risk of hypoglycemia, hence preferred in elderly patients.

OHA decreasing insulin resistance 00:09:58

Thiazolidinediones :
It acts by stimulating PPAR-γ which increases transcription factors which are required for increasing production of GLUT 1 & 4.
mainly acts by decreasing insulin resistance.
Weight gain is seen due to increased adipocyte proliferation.
Stimulation of PPAR-α leads to decreased triglycerides and increased high density lipoproteins (HDL). It has no effect on LDL levels.

Pioglitazone is the only drug available in India. It comes in a black box with warning about its risk of causing bladder cancer. The drug is banned in USA.
Side effects :

- It can stimulate epithelial sodium channels (ENaC) leading to sodium and water retention.
  Leads to edema, weight gain and precipitate congestive heart failure.
- Osteoporosis in women increasing risk of fractures. It decreases the effect of osteoblasts.

- Macular edema.
- Hepatotoxicity.

Banned drugs :

Rosiglitazone : Causes myocardial infarction.

Troglitazone : Hepatotoxic.

OHA decreasing hepatic glucose production 00:16:15

This class is called as Biguanides.

metformin is the only drug which is currently used.

Phenformin was banned as it causes severe lactic acidosis.

metformin acts by stimulating adenosine monophosphate kinase (AMPK) and blocks gluconeogenesis.

It has some effect on insulin resistance (decreases) and decreases LDL.

metformin also blocks gastric emptying leading to weight loss.

It is hence preferred in obese patients.

Uses of metformin :

- It is the drug of choice in treatment of type II diabetes mellitus and as prophylaxis in pre diabetic patients.
  In Polycystic ovarian syndrome (PCOS) to promote ovulation though not as effective as Clomiphene citrate or Letrozole.
- metabolic syndrome.
- Non-alcoholic fatty liver disease.

Side effects :

- Decreases calcium dependent vitamin B_{12} absorption leading to its deficiency.
- Calcium is given for prevention.
- Vitamin B_{12} supplement must be given if patient is symptomatic.
- Interferes with aerobic glycolysis in mitochondria. It can promote anaerobic glycolysis leading to lactic acidosis.

Contraindicated in conditions with increased risk of lactic acidosis like :

- Congestive heart failure.
- Severe lung disease.
- Renal failure (metformin is excreted by kidney).

- Hepatic failure (metformin is metabolized in liver).
- Chronic alcoholics.

Smoking is not a contraindication.

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Sodium linked glucose transporter 2 inhibitors 00:22:34

SGLT2 inhibitors include :

- Canagliflozin : Associated with increased risk of limb amputation.
- Dapagliflozin : Increased risk of bladder and breast cancer.
- Empagliflozin.

Decreases glucose absorption and are excreted via urine.
Increases glucose and sodium in the urine.
These are used in treatment of type II diabetes mellitus along with insulin or other drugs.
Fixed dose combinations (FDC) with metformin or DPP-4 inhibitors are given orally.

Side effects :
Common :

1. Urinary tract infection or genital infection like candida.
2. Low blood pressure due to loss of water along with sodium.
3. Dehydration.

Rare :

1. Diabetic ketoacidosis : Seen if used in patients with type I diabetes mellitus.
2. Urosepsis.
3. Fournier's gangrene.

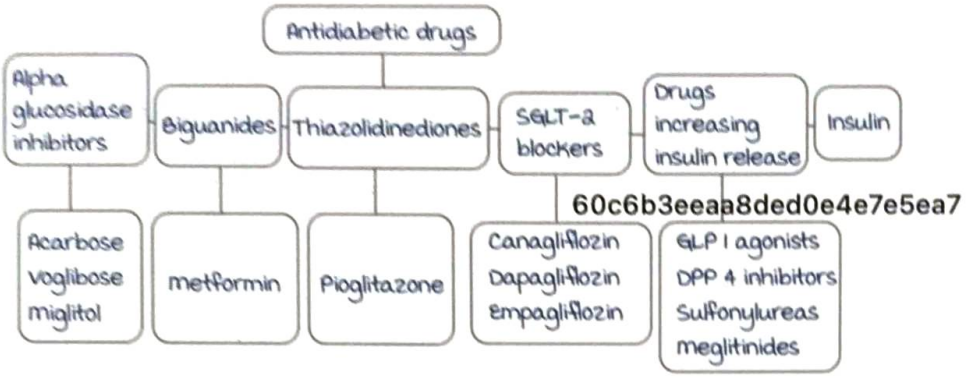
Additional beneficial effects of SGLT2 inhibitors :

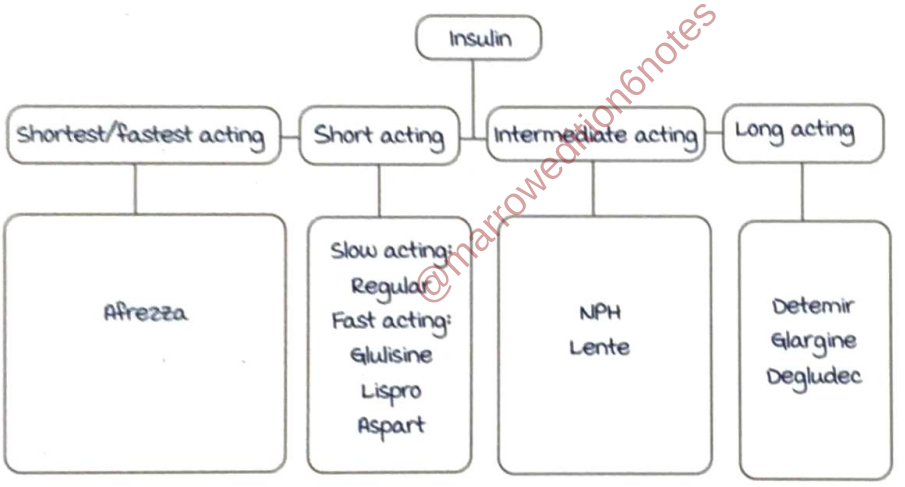
- Weight loss.
- Decreases cardiovascular mortality. GLP I agonists and SGLT2 inhibitors decreases CVS mortality.

Drugs causing weight loss :

- GLP I agonists.
- metformin.
- SGLT2 blockers.
- Amylin analogues.

DPP-4 inhibitors are weight neutral.





GROWTH HORMONE AND RELATED DRUGS

Hypothalamic pituitary axis 00:00:28

The pituitary gland has 2 subtypes of G protein coupled receptors (GPCR).
They are either G_s/G_q (stimulatory) or G_i (inhibitory) subtype.
Hypothalamus releases a substance which stimulates the G_s/G_q receptors leading to hormone release.
The substance released from the hypothalamus which binds to the G_i subtype decreases the hormone release from pituitary.
Growth hormone releasing hormone (GHRH) from the hypothalamus increases the release of growth hormone from the pituitary.

Somatostatin from the hypothalamus binds to the G_i subtype of receptors in the pituitary to decrease the release of growth hormone.
It also decreases the release of thyroid stimulating hormone (TSH) as it acts on the thyrotrophic cells.

Growth hormone (GH) binds to the growth hormone receptor and increases the linear growth.
GH acts on the liver to release insulin like growth factor 1 (IGF 1).
IGF 1 binds to the IGF 1 receptors (tyrosine kinase receptor) which brings out more GLUT 4 leading to an increased glucose uptake by the cell needed for growth.

Dwarfism & Acromegaly 00:05:01

It occurs due to a decrease in GH.
Drugs used in dwarfism :

- GHRH analogues
  1. Sermorelin.
  2. Macimorelin.

3. Tesamorelin.

- GH analogues :
  1. Somatrem.
  2. Somatropin.
  3. Somapacitan.
- IGF I analogues : IGF I is transported in plasma bound to protein called IGF binding protein 3 (IGFBP 3).
  1. Mecasermin.
  2. Mecasermin rinfabate : An analogue of IGF I bound to IGFBP 3.

Acromegaly :

It occurs due to an increase in GH.

Drugs used in acromegaly :

- Somatostatin analogues :
  1. Octreotide (short acting).
  2. Lanreotide.
  3. Pasireotide.
- GH receptor blockers are used if there is no response to somatostatin analogues :
  1. Pegvisomant : It can cause pituitary adenoma. It blocks the GH receptors in the pituitary leading to an increased GHRH release from the hypothalamus.

GHRH analogues

00:09:00

Drugs like Sermorelin, Macimorelin and Tesamorelin are used in the diagnosis of dwarfism.

Patients on GHRH analogues can elicit one of the following two responses :

- Increased GH : Indicative of hypothalamic dwarfism.
- No change in GH : Indicative of pituitary dwarfism.

GH analogues uses : (Mnemonic : SMALL)

- Small for gestational age baby.
- Malabsorption seen in short bowel syndrome. Teduglutide is a GLP 2 agonist which is also used in the treatment of malabsorption seen in short bowel syndrome. It increases proliferation of intestinal epithelial cells.

Active space

The side effect is an increased risk of colon cancer.

- AIDS related wasting.
- Decreased Length or dwarfism.

Dwarfism can be a feature of syndromes like :

1. Prader Willi syndrome.
2. Noonan syndrome.
3. Turner syndrome.

Side effects of GH analogues

00:14:33

Side effects and contraindications include :

(Mnemonic : CHILDREN)

- Carpal tunnel syndrome.
- Hyperglycemia : GH antagonizes the action of insulin.
- Increased Intracranial pressure. Can lead to papilledema. More common in children.
- Leukemia.
- Diabetes mellitus.

Contraindications :

- Retinopathy : It is contraindicated in proliferative retinopathies like diabetic retinopathy (due to neovascularization).
- Neoplasia.

IGF I related drugs :

It is used in treatment of dwarfism caused by :

- Selective decrease in IGF I.
- GH receptor mutation.
- Anti GH antibodies.

Side effects of IGF I :

- Hypoglycemia : IGF I analogues cause increased movement of glucose into the cell.
- Lipohypertrophy : The drug is given subcutaneously. It blocks hormone sensitive lipase and cause lipohypertrophy.

Somatostatin analogues

00:18:55

Drugs : Octreotide, Lanreotide and Pasireotide.

Route : subcutaneously.

They are the drug of choice (DOC) in treatment of acromegaly.

Long acting analogues used are :

- Octreotide LAR (long acting depot formulation).
- Lanreotide.

These drugs can be given once in a month.

Somatostatin analogues are DOC in secretory diarrhea.

They are DOC in tumors like :

- Glucagonoma.
- VIPoma.
- GRFoma.
- Somatostatinoma : An outside source of somatostatin leads to regression in tumor size.

Other uses :

- Insulinoma : DOC is Diazoxide.
- Acute variceal bleed : Current DOC is Terlipressin.
- Radiolabelled Octreotide can be used for diagnosis of pituitary adenoma and carcinoid tumor.
- Treatment of carcinoid tumor.
- Thyrotroph adenoma.

Paseriotide decreases adrenocorticotropic hormone and can be used in treatment of Cushing's disease.

It can decrease IGF 1 levels and lead to hyperglycemia.

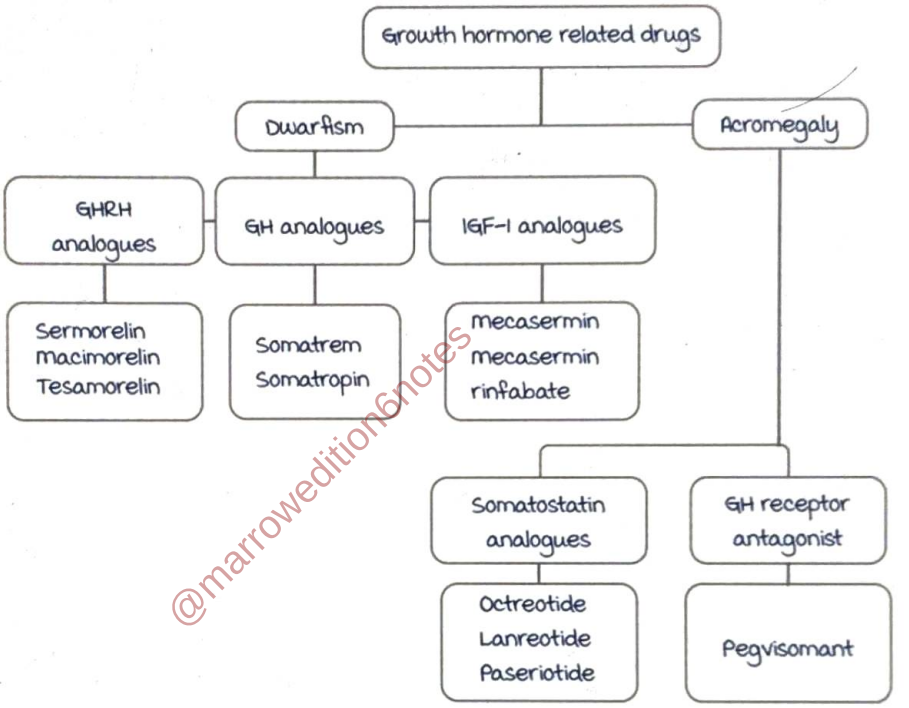
Side effects :

- Nausea and vomiting.
- Abdominal pain.
- Gall stones : Decrease the flow of bile leading to stasis and stone formation.
- Hypothyroidism : It decreases release of TSH.

Pegvisomant

00:24:56

It is used in the treatment of drug resistant acromegaly.
The aim of treatment in acromegaly is to keep the level of GH below 2.5 ng/ml.
Pegvisomant is combined with the treatment, if the drug of choice is unable to achieve adequate GH levels.
Side effect : Pituitary adenoma, thus patient must be on MRI follow up to monitor its development.

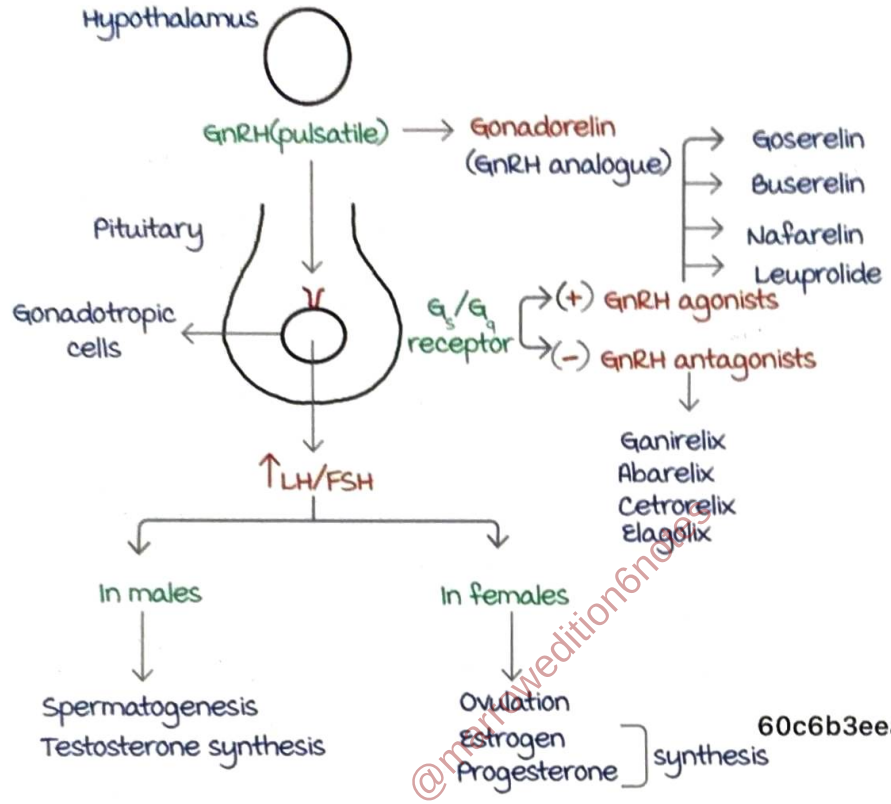


GNRH AGONISTS AND ANTAGONISTS

Physiology

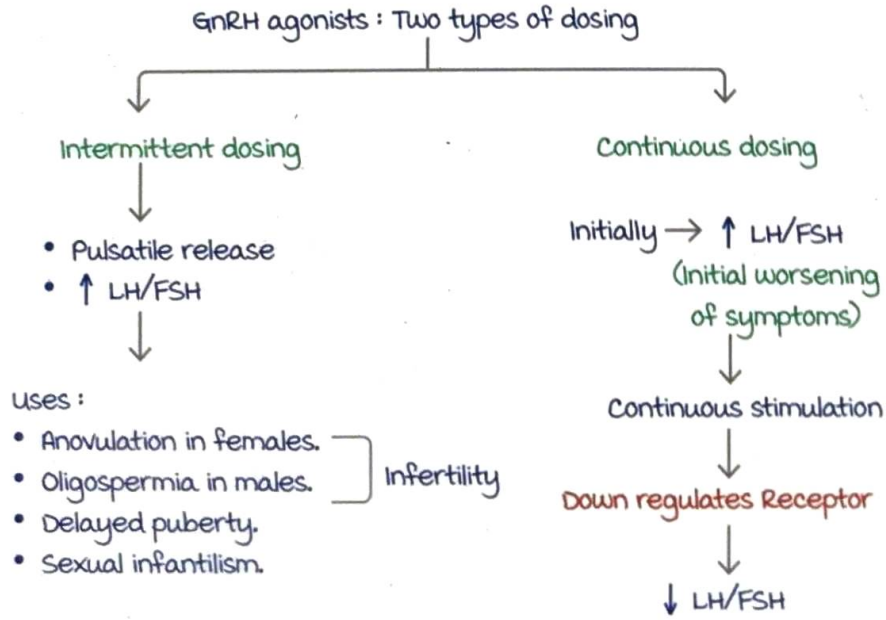
00:00:35

Gonadotropin releasing hormone axis :



GnRH agonists

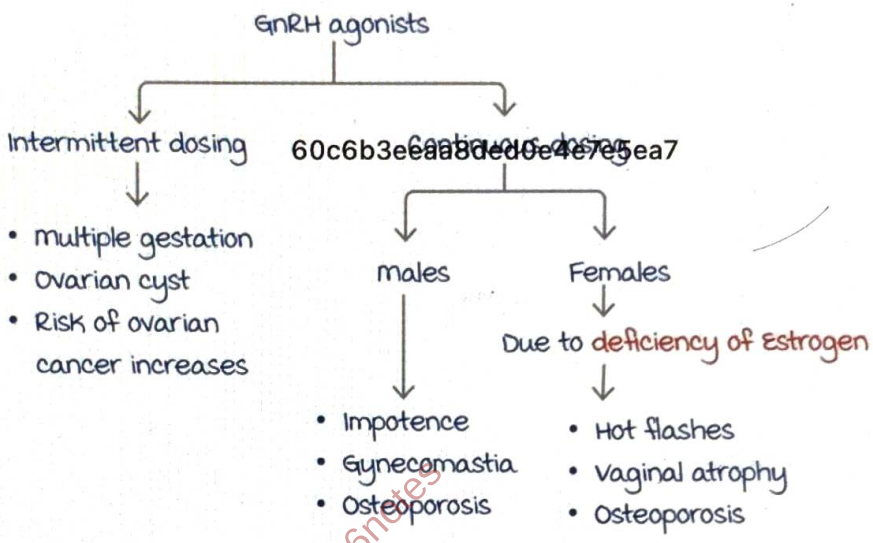
00:05:12



Uses of continuous dosing of FSH & LH :

Precocious puberty.
In females : Used in ER+ breast cancer, fibroids, endometriosis.
In males : To treat prostate cancer (DOC is Goserelin).

Side effects :



Uses and side effects of GnRH antagonists are same as GnRH agonists given as continuous dosing.

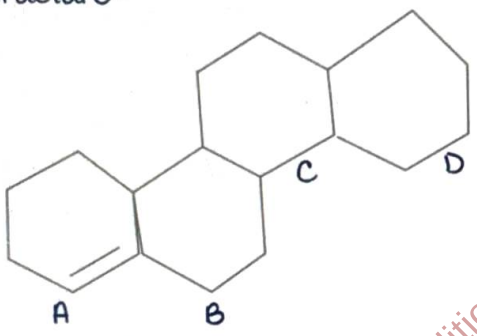
GnRH analogue :
It is called Gonadorelin.
Use :
1) To diagnose the cause of hypogonadism. (pituitary or hypothalamic)
2) Treatment of anovulation.

STEROIDS

First steroid was designed from cortisol.

Hydrocortisone 00:01:43

- Similar to cortisol.
- Drug of choice for replacement of glucocorticoids in Addison's disease, Congenital adrenal hyperplasia.
- Has both glucocorticoid and mineralocorticoid effects.
- Structure :



Prednisone and Prednisolone :

- Formed by the addition of double bond at ring A of hydrocortisone.
- Glucocorticoid effect is 4 times that of hydrocortisone and mineralocorticoid effect is 0.8 times that of hydrocortisone.
- Given by oral route.

- Used in the treatment of autoimmune disorders.

methyl prednisolone :

- Formed by addition of methyl group to Prednisolone.
- It can be given by oral as well as IV route.
- Glucocorticoid effect is 5 times that of hydrocortisone and mineralocorticoid effect is 0.8 times that of hydrocortisone.
- Used in the treatment of autoimmune disorders.

Fludrocortisone :

- Formed by addition of fluorine at ring B of hydrocortisone.

- Glucocorticoid effect is 15 times that of hydrocortisone and mineralocorticoid effect is 150 times that of hydrocortisone. Fludrocortisone is a mineralocorticoid.
- Used as replacement therapy in Addison's disease, treatment of postural hypotension.

Aldosterone :
Glucocorticoid effect is zero and mineralocorticoid effect is 500 times that of hydrocortisone.
Therefore, it is a pure mineralocorticoid.

Triamcinolone, Dexamethasone, Betamethasone :
Pure glucocorticoids.

- Formed by addition of double bond at ring A and fluorine at ring B of hydrocortisone.
- Triamcinolone : Glucocorticoid effect is 5 times that of hydrocortisone and mineralocorticoid effect is zero.
- Dexamethasone and Betamethasone : Glucocorticoid effect is 25 times that of hydrocortisone and mineralocorticoid effect is zero.

- Least potent steroid : Hydrocortisone.
- Most potent steroids : Dexamethasone & Betamethasone.
- Half-life of steroids is directly proportional to potency.
- Half-life of hydrocortisone is 8-12 hours.
- Other steroids such as Triamcinolone, Prednisone, Prednisolone, Methylprednisolone have a half-life of 12-36 hours.
- Dexamethasone & Betamethasone have a half-life of 36-72 hours → Longest acting glucocorticoids.

Sample question :
100 mg of Triamcinolone = 20 mg of Dexamethasone/ Betamethasone.

Topical steroids :

- Formed by addition of a functional group such as propionate, valerate and butyrate. This addition increases lipid solubility so that they can be used topically.
- Used in the form of cream or ointment. Ointment form is more potent.
- Most potent topical steroid is Clobetasol propionate ointment.

Effects of steroids 00:14:40

Glucose :

- Decrease GLUT 4 production → Limbs cannot utilize glucose → Increased lipolysis → Limbs become thin.
- Decrease GLUT 4 production → Increased glucose in blood → Increased insulin → Blocks hormone sensitive lipase → Block of lipolysis in trunk → Truncal obesity. This is known as lemon on stick appearance. seen in Cushing's disease or syndrome.
- Buffalo hump.
- Long term use of steroids cause diabetes.

Calcium :
Increase calcium excretion → useful in treatment of hypercalcemia.
Side effects : Osteoporosis.

Musculoskeletal system :
Osteoporosis, myopathy, growth retardation in children.

Eyes :

- Useful for ocular inflammatory disorders like uveitis, retinitis, choroiditis.
- Contraindicated in herpetic keratitis → Can cause clouding of cornea.
- Side effects :
  Systemic steroids can cause posterior subcapsular cataract.
  Long term use of topical steroids can cause glaucoma.

Gastrointestinal tract :
Decrease prostaglandin synthesis → Remove mucosal barrier of stomach → Can lead to ulcers.

Central nervous system :
Depression, insomnia, psychosis.

Skin/Hair :

- Thinning of skin and hair.
- Multiple bruises and striae.

Pregnancy :
Use : For surfactant maturation. Dose is 24 mg in 48 hours.
Either
Dexamethasone 4 doses (6 mg each dose every 12 hours) or
Betamethasone 2 doses (12 mg each dose every 24 hours)
can be used.

Antineoplastic effect :
Useful in leukemia and lymphoma.

Antiemetic effect :

- Mechanism is unknown.
- Dexamethasone can be used for chemotherapy induced nausea and vomiting (as an add on drug).

Anti inflammatory and immunosuppressive effects :
Mechanism :

- Decrease production of inflammatory mediators like IL 1, IL 6 and TNF alpha.
- Increase production of anti-inflammatory mediators like IL 10 and annexin 1.
- Induce lymphocyte apoptosis as well as cause redistribution of lymphocytes.

Uses :

Inflammatory conditions :

- Rheumatoid arthritis.
- Gout.
- Psoriasis.
- Vasculitis.

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Autoimmune disorders :

- Autoimmune hemolytic anemia.
- Immune thrombocytopenic purpura.
- Multiple sclerosis.
- Myasthenia gravis.
- Graft versus host disease.

Infections :

- Steroids are usually contraindicated.
- Exceptions : Life saving in H. influenza, meningitis, COVID pneumonia (moderate to severe).
- Only drug to decrease mortality in COVID.

Steroids summary :

Steroids	Potency with respect to hydrocortisone	Half life
Hydrocortisone	1	8-12 hours
Prednisone Prednisolone	4	12-36 hours
Methyl Prednisolone	5	12-36 hours
Triamcinolone	5	12-36 hours
Dexamethasone Betamethasone	25	36-72 hours

DRUGS ACTING ON BONES

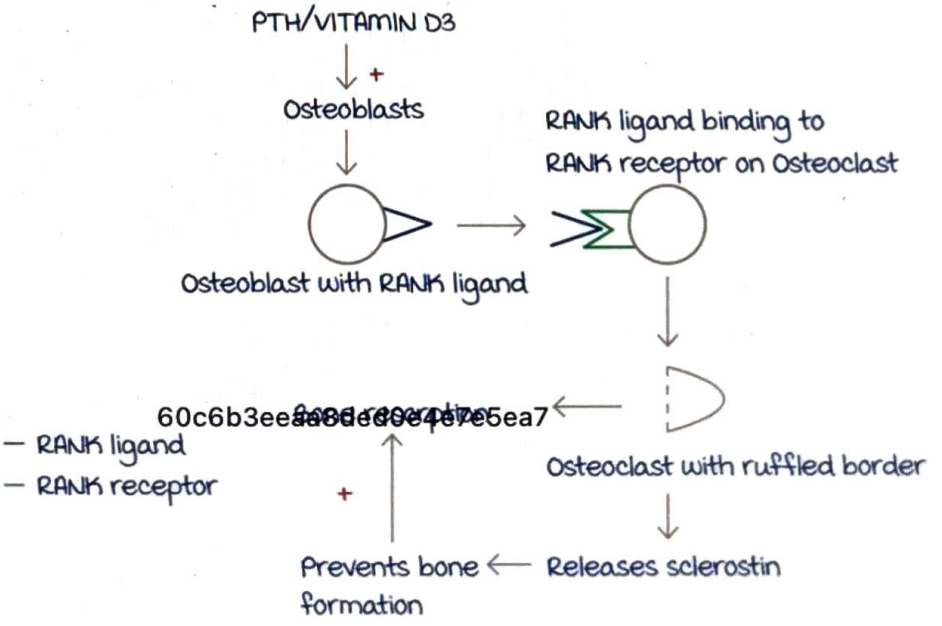
Physiology 00:00:50

Drugs acting on bones are primarily used in the treatment of osteoporosis. Accessory uses include treatment of bone metastasis and hypercalcemia.
Factors like parathyroid hormone and vitamin D3 stimulate osteoblasts to form RANK ligands.
Receptors for the ligands are present on osteoclasts called RANK receptors.
Binding of RANK ligands to the osteoclast leads to formation of spiky or ruffled borders. The osteoclasts begin to damage the bone and the process is called bone resorption.

Bone releases some factors in response to the resorption :

- Bone morphogenic proteins.
- Prostaglandins.
- Insulin like growth factor I.

These factors are stimulants for osteoblasts to induce bone formation at the site of resorption.
Physiological factor released by osteoclast is called sclerostin.
It inhibits osteoblast mediated bone formation.
Hormones like estrogen and calcitonin inhibits bone resorption.



Active space

Treatment of osteoporosis can be targeted at these mechanisms :

- Drugs that inhibit bone resorption.
- Drugs that stimulate bone formation.

Denosumab (monoclonal antibody) is an anti-RANK ligand antibody which can block the RANK ligand. It can thus inhibit bone resorption.

Bisphosphonates induce apoptosis in osteoclasts thus preventing bone resorption.
Selective estrogen receptor modulators (SERM) like Raloxifene and calcitonin can be given to prevent bone resorption.
Plicamycin is a drug that prevents bone resorption.
All drugs which inhibit bone resorption can cause a fall in serum calcium levels leading to hypocalcemia.
Hypocalcemia is maximum with Bisphosphonates and fastest with Calcitonin.
Calcium is thus given along with treatment of osteoporosis to prevent hypocalcemia.

Teriparatide and Abolaparatide are parathyroid hormone (PTH) and PTHrP analogues which stimulates osteoblast to increase bone formation.

Romosozumab is an anti-sclerostin monoclonal antibody which blocks the action of sclerostin.
Teriparatide, Abolaparatide and Romosozumab are together called as anabolic drugs.

Strontium ranelate acts on both osteoclasts and osteoblasts. It inhibits osteoclasts (bone resorption) and stimulates osteoblasts (bone formation).

Denosumab

00:10:48

It is an anti-RANK ligand monoclonal antibody.
The drug is given subcutaneously once every 6 months.

Uses :

- Treatment of giant cell tumor of bone.
- metastasis in prostate cancer.
- Hypercalcemia due to malignancy or hyperparathyroidism.
- Multiple myeloma to treat the bone changes.
- Post-menopausal osteoporosis : The drug of choice (DOC) is oral bisphosphonates. Intravenous (IV) bisphosphonates are given in case of intolerance.
  If there is intolerance to IV bisphosphonates, the next choice of treatment is based on the risk of fractures :
  - High risk of fracture : Denosumab.
  - Very high risk of fracture : Anabolic drugs.

Side effects :

- Hypocalcemia.
- Osteonecrosis of jaw.
- Secondary cancer.

Bisphosphonates 00:15:34

They are classified into :

1st generation : Low potency and currently not used.
Etidronate.
Clodronate.

2nd generation : 100 times more potent than 1st generation.
Alendronate.
Pamidronate.

3rd generation : 1000 times more potent than 2nd generation.
Risedronate.
Zoledronate : Most potent bisphosphonate.

Alendronate and Risedronate are given orally.
Its dosing is once daily to treat osteoporosis.
Pamidronate and zoledronate are given intravenously.
Dosing is once in a year to treat osteoporosis.

MOA :

1st generation drug acts by formation of an abnormal ATP which cannot be used by osteoclasts leading to its apoptosis.

2nd and 3rd generation bisphosphonates act by blocking Farnesyl pyrophosphate synthase which is required in mevalonate pathway.

mevalonate pathway is required in the synthesis of cholesterol.

Blocking the enzyme leads to apoptosis of osteoclasts.

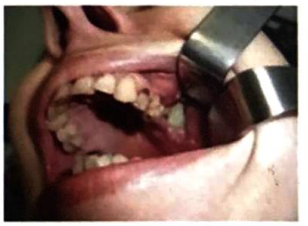
Bisphosphonates are the DOC in :

- Osteoporosis : Oral drugs (for 5 years) is preferred over IV (for 3 years).
  If the response is inadequate, the duration can be increased up to 10 years orally and 6 years IV.
- Hypercalcemia of malignancy (IV preferred).
- Pagets disease (IV preferred).

Oral bisphosphonates have poor oral absorption and are hence taken on empty stomach.

Side effects :

- Oral drugs can cause esophagitis.
- The patients must be advised to take the drug with a full glass of water and not to lie down for 30 minutes.
  (Same advice for patients taking Tetracycline.)



Osteonecrosis of jaw

- Osteonecrosis of jaw : It is more commonly seen with IV drugs.
- Bone fracture : Femoral chalk stick fracture. It is treated with teriparatide.
- Bone pain.

Zoledronate is contraindicated in patients with renal failure.

SERM

00:27:25

Raloxifene is used in treatment of post menopausal osteoporosis in women with high risk of breast cancer.
Its efficacy is limited as compared to other drugs to treat osteoporosis.
Other effects of Raloxifene include :

- Prevention of uterine cancer.
- Decreases low density lipoprotein (LDL).

Side effects :

- Hot flashes.
- Thrombosis.

Bazedoxifene is an SERM used along with estrogen to treat post menopausal osteoporosis with hot flashes and an intact uterus.

Calcitonin :
It can be given intranasally for treatment of post menopausal osteoporosis and subcutaneously for treatment of Paget's disease.
Other beneficial effects :

- Analgesia in vertebral fractures.
- Decreases risk of breast cancer.

Side effects :

- Increased risk of liver cancer.

Plicamycin can be used in treatment of post menopausal osteoporosis.

Anabolic drugs

00:32:51

Teriparatide is a PTH analogue and Abolaparatide is a PTH related peptide (PTHrP) analogue.
These drugs are given subcutaneously.
Used in treatment of post-menopausal osteoporosis (Teriparatide preferred).
Maximum duration of treatment is for 2 years due to side effects.
Osteosarcoma is a side effect.

It is contraindicated in Paget's disease.

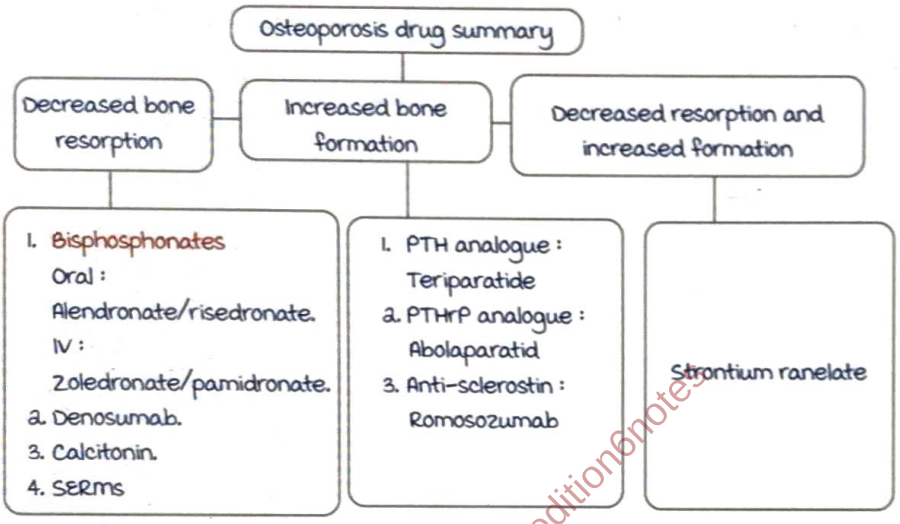
Anti Sclerostin monoclonal antibody :

Romosozumab.

It is used in treatment of post menopausal osteoporosis.

Strontium ranelate (not FDA approved) :

It is the only drug which inhibits bone resorption and stimulates bone formation.



THYROID DURGS

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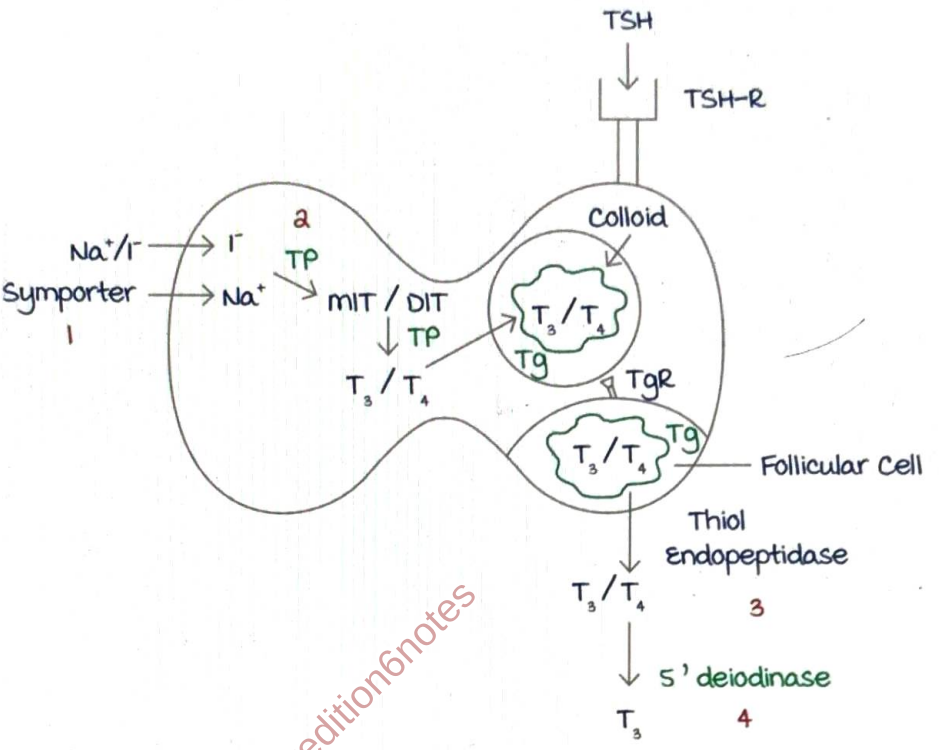
Physiology of thyroid hormones 00:00:54



TSH receptor (GPCR) when stimulated, increases production of :

- Na^+/I^- symporter.
- H_2O_2 a.k.a Thyroid Peroxidase (TP).
- Thiol Endopeptidase.

1. Na^+/I^- symporter pumps Na^+ and I^- inside the gland. Iodine forms Mono-iodo thyronine (MIT) & Di-iodo thyronine (DIT) by a process called Organification of iodine.
2. Coupling reaction by TP : MIT+DIT =T3, DIT+DIT=T4.
3. T_3,T_4 are stored in colloid packed inside a protein called Thyroglobulin (Tg).
4. Follicular cells upregulate production of thyroglobulin receptors to increase uptake of T_3,T_4 in cells.
5. Thiol endopeptidase helps in breakdown of thyroglobulin to aid in release of T_3,T_4.
6. Peripheral conversion of T_4 to T_3 (active form) occurs via 5'deiodinase.

Active space

Four classes of antithyroid drugs :
Drugs blocking Na^+/I^- symporter.
Drugs blocking Thyroid peroxidase : Block organification and coupling.
Drugs blocking Thiol Endopeptidase : Blocks release of T_3, T_4.
Inhibitors of 5' deiodinase.

Hyperthyroidism/anti-thyroid drugs 00:05:22

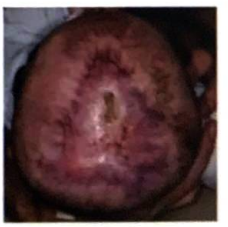
Classification of drugs :

Na^+/ I^- symporter Inhibitors :
Thiocyanate.
Perchlorate.
Fluoborate.
more toxic, so less preferred.

Thioamide drugs :
Blocks thyroid peroxidase.

Propylthiouracil	Carbimazole : Prodrug of methimazole.
Half-life : 1.5 hours Dosing : TDS	Half-life : 6 hours Dosing : OD
Side effect : Hepatotoxic	Side effects : Teratogenic : causes choanal or esophageal atresia. Cutis aplasia : Skin (scalp) formation defect. Cholestatic jaundice

Drug of choice for Hyperthyroidism/Grave's disease :
Overall : Methimazole
In pregnant females : Propylthiouracil.
In 1st trimester : Propylthiouracil.
In 2nd and 3rd trimester : Methimazole.
During lactation : Propylthiouracil.
Drug of choice for severe thyrotoxicosis/ Thyroid storm : Propylthiouracil as it blocks peripheral conversion of T4 to T3 and is shorter


Scalp defect with methimazole

acting. But the 1st drug given in case of severe thyrotoxicosis/thyroid storm is Propranolol (to prevent arrhythmia).

Common side effects of Thioamide drugs :

maculopapular rash (most common).

- Agranulocytosis.
- Arthralgia.

Iodides

00:13:00

Potassium iodide : 10%

Lugol's iodine : 5%

Mechanism of action :

- Inhibits release of T_3,T_4

  Fastest acting antithyroid drugs.

  Cannot be used long term as tolerance develops.
- Decreases vasculogenesis.
- Decreases the size and weight of thyroid gland.

This makes the gland firm and small. Hence, they can be used before thyroid surgery.

Other uses :

In nuclear accidents.

In thyroid storm : can be given after methimazole.

Side effects :

- Headache.
- Dysgeusia.
- Rash/lymphadenopathy.

Inhibitors of 5' deiodinase :

Block peripheral conversion of T_4 to T_3.

- Steroids.
- β-blockers.
- Amiodarone.
- Propylthiouracil.

Radioactive iodine :

I^{123} primarily releases gamma rays & is used for thyroid scan.

I^{131} primarily releases beta rays & is used for thyroid ablation.

I^{131} Uses :

For hyperthyroidism in elderly and cardiac patients.
For thyroid cancers (except medullary carcinoma).
For toxic nodular goiter.
To treat recurrent Grave's but radioactive iodine worsens ocular symptoms. Steroids should be given to prevent worsening.

Side effects :

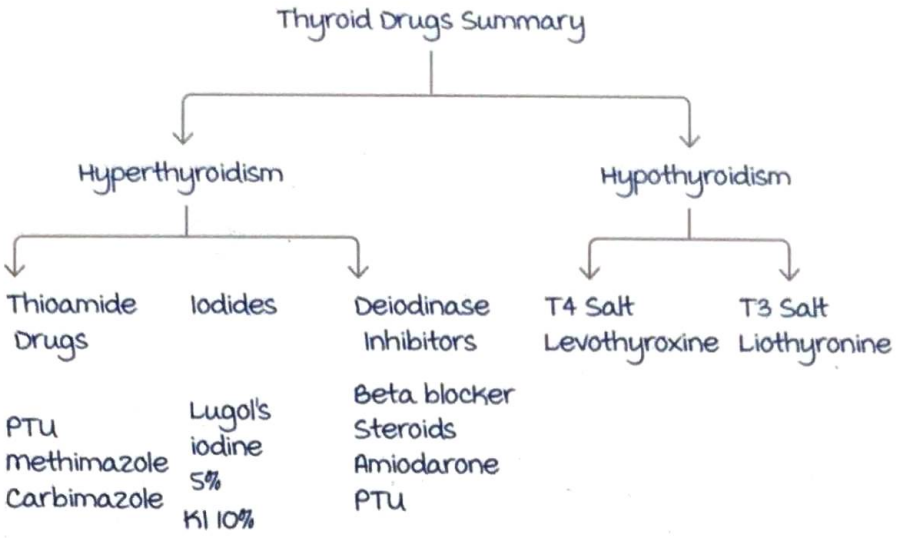
- Radiation thyroiditis : It increases the release of T3 and T4 causing arrhythmias and problems in elderly.
  So, premedicate with methimazole to decrease T_3, T_4 synthesis.
  methimazole to be stopped 3 days before and started 3 days after I^{131} treatment.
- Hypothyroidism.
- Secondary cancers.

Contraindicated in Pregnancy.

Hypothyroidism

00:22:58

T4 salt	T3 salt
Less active Longer acting Levothyroxine : Drug of choice for replacement in hypothyroidism. To be given orally on empty stomach. Oral bioavailability is 80%. Decrease intravenous dose by 20%.	more acting Shorter and faster acting Liothyronine : Oral/IV same dose can be given as bioavailability is 100%.
Uses : In thyroid cancers to reduce TSH. myxedema coma (IV route). Side effects : Osteoporosis. Increases risk of atrial fibrillation. (Reduce dose in patients of arrhythmia). Thyrotoxicosis : Palpitations, tremor, sweating, weight loss.	Uses : Myxedema coma. Prior to I^{131} therapy. After ceasing therapy, TSH increases, increasing the uptake of I^{131}.



ANTIHISTAMINICS

Autacoids

00:00:28

Histamine effects are because of it's receptors.

4 subtypes H1, H2, H3 and H4.

- All are G protein coupled receptors : H1 belongs to Gq subtype, H2 belongs to Gs subtype, H3 and H4 belong to Gi subtype.
- H1 and H2 are postsynaptic receptors.
- H3 is a presynaptic receptor.
- H4 is present on leukocytes.

Functions of receptors :

H1 increases Ca^{2+} by Gq subtype and produces the following effects :

- Bronchi : Bronchoconstriction.
- Blood vessels : Vasodilatation (increasing nitric oxide).
- GIT : Increased contraction.
- Hypothalamus : Wakefulness, decreased appetite.
- Peripheral nervous system : Itch.

H2 increases cyclic AMP and produces the following effects :

- Heart : Increases contraction and heart rate.
- Stomach (parietal cells) : Increases release of hydrochloric acid by phosphorylation of proton pump.

H3 decreases the release of histamine into the synapse thereby decreasing the effect of H1 and H2.

H4 mediates chemotaxis.

Uses :

- H1 blockers are used in allergy, motion sickness.
- H2 blockers are used in peptic ulcer disease.
  Side effects : Decrease in heart rate and contraction of heart leading to hypotension and bradycardia.
- H3 antagonist/inverse agonist (pitolisant) : To increase wakefulness in narcolepsy.
- H4 blockers : No drugs in this class. Potential site for treatment of atopic dermatitis in the future.

H1 blockers

00:12:08

Classified into 2 generations :

First generation	Second generation
Less potent	more potent
Cross blood brain barrier : Sedating antihistaminics. Contraindicated in elderly, children, pilots, and drivers.	very less amount crosses blood brain barrier : Non sedating antihistaminics.
Blocks muscarinic receptors	Do not block muscarinic receptors

First generation H1 blockers :

Promethazine, diphenhydramine and dimenhydrinate : Maximum antimuscarinic effect.

Used for their anti-muscarinic effects in

- Motion sickness : Taken 1 hour before travel.
- Treatment of extrapyramidal side effects like Acute dystonia.
- Meniere's disease (vertigo).
- Promethazine and diphenhydramine are used as local anaesthetics.
  Dimenhydrinate is used in the treatment of insomnia.
- Promethazine is also used in chemotherapy induced nausea and vomiting. Can cause hypotension due to alpha blockade.

Doxylamine :

Drug of choice for morning sickness. Formulated along with vitamin B_6 (Doxinate).

Chlorpheniramine :

Least sedating first generation drug.

Preferred first generation drug for day time use.

Hydroxyzine :

Antipruritic effect.

Anxiolytic and antiemetic.

Meclizine/cyclizine : Used in motion sickness.

Doxepin : Used as a tricyclic antidepressant.

Cyproheptadine : Used as a SHT_2 blocker.

Second generation H1 blockers 00:24:08

Cetirizine : Derivative of hydroxyzine.

- Most sedating second generation drug.
- Racemic mixture of levo and dextro isomers.

Levocetirizine : More potent isomer of cetirizine. Lesser dose requirement. More preferred.

Astemizole and terfenadine : Banned from use because of QT prolongation increasing the risk of torsades.

Fexofenadine : Derivative of terfenadine. Does not cause QT prolongation. Least sedating antihistaminic drug.

Loratadine -> desloratadine (metabolite) :
Desloratadine is the most potent of all antihistaminic drugs.

Rupatadine : Blocks platelet activating factor. Has anti-inflammatory effect.

Second generation HI blockers are drugs of choice for urticaria.
They can also be used to treat allergic rhinitis (hay fever) but the DOC is steroids.
First generation HI blockers are preferred in non-allergic rhinitis due to antimuscarinic effect.
Common side effect of both generations of HI blockers is nausea/vomiting due to delayed gastric emptying.
Topical antihistaminics :
Used for allergic rhinitis and allergic conjunctivitis.
Azelastine, alcaftadine, olopatadine, epinastine, levocarbastine.

Drugs related to bradykinin 00:32:40

Kininogens are converted into Kallidin and bradykinin by Kallikrein.

Bradykinin stimulates bradykinin 1 and bradykinin 2 receptors increasing prostaglandins (mediate pain and inflammation) and nitric oxide (causes vasodilation).

Kallikrein antagonists :

Aprotinin, lanadelumab, berotralstat, ecallantide.

60c6b3eeaa8ded0e4e7e5ea7

Bradykinin 2 receptor blocker : Icatibant.

Uses :

- Lanadelumab and berotralstat are used as alternatives for prophylaxis of hereditary angioedema.
- Icatibant and ecallantide are used as alternatives for treatment of hereditary angioedema.
- Aprotinin is used to decrease the risk of bleeding in coronary artery bypass grafting (CABG) patients as it blocks plasmin (anti fibrinolytic effect).

Hereditary angioedema:

- Drug of choice for the treatment of hereditary angioedema : C1 esterase inhibitors.
- Drug of choice for the prophylaxis of hereditary angioedema : Danazol (decreases C1 esterase).
- Prophylaxis before surgery in hereditary angioedema: Epsilon-aminocaproic acid (EACA).

Antihistaminics	
First generation	Second generation
Promethazine Diphenhydramine Dimenhydrinate Dicyclomine Chlorpheniramine Doxepin Cyproheptadine Meclizine/Cyclizine Hydroxyzine	Cetirizine Levocetirizine Astemizole Terfenadine Fexofenadine Loratadine Desloratadine Rupatadine Olopatadine Levocarbastine Ketotifen Azelastine Astemizole.

SEROTONIN AND RELATED DRUGS

7 types of receptors : SHT_1, SHT_2, SHT_3, SHT_4, SHT_5, SHT_6, SHT_7
All being GPCR (G-protein coupled receptors) except,
SHT_3 which is an ion channel receptor.

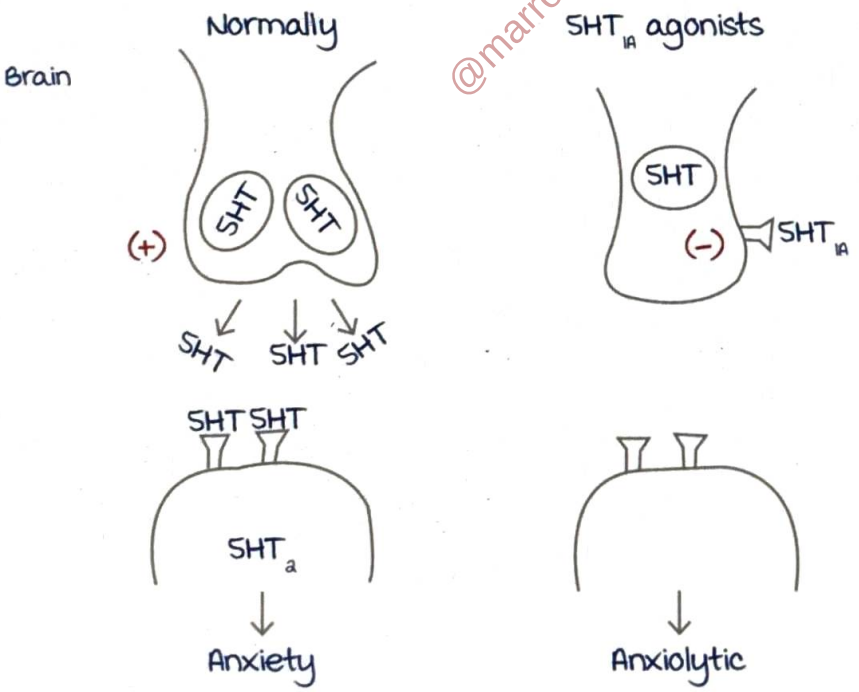
Receptors

00:01:46

SHT_1 :

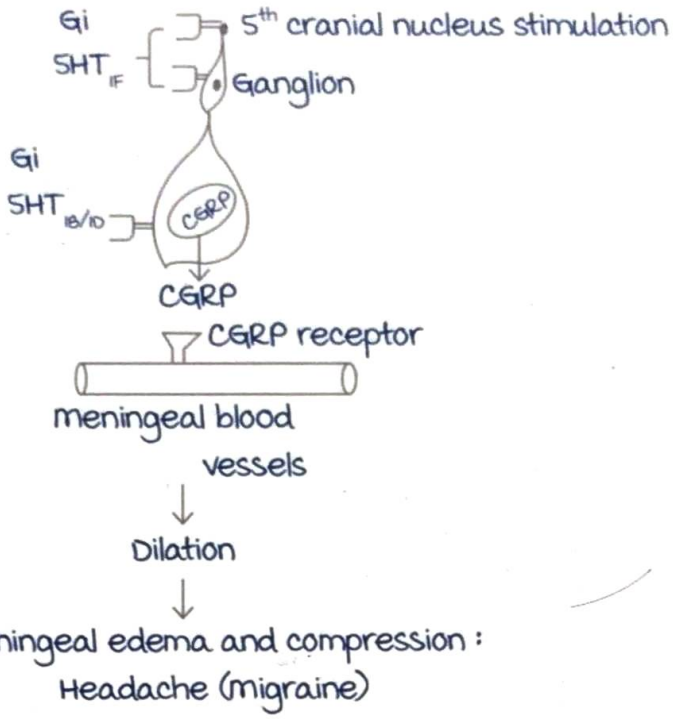
- SHT_{1A} agonists :
  Present in serotonergic neurons (pre-synaptic).
  Gi subtype receptors.

Buspirone
Ipsapirone
Gepirone
— used as anxiolytics (non-benzodiazepine)



- $SHT_{1B/1D}$ and SHT_{1F} :
  Gi subtype receptors.
  Present in 5th cranial nerve.

Active space



$SHT_{IB/ID}$ agonists : Triptans.
Decrease release of CGRP (calcitonin gene related peptide) and abort an acute attack of migraine.

SHT_{IF} agonist : Lasmiditan.
Used for treatment of acute attack of migraine.

CGRP ligand blockers :
Eptinezumab
Fremanezumab
Galcanezumab
} Given parenterally for prophylaxis of migraine.

CGRP receptor blockers :
Erenumab
Atogepant
} used for prophylaxis of migraine.
Rimegepant : Approved for treatment of acute attack of migraine.
Erenumab is given parenterally while other two drugs are given orally.

Drugs used in acute attack of migraine: 00:15:28

1. Triptans :

mechanism of action :

- Stimulators of $5HT_{1B/1D}$ decreasing the release of CGRP.
- Vasoconstrictors.

Triptans differ in pharmacokinetics and pharmacodynamics.
Rate of absorption is directly proportional to pharmacodynamics
(efficacy/potency).
So, if the rate of absorption is high, it will act faster and
lesser dose would be required.

Drugs on the basis of route of administration :
Oral drugs : Frovatriptan (acts for 27 hours) & Naratriptan
(acts for 6 hours).
Slow oral absorption, hence they are Long and slow acting.
Better for a prolonged attack.
Best drug : Frovatriptan.

Rizatriptan : Fastest acting
Sumatriptan (nasal spray)
Zolmitriptan (nasal spray)
Eletriptan
Almotriptan

} Fast oral absorption.
Fast & short acting.
Preferred in acute attacks.

Subcutaneous or rectal administration : Sumatriptan.
Overall fastest acting triptan is Subcutaneous sumatriptan.

Side effects :
Coronary vasoconstriction : Acute Chest pain.
Pain in jaw/neck.
Sweating.
Arrhythmia.

General Contraindications :

- Ischemic heart diseases.
- History of stroke/TIA.
- Ischemic bowel disease.
- HTN/PVD.

Specific contraindications :

- Naratriptan in liver and renal failure.
- Eletriptan in liver failure.
- Zolmitriptan : WPW syndrome .

2. $5HT_{1F}$ agonists : Lasmiditan.

3. CGRP receptor blockers : Rimegepant.

4. Ergot alkaloids : Ergotamine.

Mechanism of action :

- Stimulates $5HT_{1B/1D}$ (non-selective).
- Potent vasoconstrictor (>triptans).

Side effect :

Gangrene of organs with end arteries. most affected are the feet.

Dihydroergotamine :

Less potent vasoconstrictor.

Side effects and contraindications are similar to triptans.

5. D_2 blockers like chlorpromazine and metoclopramide.

6. NSAIDs :

Paracetamol : Mild to moderate attack.

Ketorolac : Severe attack.

7. Opioids :

Intranasal butorphanol.

Oral codeine.

Migraine in pregnancy 00:31:38

Drug of choice : Paracetamol.

If no response, add

- Codeine or
- Caffeine or
- metoclopramide.

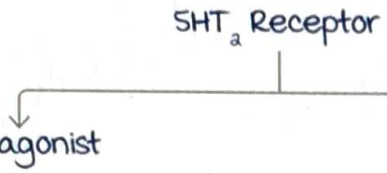
Start on triptans if all the modalities fail.

Safest triptan : Sumatriptan.

Migraine prophylaxis 00:33:21

Mnemonic : Flunarizine Can PREVENT Migraine.
Flunarizine, Cyproheptadine, candesartan, clonidine
Pizotifen, propranolol (DOC).
Drugs releasing GABA : Gabapentin.
Valproate.
Nortriptyline.
Topiramate (commonly used).
methysergide.

$5HT_2$ receptor agonists and antagonists 00:36:21



Cyproheptadine : HI, M blocker.
Uses :
Prophylaxis of migraine.
Serotonin syndrome.
Carcinoid syndrome.
Cold urticaria.
Weight gain in AIDS.

Locaserin was used to treat obesity.
Banned as it increases risk of cancer.

Pizotifen : used for prophylaxis of migraine.

methysergide : Was used for prophylaxis of migraine.
Causes Pulmonary, cardiac & retroperitoneal fibrosis.
Flibanserin :
SHT$_a$ blocker, SHT$_{1A}$ agonist.
Use to treat HSDD (Hypoactive Sexual Desire Disorder) in females.

Treatment of obesity 00:42:04

Drugs causing anorexia :
Liraglutide (Drug of choice).
Phentermine.

Inhibitor of lipase : Orlistat.

Stimulator of lipolysis : Mirabegron.

Unknown mechanism : Topiramate, naltrexone, bupropion.

Banned drugs for treatment of obesity :

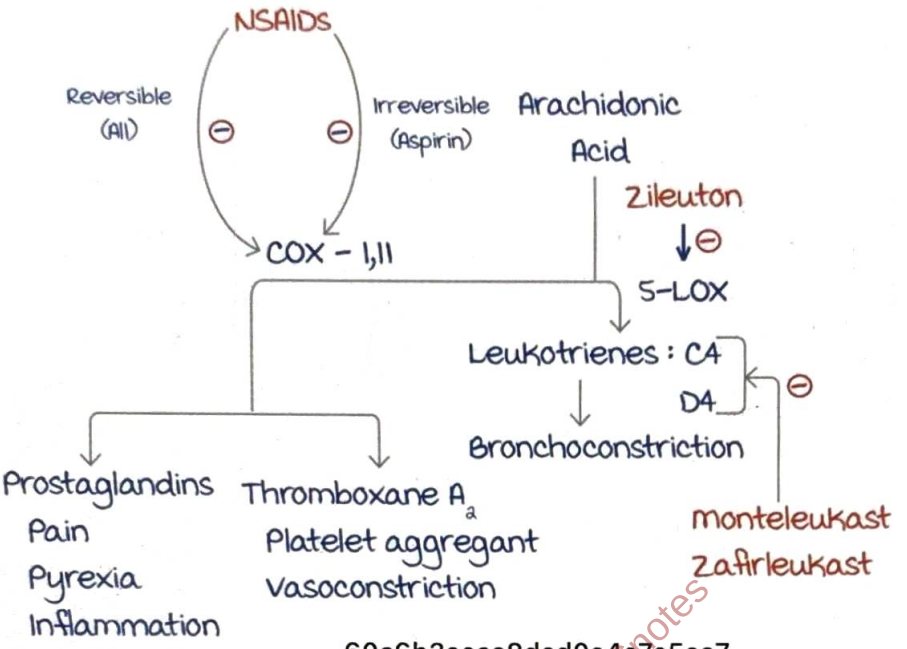
Banned drugs	Reason
Rimonabant	Suicidal tendency
Lorcaserin	Cancer
Phenylpropanolamine (norephedrine)	Stroke
Sibutramine	Myocardial Infarction

SHT_3 antagonists : Antiemetic drugs.

SHT_4 agonists : Prokinetic drugs.

EICOSANOIDS

Precursor : Arachidonic acid.



Aspirin :

Inhibits platelet aggregation by binding to cyclooxygenase (COX) irreversibly and decreases production of thromboxane A2 (TXA2).

Aspirin is the only NSAID that blocks COX irreversibly. Rest all NSAIDS are reversible inhibitors.

Aspirin induced bronchoconstriction :

Blocking of COX pathway increases availability of arachidonic acid for 5-LOX pathway.

NSAIDS : block cyclooxygenase and decrease prostaglandins therefore they decrease pain : Analgesics.

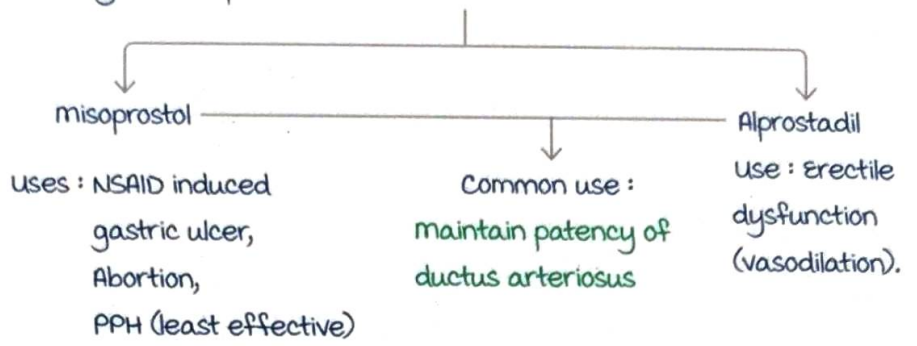
reduce pyrexia : Antipyretics.

reduce inflammation : Anti-inflammatory

Prostaglandin analogues

00:06:08

Prostaglandin E_1 :



Drugs used for erectile dysfunction :

Phentolamine.
Bremelanotide (approved for HSDD).
Naltrexone.
Ketanserin.
Sildenafil (drug of choice).
Alprostadil.
Trazadone.
Alviptadil.

Prostaglandin E_2 :
- Dinoprostone.
  - Used in PPH.
  - Drug of choice for cervical ripening.

Prostaglandin I_2 related drugs :
- Epoprostenol : Recombinant PgI_2
- Iloprost, Beraprost, Treprostinil — PgI_2 analogues
- Selexipag : PgI_2 receptor agonist.

These drugs produce vasodilation, thus used in treatment of pulmonary hypertension.

Other drugs used in pulmonary hypertension :

Endothelin antagonist : Bosentan & Ambrisentan.

$PgF_{2\alpha}$ analogues :

Carboprost : Used in PPH and abortion.

Latanoprost & Bimatoprost : Used as eye drops.

Drug of choice in open angle glaucoma.

Drug of choice for normal tension glaucoma.

Side effects :

Heterochromia iridis.

Dry eyes/ sandy eyes.

Macular edema.

Hypertrichosis (Secondary use : Approved for treatment of hypotrichosis).

Contraindication : Uveitis.

NSAIDs : non selective COX inhibitors 00:18:03

Blocks COX I and II both.

Acetaminophen (paracetamol) :

mechanism of action :

Blocks COX : Decreases prostaglandin.

Stimulate TRPV I and Cannabinoid receptors.

Effects :

Good anti pyretic.

Good analgesic effect.

Poor anti-inflammatory effect.

most common cause of drug poisoning.

Symptoms of drug poisoning :

- Renal tubular necrosis.
- Hypoglycemic coma.
- Hepatotoxicity.

Cause of hepatotoxicity :

metabolite of paracetamol called as NAPQI. It depletes glutathione (which is a free radical scavanger).

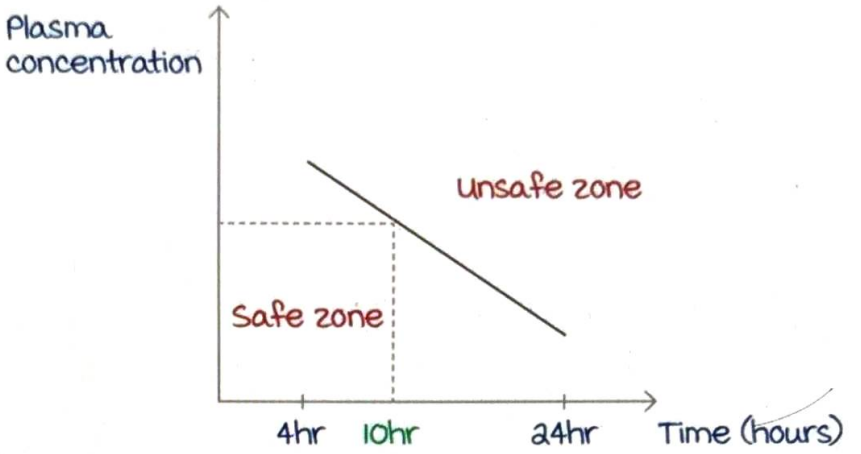
HPE : Centrilobular necrosis with periportal sparing.

Active space

Doses : > 150-250mg/kg or > 10g.

Fatal : > 20g.

Prediction of hepatotoxicity : Rumack Matthew nomogram.



Charcoal (if patient presents within 4 hours of consumption.)

Drug of choice : N-Acetyl cysteine.

If no response, patient will progress to fulminant liver failure.

MCC of drug induced liver failure : Paracetamol.

R_x of fulminant liver failure : Emergency liver transplantation.

Aspirin :

Dose dependant effect :

50 - 325 mg OD : Antiaggregant.

325 - 650 mg SOS : Analgesic/antipyretic.

Max : 4 doses/day.

3-4 gm/day (in divided doses) : Anti-inflammatory effect.

Uses :

- As an antiaggregant.
- Rheumatoid arthritis.
- Rheumatic arthritis.
- Drug of choice for Niacin induced flushing.
- Essential thrombocytopenia.
- Kawasaki disease.

Side effects :

Most common : Bleeding.

Reye's syndrome : Hepatic encephalopathy. If aspirin is used in treatment of viral fever in children.

Toxicity : > 10g causes salicylism.

- Seizures.
- Tinnitus.
- Hyperglycemia.
- metabolic acidosis.

Treatment : Symptomatic.

Dialysis (in severe cases).

Contraindications :

- Viral fever in children.
- Gout (inhibits uric acid excretion).
- With warfarin (increase risk of bleeding).

Indomethacin :

Mechanism of action :

- Inhibits COX.
- Inhibits phospholipase A & C.
- Inhibits leukocyte proliferation and migration.

Uses :

- Drug of choice for acute gout.
- Bartter syndrome.
- Paroxysmal hemicrania.

Side effect : Frontal headache.

Sulindac :

- Derivative of Indomethacin.
- Similar uses.
- Blocks FAP (familial adenomatous polyposis), thus decreases risk for colon carcinoma.
- Also decreases risk of breast cancer and prostate cancer.

Ibuprofen :

Uses :

Analgesic.

Anti-inflammatory.

Drug of choice for closure of PDA (India).

International guidelines : Indomethacin.

Side effects : Aseptic meningitis.

most common cause of drug induced aseptic meningitis is Ibuprofen.

Ocular side effects :

Toxic amblyopia.

Blurred vision.

Drug related to Ibuprofen :

Ketoprofen :

Similar uses.

Mechanism of action :

- Blocks COX.
- Inhibits LOX.
- Stabilise lysosomes.
- Inhibit bradykinin.

Flurbiprofen :

Used as eye drops to prevent intraoperative miosis.

Piroxicam :

Undergoes enterohepatic circulation.

Longest acting overall.

Slow onset of action.

Used as analgesic for chronic pain.

Diclofenac :

Short $T_{1/2}$

Long acting as it gets concentrated in the joints.

Uses :

- Rheumatoid arthritis.
- Psoriatic arthritis.
- Ankylosing spondylitis.
- Gout.
- Dysmenorrhea.
- Acute pain.

Side effect : Hepatotoxic.

Formulated with misoprostol to reduce GIT ulcers.

Ketorolac : One of the most potent analgesic.

Uses : Orally/ parenterally for acute pain. E.g. migraine, post operative pain.

Used intranasally for migraine.

Used as eye drops for ocular pain and inflammation (iridocyclitis).

Other drugs :

Naproxen : Only NSAID used as single enantiomer.

Nabumetone :

Derivative of Naproxen.

Only non-acidic NSAID.

Long acting (once daily).

Does not undergo enterohepatic circulation.

NSAIDs : selective COX-II inhibitors 00:51:46

Oral :

Celecoxib.

Etoricoxib.

Uses :

Dysmenorrhea

Acute pain.

Anti-inflammatory :

- Rheumatoid arthritis.
- Rheumatic arthritis.
- Psoriatic arthritis.
- Ankylosing spondylitis.
- Gout.

Parenteral (intravenous route)

Parecoxib :

Used in acute pain like

Postoperative pain.

Side effects :

Most common : Hypersensitivity rash.

Nephrotoxicity : Renal papillary necrosis.

Cardiotoxicity increases with selective COX II inhibitors like :

Refecoxib and Valdecoxib (banned for causing MI).

Peptic ulcer :

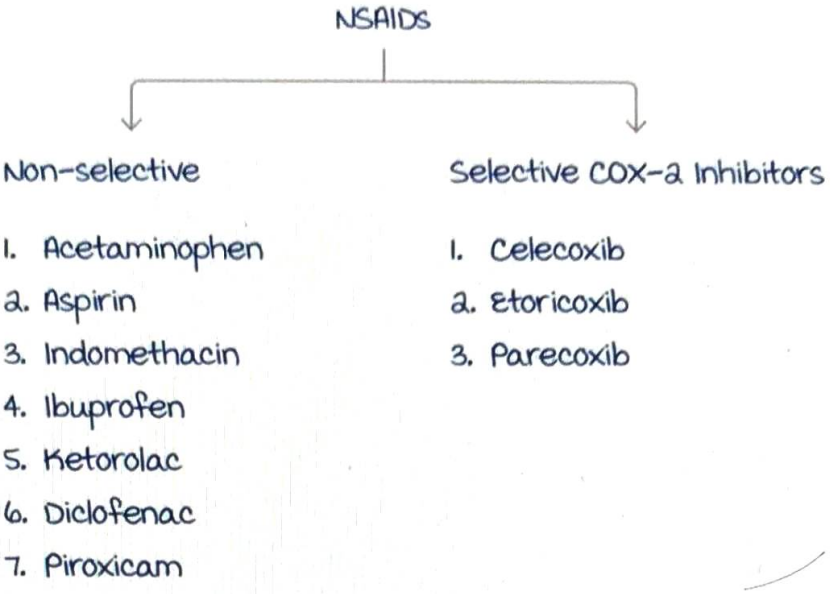
Non-selective > selective.

Drug of choice : PPIs.

Drug interactions :

Decrease the effect of antihypertensives/diuretics like Furosemide.

Decrease the clearance of Lithium, causing toxicity.



GOUT

Acute gout

00:00:36

Aim : To decrease inflammation and provide symptomatic relief.

NSAIDs :

Drug of choice : Indomethacin (act via multiple mechanisms).

If no response, start steroids.

Colchicine :

Mechanism of action :

- Inhibits microtubules → Blocks chemotaxis (migration of leucocytes).
- Decrease IL-1 from neutrophils.
- Inhibit phagocytosis.

Other uses :

- Amyloidosis.
- Prophylaxis of familial mediteranean fever.

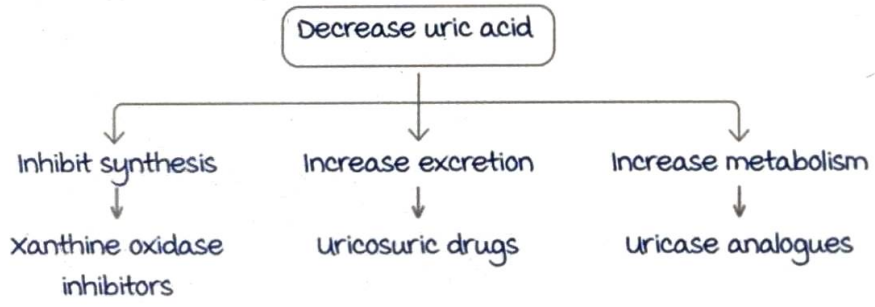
Side effects :

- Nausea, vomiting, diarrhoea.
- Bone marrow suppression.
- Alopecia.

Chronic gout

00:05:14

Aim : To prevent acute gout (decrease uric acid levels).



1. Xanthine oxidase inhibitors :

   All the drugs are competitive inhibitors of xanthine oxidase.

Allopurinol :

Drug of choice for chronic gout.

Drug of choice in hyperuricemic conditions like :

- Tumour lysis syndrome (in low to intermediate risk, mostly in chemotherapy for solid tumours).
- Lesch nyhan syndrome.
- Organ transplantation.

Side effects :

- Hypersensitivity (most common). Even leads to Steven Johnson syndrome (SJS). Associated with HLA-B-5801.
- Orotic aciduria : Inhibit Orotidylate decarboxylase.
- DRESS syndrome : Drug Related Eosinophilia causing Systemic Symptoms like fever, rash, hepatitis.

Oxypurinol :

Orphan drug.

Used in treatment of chronic gout patients with Allopurinol hypersensitivity.

Febuxostat :

Used in patients of chronic gout with Allopurinol intolerance or inadequate response to Allupurinol (better efficacy).

Side effect : Increased risk of cardiovascular death.

Common side effects of Xanthine oxidase inhibitors :

- Xanthine stones.
- Acute gout (to prevent this : Add NSAIDs or colchicine for 3-6 months as uric acid levels in blood tend to increase during initial months of treatment).

Drug interaction of xanthine oxidase inhibitors :

Inhibits the metabolism of 6-mercaptopurine or Azathioprine, increasing their toxicity.

Decrease the dose of these drugs, if given in combination.

2. Uricosuric drugs (increases uric acid excretion) :

   Probenicid.

   Sulfinpyrazone.

Benzbromarone.

Mainly used is as an add on therapy to xanthine oxidase inhibitors. Can be used as monotherapy.

Lesinurad
- Only used as an add on to xanthine oxidase inhibitors.
- Never as monotherapy.

Side effects :

- Urate stones. Contraindicated in patients with H/O renal stones. Also increases risk of calcium stones.
- Precipitate acute gout (prevent with prophylaxis for 3-6 months).

Not effective in renal failure except Benzbromarone or Lesinurad. These can be given in mild to moderate renal failure.

Miscellaneous drugs	Used in chronic gout associated with
Losartan	HTN
Atorvastatin	Increased LDL/cholesterol
Fenofibrate	Increased triglycerides.

In mammals : Uric acid is metabolized into allantoin and excreted via urine.

In humans : No such metabolism exists. Hence we use :

Uricase analogues

3. Uricase analogues :

Pegloticase :

Given intravenously once in every 2 weeks in the treatment of resistant chronic gout cases.

Rasburicase :

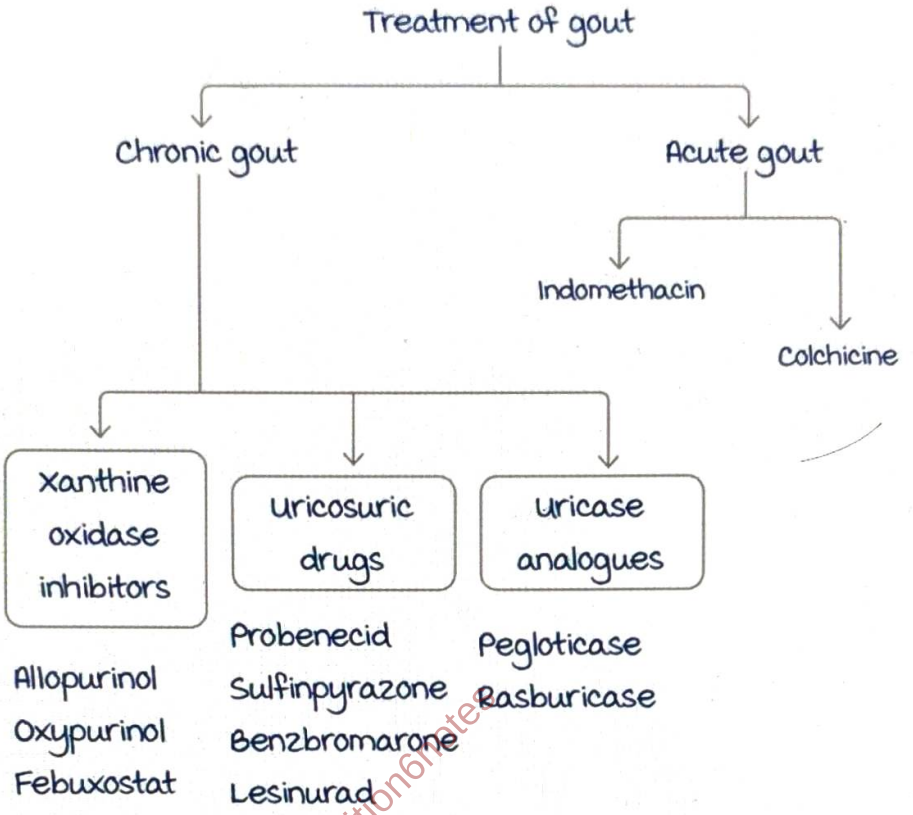
Given intravenously.

Drug of choice in high risk tumor lysis syndrome. E.g. Leukemia like CLL.

Active space

Side effects :

Hemolysis in G6PD deficiency, methemoglobinemia.



RHEUMATOID ARTHRITIS

Aim : To treat acute flares and long term management of RA.

Acute flare :

- Mild to moderate : NSAIDs like Aspirin, Diclofenac, Celecoxib (less preferred due to cardiotoxicity).
- If patient does not respond or if the flare is severe, steroids are used.
- 1-2 joints involved : Intra-articular triamcinolone.
- If > 2 joints involved : Oral prednisolone.

Long term management

00:02:28

Disease Modifying Antirheumatic Drugs (DMARDs) :

DMARDs are subclassified into Conventional, Biologics and Janus Kinase (JAK) inhibitors.

- Conventional DMARDs : Methotrexate, Hydroxychloroquine, Leflunomide, Cyclosporine, Sulphasalazine, Azathioprine, Mycophenolate Mofetil, Cyclophosphamide.
- Biologic DMARDs : TNF-alpha inhibitors, IL-1 inhibitors, IL-6 inhibitors, Abatacept, CD-20 inhibitor.
- JAK inhibitors : Tofacitinib, Baricitinib, Upadacitinib.

Biologic DMARDs, JAK inhibitors and some other drugs like cyclosporine, azathioprine, mycophenolate, mofetil suppress immune system and increase the risk of infection. These drugs should not be combined with each other.

Treatment of rheumatoid arthritis :

Drug of choice is methotrexate (also known as anchor drug).

Requires 2-4 weeks for anti inflammatory effect.

Steroids are given for 2-4 weeks.

If there is inadequate response to methotrexate after 3-6 months, add either one of the following :

1. Hydroxychloroquine + Sulfasalazine.
2. Abatacept.
3. Biological DMARDs.

If there is inadequate response, change to another biologic DMARD or JAK inhibitor.

Conventional DMARDs 00:09:50

Methotrexate :

Mechanism of action :

- Blocks dihydrofolate reductase : Decreases tetrahydrofolate and blocks purine synthesis. Can cause lymphocyte toxicity.
- Increase in adenosine gives anti-inflammatory effect. However, it can cause hepatic fibrosis.

Side effects :

- Hepatotoxicity, liver cirrhosis. ALT/AST should be monitored every 3-6 months.
- Nephrotoxicity, crystalluria.
- Bone marrow suppression.

Hydroxychloroquine :

Mechanism of action :

- Blocks lymphocyte proliferation.
- Stabilizes lysosomes.

Uses :

- Monotherapy in a mild case.
- Mostly used as an add on in moderate to severe cases.

Side effects :

Bull's eye retinopathy/maculopathy. Dose should not exceed 5 mg/kg/day. Ophthalmological examination should be done once in a year.

Sulfasalazine :

- Metabolized in gut into 5-aminosalicylic acid (not absorbed) and sulfonamide.
- 5-aminosalicylic acid is used in ulcerative colitis.
- Sulfonamide is absorbed. It blocks lymphocyte proliferation. Can be used as monotherapy in mild case of rheumatoid arthritis. Mostly used as an add on therapy in moderate to severe case.

Biologic DMARDs 00:16:40

TNF alpha blockers :

Infliximab, Adalimumab, Certolizumab, Etanercept, Golimumab.

Infliximab, Adalimumab can be given by IV route.

All the above drugs can be given by subcutaneous route.

Uses : (mnemonic : Alpha Inhibitor Prevents RA)

- Ankylosing spondylitis.
- Inflammatory bowel disease like ulcerative colitis and Crohn's disease.
- Prevents : Psoriatic arthritis, plaque psoriasis.
- Rheumatoid Arthritis.

Side effects :

- GIT ulcers, perforation.
- Increase the risk of infection.
- Increase the risk of secondary cancers (skin).

Contraindicated in hepatitis B (reactivation risk), congestive heart failure.

IL 1 inhibitors :

Anakinra : Least effective biological in rheumatoid arthritis.

IL-6 inhibitors :

Tocilizumab and sarilumab.

Also used in COVID-19 for the treatment of cytokine storm.

CD20 inhibitors :

Rituximab.

Abatacept :

- Inhibits CD 80/86 and blocks T cell activation. Down regulation of T cells gives anti-inflammatory effect.
- Belatacept is a related drug. It is used in graft versus host disease (GVHD).

Janus kinase (JAK) inhibitors 00:22:24

- Block the function of cytokines : IL 1, IL 6, TNF alpha.
- Baricitinib : used only in rheumatoid arthritis.
- Upadacitinib : used in rheumatoid arthritis, psoriatic arthritis, atopic dermatitis.

- Tofacitinib : (mnemonic : Tough PUJARA).
  Used in Psoriatic arthritis, Ulcerative colitis, Juvenile idiopathic arthritis, Ankylosing spondylitis, Rheumatoid Arthritis.
- Other drugs :

Abrocitinib : Used only in atopic dermatitis.

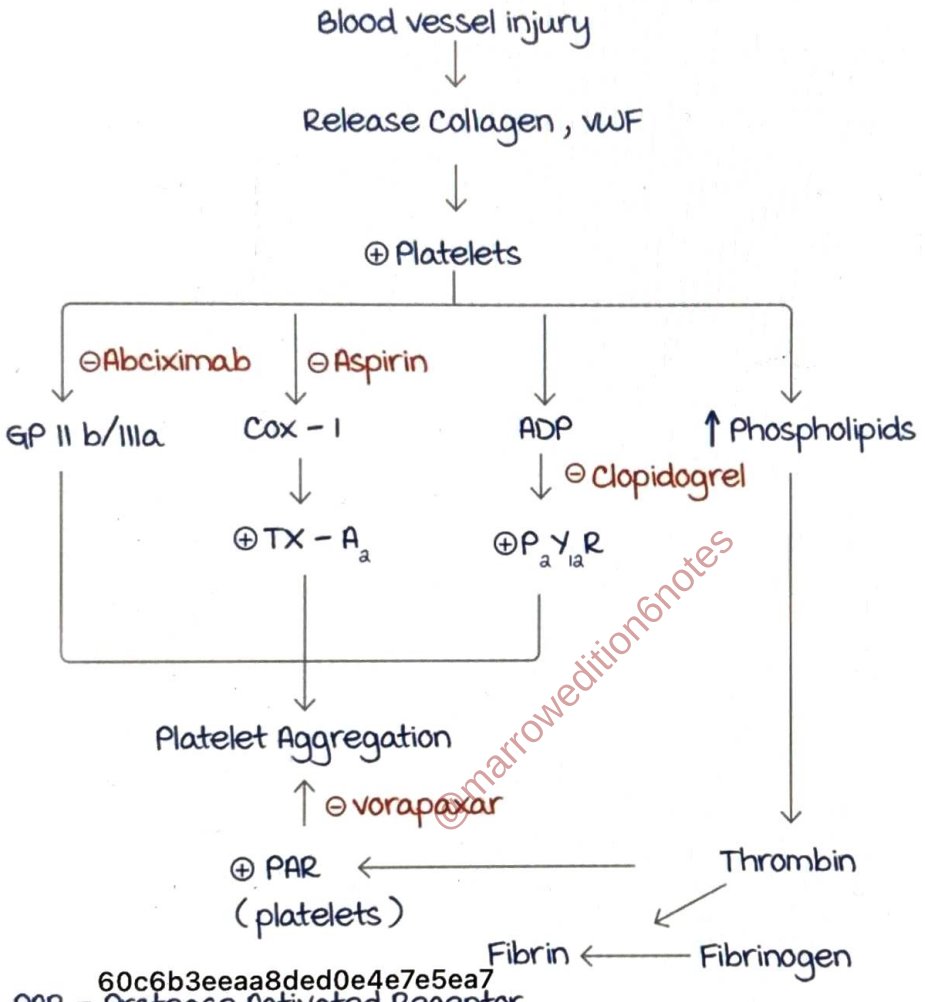
Ruxolitinib :

Used in Graft versus host disease, myelofibrosis, Polycythemia vera (not responding to Hydroxyurea).

Abnormal JAK signalling is present in myelofibrosis, polycythemia vera etc. Therefore, JAK inhibitors can be used.

ANTIAGGREGANTS AND HEMATOPOIETIC AGENTS

Physiology of blood aggregation 00:00:45



PAR = Protease Activated Receptor.

Platelet aggregation along with fibrin forms permanent clot.

Aspirin 00:06:00

Mechanism of action :

Blocks Cyclooxygenase-1 (COX-1) irreversibly & decreases Thromboxane A2.

Dose for antiaggregant action is low : 50-325mg OD.

Uses :

- Secondary prophylaxis of acute coronary syndrome (MI, unstable angina) & ischemic stroke.
- Treatment of acute coronary syndrome.

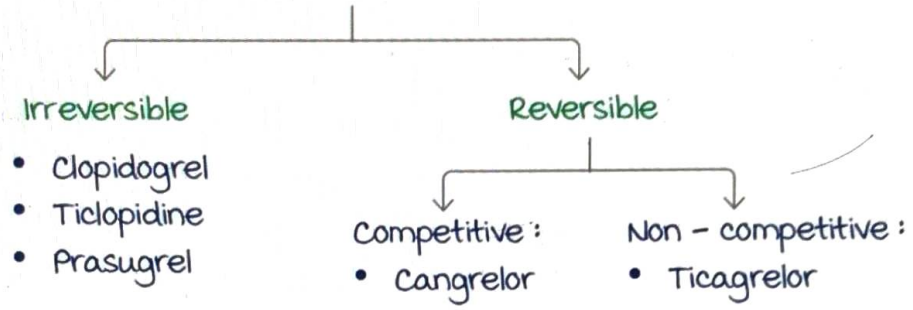
- Essential thrombocythemia.
- Kawasaki disease.
- Antiphospholipid antibody syndrome.

Side effect : Bleeding.

Continue Aspirin but stop Clopidogrel 7 days prior to surgery.

ADP inhibitors/ $P_2Y_{12}R$ inhibitors

00:12:08



Hit & run drugs :

They act longer than $T_{1/a}$ due to irreversible binding to their target.

e.g. ADP inhibitors, $P_2Y_{12}R$ inhibitors, Aspirin, PPIs.

Clopidogrel :

It is a prodrug, activated by CYP2C19.

If gene coding for CYP2C19 is less powerful, activation of Clopidogrel gets blunted. In case of CYP2C19 polymorphism, effect of Clopidogrel decreases.

Omeprazole is contraindicated with Clopidogrel.

Omeprazole is also metabolised by CYP2C19. So it competitively inhibits activation of Clopidogrel, thereby decreasing the effect of Clopidogrel.

Uses (oral route) :

Secondary prophylaxis of MI or unstable angina, stroke.

Can be combined with Aspirin for patients on stents.

Treatment of acute coronary syndrome.

Ticlopidine :

Most toxic drug.

Not preferred currently.

Side effects :

Nausea, vomiting, Diarrhoea.

Agranulocytosis.

Thrombotic Thrombocytopenic Purpura- Hemolytic Uremic Syndrome complex.

Use : Secondary prophylaxis of thromboembolic stroke.

Only in resistant cases.

Prasugrel :

Most potent and fastest acting.

Side effect : Increases risk of intracranial bleed.

Contraindications : Patients with history of cerebrovascular diseases like stroke, TIA.

Use : Percutaneous intervention (PCI) in STEMI.

Cangrelor :

Adenosine analogue.

$T_{1/2}$: 3-6 min.

Route : Intravenous.

Short acting.

Use : PCI in MI.

Ticagrelor :

Long acting.

Route : oral.

Uses : Acute coronary syndrome.

Secondary prophylaxis of MI or stroke.

Protease activated receptor inhibitor 00:26:45

Vorapaxar :

Mechanism of action :

Inhibits protease activated receptor (PAR).

Side effect : Increased risk of intracranial bleed.

Contraindications : History of stroke, TIA.

Use : Secondary prophylaxis of MI or Unstable Angina.

It can be used alone or along with Aspirin or Clopidogrel.

Glycoprotein IIb/IIIa inhibitors 00:28:32

Abciximab :

Mechanism of action : Blocks GP IIb/IIIa and inhibits vitronectin.

It is given intravenously or via intracoronary route.

Shortest $T_{1/2}$ but has maximum affinity for GP IIb/IIIa thus longest acting.

Other drugs include :

1. Tirofiban.
2. Eptifibatide : Longest $T_{1/2}$.
   Minimum affinity for GP IIb/IIIa- shortest acting.

Uses : PCI in MI.
Treatment of acute coronary syndrome.

Hematopoietic agents 00:32:25

Drugs acting on erythropoiesis :

1. Erythropoietin analogues :
   Epoetin alfa
   Darbepoetin : Longer acting and is clinically preferred.
   Use : Drug of choice for Anemia due to CRF, dialysis, Zidovudine, anticancer drugs & in premature infants.
   Side effects :
   Hypertension.
   Iron deficiency.
   Pure red cell aplasia.
   Flu like symptoms.
2. Erythropoietin receptor agonists :
   Peginesatide.
   Use : Anemia of chronic renal failure (CRF).

Drugs acting on granulopoiesis 00:37:38

1. G-CSF (Granulocyte colony stimulating factor) analogues :
   more potent, less toxic.
   E.g., Lenograstim and Filgrastim.

Filgrastim : most commonly used.
Short acting.
Can be given subcutaneously or intravenously.
It is given in multiple doses in a chemotherapy cycle.

Derivatives of Filgrastim :

- Lipefilgrastim.
- Pegfilgrastim.

These are long acting drugs and are hence given once in a chemotherapy cycle.

Uses : Neutropenia due to myelodysplasia, aplastic anemia, HIV, chemotherapy.

Side effect : bone pain.

2. GM-CSF (Granulocyte macrophage colony stimulating factor) analogues : Sargramostim.
Less potent, more toxic.
It causes capillary leak syndrome.

Drugs acting on thrombopoiesis 00:42:12

IL-11 analogue :
Oprelvekin.
Use : Chemotherapy induced thrombocytopenia.
Side effect : Fluid retention resulting in CHF/edema.

Thrombopoietin agonist :

- Romiplostim.
- Eltrombopag.

Use : Immune thrombocytopenic purpura (ITP).
Side effects : Portal vein thrombosis, acute myeloid leukemia (AML)

New drugs :

- Avatrombopag.
- Lusutrombopag.

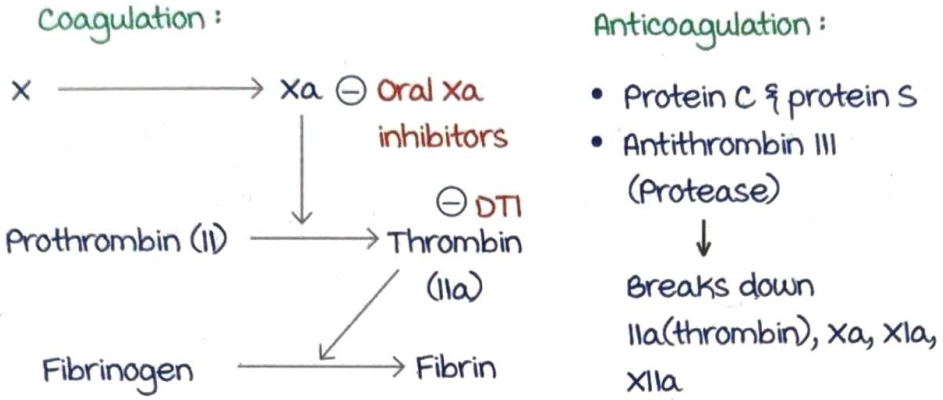
Use : To prevent procedural bleeding in patients of liver cirrhosis.

Antiaggregant drugs summary

COX – 1 Inhibitor	P2Y12 Inhibitors	PAR Inhibitors	GP IIb/IIIa Inhibitors
Aspirin	Irreversible Clopidogrel Ticlopidine Prasugrel Reversible Cangrelor Ticagrelor	Vorapaxar	Abciximab Tirofiban Eptifibatide

ANTICOAGULANTS AND FIBRINOLYTICS

Coagulation vs anticoagulation 00:01:24



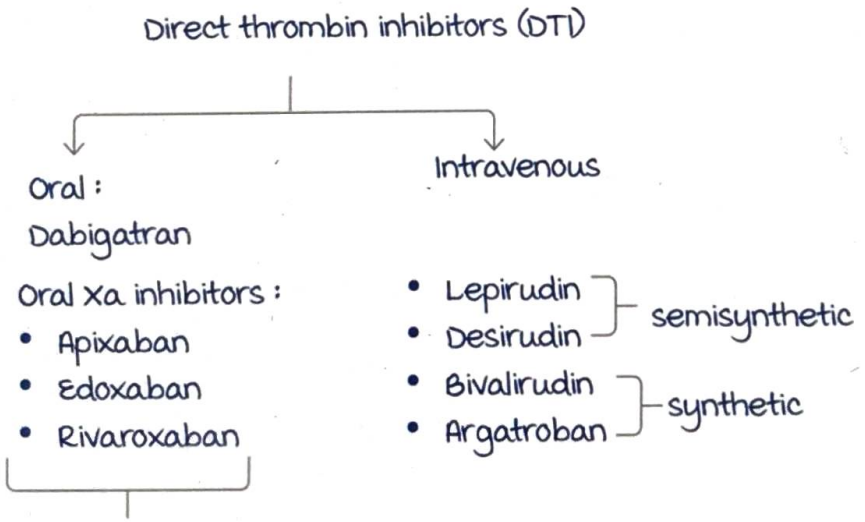
For anticoagulant effect :

- Oral Xa inhibitors
- Direct thrombin inhibitors (DTI)

} inhibits coagulation

- Indirect thrombin inhibitors : Causes anticoagulation by stimulating Antithrombin III.

Directly acting oral anticoagulants 00:05:19



Direct acting oral anticoagulants (DOAC)/ Novel oral anticoagulants (NOAC) : Oral direct thrombin inhibitors + oral Xa inhibitors.

Coagulation monitoring is not required for Dabigatran, Oral Xa inhibitors, LMWH, Fondaparinux.

Uses of DOAC/NOAC :

DOC for prophylaxis of DVT.

Treatment of DVT (DOC : LMWH).

DOC for prophylaxis of thrombosis in non-valvular atrial fibrillation.

Exceptions (Conditions where Warfarin is preferred) :

- Renal failure.
- Patient on P-glycoprotein (Pg) pump inhibitors : As these drugs are substrates for Pg pump.
- Severe mitral stenosis (area < 1.5 cm^2).

Warfarin : DOC for prophylaxis of thrombosis in atrial fibrillation with mechanical valve (extrinsic pathway).

Side effect of DOAC/NOAC : Bleeding.

Antidotes (in case of bleeding) :

Dabigatran : Idarucizumab.

Oral Xa inhibitor : Andexanet alfa (acts as a decoy).

Parenteral direct thrombin inhibitors 00:19:21

Hirudin in leech saliva has anticoagulant effect.

- Semisynthetic drugs : derivatives of Hirudin
  Lepirudin (production stopped).
  Desirudin : Subcutaneous route for DVT prophylaxis in patients undergoing hip, knee surgery.

- Synthetic drugs : Bivalirudin, Argatroban } IV route, can be used for PCI in MI.

Uses :

Heparin induced thrombocytopenia (HIT) (DOC : Argatroban).

Monitoring of aPTT is a must.

Contraindication : Renal failure
(except Argatroban : excreted by liver).

Indirect thrombin inhibitors

00:25:23

Unfractionated heparin :

- Glycosaminoglycan (mast cells).
- Source : Porcine intestinal mucosa (MALT Tissue).
- Structure : Active pentasaccharide attached to a very long chain of heteropolysaccharide (HPS).
- MOA : Active pentasaccharide binds to AT-III & Xa is broken down.
- HPS binds to factor IIa & factor IIa is broken down. Since HPS has a very long chain, activity against both Xa and IIa is equally good.

Drawbacks of UFH :

- Subcutaneous route : low bioavailability as HPS binds to local tissues.
- Hence, UFH is used subcutaneously only for prophylaxis. But IV route is needed for treatment.
- UFH → metabolized by reticuloendothelial system (macrophages).
- Short acting.
- S/C Dose : BD. (prophylaxis)
- IV dose : QID - Rx.
- Monitor aPTT.
- DOC in renal failure.

Low molecular weight Heparin :

Enoxaparin.
Tinzaparin.

- Short chain of HPS compared to UFH.
- Smaller chain restricts binding to factor IIa i.e Xa > IIa activity.
- Increased bioavailability.
- S/C route for both prophylaxis & treatment.
- Excreted unchanged by Kidney (contraindicated in renal failure).
- Long acting.
- S/C Dose : OD.
- No monitoring required except in renal failure, obese, children or elderly : Anti Xa assay.

Fondaparinux :

- Has only active pentasaccharide.
- Binds to & breaks down factor Xa only.
- No activity against IIa.
- Maximum bioavailability.
- S/C route for both prophylaxis and treatment.
- Excreted unchanged by Kidney (contraindicated in renal failure).
- Long acting.
- S/C Dose : OD.
- No monitoring required.

Antidotes :

UFH : Protamine sulfate (positively charged) binds to HPS (negatively charged) and neutralizes it.

LMWH : Protamine maybe used but less effective.

Fondaparinux : Protamine is not effective.

Side effects :

Antibodies produced against HPS cross reacts with platelet factor-4.

↓

Induces platelet aggregation

Thrombosis :	Heparin induced thrombocytopenia (HIT) – not severe.
Venous > arterial .	HIT is mostly seen with UFH use.
Females > males.	LMWH has lesser risk.
more common in surgical & cancer patients.	Fondaparinux – no risk of HIT.

Treatment : Anticoagulants (DTI).

DOC : Argatroban.

Fondaparinux. Both are used for minimum 4 weeks.

In case of major thromboembolism, minimum 3 months is required.

When platelet count > 1,50,000 : Start warfarin or DOAC.

Warfarin cannot be used for treatment.

Uses of indirect thrombin inhibitors :

UFH :

- Catheter induced thrombosis (factor XII). Only UFH has effect on factor XII.
- Anticoagulation with concurrent thrombolysis : If bleeding occurs, protamine sulfate can be used to reverse it.

LMWH/Fondaparinux :

DOC : Treatment of thrombosis in :

- DVT.
- STEMI, NSTEMI.
- Unstable angina.
- Thromboembolic stroke.
- Pulmonary embolism (massive : fibrinolytics).
- Cancer induced.

Heparin - side effects & contraindications 00:56:42

Side effects :

A : Alopecia.

H : Hemorrhage, hyperkalemia.

O : Osteoporosis.

T : Thrombosis – HIT.

Contraindications :

T : Thrombocytopenia.

E : Endocarditis.

A : Alcoholics.

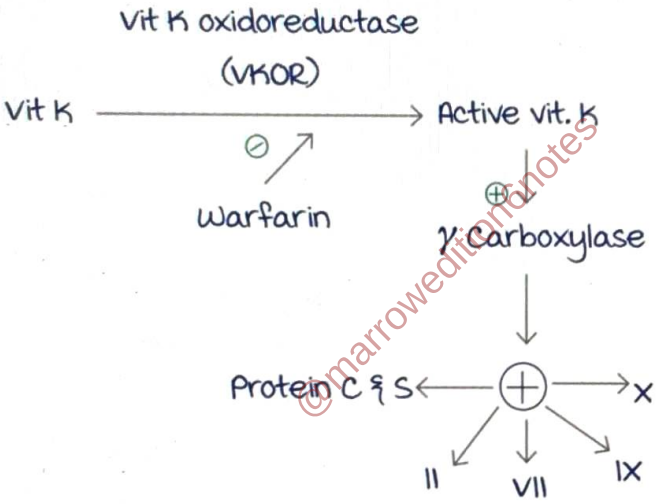
C : Cirrhosis.

H : Hypertension (severe).

E : Eye/neurosurgery.

R : Renal failure (LMWH/ Fondaparinux).

Warfarin 00:58:48



MOA :

Warfarin is VKOR inhibitor : Decreases active Vitamin K.

Thereby decreasing production of factors II, VII, IX, X causing anticoagulant effect.

Factor VII : First to decline (shortest acting).

Protein C : 2nd to decline.

Factor II : Last to decline (longest acting).

Minimum 5 days are required to produce anticoagulant effect.

In first 5 days, there is a rapid decline in protein C and S which can cause thrombosis. This leads to warfarin induced skin necrosis.

As it worsens thrombosis, warfarin is contraindicated in HIT.

Uses :

- Prophylaxis of DVT (DOC : DOAC).
- Treatment of DVT : Effective only after 5 days.
- LMWH given for first 5 days and stopped on the 5th day known as Heparin bridge.
- Prophylaxis of thrombosis : Valvular atrial fibrillation (mechanical valve).
- Prophylaxis of thrombosis in non valvular atrial fibrillation only in case of :
  - Renal failure.
  - PgP pump inhibitor.
  - Severe mitral stenosis with area < 1.5 cm^2.
- DOC for :
  - Thrombosis in antiphospholipid antibody syndrome.
  - Splanchnic vein thrombosis.

Side effects :

- Bleeding.
- Skin necrosis (more common in limbs, breast, penile area) - seen in the first 5 days.
- Worsen HIT.
- Alopecia.
- Bluish discoloration of feet.
- Teratogenicity : Nasal hypoplasia (mid facial hypoplasia). Stippled epiphyseal calcification, as it blocks osteocalcin.

Contraindication : Pregnancy.
Exception : pregnant woman with mechanical valve on prophylaxis of thrombosis.

Coagulation monitoring :
PT/INR : Normal INR is 0.9 to 1.3.
Target on warfarin is 2 to 3.
If INR >3 to 10 : Stop warfarin & restart once INR is normal.
> 10 and asymptomatic : Stop warfarin and start oral Vitamin K.
Symptomatic (bleeding) : Stop warfarin.
Treatment of choice : 4-factor Prothrombin Complex Concentrate (PTC) > FFP + Intravenous Vit K.

Anticoagulant drugs

Oral	Parenteral
1. Oral DTI :	1. PE DTI :
Dabigatran.	Desirudin.
2. Oral Xa inhibitors :	Bivalirudin.
Apixaban.	Argatroban.
Rivaroxaban.	2. ITI :
Edoxaban.	UFH.
3. Warfarin.	LMWH.
	Fondaparinux.

Recent advances 01:13:26

Ciraparantag :

Behaves as an antidote for all anticoagulants except Warfarin.

Binds to DTI, oral Xa inhibitor, Fondaparinux, LMWH.

Fibrinolytics 01:15:21

Thrombolytics :

Plasminogen —(Tissue plasminogen activator (TPA))→ Plasmin

Plasmin : Breaks fibrin.

Streptokinase :

- MOA : Binds to plasminogen. Exposes TPA binding sites. Increases plasmin.
- Clot non specific drug : Breaks fibrin both in clot and plasma. High risk of bleeding.
- High dose requirement : Due to likely neutralization of streptokinase by anti-streptococcal antibodies in the body.

Recombinant TPA (given by IV route) :

- Alteplase.
- Duteplase.
- Reteplase

Active space

- Tenecteplase : most clot specific drug. Single dose. — most preferred drug

60c6b3eeaa8ded0e4e7e5ea7

These are clot specific drugs : Break fibrin in clot much more than plasma.

Uses :

- STEMI (never in NSTEMI/Unstable angina).
- Massive pulmonary embolism.
- Peripheral thrombosis (directly injected to the site).

Contraindications :

B : Brain tumour/aneurysm.
R : Recent surgery/trauma.
A : Aortic dissection.
I : Intracranial hemorrhage history.
N : NSTEMI (risk > benefit).

Side effect : Bleeding

↓

Treatment : Antifibrinolytics – inhibit plasmin.

↓

EACA (Epsilon Amino Caproic Acid) more risk of thrombosis.	Tranexamic acid : more potent. more preferred as it is less thrombogenic.

Uses :

Thrombolytics induced bleeding.
Prevent procedural bleeding in Hemophilia.

Other uses of tranexamic acid :

- GIT bleeding (ulcer bleed/variceal bleed).
- Trauma bleed.
- Surgical bleed.
- Menorrhagia.

Contraindications :

- Not used in upper genitourinary bleed (bleed from kidney or ureter) due to risk of thrombosis and ischemia.
- Hypotension.
- Myopathy.

BRONCHIAL ASTHMA

Bronchial asthma is a progressive disease that occurs due to histamine.

Allergen exposure → mast cell lysis → Release of histamine → Bronchoconstriction and inflammation.

Drugs to counter bronchoconstriction : Bronchodilators.

Drugs to counter inflammation : Steroids.

Bronchodilators

00:01:40

60c6b3eeaa8ded0e4e7e5ea7

- β_a agonists.
- Anticholinergics.
- Methylxanthines.

Methylxanthines :

Mechanism of action : Bronchodilation and anti-inflammatory effect.

Bronchodilation is due to :

- Blockage of phosphodiesterase 3 (PDE 3) > (PDE 4) phosphodiesterase 4 → Increase in cyclic AMP → Smooth muscle relaxation.
- Adenosine receptor antagonism.

Anti-inflammatory effect is due to :

- PDE 4 inhibition.
- Stimulation of histone deacetylase.
- Increase in IL-10.
- Induce apoptosis of neutrophils.

Roflumilast is a PDE 4 inhibitor approved for the treatment of COPD.

Steroids also stimulate histone deacetylase.

Methylxanthines increase the anti-inflammatory effect of steroids.

Oral drugs :

Theophylline (preferred) > Aminophylline for treatment of persistent bronchial asthma as an add on to Inhalational Corticosteroids.

IV drugs :

Aminophylline (preferred) > Theophylline for acute exacerbation of asthma.

Side effects :

Due to blockage of PDE 4 :

- GI upset : Nausea, vomiting.
- Headache.

  Seen at levels 20-25 mg/L.

Due to blockage of adenosine receptor (Gi subtype) in heart and brain :

- Arrhythmia (also due to blockage of PDE 3).
- Seizures.

  Seen at levels >30 mg/L.

Low therapeutic index :

Theophylline normal range is 5-15 mg/L. Toxicity is seen >20 mg/L.

Steroids

00:11:52

Most commonly used steroids are Inhalational Corticosteroids (ICS).

- Examples of ICS : Fluticasone, Mometasone, Budesonide, Ciclesonide, Beclomethasone, Flunisolide.
- Most potent ICS is Fluticasone.
- Least potent ICS is Flunisolide.
- Ciclesonide and Beclomethasone are known as soft steroids due to lesser systemic side effects. They are metabolized in the airway by esterase.
- Uses of ICS :

Drugs of choice for persistent bronchial asthma (≥ 2 attacks/week), exercise induced asthma, Aspirin induced asthma (Aspirin induces bronchoconstriction).

Can be used in intermittent bronchial asthma (< 2 attacks in a week).

Treatment of intermittent asthma :

- 0–5 years : Short acting beta agonist (SABA).
- 6–11 years : SABA + ICS (SABA should be inhaled first as it produces bronchodilation and also increases the entry of ICS into the bronchi).
- > 12 years : Fixed dose combination of ICS + Formoterol in a pressurized metered dose inhaler.

If SABA has to be taken twice, 2nd dose should be taken after 1 minute as it increases the effect of second dose.

Steroids decrease the severity & number of asthma exacerbation. Hence, they are indicated in intermittent asthma.

Side effects of ICS :

- Most common side effect is hoarseness of voice.
- Oropharyngeal candidiasis : Can be prevented by using spacer & rinsing mouth after every inspiration.
- Systemic side effects are minimal.

MDI with spacer

Systemic steroids 00:21:10

Can be given by oral or IV route.

Oral drugs : Prednisone or Prednisolone.

IV drugs : Hydrocortisone (preferred as it is faster acting), Methylprednisolone.

Uses :

Persistent asthma : Oral steroids are used if there is no or inadequate response to ICS.

Acute exacerbation of asthma : Oral steroids > IV steroids.

Mechanism of action of steroids in acute exacerbation :
Steroids decrease mucus secretion and production of inflammatory mediators.
They also increase the number of β_2 receptors thereby increasing the effect of β_2 agonists (β_2 agonists also increase steroid receptors and steroid effect).

Antileukotrienes

00:25:38

Zileuton : Inhibits lipoxygenase.
Montelukast, Zafirlukast, Pranlukast : Inhibit LTC_4/LTD_4.

Uses :

- Persistent bronchial asthma : Can be used as an add on
- Exercise induced asthma.
- Montelukast has been approved for the treatment of allergic rhinitis.

Side effects :

- Hepatotoxicity, most hepatotoxic is Zileuton.
- Montelukast and zafirlukast can cause Churg Strauss syndrome.

Mast cell stabilizers :
Mechanism of action :

- Block calcium channels in mast cells → Prevent degranulation → Decreased release of histamine.

Cromolyn sodium, Nedocromil :

- Oral : Used for the treatment of food allergy and systemic mastocytosis.
- Nasal Spray : Used in allergic rhinitis.
- Eye drops : Used in allergic conjunctivitis.
- Inhalational route : Used in mild asthma. Preferred in children as they are least toxic drugs in asthma.

Ketotifen :
Along with mast cell stabilization, it also blocks H1 receptor and increases release of nitric oxide.
Used for prophylaxis of allergen induced asthma.

Monoclonal antibodies

00:32:04

Omalizumab :

- Anti IgE monoclonal antibody.
- Route : Given by subcutaneous route every 2-4 weeks.
- Uses : Resistant asthma, allergic rhinitis, chronic urticaria, peanut allergy.
- Dose : Based upon weight of patient and IgE titer.
- Contraindication : Atopic dermatitis (due to high IgE titers).

IL-4 and IL-5 related monoclonal antibodies :

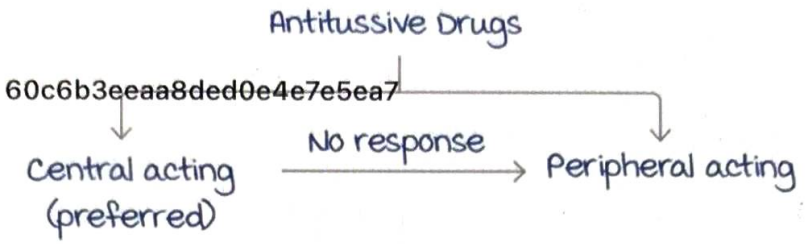
- IL-4 receptor is present on T helper cells.
  IL-4 binds to its receptor → release of IL-5 from T helper cells → IL-5 binds to IL-5 receptor on eosinophils → maturation and survival of eosinophils.
- Dupilumab : IL-4 receptor blocker.
- Reslizumab, Mepolizumab : Inhibits IL-5.
- Benralizumab : IL-5 receptor blocker.

Uses : Severe eosinophilic asthma.
Dupilumab has also been approved for the treatment of atopic dermatitis.

Anti asthmatic drugs

Bronchodilators	steroids	Anti leukotrienes	mast cell stabilizers	monoclonal antibodies
1. β_2 agonists	1. Inhalational	1. LOX inhibitor : Zileuton	1. Cromolyn sodium	1. Omalizumab
2. Anticholinergics	2. Oral	2. LTC_4/D_4 inhibitor : Montelukast, Zafirlukast, Pranlukast	2. Nedocromil	2. Dupilumab
3. Methylxanthines	3. IV			3. Reslizumab/ Mepolizumab
				4. Benralizumab

ANTITUSSIVE DRUGS



Central antitussive drugs

00:01:17

Used in dry cough.

Opioids :

- Codeine (Doc), Pholcodine, Ethylmorphine — mild to moderate cough
- Morphine, Methadone — Severe cough e.g. Bronchial cancer

Side effect : Constipation

(least with Ethylmorphine)

Maximum abuse potential.

Non opioids :

Dextromethorphan :

MOA : Blocks NMDA receptor.

Use : Mild cough.

OTC drug.

Side effects : Hallucinations, agitation, abuse potential.

Noscapine :

Use : Spasmodic cough.

Levopropoxyphene.

Used in mild cough.

Miscellaneous drugs :

Diphenhydramine :

MOA : H1 and muscarinic blocker.

Use : Mild cough.

Aprepitant :

MOA : Blocks NeuroKinin I.

Use : Severe cough.

Gabapentin/Pregabalin : Used in chronic idiopathic cough.

Peripheral antitussive drugs

00:07:23

Local anaesthetics : Block stretch receptors in the lungs.

- Lidocaine.
- Bupivacaine.
- Mexiletine.

Moguisteine : Opens K^+ channels in peripheral nerves in the lungs (cannot send action potential for cough reflex).
Cromolyn : Persistent depolarization of the peripheral nerves in the lungs.

Expectorants and mucolytics 00:09:41

Expectorants :
MOA : Gastric irritation → Reflex irritation of bronchi → gradual removal of secretion from respiratory tract.

- Guaifenesin (only FDA approved expectorant).
- Use : Antitussive effect (no role in COPD).
- Iodides.
- Hypertonic saline (non-FDA approved).

Mucolytics :
MOA : Breaks down mucus, liquifies it and facilitate removal.

- N-acetyl cysteine.
- Ethyl cysteine.
- Methyl cysteine.

} Have sulfhydral group which breaks disulphide bond in mucus.

- Carbocisteine.
- Erdosteine.
- Letosteine.
- Stepronine.

} Increase production of sialomucins which liquifies mucus.

- Bromhexine
- Ambroxol

} Depolymerise mucopolysaccharides. Mucus structure breaks down and liquifies.

- DNAse → Used in cystic fibrosis. To break thick secretions.

Components of productive cough syrup :
Guaifenesin (expectorant) + Salbutamol (bronchodilator) + Phenylephrine (nasal decongestant) + Ambroxol/Bromhexine (mucolytic).

Active space

PEPTIC ULCER DISEASE

Aim : Ulcer healing.

Treatment and classes of drugs :

- Decrease HCl secretion : Anti acid secretory agents.
- Cover the ulcer : Gastroprotective agents.
- Neutralize HCl : Antacids.

Most effective : Anti acid secretory agents.

Gastric acid secretion

00:04:16
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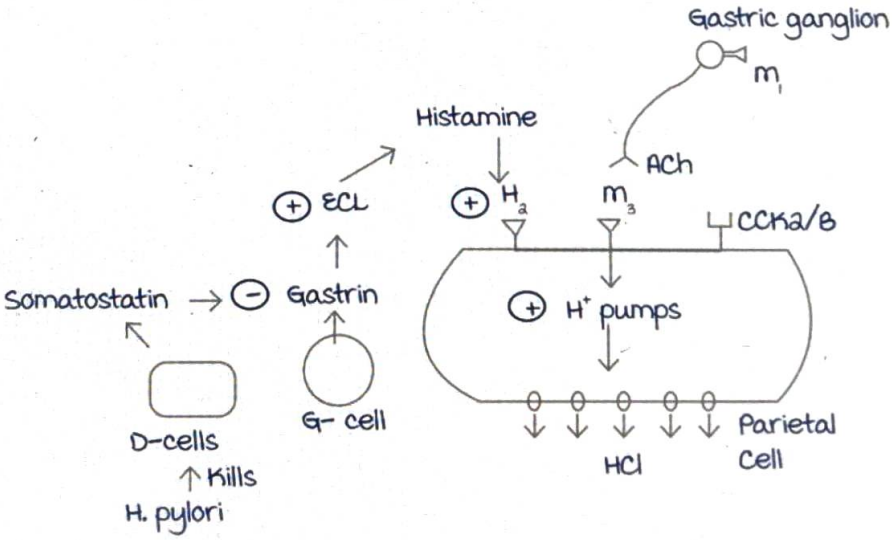
- Parietal cells have different types of receptors : CCK2/B, M_3 and H_2.
- Gastric neural ganglion (M_1 receptors) innervates parietal cells → Ach released stimulates M_3 receptors of parietal cells.
- G cell releases gastrin. Gastrin stimulates CCK 2/B receptors and enterochromaffin like cells which release histamine.
- Histamine stimulates H_2 receptors.



- Stimulation of CCK 2/B, M_3 and H_2 receptors activate proton pumps which secrete HCl.
- D cells release somatostatin that blocks gastrin.

Active space

H. pylori kills D cells → Leads to increased gastrin and histamine → Increased HCl secretion → Peptic ulcer.

Anti-acid secretory agents :

- M_1 receptor blockers : Pirenzepine, Telenzepine.
- CCK 2/B receptor blockers : Natezepide → Approved for treatment of gastrinoma. Not an anti acid secretory agent.
- H_2 receptor blockers : Cimetidine.
- Proton pump inhibitors.

Proton pump inhibitors (PPIs) 00:09:41

Drugs of choice for peptic ulcer disease.
Examples : Omeprazole, Rabeprazole, Lansoprazole, Esomeprazole, Dexlansoprazole, Pantoprazole.

Pharmacokinetics :

- Half life : 1.5 to 2 hours.
- Long acting drugs as they are irreversible inhibitors.
- Full effect is seen 3-5 days after administration. Effect stops 3-5 days after stopping the drug.
- Acid labile : Broken down by HCl. Maximum with Rabeprazole and minimum with Pantoprazole. Enteric coated capsules are used.
- Oral PPIs → Absorbed from small intestine into plasma → Secreted to parietal cells → PPI is activated by HCl (food intake is the stimulus for HCl secretion) in parietal cells.
- Oral PPIs are taken at least 30-60 minutes before food intake.

Omeprazole :

- Most potent enzyme inhibitor.
- Inhibits CYP_2D_6 → Blocks metabolism of antidepressants and antipsychotics (increased risk of toxicity). Also blocks activation of Tamoxifen (decreased effect).
- Drug interactions can occur.

- Can block activation of Clopidogrel decreasing its effect. Contraindicated with Clopidogrel.
- Omeprazole is a racemic mixture of R and S enantiomer. S enantiomer is known for slow elimination.
- Esomeprazole is derived from S enantiomers. It is longer acting than omeprazole.

Pantoprazole : Least potent enzyme inhibitor.

Rabeprazole : Longest and fastest acting PPI. It is the most potent PPI.

Uses of PPIs :

- Drugs of choice for peptic ulcer disease, stress ulcers, NSAIDs induced ulcers, gastroesophageal reflux disease, Zollinger Ellison syndrome & Barrett's esophagus (lifelong treatment is required).
- Can be used in acute gastric bleed (IV route).

Side effects of PPIs :

Decreased HCl :

- GIT upset : Diarrhoea/constipation, nausea/vomiting.
- Increased microbial growth in stomach : Increased risk of pneumonia & pseudomembranous enterocolitis.

Atrophic gastritis :

- Decreased absorption of calcium, magnesium, vitamin B_{12}, iron.
- Can cause osteoporosis due to hypocalcemia (hip fracture is characteristic).

Increases the levels of gastrin.

H2 receptor blockers

00:25:42

Cimetidine, Ranitidine, Nizatidine, Famotidine.

Cimetidine : Least potent and shortest acting H_a receptor blocker.

Famotidine : Most potent and longest acting H_a receptor blocker.

Uses :

- Similar to PPIs.
- Drugs of choice for prevention of post operative aspiration pneumonia (occurs due to basal acid secretion).

Side effects :

- Similar to PPIs.
- Can cause neurotoxicity : Agitation/hallucination. It is seen with IV route, elderly and more common with Cimetidine.
- Can cause cardiotoxicity : Bradycardia and hypotension. Seen with rapid IV infusion. Infusion should be given over 30 minutes to prevent cardiotoxicity.
- Cimetidine has antiandrogenic effect : Can cause gynecomastia and impotence in males. Can increase prolactin and cause galactorrhea in females.

Anticholinergics : M 1 receptor blockers : Pirenzepine and Telenzepine.

Gastroprotective agents 00:36:54

Misoprostol :

- Prostaglandin E1 analogue → Stimulates EP2 (Gs subtype), EP3 (Gi subtype), EP4 (Gs subtype) receptors.
- Stimulation of EP2 and EP4 receptors results in increased synthesis of mucin and bicarbonate.
- Stimulation of EP3 receptors decreases hydrochloric acid.

Uses :

QID dose 200 mcg for NSAID induced ulcer.

Most specific drug for NSAID induced ulcer : Misoprostol.

Drug of choice for NSAID induced ulcer is PPI.

Side effects : Severe abdominal cramps and diarrhoea.

Contraindication : Inflammatory bowel disease.

Sucralfate :

- Made up of octasulphate of sucrose and aluminum.
- Contraindicated in renal failure due to risk of aluminium toxicity (presents as osteoporosis and encephalopathy).
- Mechanism of action :
  Oral route → Polymerized by gastric HCl into thick viscous substance which covers the ulcer base.
  Contraindicated with antacids.
- Uses :
  Peptic ulcer disease, esophageal ulcer, prophylaxis of radiation proctitis.
- Side effects :
  Hypophosphatemia, gastric bezoars and constipation.
- Contraindications : (mnemonic : OKSANA)
  Other drugs (Sucralfate can be taken after 2 hours).
  Khana = Food (sucralfate can be taken after 1 hour of food intake).
  Sucralfate.
  Antacids (can be taken only after 30 minutes of sucralfate use).
  NA : No.

Bismuth compounds :

Bismuth subsalicylate and bismuth subcitrate.

Mechanism of action :

- Cover ulcer base.
- Induce synthesis of mucin and bicarbonate at the site of ulcer.
- Have anti bacterial effect.

Uses : Can be used in PUD, traveller's diarrhea and H. pylori.

Side effects :

- Common side effect is blackish discoloration of tongue and stool.
- Bismuth subsalicylate can cause Reye's syndrome.
  Contraindicated in children with fever.
- Bismuth subcitrate is neurotoxic.

Antacids

00:43:56

Salts of magnesium and aluminum (magnesium causes diarrhoea and aluminum causes constipation cancelling each other's effect).

Examples : Gelusil, Maalox, Riopan, Digene etc.,

Uses :

1. Peptic ulcer disease :
   - Primary aim is ulcer healing.
     Secondary aim is treatment of dyspepsia.
   - If complicated ulcer (bleeding) → To be taken every 30 minutes.
   - If uncomplicated ulcer → To be taken at 1st and 3rd hours after food.
2. GERD : Drug of choice in pregnancy and children.

Contraindicated with other drugs and renal failure (as they bind to other drugs due to presence of aluminium).

Add on to antacids :

Alginate : Absorbs water in stomach and floats above the food like a sponge.

Use : GERD.

Simethicone : Surfactant that decreases surface tension of gas bubbles in stomach. Gas bubbles rupture.

Eases passage of gas.

Use : Flatulence, GERD.

Peptic Ulcer Disease Drugs Summary

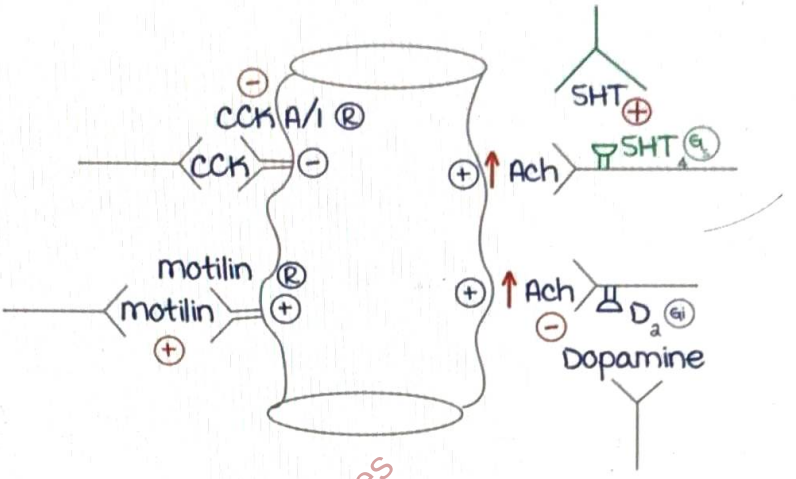
Anti-acid secretory agents	Gastroprotective Agents	Antacids
1. PPI	1. Sucralfate	
2. H_a blockers	2. Bismuth compounds	
3. Anticholinergics	3. Misoprostol	

PROKINETICS & ANTIEMETICS

Prokinetics

00:00:13

Drugs that increase the movement or contraction of gastro intestinal tract in the cranio-caudal direction.



Most important neurotransmitter responsible for contraction of GIT is Acetylcholine.
Further, serotonin and dopamine regulate acetylcholine release. Serotonin (5HT) increases the GI contraction through G_s receptors, while Dopamine decreases the contractions through Gi receptors. Therefore, $5HT_4$ agonist and D2 antagonist increase Acetylcholine.
Cholecystokinin (CCK) or gastrin acts on CCK A/1 receptors and inhibits contraction of GIT.
Motilin stimulates motilin receptors causing GI contraction.

$CCK_{A/1}$ inhibitors :
Dexloxiglumide
Motilin receptor stimulants :
Erythromycin
Mitemcinal
→ Use : Gastroparesis.

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Heteroreceptors : One receptor from a system is present on another system. Eg : serotonergic or dopaminergic receptors present on cholinergic system.

5HT4 agonists

00:05:06

Cisapride, Tegaserod — Banned
As they cause QT prolongation.

Mosapride, Prucalopride — Use : GERD (Gastro esophageal reflux disease).
Chronic constipation.

Side effect : Diarrhoea.

D2 blockers

00:06:30

Metoclopramide :

Mechanism of action :

At normal doses blocks D_2 receptors.

At high doses, stimulates $5HT_4$ and blocks $5HT_3$ and D_2.

$5HT_3$ and D_2 blocking provides prokinetic as well as antiemetic action.

D_2 block and $5HT_4$ stimulation provides prominent prokinetic effect.

Use :

- Chemotherapy induced nausea and vomiting.
- Gastroparesis.
- Paralytic ileus.
- Hiccups.
- Bowel cleaning.

Side effects :

Crosses BBB (Blood brain barrier) significantly.

Develops extrapyramidal symptoms : Acute dystonia (abnormal posturing).

Causes significant hyperprolactinemia.

Domperidone :

Only D_2 blocker.

Provides antiemetic and prokinetic properties.

Use :

- Antiemetic in mild to moderate cases.
- GERD

Active space

Cross BBB but very less, thus insignificant EPS.
Hyperprolactinemia is less significant and therefore, can be used for prolactin stimulation.

Anti-emetics

00:11:34

$5HT_3$ antagonists :

Ondansetron (can be given i.m.) : shortest acting.
Palonosetron : longest acting, most potent.
Dolosetron
Toposetron
Granisetron

All these drugs can be given by oral route.

Uses :

- Very potent antiemetic.
- Drug of choice for early onset chemo induced nausea and vomiting : Ondansetron
- For late onset : Palonosetron
- Drug of choice for post operative and post radiotherapy nausea and vomiting.
- Morning sickness (not effective in motion sickness).

Side effects :

- Constipation/ diarrhoea.
- Headache.
- QT prolongation (maximum with Dolosetron, minimum with Palonosetron).
- Hypotension.

Contraindication :

In treatment of Apomorphine induced nausea and vomiting as increases risk of hypotension.

Neurokinin 1 inhibitors :

Aprepitant : given oral, intravenously.
Fosaprepitant : given only intravenously.
Netupitant
Rolapitant

These are long acting, so drug of choice for late onset chemotherapy induced nausea and vomiting.
Aprepitant can be used for treatment of severe cough.

Cannabinoid receptor agonist :

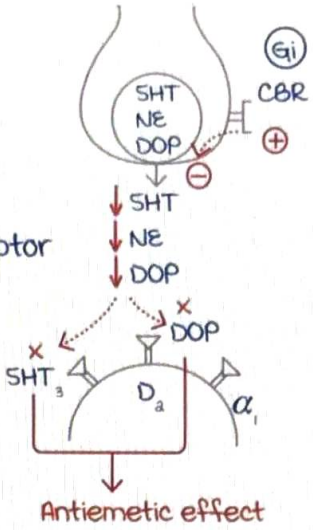
Dronabinol

Nabilone

Cannabinoid receptor : Gi subtype presynaptic receptor

Cannabinoid receptor agonists stimulate this receptor & decrease the release of SHT, dopamine, norepinephrine.

Provides antiemetic action : No effect on SHT_3 and D_2 receptors.



Side effects : Due to no effect on α_1 receptor :

Hypotension (so monitor BP)

Blood shot eyes (eye congestion).

D_2 blockers :

Metoclopramide

Domperidone

Antipsychotics :

Levosulpiride : Used in post op nausea & vomitng, Gastroparesis

Olanzapine : Chemotherapy induced nausea & vomitng

Anticholinergics :

Scopolamine : Drug of choice in motion sickness. Used as transdermal patch : 4 to 5 hrs before travel.

Antihistaminics :

Doxylamine : morning sickness.

Diphenhydramine
Dimenhydrinate
Promethazine
Cyclizine/meclizine
} motion sickness

Dexamethasone : Chemotherapy induced nausea & vomiting (as an add on)

LAXATIVES /PURGATIVES & ANTI DIARRHEAL DRUGS

Laxatives ease passage of formed stools. Used in treatment of constipation. At high doses, laxatives can behave as purgatives.
Purgatives ease passage of formed and preformed stools. Used for bowel cleaning before any procedure or surgery.

Probiotics & Prebiotics

00:02:00

Probiotics :
Beneficial microorganisms for our intestine. Eg : Lactobacillus, B. clausii, saccharomyces.
Uses :

- Constipation : Bulk of stool is formed by microbes. These drugs will increase stool formation, causing stretching and contraction of large intestine, thereby enabling passage of stools.
- Antibiotic associated diarrhea.

Prebiotics :
Dietary fibers : Feed for the micro organisms.
E.g : Psyllium husk, Bran, methyl cellulose.
Used in constipation.

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Symbiotics : Probiotics + Prebiotics.

Stimulant laxatives : Bisacodyl, senna, cascara.
Mechanism of action (MOA) : Promote low grade inflammation in intestine.
↓
Irritation of nerve endings
↓
Contraction of intestine
Effect is seen after 6-8 hours. Hence to be taken at night.

Side effects :

- Atonic colon : Continuous stretching and contraction of bowel can lead to atonicity, hence should not be used for more than 10 days.
- Bisacodyl : Hypokalemia.
- Senna, Cascara : Melanosis coli (black pigmentation of intestinal mucosa).

Contraindication : Intestinal obstruction (can cause rupture of intestine).

Castor oil :

MOA : metabolized into ricenolenic acid, which is a stimulant.

Osmotic laxatives

00:09:25

Saline laxatives : Salts of Magnesium/Sodium.

Eg : Sodium phosphate, magnesium hydroxide, magnesium citrate.

Uses : Bowel cleaning before surgery or procedure.

Contraindications :

- Magnesium salts are contraindicated in renal failure due to risk of Mg toxicity.
- Sodium salts are contraindicated in CHF as sodium retention can cause edema and worsening of CHF.

Non-digestible sugars : Lactulose, Mannitol, Sorbitol, Lactitol.

MOA : metabolized into saturated fatty acid → Draws water into gut. Costly, hence used as 2nd line drug.

Side effects : Flatulence as bacteria feed on the drug and generates huge amount of gas.

Lactulose : Makes the intestine pH acidic → Converts ammonia to polar ammonium ion (water soluble ion) → Excreted out easily.

Hence used in hepatic encephalopathy.

Polyethylene Glycol (PEG) : DOC for IBS associated with constipation.

Stool softening agents :

Surfactants :

Docusate sodium, Docusate calcium.

MOA : Decrease surface tension of the stool, causing stool to collapse and move out easily.

Mineral oil : Rarely used as accidental aspiration can cause aspiration pneumonitis.

Tenapanor

00:15:18

MOA : Blocker of sodium-proton exchanger.

Use : Treatment of IBS with constipation.

Chloride secreting agents :

MOA : Increases Cl^- ions in intestine which pulls water into lumen.

Lubiprostone :

MOA : Stimulate Type-II Cl^- channels present in intestinal epithelial cells which increases excretion of water and chloride.

Linaclotide/Plecanatide :

MOA : Stimulate guanylate cyclase

↓

increases cyclic GMP

↓

Stimulate CFTR (Cystic Fibrosis Transmembrane Regulator)

↓

Increases secretion of Cl^- and water

Uses : IBS with constipation.

Anti-diarrhoeal drugs

00:18:40

Opioids :

- Loperamide (DOC).
- Diphenoxylate.
- Difenoxin.

} Used in IBS associated with diarrhea : Non secretory diarrhea

Eluxadoline :

MOA : Agonists (μ and κ), antagonist (δ opioid receptor)

Used for IBS with diarrhea.

Bile acid binding resins :

- Cholesteramine
- Colesevelam
- Colestipol

Uses : Biliary diarrhoea.

SHT_3 Antagonist :

Alosetron → Used in IBS associated with diarrhoea in females.

Side effects : Ischemic colitis.

Octreotide :

MOA : Decrease secretion of gastrin and Vaso-intestinal peptide (VIP) which in turn decreases both GIT contraction and secretion.

Uses :

- DOC in secretory diarrhea in HIV, DM, chemotherapy.
- Pancreatitis.
- Dumping syndrome (short bowel syndrome).

Racecadotril : MOA : Inhibit enkephalinase → Increase enkephalin (endogenous opioid).

Uses : Acute diarrhoea in children.

Crofelemer :

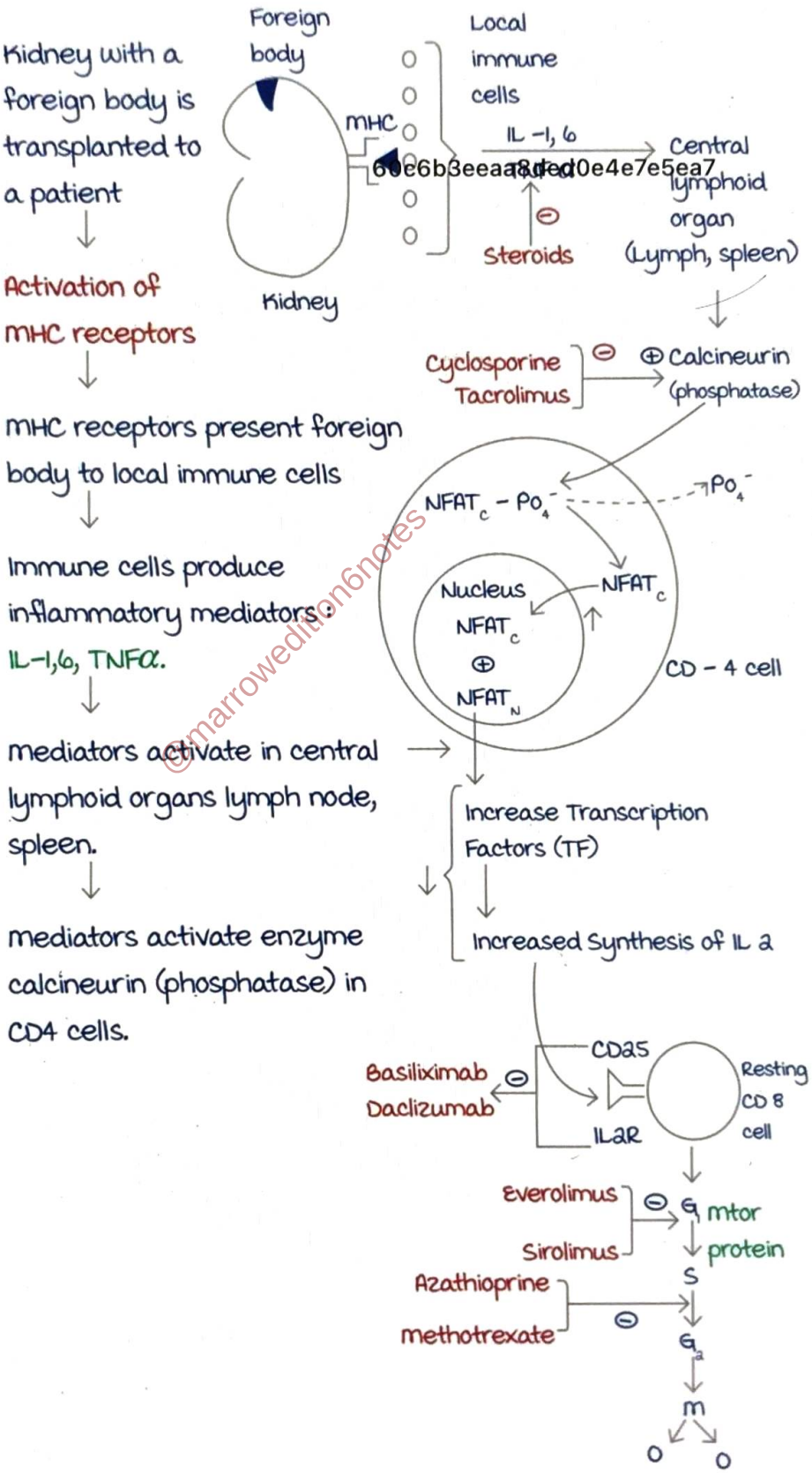
MOA : Inhibit CFTR → Decrease Cl^- and water.

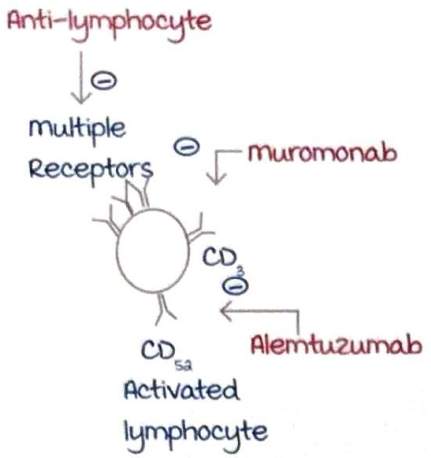
Used for HIV associated diarrhoea.

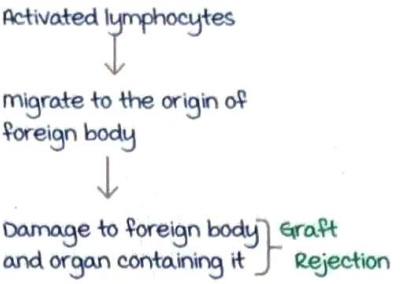
IMMUNOMODULATORS

Graft rejection

00:00:44







Blockers of graft rejection

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1. Steroids :
   Blocks production of inflammatory mediators by local immune cells.
   Induce apoptosis of activated lymphocytes.
2. Cyclosporins, tacrolimus : blocks calcineurin
3. Basiliximab, Daclizumab : blocks CD 25, IL-2 receptor
4. Everolimus, sirolimus : Blocks mTOR for protein.
5. Azathioprine, methotrexate : Blocks S-phase in cell cycle
6. Muromonab : Blocks CD3.
7. Alemtuzumab : Blocks CD 52.
8. Anti lymphocyte, anti thymocyte : Blocks multiple receptors.

Graft vs Host disease (GVHD) → Treatment, Prophylaxis → All drugs

Graft rejection → Prophylaxis – all drugs
Treatment : Drugs which act on activated lymphocytes

Calcineurin inhibitors

00:12:29

MOA : Decrease transcription of IL – 2.

Use : 1st line – GVHD, Graft rejection : Cyclosporine
No response ↓
Tacrolimus (rescue therapy)

Cyclosporine, Tacrolimus → used topically in Skin disorders
Eg : lichen planus, atopic dermatitis

Cyclosporine
Drug of choice in :

- Steroid resistant Nephrotic syndrome & Ulcerative colitis.
- Myasthenia gravis.
- Rheumatoid arthritis.
- Bechet's disease.

Side effects : Tacrolimus is more toxic than cyclosporine.
Tacrolimus and Cyclosporine :

- Nephrotoxicity
- HyperKalemia
- Hepatotoxicity
- Neurotoxicity
- Hyperglycaemia

Cyclosporine : Hirsutism.
Hyperplasia of gums.
Hyperlipidemia.
Hyperuricemia.

mTOR inhibitors

00:17:49

MOA : Blocking G1-S phase of CD 8 cell proliferation.
In other cells as anti cancer effect.

1. MC used Drug : Sirolimus (Rapamycin)
   Use : GVHD.
   Graft rejection. → Along with Cyclosporine or Tacrolimus
   Cardiac stent coating.
   Uveoretinitis : Along with Cyclosporine.
   Temsirolimus : In Renal cell carcinoma.

Everolimus is used in :

- Renal cell carcinoma.
- Renal angiomyolipoma (Tuberous sclerosis).

- Pancreatic cancer.
- ER (+) breast cancer.
- Astrocytoma.

Side effects : (mnemonic : lymphocytes HATE mTOR)

Lymphocele.

Hemolytic uremic syndrome, hypokalemia.

myelosuppression.

Thrombocytopenia.

Oral ulcers.

Raised lipids (hyperlipidemia).

IL 2 receptor blocker/ CD 25 blocker 00:21:22

Daclizumab : used in multiple sclerosis only now.

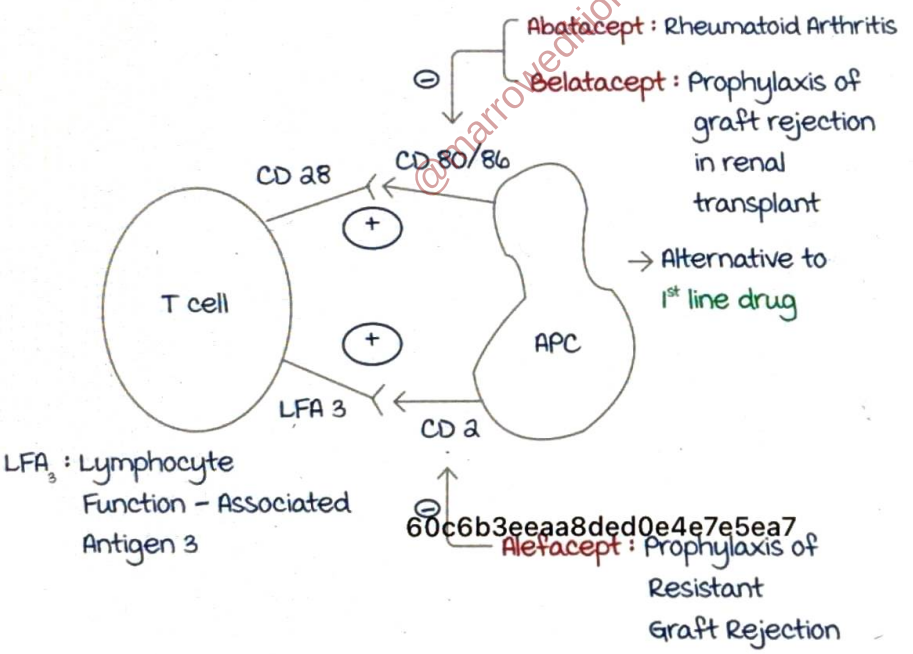
Basiliximab : used for prophylaxis of acute graft rejection.

Muromonab : MOA : CD_3 blockade.

used for treatment of acute graft rejection.

Side effect : Cytokine release syndrome (fever & chills).

T- cell activation inhibitors :



Alemtuzumab :

Anti CD_{52} monoclonal antibodies.

Uses : Graft rejection.

multiple sclerosis.

Azathioprine and Mycophenolate mofetil 00:26:55

Prodrug of 6 mercaptopurine.

MOA : Blocks S-phase.

Uses :

- Graft rejection prophylaxis.
- Rheumatoid arthritis.
- Ulcerative colitis.
- Multiple sclerosis.

Side effects : Bone marrow suppression and hepatotoxicity.

Pharmacokinetics :

Azathioprine ⇄ 6 mercaptopurine — metabolised by thiopurine methyl transferase

↓

Decreased production of this enzyme causes increased toxicity of drug.

mycophenolate mofetil (MMF) :

MOA : Blocks IMP dehydrogenase and blocks de-novo purine synthesis (only pathway in lymphocytes. If blocked, leads to selective toxicity of lymphocytes).

Uses :

- 1st line drug in Cardiac transplant & Bone marrow transplant.
- 2nd line in other transplants.
- Rheumatoid arthritis.
- Myasthenia gravis.
- Inflammtory bowel disease.

Side effects : GIT upset + bone marrow suppression.

Contraindicated with azathioprine (same MOA).

IL-1 blocker and Thalidomide 00:31:59

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IL-1 blocker :

Drug : Anakinra.

Uses :

- Rheumatoid arthritis.
- DOC : Cryopyrin associated periodic syndrome (CAPS).
- Treatment of idiopathic juvenile arthritis (Stills disease).

Canakinumab : Also used in CAPS and Stills disease.

Rilonacept : Acute gout.

Thalidomide : Introduced as a sedative/ hypnotic.

Use : morning sickness.

Side effects : Phocomelia (limb deformities).

Re-introduced due to :

- Anti-inflammatory effects.
- Immunomodulatory effects.
- Anti-neoplastic effects.
- Anti-angiogenic effects.

Uses : (Mnemonic : CATCH PROGRAMMES)

CML.

Pancreatic cancer.

Rheumatoid arthritis.

Oro-ocular genital syndrome.

Graft versus host disease.

AIDS related aphthous ulcer.

Multiple myeloma.

Malignant melanoma.

Erythema nodosum leprosum (best).

Sarcoidosis.

Side effects : (Mnemonic : SPORT Channel)

Sedation.

Peripheral neuropathy, phocomelia.

Ocular side effect.

Rash.

Thrombosis.

Constipation.

ANTI-CANCER DRUGS : INTRODUCTION

Neoplasia : Abnormal & rapid proliferation of cells.

Cell cycle : G1 → S → G2 → M

Classification of Anti-cancer drugs 00:04:41

- Non-cell cycle Specific drugs
  - Alkylating agents
  - Platinum compounds
  - Anti tumour antibiotics
- Cell cycle Specific drugs
  - S phase inhibitors
    - S-Phase inhibitors
      - Anti metabolites
        - a) Antifolate
        - b) Pyrimidine analogs
        - c) Purine analogs
      - Topoisomerase inhibitors
      - Hydroxyurea
      - Histone deacetylase inhibitors
  - M Phase Inhibitors
    - M-Phase inhibitors
      - Vinca alkaloids
      - Taxanes
      - Epothilones
      - Eribulin
      - Estramustine

Common Side-effects 00:10:12

Because they block replication of rapidly dividing normal cells.

- Bone marrow suppression :
  MC dose limiting toxicity of anti cancer drugs.
  Maximum with Alkylating agents > Antifolate drugs.
  Not seen with Cisplatin, Vincristine & Bleomycin.
- Hair follicles : Alopecia.

- Germ cell :
  Oligospermia, Anovulation] Infertility
- GIT mucosa cells : mucositis, diarrhoea.
- Enterochromaffin cells lysis → Release Serotonin & Substance- P → Stimulates SHT3 & NeuroKinin 1 → Nausea and vomiting (mc side effect).
  Maximum with Cisplatin.

Prevention of nausea and vomiting :

Antiemetics :

- SHT_3 blockers : Ondansetron, Palonosetron.
  Ondansetron : Short acting → DOC for early onset nausea & vomiting.
  Palonosetron] Long acting, DOC for late onset nausea & vomiting.
- NK 1 blocker : Aprepitant]
  Overall DOC → Ondansetron.
- Dexamethasone
- D2 receptor blockers :
  metoclopramide
  Anti-psychotics :
  1. Typical : Prochlorperazine.
  2. Atypical : Olanzapine.
- Cannabinoid receptor agonists (Gi subtype receptor) :
  Dronabinol, Nabilone] No SHT & Dopamine action on SHT3 & D2: Anti emetic.
  S/E : Hypotension (no NE action on α1 → vasodilation).
  Bloodshot eyes (Corneal & Conjunctival congestion).

Regimen for chemotherapy-induced nausea & vomiting :

Severe	moderate	Mild
Ondansetron	Ondansetron	Ondansetron or Dexamethasone
Dexamethasone	Dexamethasone	
Aprepitant	Aprepitant	
Olanzapine		

Non-cell cycle specific drugs 00:22:54

Alkylating agents :

MOA :

Alkyl group of drugs is devoid of H atom.

It binds to the free hydrogen present at N7 of Guanine → abnormal Guanine – thymidine pairing → abnormal DNA → at functional cell cycle check gate : Undergoes apopotosis i.e they are cytotoxic.

If check point is non-functional, secondary cancers develop.

MC : AML (4 years to develop).

MC complication is with Melphalan.

Least common is with Cyclophosphamide.

Classification of alkylating agents 00:26:38

Nitrogen mustards	Nitrosoureas	Agents acting by DNA methylation	Miscellaneous
Cyclophosphamide : Neoplastic uses : • Pediatric solid tumor : Wilm's tumor, Neuroblastoma. • Breast cancer, Ovarian cancer. • NHL, CLL. Non-neoplastic uses : • DOC : Wegener's granulomatosis. • DOC : Steroid dependent nephrotic syndrome. • Rheumatoid arthritis. • IBD. Ifosfamide : Used in Osteosarcoma & Testicular cancer.	Carmustine Lomustine Semustine • High lipid solubility → Cross BBB. • Used in Brain tumor. • S/E : Sustained neutropenia. Streptozocin : Uses : • Pancreatic β islet cell cancer. • Malignant carcinoid tumor.	Dacarbazine Procarbazine Use : Hodgkin's disease. S/E : Procarbazine : • Disulfiram-like reaction. • Weak MAO inhibitor → Cheese reaction, serotonin syndrome. Temozolomide : DOC : Brain tumor.	Busulfan : Use in CML. S/E : Pulmonary fibrosis. Thiotepa Trabectedin Altretamine Used in the Rx of Drug resistant ovarian cancer.

S/E : Ifosfamide > Cyclophosphamide. Ifosfamide produces more toxic metabolites like • Chloroacetyldehyde : • Neurotoxicity : SIADH, seizure, coma. • Acrolein : Haemorrhagic cystitis. Prevented by Mesna (Oral/IV). Dose : 60% dose of Ifosfamide/ Cyclophosphamide. Mechlorethamine : • Used for Rx of Hodgkin's disease (Old regimen) MOPP : Mechlorethamine, Oncovin, Prednisolone, Procarbazine. • New regimen : ABVD : Adriamycin, Bleomycin, Vinblastine, Dacarbazine. S/E : Vesication. Can also be seen with Doxorubicin. Prevention by rapid IV infusion. Melphalan : Use : Multiple myeloma. Chlorambucil : Use : CLL.			

PLATINUM COMPOUNDS

Mechanism of action 00:00:28

Free e^- of platinum compounds

↓

Bind to free e^- at N 7 of guanine and forms covalent bonds

↓

Abnormal DNA formation

↓

Cytotoxicity

Secondary cancers

mc : AML, develops around 4 yrs

Types

Bivalent compounds (2 free e^-)

Cisplatin

Carboplatin

Quadrivalent compounds (4 free e^-)

Oxaliplatin

Cisplatin 00:02:58

most wide spectrum anticancer drug overall.

Uses of Cisplatin :

Cisplatin has most wide spectrum amongst anti-cancer drugs.

1. DOC : Head and neck CA (oral cancer)
   Esophageal CA
   Gastric CA
   ] DOC : Cisplatin
2. Colorectal CA : 5 FU + Folinic acid + Oxaliplatin or Irinotecan.
3. Anal CA : 5 FU + topical Mitomycin C.

Regimens :

Fofox.

Folfiri.

Folfirinox.

4. DOC in urogenital CA : Cisplatin

Bladder CA	Ovary CA	Cervical CA	Testicular CA
Gemcitabine	Taxanes	–	Bleomycin Etoposide Platinum compounds

5. DOC for Osteosarcoma : Cisplatin
6. DOC in lung carcinoma (cisplatin + etoposide)

Non small cell CA — Small cell CA

Vinorelbine +

Squamous CA: Gemcitabine

Non-squamous CA: Pemetrexed

Side effects of cisplatin 00:15:02

Maximum nausea and vomiting. DOC : Ondansetron.
Ototoxicity.
Peripheral neuropathy : Coasting effect.
(Worsening of symptoms after stopping cisplatin).
Raynaud's phenomenon.
Nephrotoxicity.

Prevention :

1. Preload with 1 -2 L of NaCl,
   Cl^- diuresis : Cl^- inactivates cisplatin.
2. Diuresis causes washout of inactivated cisplatin.
   Mannitol : Forced diuresis of inactivated cisplatin.
3. Amifostine : Radioprotective as free radical scavanger.

Carboplatin and oxaliplatin 00:19:08

Carboplatin :
Uses : Similar to cisplatin.
Side effects : Bone marrow suppression (dose limiting toxicity)

Oxaliplatin :
Blocks Thymidylate synthase.
Used along with 5-FU in colorectal CA.
Side effect : Peripheral neuropathy (dose limiting toxicity).

Active space

ANTI TUMOR ANTIBIOTICS

Bleomycin 00:00:32

MOA :

- Inhibits Topoisomerase II : Blocks S phase
- Free radical induced DNA damage : Blocks G_2 phase.

Uses :

- AML.
- Hodgkin's disease (Regimen ABVD).
- Testicular Cancer (Regimen BEP).

Pharmacokinetics : metabolised by Bleomycin hydrolase.

Deficient in Lungs : Type I pneumocyte damage leading to pulmonary fibrosis.

Skin : Flagellate dermatitis (Longitudinal treaks of hyperpigmentation on back).

Actinomycin-D/Dactinomycin 00:05:04

MOA : Binds to DNA → Drug – DNA complex formed → blocks RNA polymerase in the tumor cell.

Uses :

- Choriocarcinoma.
- Wilm's tumor.

Side effects :

Radiation recall syndrome : Chemotherapy triggers inflammatory reaction to previously irradiated areas.

Seen with Dactinomycin, Doxorubicin, Daunorubicin (3D's).

Mitomycin-C 00:08:29

MOA : Inhibits Topoisomerase II & alkylates DNA.

Uses :

- Topical : Anal Cancer.
  Bladder Cancer (Intravesicular).
- Prevents laryngotracheal stenosis (prevents fibroblast proliferation).

- Prevents synechiae formation post nasal surgery.

S/E : Hemolytic Uremic Syndrome
(Seen also with Gemcitabine).

Anthracycline group 00:11:42

MOA :

- Inhibits Topoisomerase II : Blocks S phase.
- Free radical : Blocks G2 phase.
  Depends on iron.
  S/E : Cardiotoxicity.
  Prevention : Dexrazoxane
  (Iron chelating agent)

Drugs :

- Daunorubicin (or) } In AML along with Cytarabine (TOC).
- Idarubicin
- Doxorubicin : Osteosarcoma, Hodgkin's disease.
  DOC in Kaposi sarcoma.
- Epirubicin : Breast cancer.
- Valrubicin : Bladder cancer.
- Mitoxantrone : AML, MS.

S/E :

Cardiotoxicity :
Maximum : Doxorubicin & Daunorubicin (red discoloration of urine).
Minimum : Mitoxantrone.

Acute toxicity :
Pericarditis/myocarditis syndrome which presents as arrhythmia.

Chronic toxicity : Dilated cardiomyopathy which presents as CHF.
HPE of myocardial cells : Vacuolar myofibril degeneration.

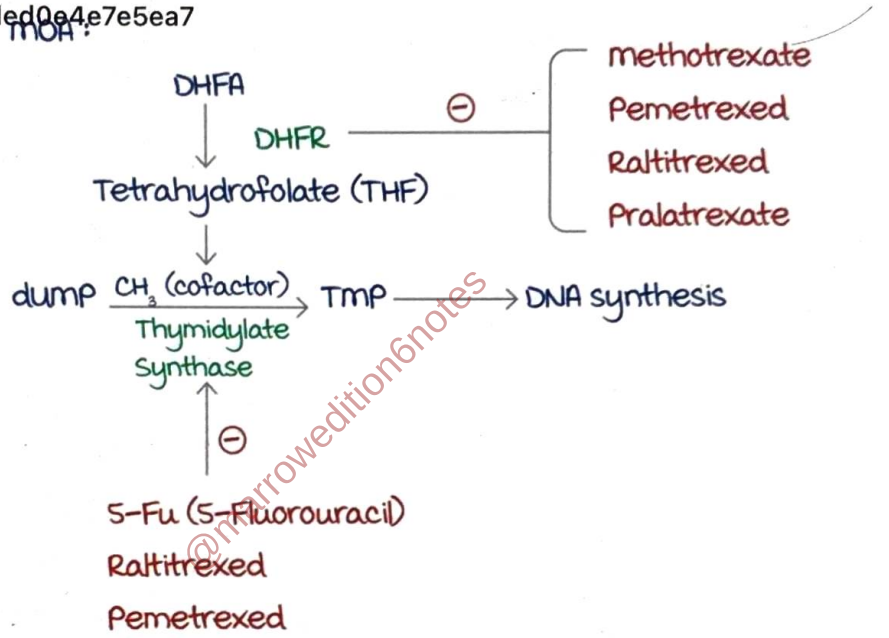
CELL CYCLE SPECIFIC DRUGS

S phase blockers 00:00:23

1. Anti-metabolites
   - A. Antifolate drugs
   - B. Pyrimidine analogue
   - C. Purine analogue

Antifolate drugs 00:01:30

MOA:



Folinic acid : Binds to 5-FU and Thymidylate synthase and forms a tertiary complex (increase sensitivity of 5-FU).

5-FU & Raltitrexed : Used in GIT cancer (block thymidylate synthase)

Decreased THF

Bone marrow Suppression

1. Methotrexate :
   Block purine synthesis.
   Bone marrow suppression
   Prevention : Folinic acid (Leucovorin) > Folic acid.

Block purine synthesis

Toxicity to lymphocytes (anti inflammatory effect)

2. Pemetrexed :

Blocks both purine and pyrimidine synthesis.

Bone marrow suppression (more than methotrexate).

Prevention : Folinic acid (Leucovorin) > Folic acid

+ Inj Vit B_{12}

mechanism of resistance :

DHFR

- Enzyme induction (< 24 hrs : Acute)
- Gene mutation/Amplification (>24 hrs : Chronic)

- Decreased receptor on cell : Decreaseed entry of drug.
- Decreased enzyme : Decreased activation of drugs
- Increased drug efflux.

Methotrexate 00:16:19

Uses of methotrexate :

Neoplastic

- DOC : Choriocarcinoma
  Carcinomatous meningitis (intrathecal)
- CNS leukemia (intrathecal route)
- Osteosarcoma

Other drugs for Osteosarcoma :

1. Ifosfamide.
2. Cisplatin.
3. Doxorubicin.
4. methotrexate (high dose).

TOC : Combination of any 2 drugs.

Non-neoplastic

DOC : Rheumatoid arthritis
Psoriatic arthritis.
GVHD.
Ectopic pregnancy.
Wegener's granulomatosis.

Side effects of methotrexate :

Bone marrow suppression.

Hepatotoxicity (liver cirrhosis) : In rheumatoid arthritis and psoriatic arthritis.

Nephrotoxic : Crystalluria (prevented by urine alkalization by bicarbonate).

Contraindicated in renal failure. But can be used with Glucarpidase (it metabolizes methotrexate into a metabolite which is excreted by liver).

Intrathecal route side effects : meningismus.
Arachnoiditis.
Seizure.

Pemetrexed, Pralatrexate, Raltitrexed 00:24:16

Pemetrexed :

Uses : mesothelioma.
Lung cancer (non small cell).

Side effects : Bone marrow suppression.

Pralatrexate :

Use : Peripheral T cell lymphoma.

Raltitrexed :

Use : mesothelioma.
GIT cancer (blocks Thymidylate synthase).

Pyrimidine analogues 00:26:24

- 5-FU :
  It is a Prodrug that is activated to f dUMP and inhibits Thymidylate synthase
  Combined with folinic acid to increase sensitivity.
  Route : IV.
  Use : GIT cancer.
  DOC in lower GIT cancer (colorectal ca, anal ca).
  Add on drug in upper GIT cancer (esophageal cancer and gastric cancer).
  Resistant pancreatic cancer.

- Capecitabine :
  Oral prodrug of 5-FU.
  Uses : Similar to 5-FU and used in breast cancer.
  S/E : more than 5-FU.
  Hand and foot syndrome : Desquamation of hand and foot. Prevention by Vit B_6 (Pyridoxine).

- Cytarabine (Ara-C):
  Very short half life.
  Route: Continuous IV infusion.
  Use: AML (TOC: Idarubicin/Daunorubicin + Ara-C)
  High grade lymphoma.
  Histiocytosis:
  Cytarabine.
  Vinblastin (DOC) + prednisolone.
  Clodribine (in resistant cases).
  S/E: Non cardiogenic pulmonary edema.
  CNS: Cerebral toxicity (seizure, dementia).
  Cerebellar toxicity (ataxia, dysarthria).

- Gemcitabine:
  DOC in pancreatic cancer.
  Add on drug in Bladder cancer and Non small cell cancer of lungs.
  S/E: HUS.
  Interstitial pneumonitis.
  Posterior leukoencephalopathy syndrome.

- Azacytidine and Decitabine:
  MOA: Demethylation of DNA.
  DOC for myelodysplasia.
  Exception: Myelodysplasia with 5q syndrome (anemia)
  Lenalidomide is preferred.

Purine analogues 00:39:10

6 mercaptopurine (6-MP).
6 Thioguanine.

MOA: Interfere with De Novo purine synthesis.
Lymphocytes have only De Novo pathway.
All other cells have both De Novo and salvage pathway.

Use: Leukemia.

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S/E:

- Tumor lysis syndrome(DOC of prevention: Allopurinol).
  6 MP is metabolized by Xanthine oxidase. If

allopurinol (xanthine oxidase inhibitor) is used concurrently, the dose of 6 MP should be reduced by 75%.

- Hepatotoxicity.
- Bone marrow suppression.

Fludarabine :

DOC in CLL : TOC → F : Fludarabine
C : Cyclophosphamide
R : Rituximab

S/E : Pulmonary toxicity.

Pentostatin :

MOA : Inhibit adenosine deaminase.
Use : HCL (Hairy cell Leukemia).
S/E : Pulmonary toxicity.

Cladribine :

DOC for HCL and refractory histiocytosis.

Clofarabine and Nelarabine :

Use : Resistant ALL.

Topoisomerase inhibitor

00:46:12

Topoisomerase removes the torsional stress in DNA strands and helps in unwinding and rewinding of DNA multiple times.

Topoisomerase I inhibitor :

- Irinotecan : Used for colorectal & pancreatic cancer.
  S/E : Delayed diarrhea (DOC is Loperamide).
- Topotecan :
  Use : Ovarian cancer.
  S/E : Neutropenia.

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Topoisomerase II inhibitor :

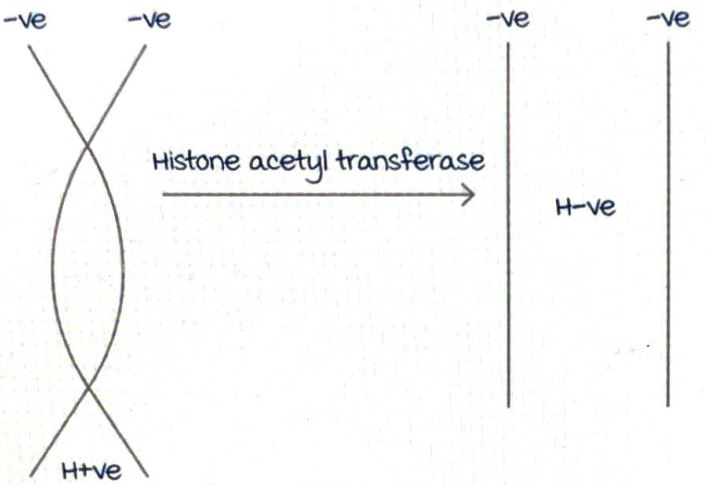
- Etoposide :
  Use : Testicular cancer
  Lung cancer.
  Prostate cancer.
  S/E : Bone marrow suppression.

- Teniposide :

  Use : Resistant ALL (synergistic with Clofarabine)

Histone deacetylase inhibitor :

MOA : Inhibit histone deacetylase → Inhibit DNA rewinding



H Histone (binds DNA strands) Unwound DNA strands

Vornistat
Romidepsin } Cutaneous T cell lymphoma.
Belinostat

Panobinostat : multiple myeloma.

S/E : QT prolongation.

Hydroxyurea :

MOA : Block RNR (Ribonucleotide diphosphate reductase)

↓

Prevent conversion of ribonucleotides to deoxyribonucleotides.

↓

Inhibit DNA synthesis

Uses :

DOC for sickle cell anemia.

(MOA : ↑ HbF → high solubility → ↓ sickling)

DOC for Polycythemia Vera : (newer drug : Anagrelide)

DOC for essential thrombocytemia.

CML.

S/E : Painful leg ulcer, Skin and nail pigmentation.

Active space

M phase inhibitors

00:58:22

Microtubules help in axonal transport & phagocytosis.

Inhibition of these functions leads to S/E as Neurotoxicity.

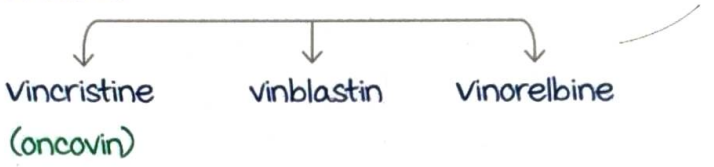
MOA :

Vinca alkaloids : Block beta tubulin → Reduce polymerization of microtubules.

Taxanes : Stimulate beta tubulin → Increase polymerization of microtubules → Prevent depolymerization.

Epothilones : Stabilize microtubules.

1. Vinca alkaloids :



S/E : SIADH, Peripheral Neuropathy.

	Vincristine	Vinblastine	Vinorelbine
Side effects	maximum	medium	minimum
BM ↓	not seen	seen	seen

Uses of Vinblastin :

Testicular cancer.

Hodgkin's disease.

DOC for Histiocytosis.

Uses of Vinorelbine : Non small cell cancer of lungs.

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Uses of Vincristine :

Pediatric solid tumors : Neuroblastoma, Wilms tumor.

Pediatric ALL : Regimen VPAD : Vincristine.
Prednisolone.
Asparaginase.
Daunorubicin.

Malignant pheochromocytoma → Vincristine.
(Regimen VCD) Cyclophosphamide.
Dacarbazine.

Retinoblastoma → Vincristine.
(Regimen VEC) Etoposide.
Carboplatin.

Non-Hodgkin lymphoma

a. Low grade : Fludarabine
(Regimen FCR Same as CLL) Cyclophosphamide
Rituximab

b. High grade : Cyclophosphamide
(Regimen CHOPR) Hydroxydaunorubicin
Oncovin
Prednisolone, Rituximab.

2. Taxanes :

Use : GIT cancer.
Breast cancer and ovary cancer, prostate cancer.
Head & neck cancer.

Paclitaxel :

High lipid solubility.
Inject with castor oil and ethanol (cremophor vehicle).

S/E : Hypersensitivity to caster oil (most common).
Peripheral neuropathy.

Nab-paclitaxel :

Water soluble.
Cremophor is not required.
S/E : Peripheral neuropathy.

Docetaxel :

Injected with polysorb 80 → water retention.
S/E : Edema : Peripheral/pulmonary edema.

Cabazitaxel :

Use : Prostate cancer (resistant to hormonal drugs).

3. Epothilones : Ixobepilone
4. Eribulin
} Use : Resistant triple -ve breast cancer.

(Regimen FEC) 5-FU.
Epirubicin.
Cyclophosphamide
f/b Paclitaxel.

5. Estramustine :

Consists of Estradiol normustine (alkylating agent).
Use : Prostate cancer.

S/E : Gynecomastia.

MISCELLANEOUS ANTI-CANCER DRUGS

Hormonal agents :

Selective estrogen receptor modulators 00:00:44

- Tamoxifen.
- Raloxifene.
- Toremifene
- Ospemifene.

Effect on estrogen receptors	Tamoxifen	Raloxifene
Breast	Antagonist, DOC in treatment and prophylaxis of ER +ve breast cancer in premenopausal woman.	Antagonist, used for prophylaxis of ER +ve breast cancer in post menopausal women.
Uterus	Agonist, hence may cause uterine cancer.	Antagonist : protective role.
Bone	Agonist : prevents resorption.	Agonist hence used in postmenopausal osteoporosis.
Lipids	Agonist : decreases LDL levels	Agonist : decreases LDL levels
Coagulation	Agonist : Thromboembolism	Agonist : Thromboembolism may occur
Hot flashes	Causes hot flashes	Causes hot flashes

Other uses of Tamoxifen :

- Treatment of acromegaly as it decreases insulin like growth factor- 1.
- Drug of choice for Riedel's thyroiditis.

Duration of use in breast cancer treatment is 5-10 years and for prophylaxis is 5 years for Tamoxifen & the dose is 20 mg. Raloxifene dose is 60 mg for 5 years.

Other drugs :

Toremifene : Used in cases of Tamoxifen resistant breast cancer.

Ospemifene : Used in treatment of postmenopausal dyspareunia.

SERD : Selective estrogen receptor down regulators

00:10:43

1. Clomiphene.
2. Fluvestrant :
   - Action is limited only to the breast where it blocks estrogen receptors.
   - 100 times more potent than tamoxifen and safer too.
   - DOC in treatment of Tamoxifen or Letrozole resistant ER positive breast cancer in post-menopausal female (Letrozole is the DOC if resistance is not present).
   - Dosage : Subcutaneous route 250 mg once a month.

Aromatase inhibitors :

In the adipocytes of post menopausal females an enzyme aromatase is present.

Aromatase converts testosterone into estrogen, thus it is the only source of estrogen in post menopausal women developing breast cancer. 60c6b3eeaa8ded0e4e7e5ea7

Classification

Steroidal	Non-steroidal
(Irreversible).	(Reversible)
Exemestane	Letrozole & Anastrozole

These are DOC for treatment and prophylaxis of ER positive breast cancer in post menopausal female.

Also used in treatment of precocious puberty, hirsutism and infertility caused by anovulation.

These are better than clomiphene.

Side effects : Decreases estrogen hence,

- Increases the risk of osteoporosis and bone fracture.
- Vaginal atrophy (Bleeding).
- Hot flushes (Lesser than SERM).

Anti-androgen drug

00:18:10

Androgen receptor antagonist

Progesterone derivative	Synthetic
Cyproterone.	Flutamide
Megestrol.	Bicalutamide
Not preferred nowadays.	Enzalutamide
	Nilutamide
	Apalutamide

Synthetic drugs are preferred and are used in treatment of prostate cancer along with GnRH agonist.

Also used In treatment of hirsutism.

Side effects : Impotence and gynaecomastia.

Flutamide & Cyproterone are hepatotoxic.

Enzalutamide can cause epilepsy and seizure.

Nilutamide causes interstitial pneumonitis.

5 α reductase inhibitors :

- Finasteride : Blocks type 2 (5α reductase).
- Dutasteride : Blocks both type 1 and 2.

Uses : DOC for treatment of androgenic alopecia.

Treatment of hirsutism.

Treatment of benign prostatic hyperplasia by reducing the proliferation of smooth muscles.

Side effects : Impotence and gynaecomastia.

L-Asparaginase 00:24:44

It is an enzyme and route of administration is intravenous.

MOA : Breaks asparagine (Depletion of asparagine).
Lymphocytes cannot synthesis asparagine whereas other cells can synthesis.

Administration of L- Asparaginase causes selective toxicity to lymphocytes

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Uses : Leukaemia (ALL) and lymphoma.

Side effects : Decreases protein synthesis thereby causing,

- Decreases insulin production causing hyperglycemia.
- Decreases apo-lipoprotein thereby causing hyperlipidemia.
- Decreases coagulation factors causing haemorrhage.
- Decreases anticoagulation factors causing hypercoagulation or thrombosis.
- It is an exogenous protein hence causes hypersensitivity.

Proteasome inhibitors 00:29:35

Drugs :
Carfilzomib
Bortezomib } used in treatment of multiple myeloma.
Ixazomib

Regimen :

Induction chemotherapy
Bortezomib + Dexamethasone + Lenalidomide
↓
Stem cell transplantation
↓
Consolidation
Good prognosis : Lenalidomide
Poor prognosis : Lenalidomide + Bortezomib.

Side effects : Thrombocytopenia (most common), Peripheral neuropathy.

Cyclin dependent kinase 4 & 6 inhibitors :
Function : Inhibits The movement of cell from G1 phase to S phase.

Drugs :

- Palbociclib.
- Rivociclib.
- Abemaciclib.

Uses :

In ER+ve breast cancer which is resistant to either Fluvestrant or Letrozole.

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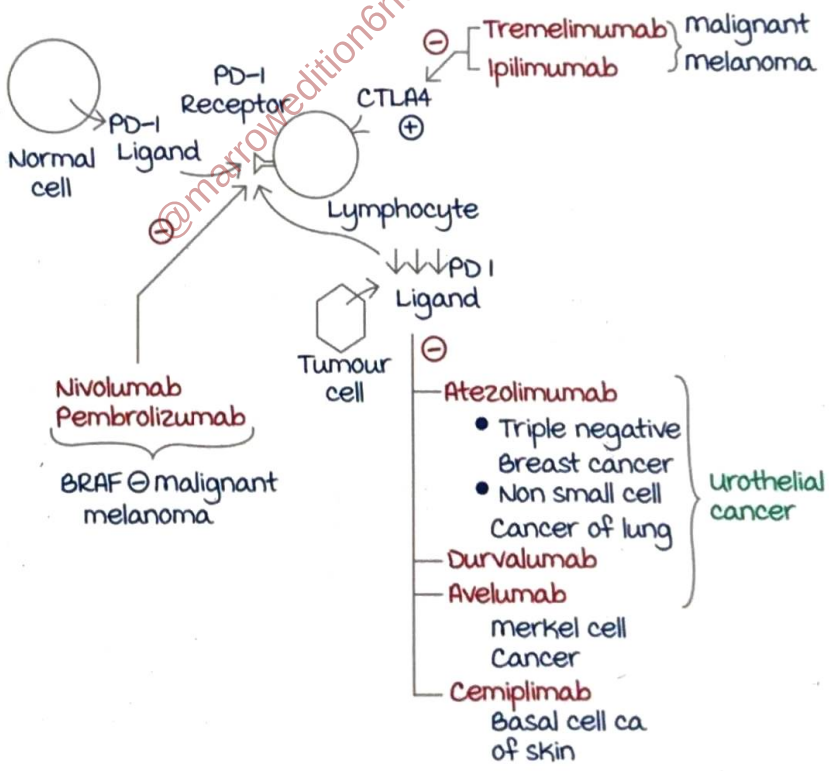
Immune checkpoint inhibitors

00:34:37

Normal cells produce programmed death cell ligand.
It binds to PD-1 receptor, thereby blocking lymphocytes from damaging cells (protective mechanism).

- Same effect is produced by CTLA-4 receptor.
- Tumour cells produce increased amount of PD-1 ligand and Ligands for CTLA-4 receptor and thus evades immune system.



Poly ADP ribose polymerase inhibitor(PARP inhibitor) :
mechanism of action :
Can be used in patients with BRCA mutation as partial repair occurs in these patients.
PARP inhibitors causes DNA breakdown by stopping the repair.
Uses : Increases the effect of cisplatin.

Drugs : Olaparib, Niraparib.

Used in treatment of BRCA positive cancers like

- Fallopian tube cancer.
- Ovarian cancer.
- Primary peritoneal cancer.

Talazoparib : BRCA positive breast cancer.

Aldesleukin :

Interleukin 2 analogue : Activates CD8 cells.

Uses : Malignant melanoma and renal cell carcinoma.

Hedgehog pathway :

Active during embryogenesis.

If active in adults causes cancer.

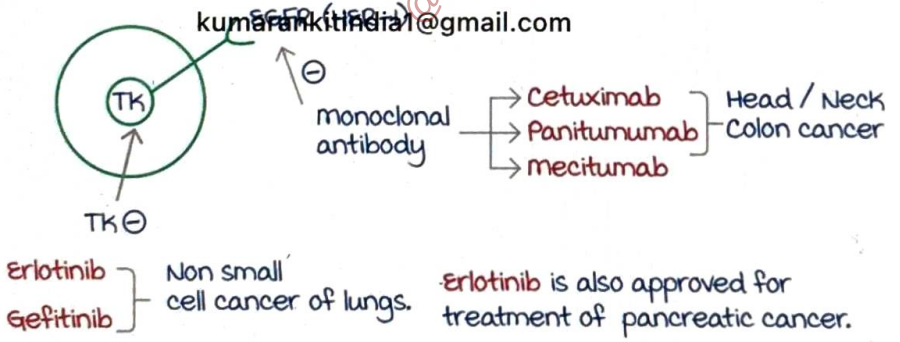
Inhibitors :

- Sonedigib : Treatment of basal cell carcinoma of skin.
- Glasdegib : Acute myeloid leukaemia.

Targeted therapy 00:47:03

Drugs are tyrosine kinase inhibitor and monoclonal antibody.

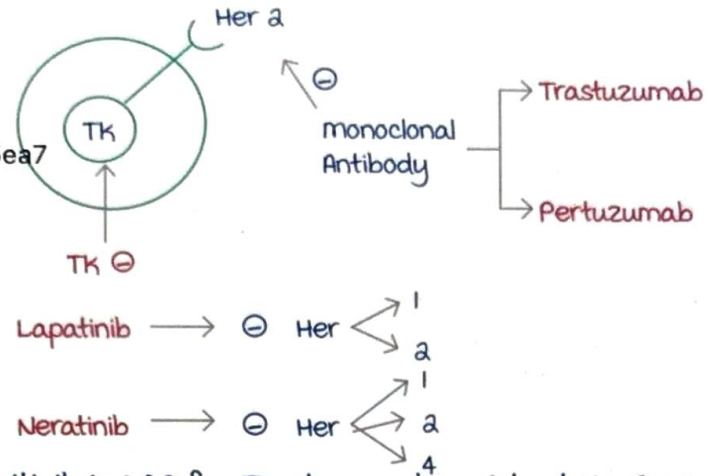
Tyrosine kinase receptor : EGFR



Her 2 receptor :

Present in breast, stomach and heart.

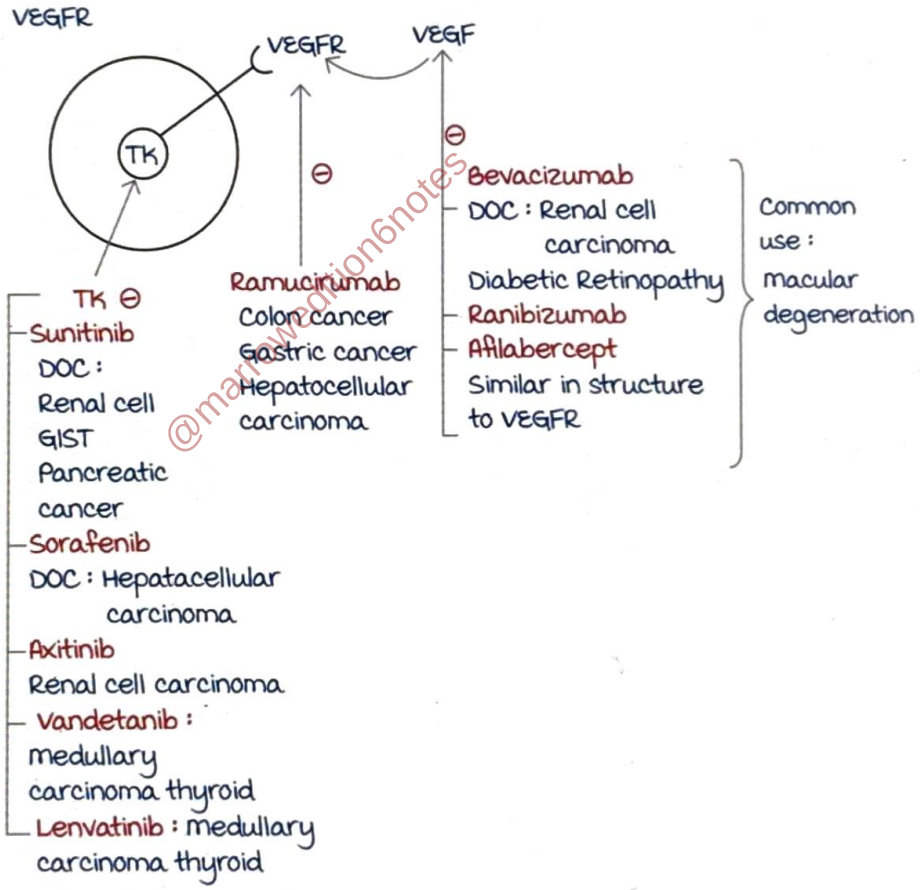
Trastuzumab and Pertuzumab : DOC in Her 2 positive breast cancer and gastric cancer.



Lapitinib is DOC for Trastuzumab resistant Her2 +ve breast cancer.

VEGFR

00:52:27



Other tyrosine kinase inhibitors

00:57:45

BCR-ABL tyrosine kinase inhibitor :

Used in treatment of chronic myeloid leukaemia.

Drug of choice is Imatinib (1st generation).

If there is no response use second generation drugs,

- Bosutinib.
- Nilotinib.
- Dasatinib.

If there is no response due to T315-I mutation, use Ponatinib.

Multi tyrosine kinase inhibitor resistant CML : Resistance for more than 2 drugs.

DOC : Omacetaxine, Inhibits synthesis of BCR-ABL protein.

Bruton's Tyrosine Kinase inhibitor :

Ibrutinib : Used in Treatment of,

- Mantle cell lymphoma.
- Marginal zone lymphoma.
- Waldenstrom macroglobulinemia.
- Chronic lymphoid leukemia.

Function : Increases proliferation and inhibits apoptosis of B cells hence used in treatment of B cell neoplasm.

Acalabrutinib: Ibrutinib resistant mantle cell lymphoma.

Anaplastic lymphoma kinase inhibitor/ALK 3 01:02:57

Active during embryogenesis cell proliferation.

It can be reactivated in adults by ALK -3 mutation causing non small cell carcinoma of lungs.

ALK 3 inhibitors :

Crizotinib (1st generation)

↓

Alcetinib, Brigatinib, Ceritinib (2nd generation)

↓

Lorlatinib (3rd generation)

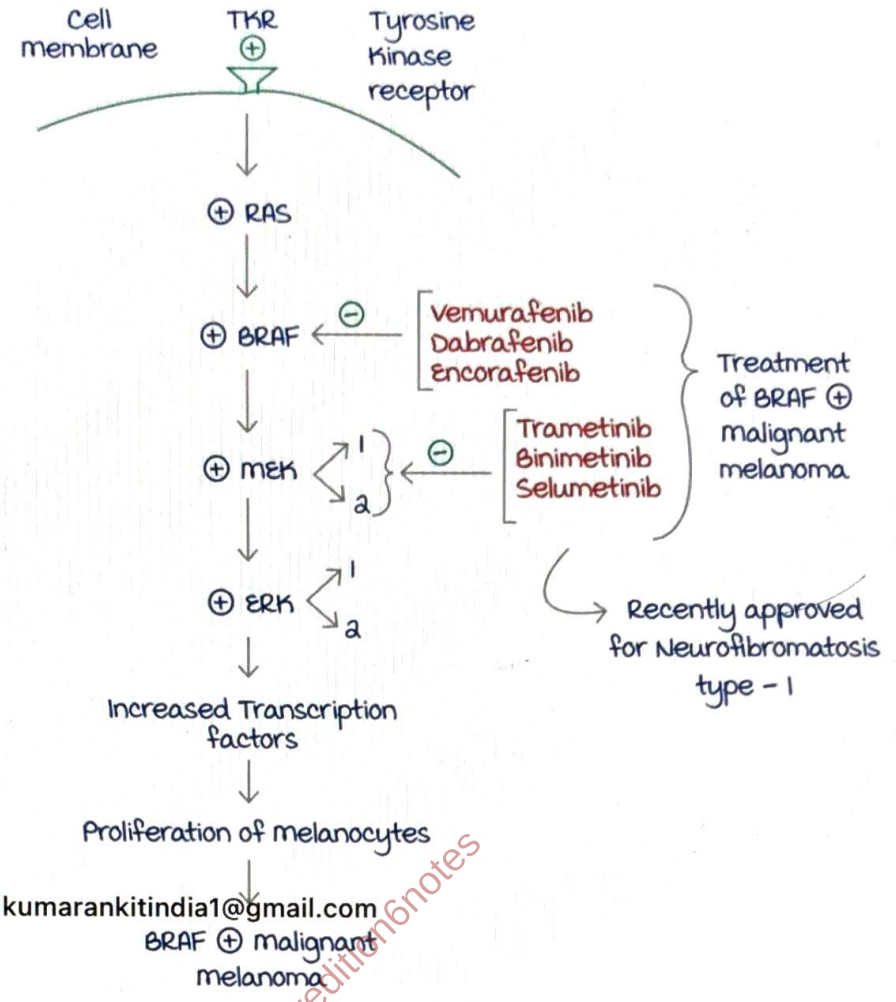
FMS like Tyrosine Kinase inhibitor (FLT 3 inhibitor)

Function : Proliferation of myelocytes.

Drugs :

- Midostaurin : Used in AML with FLT 3 mutation, mastocytosis and mast cell leukoma.
- Gilteritinib : Used in treatment of AML.

Mitogen activated protein Kinase inhibitor (MAPK inhibitor)



Phosphoinositide Kinase 3 inhibitor (PIK-3)

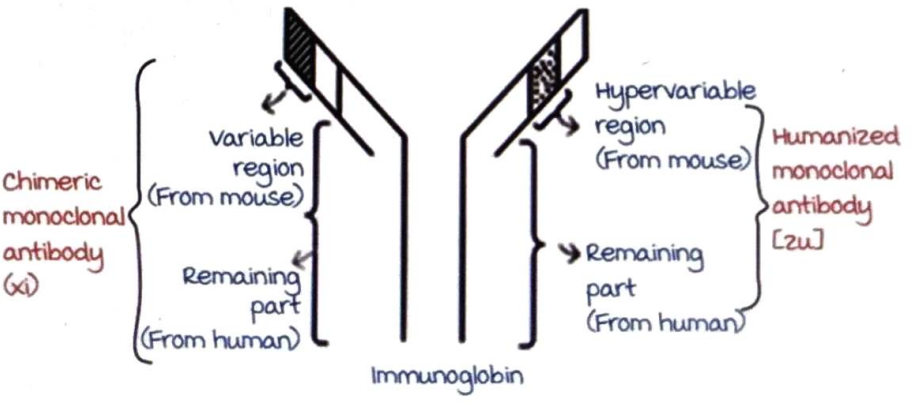
Idelalisib — Chronic lymphoid leukaemia.

Duvelisib — Non-Hodgkin's lymphoma. small lymphocytic leukaemia.

Alpelisib : ER +ve breast cancer with PIK 3 CA mutation.

Monoclonal antibody

01:12:02



Eg : Abciximab
Source : Chimeric
Use : Acts on circulation

Eg : Trastuzumab
Source : humanized
Use : Acts on tumour

Total antibody can be derived from either mouse or human.

Mouse :

Murine monoclonal antibody (o)

Ibritumomab, source : Murine, Acts on tumour.

Human : Human monoclonal antibody (u)

Adalimumab, Source : Human, target lymphocytes.

The name of a monoclonal antibody :

Mab : monoclonal antibody.

Denosumab/Romosozumab :

Monoclonal antibody, source: human, used in osteoporosis.

Palivizumab :

Monoclonal antibody, source: humanised, used as a prophylaxis for Respiratory syncytial virus.

Raxibacumab : Anti bacterial. Treatment of anthrax.

Bezlotoxumab :

Against toxin b of Clostridium difficile.

Prophylaxis of pseudomembranous enterocolitis.

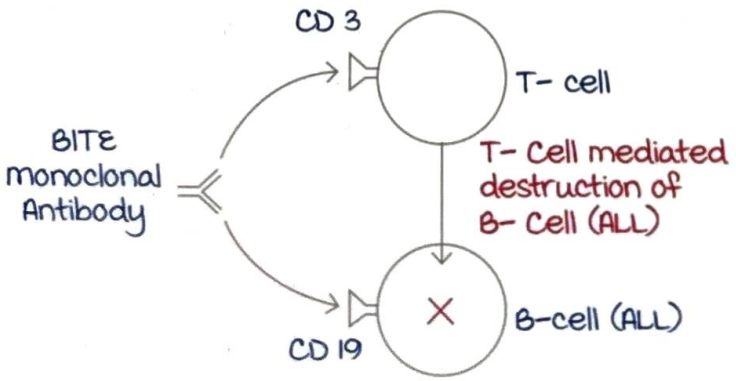
Fremanezumab/Erenumab/Galcanezumab : Prophylaxis of migraine.

Evolocumab/Alirocumab : PCSK-9 inhibitor, decreases LDL, used as an add on with statins.

Bite mab :

Bispecific T cell engager.

Blinatumomab, has two binding sites. Used in B cell precursor ALL



Anti CD20 monoclonal antibodies

01:25:09

Rituximab : (mnemonic : CANT MISS Ritu)

- Chronic lymphoid leukaemia.
- Autoimmune haemolytic anaemia.
- Non-Hodgkin's lymphoma.
- Thrombotic thrombocytopenic purpura.
- Multiple sclerosis
- Myasthenia gravis.
- Idiopathic thrombocytopenic purpura.
- SLE.
- Rheumatoid arthritis.

Ofatumumab : CLL resistant to Rituximab.

Ocrelizumab : Rheumatoid arthritis.

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