

Quality is our Passion

General pharmacology



L1 & 2 pharma

Absorption & Distribution

Introduction

Pharmacology:

- ✓ Science of drugs that have beneficial therapeutic effect on the patient or toxic effects on parasites infecting the patient
(used in treatment , diagnosis and prevention of diseases)
- ✓ Science deals with study of **drugs** and its effect on **body systems**

Drugs :

- ✓ Substances that interact **with living systems** by chemical processes .
- ✓ Drugs are either synthesized in the body e.g. hormones or not i.e. **xenobiotics**

Divisions of Medical Pharmacology : (What to study about drugs ?)

- ✓ In order to study pharmacology , you have to know about :

 1. Source and chemical structure
 2. Drug-body interaction
 - Pharmacokinetics : what the body does to the drug ? (ADME)
 - Pharmacodynamics : what the drug does to the body ? (Actions and Mechanism of action)
 3. Preparations (Dosage forms)
 4. Therapeutic uses (indications) and Doses
 5. Side effects (adverse drug reactions) and Toxicity
 6. Contraindications موانع الاستخدام and Precautions
 7. Drug interactions .

Drug names :

1. **Chemical name** : e.g. N - acetyl - para - aminophenol (APAP)
2. **Non - proprietary name** (Generic - Scientific - Approved) : e.g. paracetamol , acetaminophen
3. **Proprietary name** (Commercial - Brand) : e.g. Panadol

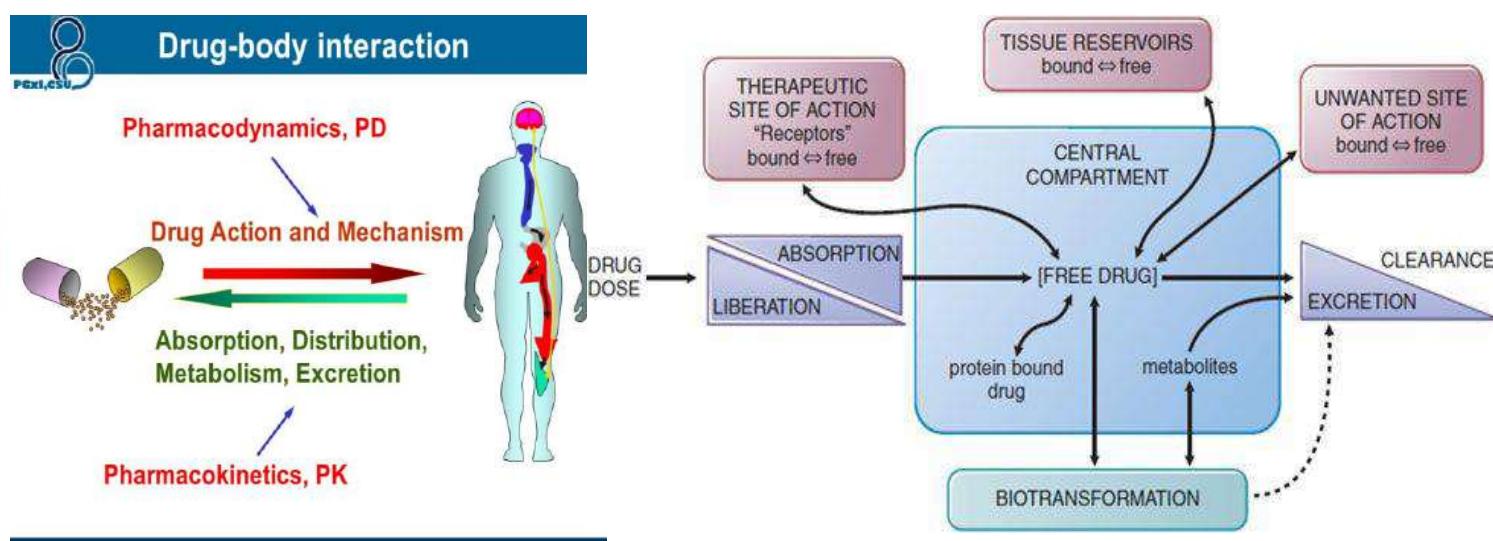
N.B : Drugs are purchased as :

- Prescription Only Medications (POM) : Most drugs
- Over The Counter Medications (OTC) : Antipyretics (paracetamol) , common cold preparations , laxatives and others.



Pharmaco-Kinetics

Pharmaco-Kinetics		Pharmaco-dynamic
Def	What the body does on the drug? تأثير الجسم على الدواء	What the drug does on the body? تأثير الدواء على الجسم
Include	ADME <ul style="list-style-type: none"> Absorption : Transfer of a drug from site of administration to systemic circulation Distribution : Transfer of a drug from systemic circulation to tissues Metabolism : Chemical alterations that occur to a drug to promote its excretion Excretion (Elimination) : Drug movement out of the body <p>N.B. Biodisposition = metabolism and excretion</p>	<ul style="list-style-type: none"> Drug action Mechanism Uses Side effects& contraindications



Importance : It helps to :

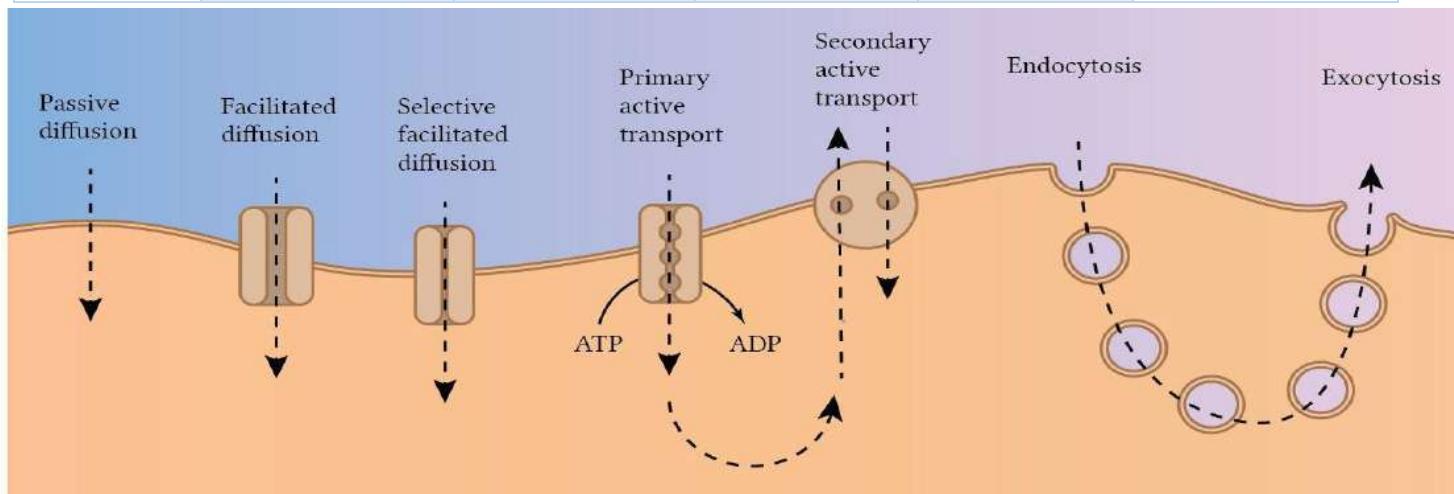
- Determine clinically important pharmacokinetic parameters e.g. bioavailability , volume of distribution (Vd) , elimination half life (t_{1/2}) , clearance (CL) and steady state concentration (Css)
- Design the proper dosage schedules (dose , route , frequency of administration) for individual patients based on their body characteristics .




Absorption

- Definition: Transfer of a drug from site of administration to systemic ABSORPTION circulation . It requires passage of drugs across cell membranes
- Modes of drug transport across cell membrane

	Passive transport		Specialized transport		
	Simple diffusion	Filtration Pores or Spaces	Facilitated diffusion	Active transport	Pinocytosis (endocytosis)
Nature of substance	-Small MW -Lipophilic -Unionized e.g. Most drugs	-Small MW -Hydrophilic -Ionized e.g. ions . hydrophilic drugs -Glomerular filtration	Large MW Hydrophilic - e.g. Glucose Aminoacids	e.g. Na + / K + Pump - Renal secretion of Penicillin	e.g. Vit . B12 + Intrinsic factor - Fat soluble Vitamines (A- D - E - K)
Way	Along conc gradient	Along hydrostatic , osmotic pressure	Along conc . gradient	Against conc . gradient	Material is engulfed by invagination of cell membrane
Energy	No	No	No	Required	Required
Carriers	No	No	Required	Required	No
Specificity	No	No	Specific	Specific	No
Saturation	No	No	Saturable	Saturable	No



- Most drugs are transported by simple diffusion :

It depends on :

1. Concentration gradient : Higher conc . gradient Faster absorption .

2. Molecular size : Smaller molecular size → faster absorption .

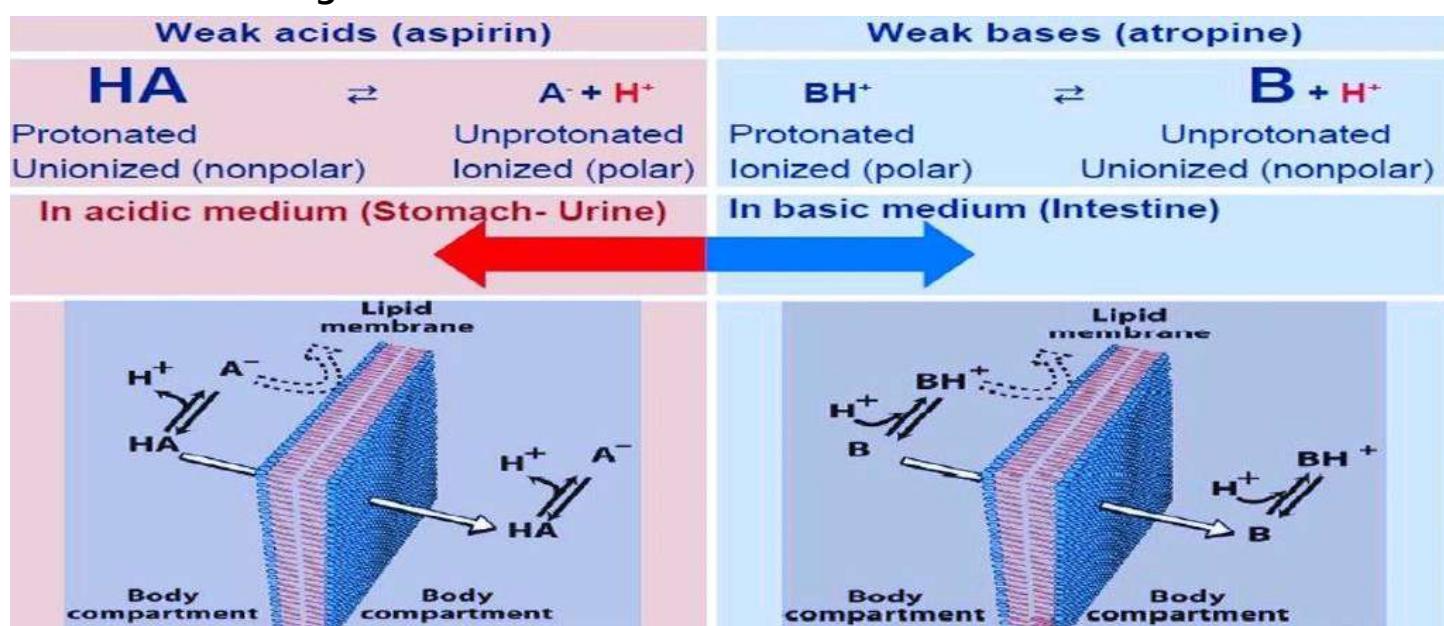
3. Lipid solubility : Higher lipid solubility → Faster absorption .

- It is measured by lipid / water partition coefficient (Higher Coefficient → Faster absorption)
- Lipid / water PC = Portion of drug dissolved in lipid/ Portion of drug dissolved in water

e.g. Streptomycin is not absorbed orally (low lipid solubility - ionized)

4. Degree of Ionization :

- Less ionization→ Faster absorption .
- Unionized drug (nonpolar - lipophilic) → More absorption
- Ionized drug (polar - hydrophilic) → Less absorption
- It depends on pH of the medium and pKa of the drug .
- Most drugs are either weak acids or weak bases .



Henderson Hasselbalch equation: $\text{Log } \frac{\text{Protonated}}{\text{Unprotonated}} = \text{pKa} - \text{pH}$

pKa (ionization constant) = pH at which 50% of the drug exists in ionized form and 50% in unionized form

pH = pH of the medium (Site of absorption or excretion)

E.g. For weak acids: → Aspirin pKa = 3.5 Gastric pH = 1.5 Intestinal pH = 7.5

What is the ratio between unionized fraction and ionized fraction at gastric pH and at intestinal pH?

$$\text{Log } \frac{\text{AH}}{\text{A}^-} = 3.5 - 1.5 = 2$$

$$\text{Unionized fraction / Ionized fraction} = 100 / 1$$

$$\text{Log } \frac{\text{Unionized}}{\text{Ionized}} = 2$$

Aspirin is better absorbed from the stomach



Weak acids e.g. Aspirin are better absorbed from the stomach

Alkalization of urine (by IV NaHCO₃) → ↑ excretion of weak acids e.g. aspirin (↑ ionized form) → helps treatment of toxicity

Weak bases e.g. Atropine are better absorbed from the intestine

Acidification of urine (by oral Vit. C) → ↑ excretion of weak bases e.g. atropine (↑ ionized form) → helps treatment of toxicity

Significance of PKa:

- 1- Affects site and rate of absorption, distribution, metabolism and excretion.
- 2- Guide for treatment of toxicity (by changing urine PH)
- 3- Explains some adverse effects e.g. Peptic ulceration caused by Aspirin

For aspirin (weak acid)- in stomach

$$-\log(\text{protonated}/\text{un protonated}) = \text{Pka-PH}$$

$$-\log(AH/A^-) = 3.5 - 1.5 = 2$$

$$(\text{unionized}/\text{ionized}) = 100$$

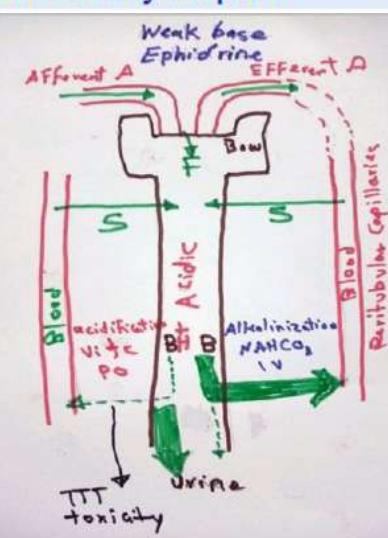
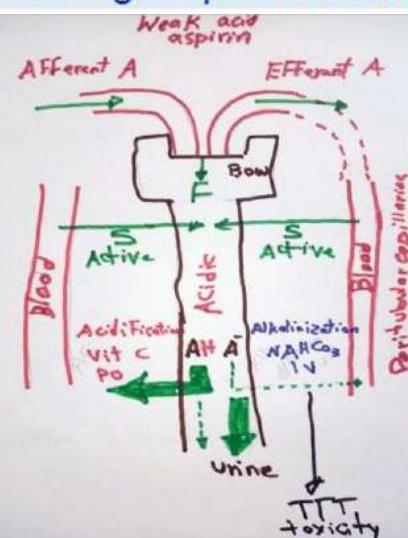
يعني

For aspirin -in intestine

$$\log(AH/A^-) = 3.5 - 7.5 = -4$$

يعني

$$(\text{unionized}/\text{ionized}) = 1/10000$$



Bioavailability

- Definition : Fraction of unchanged drug (Bioactive drug) that reaches systemic circulation following administration by any route . النسبة بين الجرعة المعطاة الى الجرعة . الممتصة (الى وصلت الدم)

- Bioavailability After IV administration = 100 % (by definition)

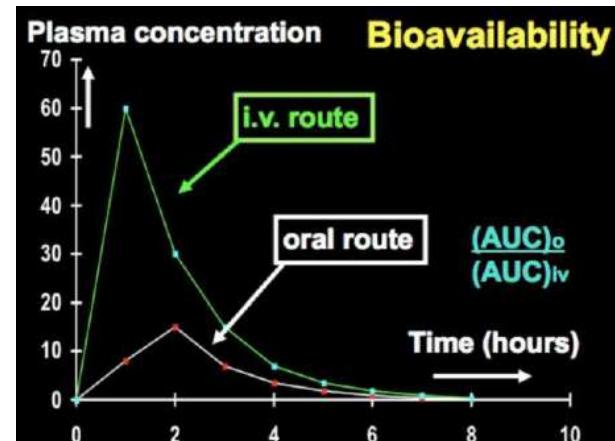
- Bioavailability After any route of administration =

$$\text{AUC (Route)} / \text{AUC (IV)} \times 100 \%$$

- N.B : AUC (Area Under time concentration Curve) is a measure of the total amount of a drug in the body and is useful to calculate of the dose , clearance (CL) and bioavailability :

$$CL = \text{Dose} / \text{AUC}$$

$$CL : \text{Total body clearance}$$



Factors affecting bioavailability

1- Factors Affecting Drug Absorption

A - Factors related to the drug

1. Lipid solubility , Molecular size , Degree of ionization : See simple diffusion .
2. Chemical nature and valency : Inorganic drug is better absorbed than organic , Ferrous salts (Fe⁺²) are better absorbed than Ferric (Fe⁺³) salts .
3. Dosage form : absorption of Solutions > Suspension > Solid
4. Rate of disintegration and dissolution (compression + excipients)

B- Factors related to patient

1. Dosage : ↑ Dose →↑ Absorption
2. Route of administration : Intravenous (IV) > Alveolar (Very large surface area) > Sublingual (SL) > Intramuscular (IM) > Subcutaneous (SC) > Intestinal > Gastric > Rectal > Skin (topical) .
3. Area , vascularity and state of health of absorbing surface :
 - Absorption is directly proportional to both area and vascularity of absorbing surface
 - Rubbing at injection site Vasodilation (VD) (↑ vascularity) →↑ absorption .
 - Atrophic gastritis , malabsorption syndrome → ↓ absorption
4. Rate of general circulation : Shock Drug absorption from SC and IM injection sites (Avoid SC or IM injection in shock)
5. Presence of food or other drugs : e.g.
 - ✓ GIT secretions and Food may affect drug absorption e.g. Penicillin G (destroyed by gastric secretions - Used only IV)
 - ✓ Adrenaline →Vasoconstriction (VC) →→ ↓ absorption of companion local anesthetic from site of injection →→ prolongs its effect (Adrenaline is added to local anesthetics to prolong their effect)
 - ✓ Calcium → ↓ oral absorption of Tetracyclines (Tetracyclines should not be coadministered with Calcium containing foods or drugs)
6. Specific factors : e.g. Intrinsic factor is essential for absorption of vitamin B12



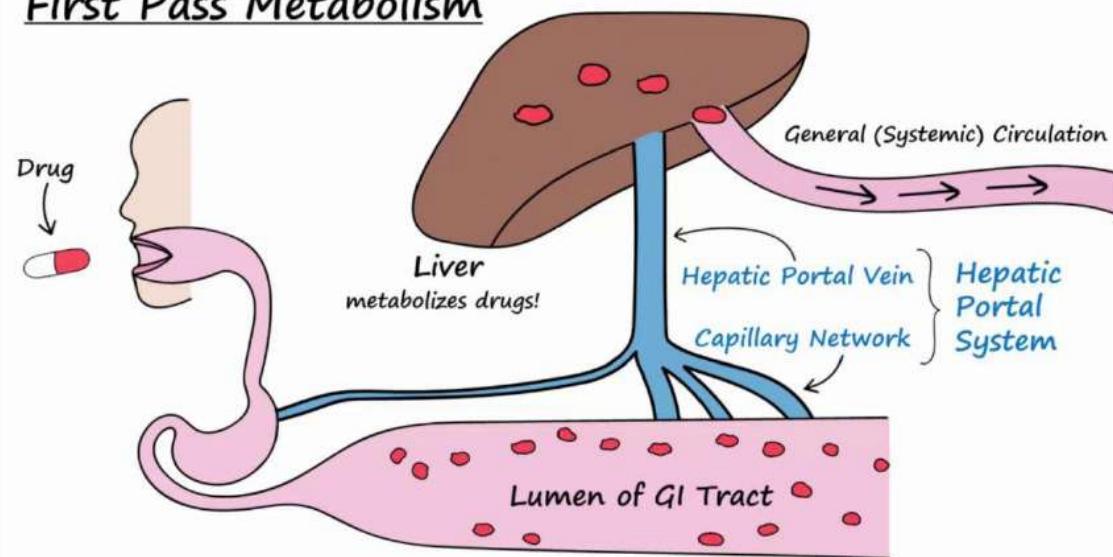
II- First pass metabolism :

- **Definition :** Metabolism of a drug before reaching the central compartment (general circulation)
- **Sites :**
 - **Liver** : For propranolol , nitroglycerine
 - **Intestinal wall** : For tyramine , alpha methyl dopa , estrogen
 - **Lung** : For nicotine , isoprenaline .
- **Importance :**
 - Drugs which undergo **high first pass metabolism** → Have low bioavailability e.g. Propranolol , Nitroglycerine (**Propranolol** : IV dose = 1 mg)
 - Oral dose = 40 times IV dose) Routes of administration that bypass first pass metabolism : parenteral , sublingual and rectal (to some extent)
- **Factors that decrease hepatic first pass metabolism :**
 - ↓ Portal blood flow e.g. portal hypertension , propranolol
 - ↓ Hepatic enzymes e.g. liver failure , enzyme inhibitors as erythromycin .

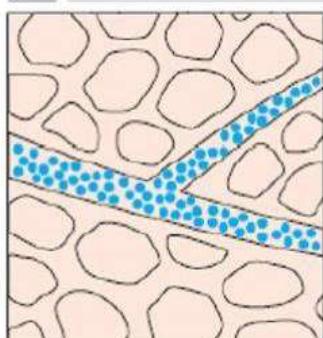
III- Enterohepatic circulation (Recycling) :

- **Definition :** recycling of a drug between intestine and liver . Drugs which undergo enterohepatic recycling are conjugated in liver excreted in bile to small intestine → deconjugated (reactivated) by enzymes from intestinal bacteria →→ reabsorbed .
- **Importance :** Drugs which undergo enterohepatic recycling → have prolonged high plasma levels prolonged effect e.g. **Ceftriaxone , Rifampin , Doxycycline , indomethacin**

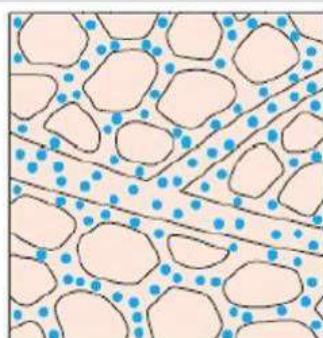
First Pass Metabolism



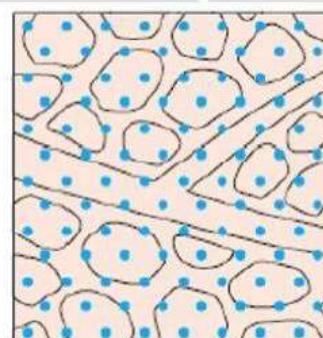
 Distribution

PATTERNS OF DISTRIBUTION


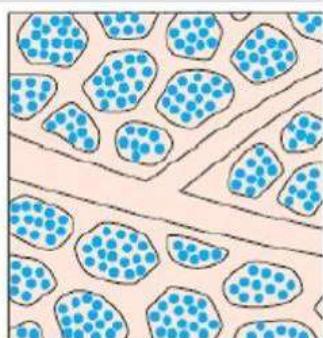
Intravascular



Intravascular and interstitial



Extra- and intracellular



Tissue binding

	Pattern Of Distribution (Model)	Examples of drugs
A	Single compartment (intravascular): Drugs which cannot cross capillary wall → retained in plasma	Drugs with relatively high MW e.g. Dextran, Heparin
B	Two compartments (intravascular and interstitial): Drugs which cross capillary wall but cannot cross cell membranes → remain localized in plasma and extracellular fluid	Quaternary ammonium compounds (N ⁺), Mannitol.
C	Multicompartment (extracellular and intracellular): Drugs which cross cell membranes are distributed all over the body (plasma, interstitial fluid and intracellular fluid)	Drugs with low MW and lipophilic e.g. Alcohol.
D	Tissue Reservoirs: Drugs which have special affinity for specific tissues → concentrated in these tissues	- Calcium, Tetracyclines precipitate in bones - Iodide in thyroid gland

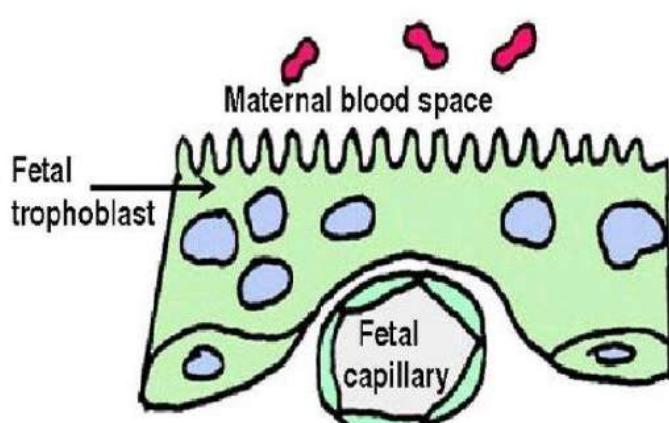
❖ Blood tissue barriers
❖ Blood brain barrier (BBB) :

- **It consists of** : endothelial cells and basement membrane cells (astrocytes) with no pores or gaps (Tight barrier)
- **To cross BBB , Drugs must be lipophilic and highly unionized**
- **Passage of drugs to CNS : BLOOD TISSUE BARRIERS**
 - ✓ Lipophilic drugs cross freely through BBB e.g. General anesthetics and other CNS depressants
 - ✓ Secondary and tertiary amines (e.g. physostigmine) can cross BBB but Quaternary ammonium compounds NH₄ + (e.g. neostigmine) cannot
 - ✓ Dopamine can't penetrate to CNS → L- **dopa** is used in parkinsonism as it penetrates to CNS to be decarboxylated → dopamine
 - ✓ Inflammation → ↑ permeability of BBB **Penicillins** can cross BBB in meningitis (cannot cross in normal conditions).

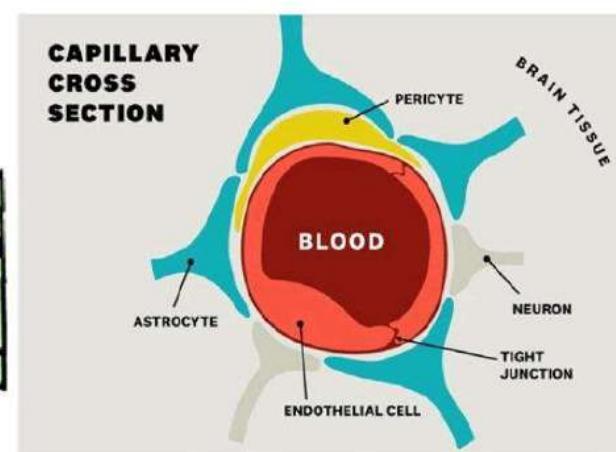


- Placental barrier :

- Drugs cross the placenta by simple diffusion depending on their lipid solubility , molecular size , degree of ionization (\uparrow lipid solubility \rightarrow \uparrow drug uptake by fetus) .
- Most drugs taken by mother can cross the placenta to fetal circulation \rightarrow high , prolonged fetal drug levels due to underdeveloped fetal mechanisms of metabolism and excretion \rightarrow
 - ✓ Drugs used during first trimester \rightarrow Congenital malformations (**teratogenic** effects) e.g. **Thalidomide** \rightarrow **Phocomelia**
 - ✓ Morphine \rightarrow neonatal asphyxia
 - ✓ Oral hypoglycemic drugs \rightarrow prolonged neonatal hypoglycemia
 - ✓ Oral anticoagulants \rightarrow neonatal hemorrhage
 - ✓ Antithyroid drugs \rightarrow neonatal hypothyroidism and goiter



Placental Barrier



Blood Brain Barrier

❖ BINDING OF DRUGS TO PLASMA PROTEINS

- **Drugs circulate in plasma**

- partially bound to plasma proteins (Bound fraction) and partially unbound (Free fraction) .
- Both fractions are in equilibrium . Binding to plasma proteins is reversible and non selective

- **Sites of plasma protein binding :**

1. **Albumin** : Binds with high affinity to acidic drugs e.g. warfarin , indomethacin .
2. **Alfa - 1 - acidic glycoprotein** : Binds with high affinity to basic drugs e.g. propranolol , quinidine
3. **Globulins binds hormones** : e.g. thyroxin , sex hormones , glucocorticoids



Fetal hydantoin syndrome include:

- cleft lip, cleft palate
- congenital heart disease
- slowed growth
- mental deficiency



**Phocomelia
(Thalidomide)**

Bound fraction (mainly to albumin)	Free fraction
Inactive (Cannot access to its receptor)	Active (Can access to its receptor)
Cannot be distributed	Can be distributed
Cannot be metabolized	Can be metabolized
Cannot be excreted	Can be excreted
Act as reservoir	Eliminated and continuously compensated from bound fraction

▪ Factors affecting plasma protein binding

1. Renal diseases , hepatic diseases , hypoalbuminemia , uremia , burns neoplastic diseases, $\rightarrow \downarrow$ Conc . of plasma proteins $\rightarrow \uparrow$ free fraction of some drugs $\rightarrow \uparrow$ drug distribution

2. Presence of drug receptors in specific tissues : e.g. skeletal muscles have high expression of Na^+ / K^+ ATPase (target for digoxin) digoxin is highly concentrated in skeletal muscles.

3. Age : neonates have low conc . of plasma proteins $\rightarrow \uparrow$ drug distribution

N.B :: Drugs with high plasma protein binding are characterized by

1 - \uparrow Absorption & t 1/2

2- \downarrow Metabolism & Distribution and Excretion.

3. More liable for drug interactions



- Drug interactions at plasma protein binding sites :

Drugs with high affinity to plasma proteins (slow dissociation rate) can displace other drugs with lower affinity (rapid dissociation rate) → ↑ Free (active) fraction of displaced drug → ↑ its effect and toxicity e.g.

- Non - steroidal anti - inflammatory drugs (NSAIDs) e.g. salicylates can displace oral hypoglycemic agents (e.g. tolbutamide) → ↑ their hypoglycemic effect transient hypoglycemia .
- NSAIDs can displace oral anticoagulants (e.g. warfarin) their anticoagulant effect → bleeding .
- Sulfonamides (Antibacterial drugs) can displace bilirubin → ↑ Free bilirubin fraction Bilirubin deposits in basal ganglia (extrapyramidal motor center in CNS) → kernicterus in infants (Lethargy , decreased feeding , involuntary movements) .

❖ Apparent volume of distribution (Vd)

✓ **Definition :** The volume of fluid that would accommodate the total amount of the drug in the body if its concentration in the entire volume was the same as that in plasma (*It is Not a real volume*)

✓ **It equals :**

$$Vd = Q / Cp$$

✓ **Factors affecting Vd :**

1. Blood flow to different organs .
2. Lipid solubility of the drug .
3. Binding of drugs to plasma proteins .

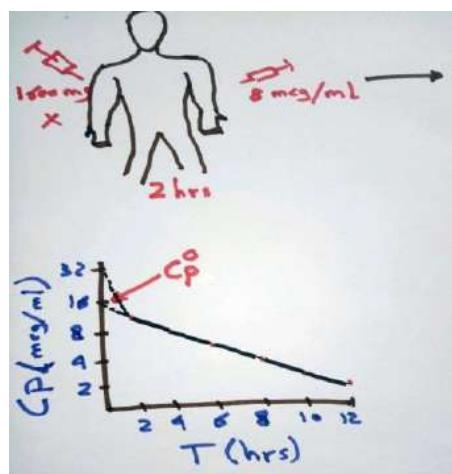
4. Binding to cell and tissue constituents (tissue reservoir) : see before .

Vd : Drug's Volume of distribution

(L or L / Kg)

Q : Total amount of the drug in the body
(Dose by mg)

Cp : Plasma concentration of the drug
(mg / ml)



$C_p = \frac{Q}{V_d}$
 $V_d = \frac{Q}{C_p}$

$$\begin{aligned}
 Vd &= \frac{Q}{C_p} = \frac{1600}{8} \frac{\text{mg}}{\text{mg/L}} \\
 &= \frac{1600000}{16} \frac{\text{mg}}{\text{mg/L}} \\
 &= 100000 \text{ mL} \\
 &= 100 \text{ L} \\
 &\text{لـ الوزن} \\
 &Vd = \frac{100}{70} = 1.4 \text{ L/Kg} \\
 &\begin{array}{l|l}
 \text{70 L} & \text{Dose} \\
 \hline
 50 \text{ L} & \text{Ethanol} \\
 15 \text{ L} & \text{Heparin} \\
 5 \text{ L} &
 \end{array}
 \end{aligned}$$



N.B : Drugs with high volume of distribution are characterized by :

1. High lipid solubility : ↑ Absorption , ↑ Distribution , ↑ Metabolism , ↓ Excretion
2. High tissue binding (tissue uptake)
3. Low plasma protein binding
4. ↑ Dose (Loading)
5. ↑ t 1/2
6. Dialysis is not useful for treatment of toxicity .

✓ Importance :**1. An estimate for the extent of tissue uptake of drugs :**

- Frusemide (diuretic) has Small Vd → very low tissue uptake
- Digoxin (+ ve inotropic) has Large Vd → extensive tissue uptake

2. In case of toxicity :

- Dialysis is not useful for drugs with Large Vd (most of the drug is retained in tissues and is hard to be dialyzed)
- Dialysis is useful for drugs with Small Vd (most of the drug is retained in circulation and is easy to be dialyzed)

3. Calculation of loading dose (LD) :

$$LD = Vd \times Css$$

Vd : Volume of distribution of the drug (L or L / Kg)

LD : Loading dose (mg)

Css : Steady state plasma concentration of the drug (mg / ml)

4. Vd is directly proportional to half - life (t 1/2) and inversely proportional to the rate of drug elimination : e.g. Digoxin has high Vd , long t 1/2 , slow rate of elimination → cumulation (so taken once daily with digoxin free days)**Useful pharmacokinetic equations**

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

t 1/2 : Drug's Plasma half life

Vd: Drug's Volume of distribution

CL: Total body clearance of the drug

$$CL = \frac{\text{Rate of elimination}}{Css}$$

Css = Steady state plasma concentration of the drug (mg/ml)



Thank You!

METABOLISM (BIOTRANSFORMATION)

- **Definition:** Metabolic conversion of drug molecules from lipophilic form to Hydrophilic form to be easily excreted.

- **Sites:**

1. The liver:

- The major site of metabolism for many drugs.
- Metabolism is catalyzed mainly by hepatic microsomal enzymes.
- Responsible for glucuronide conjugation and most oxidation processes

2. Non-hepatic sites: Lung, kidney, adrenal gland, plasma.

- **It results in:**

- Inactivation of drugs e.g. Most drugs.
- Conversion of active drug → more active metabolite e.g. codeine to morphine and morphine to morphine -6- glucuronide
- Conversion of inactive drug (Prodrug) → active metabolite e.g. Prednisone to Prednisolone.
- Conversion of active drug → toxic metabolite e.g. paracetamol to N-acetyl-p-benzoquinone imine (NAPQI) which is then conjugated to reduced glutathione (GSH)

- **Phases: two phases:**

1. **Phase I (Non Synthetic Reactions):** usually precedes phase II

- **Definition:** Modification of drug molecules via oxidation, reduction or hydrolysis.
- **It results in:** addition or unmasking of a polar group (-OH, -SH, -NH2) → ionized metabolite → easily excreted or Conjugated (phase II)
- **Oxidation by cytochrome P450 enzymes** is the most important reaction

2. **Phase II (Synthetic reactions or Conjugation reactions):**

- **Definition:** Conjugation of drug molecules with endogenous substrates with the help of transferases.
- **It results in:** Usually inactivation of drugs → easily excreted

- Conjugation substrates and enzymes:

Drug	Substrate	Enzyme
Chloramphenicol, Morphine	Glucuronic acid	UDP-Glucuronosyl transferase (UGT)
Sulfonamides, Hydralazine, Isoniazid.	Acetic acid	N-Acetyl transferase (NAT)
Salicylates.	Glycine	Glycine N-acetyl transferase (GLYAT)
Catecholamines, Histamine, Xanthines	Methyl group	COMT, Thiopurine methyl transferase (TPMT)
Paracetamol	Sulfate	Sulfotransferase (SULT)

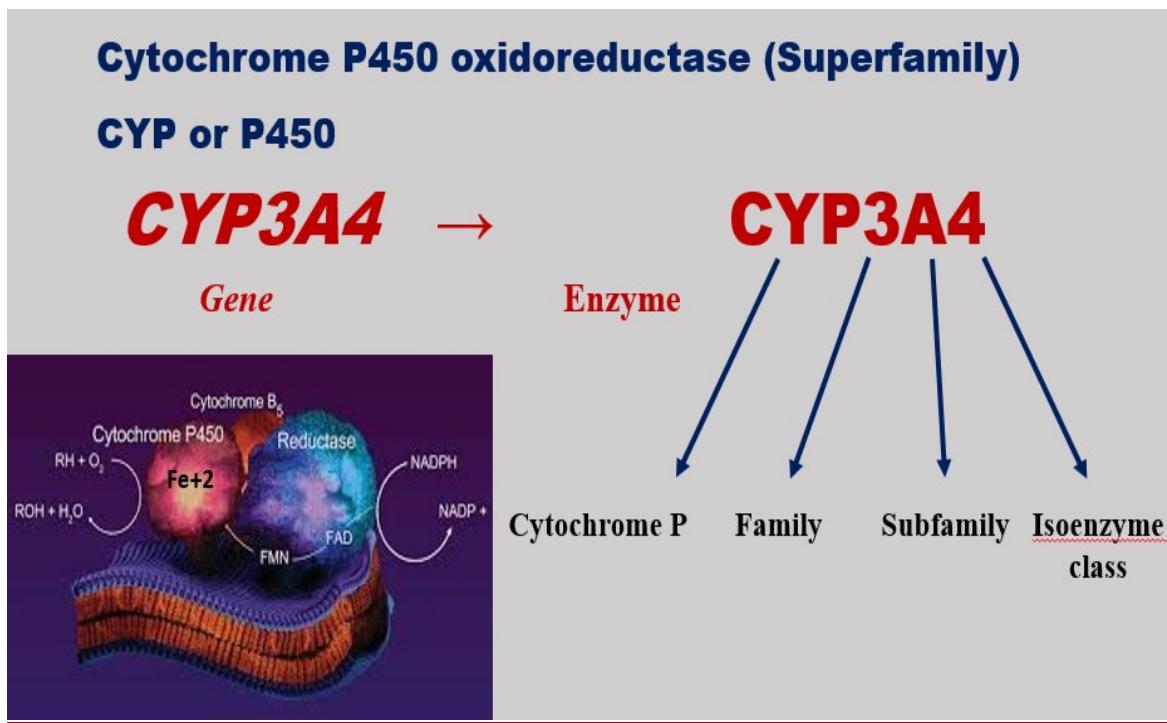
N.B.: Phase I reactions usually precede phase II reactions but the reverse may occur with some drugs e.g. isoniazid → It is first acetylated (phase II) → Acetyl isoniazid → hydrolyzed to isonicotinic acid (phase I).

- Types of metabolic enzymes:

	A- Microsomal Enzymes	B- Non Microsomal Enzymes
Site	Smooth endoplasmic reticulum of the liver.	Cytoplasm, mitochondria of all organs
Reactions	Oxidation, Reduction, Hydrolysis Conjugation (glucuronic acid)	Oxidation, Reduction, Hydrolysis, Conjugation (All except glucuronic)
Substrate	- Lipid soluble drugs - Bilirubin, nicotine, steroids	- Water soluble drugs - Endogenous substrates e.g. NT
Specificity	Non specific	Specific
Induction	Inducible by drugs	Non-inducible by drugs
Neonates	Small amount in neonates	Large amount in neonates
Examples	Cytochrome p450 oxidase (CYP450), UDP- Glucuronosyl transferase (UGT)	- Mono-amine oxidase (MAO) - N- Acetyl transferase (NAT) - Esterases

N.B.:

- CYP450 oxidases (CYP are a superfamily of enzymes related to Mixed Function Oxidases (MFO)).
- CYP3A4 isoenzyme is responsible for metabolism of 40% of prescribed drugs:



▪ **Factors affecting hepatic microsomal enzyme Activity:**

1) Drugs (enzyme inducers and enzyme inhibitors):

	A- Enzyme Inducers		B- Enzyme Inhibitors	
Mech.	↑ enzyme synthesis		Direct enzyme inhibition or damage	
Rate	Slow (Delayed onset)		Fast (Rapid onset)	
Ex.	Phenobarbitone Phenytoin Carbamazepine	Rifampicin Androgens Smoking	Chloramphenicol Erythromycin Ciprofloxacin	Ketoconazole Estrogen Grapefruit
Effect	<ul style="list-style-type: none"> • ↓ activity of coadministered drugs e.g. oral anticoagulants (→ thrombosis); oral contraceptives (Not relied); corticosteroids (Inflammation relapse) • Tolerance e.g. Phenobarbitone → ↑ its own metabolism → tolerance to its sedative effect 			
	↑ Effect of coadministered drugs → Toxicity (may be serious)			

2) Age and sex:

- Defective glucuronide conjugation in premature → ↑ Risk of toxicity with some drugs e.g. Chloramphenicol → Grey baby syndrome
- Defective metabolism in elderly → ↑ Risk of toxicity with CNS depressants e.g. Benzodiazepines
- Androgens →↑ drug metabolism - female sex hormones →↓ drug metabolism.

3) Starvation → ↓ enzyme activity and ↓ substrates needed for conjugation

4) Pathological conditions: liver disease →↓ metabolism of many drugs (dose adjustment is required).

5) Pharmacogenetics: genetic variations may occur in drug metabolizing enzymes e.g. Succinylcholine (a depolarizing skeletal muscle relaxant) → prolonged apnea in patients with genetic deficiency of pseudocholine esterase.

EXCRETION

- Drugs are eliminated in the form of free or metabolized product through one or more of the following routes.

Routes of drug excretion:

1- Renal (main site): Three processes:

A. Glomerular filtration: Drug should be:

- Small molecular size, Hydrophilic
- Unbound

B. Active tubular secretion: through specific transporters e.g.:

- ® Organic anion transporters for weak acids as Penicillin
- ® Organic cation transporters for weak bases as Metformin

C. Passive tubular reabsorption: Drug should be:

- Small molecular size, Lipophilic
- Unionized → Affected by urine pH and drug pKa

2- GIT:

a) Salivary glands: e.g. Iodides

b) Liver → Bile → Intestine: e.g. Ceftriaxone, Doxycycline

3- Skin: e.g. Rifampicin (red sweat)

4- Lungs: Volatile lipid soluble drugs e.g. general anesthetics, alcohol

5- Breast milk:

- Breast milk is slightly acidic than plasma with high fat content → Basic and Lipophilic drugs have high tendency to be trapped in breast milk
- Most drugs excreted in breast milk undergo first pass metabolism in the liver of suckling baby → Low bioavailability → Rarely cause symptoms e.g. sedation or diarrhea.
- To decrease the risk for these side effects, the nursing mother should take her medications immediately after lactation and/or 3-4 hours before the next feeding.
- Drugs contraindicated during breast feeding:
 - Antibiotics e.g. chloramphenicol, tetracyclines, sulfonamides and Laxatives e.g. senna, cascara → diarrhea
 - CNS drugs: morphine, benzodiazepines, alcohol → Sedation
 - Glucocorticoids → ↓ fetal growth.
 - Bromocriptine and female sex hormones → suppress lactation.

6- Other routes: fetal circulation, hairs, nails.

SOME PHARMACOKINETICS PRINCIPLES

Drug Clearance (CL):

- **Definition:** Volume of blood cleared from a drug / unit time.

$$CL = \frac{\text{Rate of elimination}}{C_p}$$

*CL: Systemic clearance (ml/min)
Cp: Concentration of the drug in plasma (mg/ml)*

- **The major routes of drug clearance:** kidney (CL renal) and liver (CL hepatic).
- **Systemic clearance is equal to:** The sum of clearance by individual organs (kidney, liver, lungs, others)

$$\text{CL Systemic} = \text{CL renal} + \text{CL non renal}$$

▪ **Factors affecting drug clearance**

1. Blood flow to the organ of clearance (directly proportional).
2. Activity of elimination mechanisms e.g. glomerular filtration, tubular secretion, hepatic microsomal enzymes (directly proportional)
3. Plasma protein binding (inversely proportional)

1. Renal drug clearance: Volume of blood cleared from a drug by the kidney / unit time

$$\text{CL renal} = \frac{U \times V}{C_p}$$

U: Concentration of the drug in urine (mg/ml)

V: Volume of urine (ml)

C_p: Concentration of the drug in plasma (mg/ml)

2. Hepatic drug clearance: Volume of blood cleared from a drug by the liver/ Unit time

$$\text{CL Hepatic} = Q \times E$$

Q: Hepatic blood flow (ml/min)

E: Extraction ratio (%)

⊗ **Extraction ratio:** the fraction (%) of a drug eliminated by the liver.

$$E = \frac{(CA - CV)}{CA}$$

CA: Arterial drug concentration (mg/ml)

CV: Venous drug concentration (mg/ml)

⊗ **Drugs may be:**

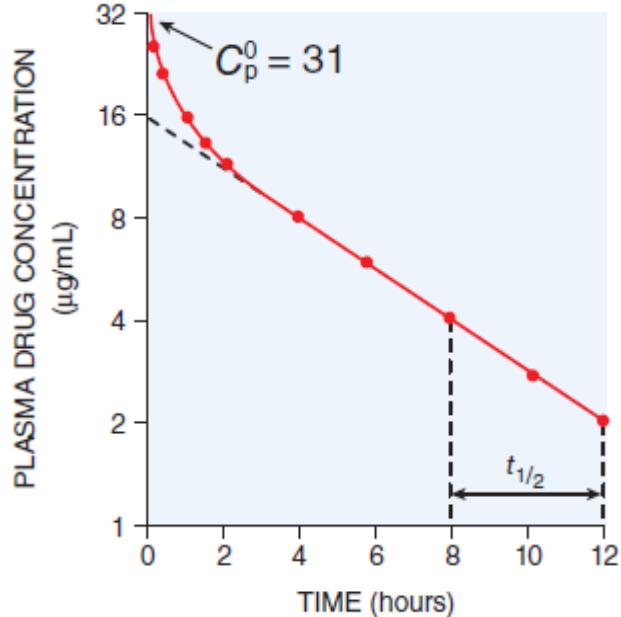
- Drugs with high E (Flow dependent elimination): e.g. Propranolol.
- Drugs with low E (Enzyme dependent elimination): e.g. Warfarin.
- Drugs with intermediate E (Both flow and enzyme dependent elimination): e.g. Acetaminophen

- **Importance of Clearance:**

- 1- Calculation of maintenance dose: **Maintenance dose = CL X Css**
- 2- Adjustment of the dose according to Creatinine Clearance (CLcr – normal =120 ml/min)
 - e.g. for drugs eliminated by tubular secretion as penicillins or glomerular filtration as gentamycin →
 - If CLcr < 50 ml/min → ½ adult dose is required
 - If CLcr < 30 ml/min → 1/3 - ½ adult dose is required

Plasma half-life of drugs ($t_{1/2}$):

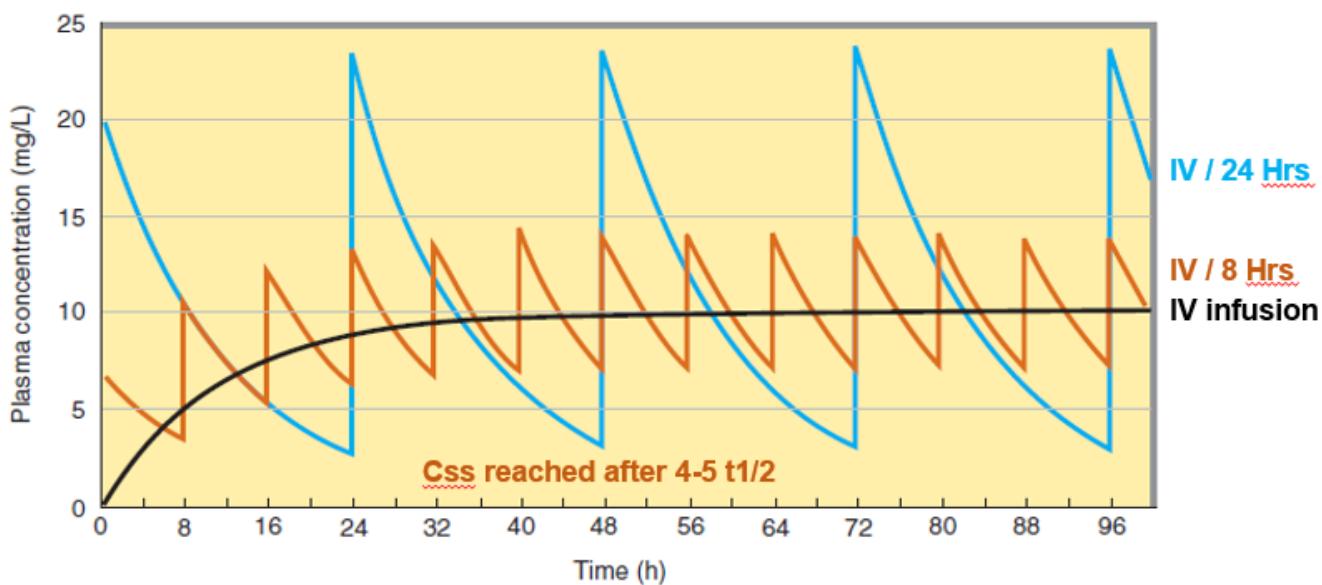
- **Definition:** Time required by the body to reduce plasma concentration of a drug by 50%. It depends on kinetics of drug elimination (metabolism and excretion).
- **About 90%** of a drug is eliminated within 4 $t_{1/2}$
- **Importance:** It determines:
 1. **Dosage interval (T):** frequency of drug administration (every $t_{1/2}$ is accepted)
 2. **Time taken by the drug to reach Css:** $4-5 t_{1/2}$ for 1st order kinetics
 3. **Drug toxicity:** Prolonged $t_{1/2}$ → drug accumulation and toxicity.



N.B.: Drugs with short $t_{1/2}$ e.g. penicillins can be administered by IV infusion, sustained release (SR) preparation or large infrequent doses (if the drug is safe - maximal dose strategy e.g. Amoxicillin 1g/ 12 Hrs).

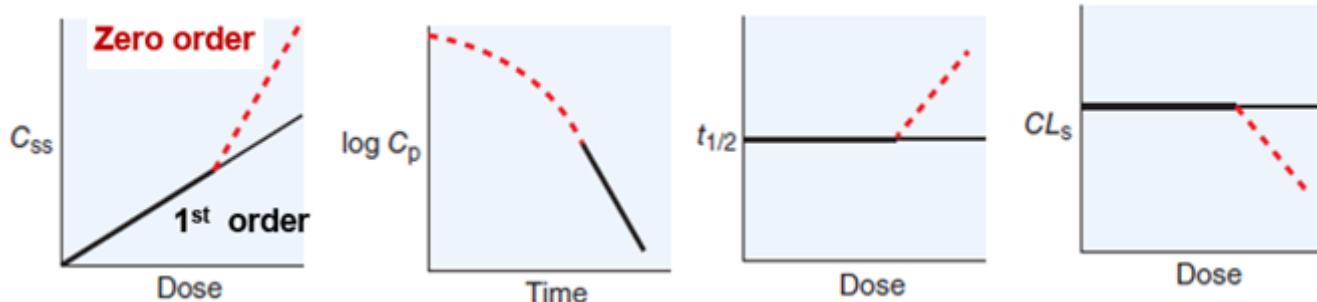
Steady state concentration C_{ss} :

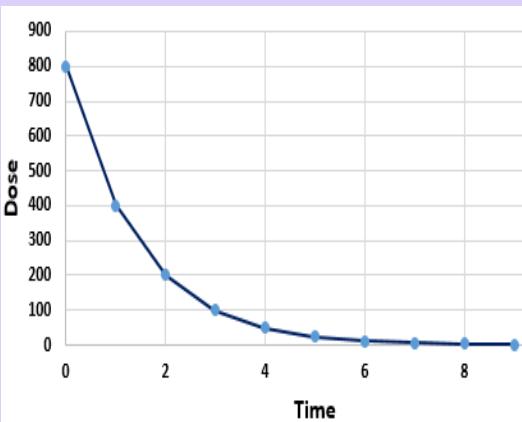
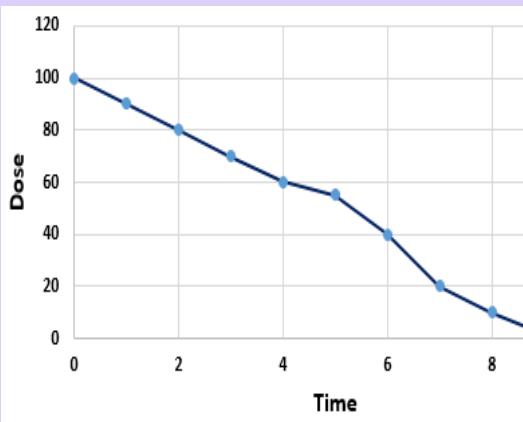
- **Definition:** Plasma concentration of a drug at which rate of absorption = rate of elimination.
- **In first order kinetic:** 95 % of C_{ss} is reached after $4-5 t \frac{1}{2}$
- **In zero order kinetics:** No C_{ss}
- **Factors affecting C_{ss} :**
 1. Infusion rate (directly proportional)
 2. Apparent volume of distribution (V_d) (inversely proportional)
 3. Total body clearance (Cl_{total}) (Inversely proportional)



Patterns of drug kinetics:

- Drugs may follow one of two pharmacokinetic patterns:



	First - Order kinetics	Zero - Order kinetics
Description	<ul style="list-style-type: none"> - <u>Constant fraction (%)</u> of the drug is eliminated / unit time which is <u>proportional</u> to its plasma concentration - i.e. 100 mg → 4h → 50 mg → 4h → 25 mg → 4h → 12.5 mg. 	<ul style="list-style-type: none"> - <u>Constant amount (mg)</u> of the drug is eliminated / unit time which is <u>not proportional</u> to its plasma concentration - i.e. 80 mg → 4h → 70mg → 4h → 60 mg → 4h 50 mg → 4h 40
Rate of drug elimination	<ul style="list-style-type: none"> - <u>Variable</u> (Concentration dependent) - ↑ plasma drug concentration → ↑ rate of elimination 	<ul style="list-style-type: none"> - <u>Constant</u> (not concentration dependent) - ↑ plasma drug concentration → No ↑ rate of elimination
t $\frac{1}{2}$	<u>Constant</u> with ↑ dose	<u>Variable</u> with ↑ dose
CL	<u>Constant</u> with ↑ dose	<u>Decreases</u> with ↑ dose
C _{ss}	<p>After 1 t $\frac{1}{2}$ → 50% of C_{ss}</p> <p>After 3 t $\frac{1}{2}$ → 75% of C_{ss}</p> <p>After 4-5 t $\frac{1}{2}$ → 95% of C_{ss}</p>	<u>No C_{ss}</u>
Conc. Time curve	<p>Linear</p>  $Ct = C_0 * e^{-kt}$	<p>Non linear</p> 
Toxicity	Less toxic	More toxic (cumulative)
Example	Most drugs	Ethanol (most drugs had been withdrawn due to toxicity)
Dose	No need for monitoring of plasma conc. or dose adjustment	Needs monitoring of plasma conc. and dose adjustment according to clinical condition

N.B.: Phenytoin, Aspirin, Theophylline exhibit saturation kinetics:

- At small doses → They follow 1st order kinetics
At larger doses → All mechanisms of elimination become saturated → They follow zero order kinetics
- Modest change in the dose may lead to unexpected toxicity and drug interactions are common

DOSAGE OF DRUGS (POSOLOGY)

⑧ **Therapeutic dose:** Average adult dose required to produce a therapeutic effect.

⑧ **Maximal tolerated dose:** Largest dose that can be taken safely.

⑧ **Loading dose:** Dose required to increase plasma concentration to therapeutic level.

Or dose needed to reach Css

$$LD = Vd \times Css$$

⑧ **Maintenance dose:** Dose required to maintain plasma concentration at therapeutic level attained by initial dose

Or dose needed to keep Css

$$MD = Cl \times Css$$

⑧ **Lethal or fatal dose:** Dose that produces death.

- **LD50** = Dose that induces death in 50% of experimental animals.

- **ED50** = Dose that induces a certain therapeutic effect in 50% of experimental animals

- **Therapeutic index (TI):**

$$TI = \frac{LD\ 50}{ED\ 50}$$

- It is a measure for drug's safety
- The higher the index → the safer the drug.
- Some drugs have narrow safety margin as digoxin, warfarin and phenytoin, theophylline → should be administered cautiously and may require monitoring of their plasma concentration.

Pharmacodynamics

Pharmacology:

The science that deals with the drugs as regards:

- Source, physical and chemical properties.
- Pharmacokinetics (kinetics of absorption, distribution, metabolism and excretion).
- Pharmacodynamics (biological effect and mechanism of action on different body organs = what the drug does to the body).
- Pharmacotherapeutics (uses in treatment of diseases in specific dosage forms and interactions with other drugs).
- Adverse effects (unwanted actions) and contraindications (toxicology)

Types of pharmacodynamics effects:

The drugs exert their effects by acting:

- 1- Local or topical action, where drugs act on site of application e.g. ointment or eye drops.
- 2- Systemic or general action, where the drug acts after administration and distribution by circulation to various tissues.
- 3- Reflex or remote action, where the drug acts locally at one site to produce reflex action elsewhere.

Mechanisms of drug actions:

- 1- Physical action: As adsorption e.g. kaolin and pectin in cases of diarrhea.
- 2- Chemical action: As neutralization of hyperacidity by antacids.
- 3- Interference with cell division as cytotoxic drugs.
- 4- Inhibition of enzymes e.g. choline esterase inhibitor drugs.
- 5- Interference with normal metabolic pathways e.g. sulfonamide interfere with para-aminobenzoic acid which is essential metabolite for bacteria.
- 6- Action on cell membrane: e.g. local anesthetics.
- 7- Action on cell receptors: The most common method by which most drugs generally act e.g. acetyl choline on cholinergic receptors, adrenaline on adrenergic receptors.

Receptor

- It is a chemically reactive (chemosensitive) macromolecule, protein in nature, present inside or on the surface of the cell .it is the site of drug attachment and action, can be stimulated by agonist drugs and blocked by antagonist drugs

Classification of receptors:

1- Ligand gated ion channels:

- They act by regulation of the flow of ions across cell membranes
- Response is very rapid
- Examples: Nicotinic Receptors: Stimulated by acetylcholine and results in sodium influx, activation of contractions in skeletal muscle

2- G-Protein Coupled

- linked to a G-protein
- Binding of appropriate ligand to extracellular region → activates G-Protein → activated G-protein changes the activity of an enzyme.
- Response last several seconds to minutes.
- **They are subdivided according to secondary messenger into:**
 - a. **Gs protein:** stimulate adenyl cyclase or guanyl cyclase e.g. B1&B2 &D1 receptors.
 - b. **Gi proteins:** decrease adenyl cyclase or guanyl cyclase e.g. α_2 , M2 and D2 receptors.
 - c. **Gq proteins:** stimulate phospholipase C e.g. α_1 , M1, M3, H1 and 5HT1 receptors.

3- Enzyme-Linked

- Have a cytosolic enzyme activity as an integral component of their structure/function.
- Binding of a ligand to extracellular domain activates or inhibits cytosolic enzyme activity.
- **Examples:** Insulin receptors which activate tyrosine kinase enzyme.
- **Duration of response:** minutes to hours

4- Intracellular receptors:

- Entirely intracellular, ligand must diffuse into the cell to interact with it.
- The ligand must have sufficient lipid solubility to be able to move across cell membrane.
- Activated ligand-receptor complex migrated to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of gene expression.
- **Example:** Steroid receptors
- **Duration of response:** Much longer, hours to days

Drugs are classified into agonist, antagonist, partial agonist and inverse agonists according to action on cell receptors:

I. Agonist: a drug which has the following properties:

- a. Affinity for a specific receptor i.e. the drug can fit into this receptor and bind with it producing drug-receptor complex.
- b. High efficacy (intrinsic activity): The ability of the drug to produce a biological or pharmacological response. (The drug produces its effect by inducing changes in the receptor and hence in the effector tissue)
- c. Rapid association and dissociation rate of the drug receptor complex to allow receptors to combine with fresh agonist e.g. Acetylcholine on cholinergic receptors, adrenaline on adrenergic receptors.

II. Antagonist: a drug that inhibits the action of full agonist:

Types of antagonist drugs:

1- Competitive antagonist: has the following properties:

- a. Affinity to specific receptor.
- b. No efficacy i.e. the drug receptor complex can-not produce pharmacological response (the antagonist can-not produce changes in receptors and hence in the effector tissue.)
- c. Slow dissociation rate of the drug receptor complex, consequently, prevents or blocks the action of the agonist by occupying its receptors.

- d. Both the agonist and the antagonist compete for the receptors. The action of the antagonist is reversible and can be abolished by excess of agonist.
- e. The addition of competitive antagonist decreases the affinity and potency but does not affect maximal efficacy (the maximal efficacy of agonist can be reached in the presence of competitive antagonist by addition of excess agonist).
- f. **Examples:** atropine on cholinergic receptors and beta adrenergic blockers on adrenergic receptors.

2. Non-competitive antagonist:

- a. Both the agonist and antagonist do-not compete for the receptors.
- b. The action of the antagonist can-not be overcome by excess of the agonist.
- c. The addition of non-competitive antagonist not affect potency but decrease affinity and maximal efficacy of full agonist.
- d. **Example:** Hexamethonium blocks the effect of acetyl choline on nicotinic receptors in autonomic ganglia by blocking sodium channels associated with receptors.

III. Partial agonist (dualist): a drug which has the following properties:

- a. Affinity for specific receptor
- b. Low efficacy: it can occupy all available receptors but evoke response less than that of an active agonist.
- c. Moderate dissociation rate, consequently, the partial agonist at first stimulates receptors and lastly blocks the effect of true agonist.
- d. **Examples:** dichlorisoprenaline is partial agonist for beta adrenergic receptors.

IV. Inverse agonist: a drug which has the following properties:

- a. Affinity for specific receptor.
- b. Efficacy is opposite to that of endogenous agonists
- c. **Examples:**
 - Valsartan binds to angiotensin AT1 receptors and decreases cardiac cell proliferation which is opposite to the effect of endogenous agonist angiotensin II that increase proliferation of cardiac cell.

Factors affecting drug action

1. Dose: It is the amount of the drug given to the patient at a time.

- a. **Therapeutic dose:** the average dose given to adult patient to produce therapeutic effect.
- b. **Maximal tolerated dose:** the largest dose of drug that can be taken safely.
- c. **Initial dose:** the dose used at start of treatment.
- d. **Maintenance dose:** the dose required to maintain the therapeutic effect.
- e. **Toxic or lethal dose:** dose that produces death.

LD₅₀ = dose that produces death in 50% of experimental animal.

ED₅₀ = median effective dose of a drug in 50% of animals.

Therapeutic index: LD₅₀ / ED₅₀. It is a measure for safety of drugs. The higher the index the safer the drug. Some drugs have narrow safety margin as digoxin, warfarin and phenytoin.

2. Age, weight and surface area:

➤ **Adult dose** is calculated depending on age from 20 to 60 years old, and weight about 70 kg.

➤ **Children dose:**

According to age:

Young formula:

$$\text{Child dose} = \text{adult dose} \times \text{age in years} / \text{age in years} + 12$$

Diluting formula:

$$\text{Child dose} = \text{adult dose} \times \text{age in years} / 20$$

According to weight (for infant less than 1 year):

$$\text{Infant dose} = \text{adult dose in pounds} / 150$$

- Newborn infant especially premature infants are more susceptible to the effect of the drugs because:

- a. Underdevelopment of many hepatic microsomal enzymes that detoxify drugs.

- b. Reduced renal excretion of drugs due to low glomerular filtration and renal blood flow
 - c. Lower total plasma protein levels.
 - d. Immaturity of blood brain barriers (B.B.B), e.g. Infants are more sensitive to morphine and chloramphenicol.
- Elderly patients have impaired ability to detoxify and excrete drugs.
 - **The elderly dose:**
 - From 60 - 80 years old = 3/4 adult dose.
 - Above 80 years old = 1/2 adult dose

2- Sex:

- Female patients need less dose than male patients because:
 - a. Female contain more fatty tissues (which have low oxidation rate and are inert tissues).
 - b. Estrogens inhibit hepatic microsomal enzymes, while androgens stimulate these enzymes.
- During menstrual period: salicylate and strong cathartics should be avoided as these drugs increase bleeding.
- During pregnancy: teratogenic drugs, uterine stimulants and strong cathartics should be avoided.
- During labour: morphine should be avoided as it causes respiratory depression of fetus.
- During lactation: drugs as oral anticoagulants and chloramphenicol can be excreted into milk and cause harmful effects to infant

3- Route of administration

- Magnesium sulfate, when given orally act as a purgative, while when given IV it cause depression to cardiac, skeletal, smooth muscles and C.N.S.
- Doses of drugs given by injection route are less than that by oral route and have rapid onset of action.

4- Time of administration:

- Non-irritant drugs are given before meals to enhance absorption of these drugs.
- Irritant drugs are given after meals to avoid gastric irritation.
- Drugs with C.N.S stimulant effect, as ephedrine should not be given at night to avoid insomnia.
- Drugs which cause drowsiness as antihistamine drugs should not be given at day time.

5- Tolerance: Failure of responsiveness to the usual dose of a drug.

Types:

I. Acquired tolerance:

- It is acquired failure of responsiveness to the usual dose of the drug.
 - It occurs on repeated administration of the drug.
 - More drugs is needed to obtain the original effect.
 - It is reversible i.e. it disappears when the drug is stopped for some time.
 - **Examples** of drugs causing tolerance: morphine, nitrates, xanthines and barbiturates.
- **Mechanism of acquired tolerance:** It is due to one or more of the following factors:
- a. Decreased intestinal absorption of drugs.
 - b. Increased renal excretion of drugs.
 - c. Increased metabolism of drugs due to enzyme induction.
 - d. Cellular adaptation to the presence of the drug.
 - e. Decrease sensitivity of receptors.
 - f. Down regulation: Decreased number of receptors due to eating of receptors. It occurs with agonist drugs e.g. ephedrine.
 - g. Development of anti-hormone against insulin and parathormone.

➤ **Special types of acquired tolerance:**

1. Tachyphylaxis:

- It is acute rapid development of acquired tolerance. The original effect can-not be obtained by increasing the dose.
- **Example:** tachyphylaxis to action of ephedrine on blood pressure.

If ephedrine is given to anaesthetized animal, it increases PB but subsequent equal doses of ephedrine at regular short intervals produce gradually decreasing responses and finally no change of BP.

Mechanism of tachyphylaxis to ephedrine:

- a. Rate of dissociation of ephedrine is moderate so fewer and fewer receptors are available.
- b. Down regulation of receptors
- c. Depletion of noradrenaline stores as ephedrine act directly on receptors and indirectly by release of noradrenaline so subsequent doses lead to depletion of stores.

2. Cross-tolerance: tolerance for drugs of related groups e.g. morphine and pethidine.

3. Tissue tolerance: to some actions of the drug. e.g. morphine tolerance to analgesic and respiratory depressant actions but not to its miotic and constipating actions.

4. Bacterial resistance to antibiotics.

II. Congenital tolerance:

1. Racial: ephedrine is not mydriatic in negros.

2. Species: rabbits tolerate large amounts of belledona as rabbits blood and plasma contain atropinase enzyme which rapidly detoxicate atropine.

3. Individual tolerance: biological variation that exists within any population, thus a certain individual may be tolerated to a certain drug, but not the rest of this community. This may be due to genetic factors.

6- Drug intolerance (hypersusceptibility):

- It is exaggerated pharmacological response to the usual dose of the drug e.g. adrenaline in thyrotoxicosis.

7- Genetic abnormalities (idiosyncrasy):

- It is congenital abnormal reactions to drugs due to genetic abnormality. It is commonly due to genetic deficiency of certain enzymes.

- It occurs with some drugs.
- It occurs in some individuals.

➤ Examples:

- a. Some drugs as antimalarial, sulphonamide, salicylates may induce hemolytic anemia in patients with congenital deficiency of glucose-6-phosphate dehydrogenase enzyme in R.B.Cs because these drugs are oxidizing agents, render RBCs more readily haemolyzable in presence of G-6-P dehydrogenase deficiency.
- b. Succinyl-choline apnea: occur in patients with congenital deficiency of plasma pseudo-choline esterase enzyme.

8- Drug allergy (hypersensitivity):

- It is acquired abnormal reactions to drugs due to antigen - antibody reaction.
- It is unrelated to the dose.
- It occurs when the drug is given repeatedly.
- Not all people are sensitive to the same drug.
- It may occur with many drugs as penicillin, aspirin, thiouracil etc.

Mechanism of hypersensitivity:

1- Exposure to the antigen which may be:

- a. The drug itself if it is protein in nature or of high molecular weight.
- b. The drug of low molecular weight or one of its metabolites may combine with one of body proteins to form antigenic compound The drug is called hapten in this case.

2- The antigen (drug) sensitizes the tissue to produce specific antibodies for each

antigen. These antibodies are either circulating in blood or fixed on the walls of the mast cells.

- 3- Re-exposure to the same antigen (drug) lead to antigen-antibody reaction on the walls of mast cells with degranulation of these cells and release of mediators of allergy (autacoids) as histamine, serotonin, bradykinins and slowly reacting substance of anaphylaxis, which produce manifestations of allergy.

Manifestations of drug allergy:

- 1- **Acute allergy (anaphylactic reactions):** Occurs within one hour from drug administration in form of anaphylactic shock, acute bronchial asthma, laryngeal edema, generalized urticaria and conjunctivitis
- 2- **Sub-acute allergy:** Occurs between 1 - 24 hours in form of skin rash, bronchial asthma, rhinitis, fever and photosensitivity.
- 3- **Delayed allergy:** occurs in form of blood reactions (blood dyscrasias) e.g. thrombocytopenic purpura, agranulocytosis and haemolytic reactions.

9- Pathological state:

Some drugs act in presence of disease. e.g.:

- Aspirin lower body temperature in case of fever but without effect on normal body temperature.
- The dose of most drugs should be reduced in patients with renal impairment due to decreased drug excretion
- The dose of most drugs should be reduced in patients with hepatic impairment due to decrease hepatic drug metabolism.
- The effect of subcutaneous drugs is delayed in patients with shock or heart failure due to slow of cutaneous circulation
- Iron absorption is increased in anemic patients.
- The bronco-constrictor effect of cholinomimetics, non-steroidal anti-inflammatory drugs is exaggerated in patients with bronchial asthma.

10- Cumulation:

This occurs when the rate of administration of the drug exceeds the rate of its metabolism or excretion which leads to drug accumulation in the body and toxic effect e.g. digitalis.

11- Emotional factors:

- Administration of placebo (inert medication formed of sucrose or lactose) may give therapeutic effect in psychic patient (just to please him).

➤ Uses of placebo:

- 1- Evaluation of new drugs. 2- Psychotherapy.

12- Drug dependence:

It is a phenomenon which is related to tolerance. It takes the form of habituation or addiction:

- a. Habituation:** it is psychological or emotional dependence for a drug. If the drug is suddenly stopped, the individual may develop some emotional distress for short period of time but no physical disturbance occur e.g. coffee and tea habits.
 - b. Addiction:** it involves psychic and physical dependence for a drug. The body tissues become adapted on the drug to function normally on repeated administration of the drug. When the drug is stopped suddenly severe withdrawal symptoms or an abstinence syndrome occur, some of these symptoms are the reverse of the normal pharmacological actions of the drug e.g. morphine, heroin and tobacco smoking.

13- Drug interactions:

It is the biological response mediated by simultaneous administration of more than one drug. The mechanisms by which drug interact include:

- a- Addition or summation:** the resultant action is the algebraic sum of the individual actions of the two drugs combined. In such case only half the normal dose of each drug is required to produce the desired effect. e.g. histamine and ACH on B.P.

- b- **Synergism:** both drugs are biologically active, but when combined, the net effect is more than the sum of their individual effects e.g. sulphonamide and trimethoprim.
- c- **Potentiation:** this occurs when one drug has no apparent action on one system but increase the effect of another drug on that system. e.g. barbiturates potentiate the analgesic effect of salicylates.
- d- **Antagonism:** this occurs when drugs with opposing actions are given simultaneously it may be:
- 1- Physiological antagonism: drugs with opposing actions on the same physiological system e.g. histamine and adrenaline.
 - 2- Chemical antagonism: one drug reacts chemically with an active drug to form an inactive compound e.g. heparin and protamine sulphate.
 - 3- Pharmacological antagonism:
 - Competitive antagonism
 - Non-competitive antagonism

Adverse and Toxic Effects of Drugs

A. Predictable Adverse Effects (Type A)

1. **Side effects:** Unavoidable, undesirable normal actions of drug e.g., Captopril as antihypertensive causes hyperkalemia.
2. **Secondary effects:** Long use of oral broad spectrum antibiotics may lead to superinfection by monilia.
3. **Overdose:** Exaggerated normal action of drug either by single large dose (Insulin LD) or cumulation of several small doses (Digitalis).
4. **Supersensitivity (Drug intolerance).**
5. **Tolerance.**
6. **Drug Dependence (Drug – abuse).**
7. **Iatrogenic Drug (Induction of disease)** e.g., Chlorpromazine induces parkinsonism.
8. **Cytotoxic effect: Drugs may produce cell damage e.g.,**
 - Hepatic damage (Halothane, paracetamol).
 - 8th Cranial nerve damage (Streptomycin).
 - Bone marrow depression (Chloramphenicol).
 - Nephrotoxicity (Sulphonamides, Aminoglycosides).
9. **Drug Interactions.**

B. Unpredictable Abnormal Response (Type B)

1. **Hypersensitivity (Allergic) reaction**
2. **Idiosyncrasy = Phamacogenetics**

C. Continuous (Type C)

Adverse reactions due to long term (chronic) use of drug e.g., osteoporosis and corticosteroids.

D. Delayed effect (Type D)

Occurs after latent period from chronic administration of the drug, it includes teratogenicity and carcinogenicity e.g.,

1. Teratogenicity: Drug induces fetal abnormalities especially in first trimester e.g. Tetracyclines and Phenytoin.

2. Carcinogenicity: e.g. Tobacco smoking induces bronchogenic carcinoma.

E. End (Type E)

Adverse reactions after drug withdrawal e.g., acute addisonial crisis with sudden withdrawal of chronic corticosteroid therapy.

Drug interaction

Definition:

It is the biological response mediated by simultaneous administration of more than one drug.

Types of drug interactions:

1-pharmaceutical interaction.

Result from chemical or physical reaction between drugs outside the body

2-pharmacokinetic interaction.

a- Absorption

➤ Gastric motility

- Metochlopramide increases gastric motility → decreases absorption of drugs absorbed from the stomach e.g. digoxin.
- Atropine has opposite effects

➤ Intestinal motility

- The more intestinal motility → the less absorption.
- Diarrhea decreases gastrointestinal drug absorption.
e.g.: Purgatives decrease absorption of co-administered drugs.

b- Gastric pH

- Acidic drugs (aspirin) absorbed in the stomach
- Antacid → decrease absorption of aspirin
- Basic drugs (ephedrine) absorbed in the intestine

c- Food:

- Increase secretion of gastric juice → decrease absorption of ampicillin
- Increases bile secretion → increase absorption of fat soluble drugs e.g. propranolol

d- Distribution:

- Sulphonamides can displace bilirubin producing hyperbilirubinemia and kernicterus in infants
- Aspirin can displace oral anticoagulants

e- metabolism:

- Estrogen is hepatic enzyme inhibitor → decrease the metabolism of oral anticoagulants

f- Excretion:

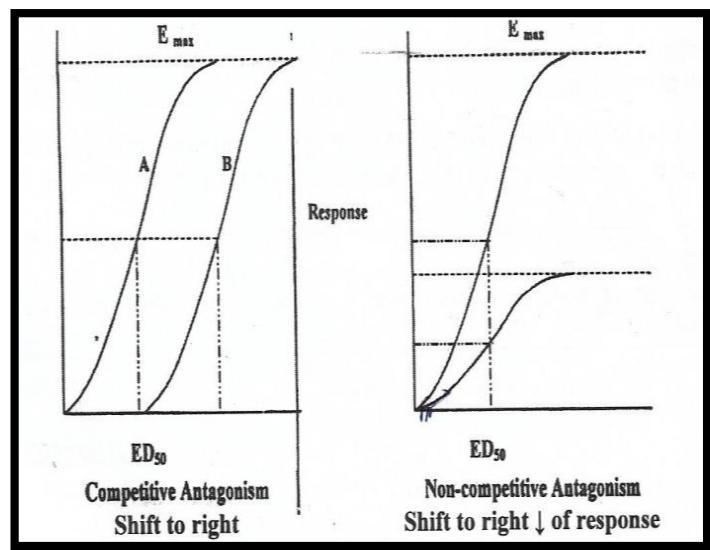
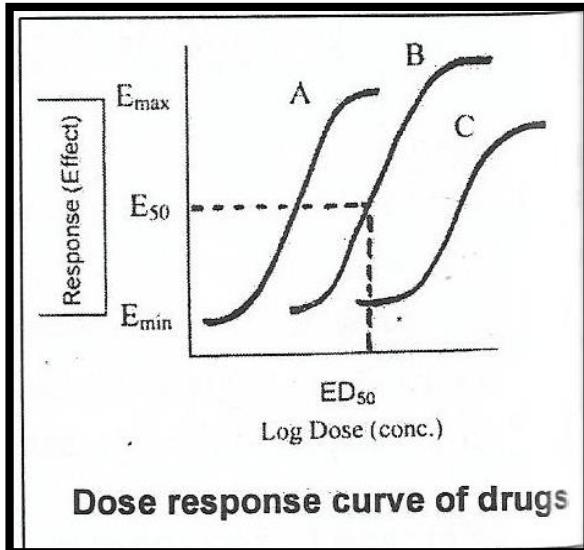
- Alkalization of urine → increase excretion of acidic drugs (aspirin)
- Acidification of urine → increase excretion of basic drugs (ephedrine)

3-pharmacodynamic-interaction.

- a. **Interaction at receptor = pharmacological antagonism (competitive and non-competitive antagonism).**
- b. **Interaction at the same physiological system:** e.g: adrenaline &histamine
- c. **Interaction involved combined effects:** Combined use of 2 or more drugs with toxic effect on the same organ can greatly increase the organ damage. Results of drug interaction (Addition or summation, Synergism, Potentiation and antagonism).

Dose Response Curve of Drugs

1. Shows relation between Log Dose and Response (Effect) of a drug.
2. It is useful to know Effects (responses):
 - Minimal effect (E_{\min}). Maximal effect (E_{\max}) and Submaximal effect 50% (E_{50}).
3. It is useful to know doses that produce minimal effect (ED_{\min}). Maximal effect (ED_{\max}) and submaximal effect 50% ED_{50} .
4. It is useful to compare drugs:
 - Efficacy:** is the maximal response produced by the drug $B > A > C$.
 - Potency:** is a measure of how much drug is required to elicit a response $A > B > C$.
5. It is useful to determine the type of a blocker (antagonist) whether:
 - a. Competitive → parallel shift to right (\downarrow potency) with same E_{\max} (Same efficacy).
 - Excess agonist can displace the antagonist from receptors.
 - b. Non-competitive → Non-parallel shift to right with decreased E_{\max} (\downarrow efficacy).
 - Excess agonist cannot displace the antagonist from receptors.



GRADED DOSE-RESPONSE CURVE

&

VOLUME OF DISTRIBUTION

dose-response curve:

it is a relationship between the drug dose(log dose) on the X-axis and the response (drug effect) on the Y-axis.

Advantages of dose response curve:

1. Useful to know effect of drug (response):-
 - minimal effect (E_{min}) -maximal effect (E_{max})
 - sub maximal effect 50% (E_{50})
2. Useful to know doses that produce :
 - minimal effect (ED_{min}) -maximal effect (ED_{max})
 - sub maximal effect 50% (ED_{50})
3. useful to compare drugs:

Efficacy: is the maximal response produced by the drug B>A>C

Potency: a measure of how much drug is required to elicit a response A>B>C

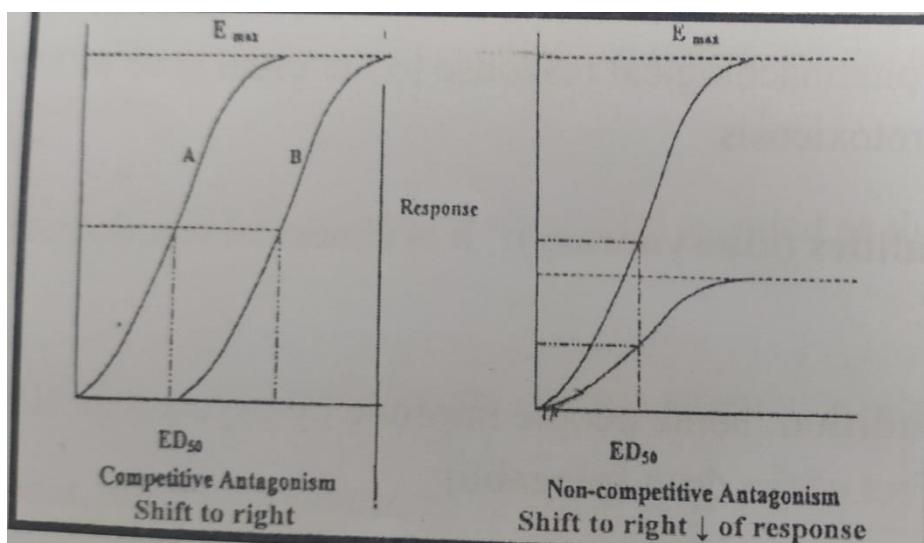
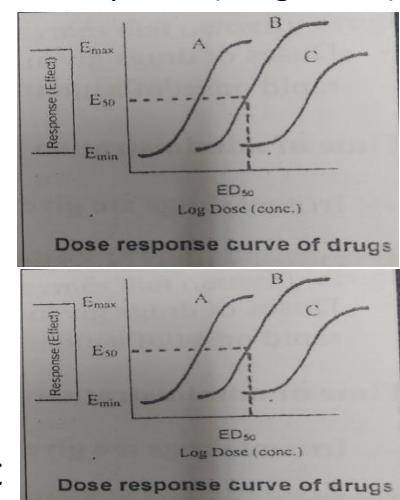
4. useful to determine type of blocker (antagonist):-

competitive:

- parallel shift to right (decrease potency) with same E_{max} (same efficacy)
- excess agonist can displace the antagonist from the receptor

Non competitive:

- No parallel shift to right (decrease potency) with decrease E_{max} (decreased efficacy)
- excess agonist can not displace the antagonist from the receptor, it may be reversible or irreversible.



Bioavailability:

- ❖ It is a term used to describe the proportion of administered drug reaching the systemic circulation in unchanged manner.
- ❖ Bioavailability is 100% following IV but drugs given by other routes of administration, the proportions varies in different patients .

Factors affecting bioavailability:

1. **Factors related to the drug** :drug dosage, lipid solubility and pKa.
2. **Factors related to drug formulation** :the rate of disintegration and dissolution.
3. **Factors related to patient** : pH and surface area of absorbing site, presence of food or other drugs .
4. **Enterohepatic circulation** : recycling of the drug between the intestine and the liver .
N.B: The drugs undergoing enterohepatic circulation are conjugated in liver and excreted in bile into small intestine where they are deconjugated and reabsorbed from intestine to liver .This leads to increase plasma concentration and duration of drug action.
5. **First pass metabolism** : metabolism of the drug before reaching the central compartment (general circulation) .
Sites of first pass metabolism are:
 - Liver : for propranolol ,verapamil ,nitroglycerine.
 - Intestinal wall: for tyramine , alpha methyl dopa.
 - Lung for nicotine and isoprenaline.

Apparent volume of distribution(Vd):

- ❖ It is a measure of drug distribution.
- ❖ It is the volume of biological fluids required to contain the total amount of the drug (Q) at the same concentration as that in plasma (Cp).

$$V_d = \frac{Q \text{ Amount of the drug in the body (drug dose)}}{C_p \text{ drug concentration}}$$



Significance of volume of distribution:

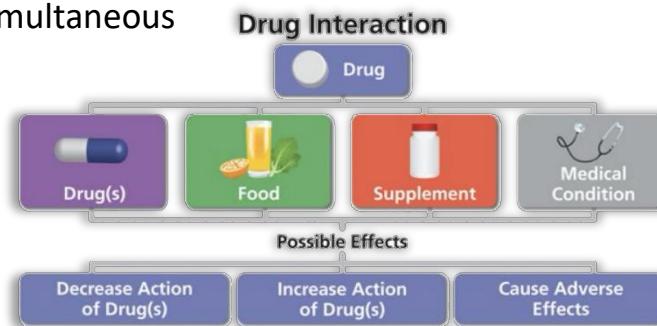
- ❖ It is a measure of drug **distribution and storage**. Drugs with high Vd are more likely to be stored and have long half life.
- ❖ It is a measure of **tissue uptake** of the drug :
 - low Vd -----limited tissue uptake.
- ❖ It may predict the ability of the drug to be **removed** from plasma by **hemodialysis** e.g. drugs with high Vd are not suitable for removal by hemodialysis.
- ❖ It is required to **calculate the loading doses** of cumulative drugs.

Drug interactions

Definition: It is the biological response mediated by simultaneous administration of more than one drug.

Types of drug interactions:

- Interactions occurring before drug administration (outside the body).
- Interactions occurring after drug administration (inside the body).
 - Pharmacokinetic drug interaction.
 - Pharmacodynamic drug interactions.



Interactions occurring before drug administration: This usually occurs as a result of physical or chemical reactions between two drugs.

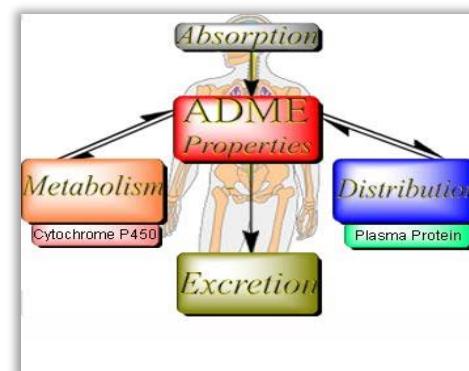
- **During pharmaceutical formulation.**
 - e.g. Calcium lactate as a diluent with tetracyclines → insoluble chelate
- **Mixing of drugs with intravenous infusions.**
 - May affect PH, solubility or activity of components, Examples:
 - Calcium chloride should not be mixed with tetracyclines
 - Hydrocortisone should not be mixed with heparin.
 - Vitamin B12 should not be mixed with vitamin C and vitamin K.
- **Simple mixing of drugs before administration.**
 - Thiopentane (alkaline) + succinylcholine (acidic) → neutralization.
 - Protamine sulfate (basic) + heparin (acidic) → inactivation

Pharmacokinetic interactions

Interactions occurring after drug administration (inside the body).

❖ Absorption:

- **Gastric motility.**
 - Metoclopramide ↑ gastric motility → ↑ absorption of propranolol and paracetamol and ↓ absorption of digoxin
 - Atropine has opposite effects
- **Intestinal motility.**
 - The more intestinal motility → the less absorption.
 - Diarrhea decreases gastrointestinal drug absorption. e.g. Purgatives decrease absorption of coadministered drugs.



- **pH changes.**

- Gastric acidity → ↑ absorption of weak acids e.g. aspirin and phenobarbitone.
- Intestinal alkalinity → ↑ absorption of weak base e.g. atropine and ephedrine.

- **Food.**

- Increase secretion of gastric juice → decrease absorption of ampicillin
- Increases bile secretion → increase absorption of fat soluble drugs e.g. propranolol

- **Binding or Chelation.**

- Tetracyclines form chelates with salts of Mg, Ca, Al and Fe → insoluble complexes.
- Activated charcoal may adsorb sulphonamides and aspirin.

❖ Distribution

- The protein bound fraction is pharmacologically inactive while the activity as well as the toxicity of the drug depends on the concentration of the free fraction.
- One drug may displace another from its binding sites on plasma proteins depending on their relative concentrations and on the affinity of each drug for these sites. The displaced drug will show higher free blood levels associated with enhanced activity and possibly enhanced toxicity. **Examples:**

- Phenylbutazone and sulphonamides can displace warfarin → haemorrhage.
- Phenylbutazone, salicylates and sulphonamides displace tolbutamide and chlorpropamide → hypoglycemia.
- Salicylates and sulphonamides can displace bilirubin → hyperbilirubinemia.

- In infants since they lack sufficient quantities of glucuronyl transferase to conjugate the excessive amounts of free bilirubin. In consequence, bilirubin passes the blood brain barrier leading to kernicterus.

❖ Metabolism

Metabolism is mainly controlled by cellular hepatic enzymes:

- **Enzyme activators (inducers)**

- They increase the rate of enzyme synthesis e.g. rifampicin, phenytoin, phenobarbitone and androgen.
- Enzyme induction results in:
Decrease activity of some drugs as oral anticoagulants, oral contraceptives due to increase metabolism.

- **Enzyme inhibitors**

- As cimetidine, estrogen, progesterone, tolbutamide increase the effects of other drugs (exaggeration)

❖ Excretion

- **Competition for active renal tubular secretion.**

- e.g. Probenecid # renal tubular secretion of penicillin. Probenecid interferes in the same way with the active transport of other acidic drugs, e.g. indomethacin.

- **Changes in urinary pH.**

- Acidification of urine → ↑ excretion of basic drugs e.g. amphetamine and antihistaminics.
- Alkalization of urine → ↑ excretion of acidic drugs e.g. barbiturates and salicylates.

Pharmacodynamic interaction

❖ Inter action at receptor = pharmacological antagonism

Competitive antagonism	Non-competitive antagonist
Agonist and the antagonist compete for the receptor	Agonist and the antagonist does not compete for the receptor
Action of the antagonist can be overcomed by excess of the agonist Eg: atropine, propranolol	Action of the antagonist cannot be overcomed by excess of the agonist Eg: phenoxybenzamine
<p>Competitive Antagonism</p> <p>Maximum efficacy remains unchanged in the presence of a competitive antagonist</p>	<p>NON COMPETITIVE ANTAGONISM</p> <p>Maximum efficacy is reduced</p>

Efficacy: is the maximal response produced by the drug

Potency: is a measure of how much drug is required to elicit a response

❖ **Interaction at the same physiological system:**

- Eg: adrenaline & histamine.

❖ **Interaction involved combined:**

- Combined use of 2 or more drugs with toxic effect on the same organ can greatly increase the organ damage.
- Results of drug interaction (Addition or summation, Synergism, Potentiation and antagonism).

Results of drug interaction

• **Addition or summation:**

- The resultant action is the algebraic sum of the individual actions of the two drugs combined. In such case only half the normal dose of each drug is required to produce the desired effect.
- e.g. histamine and ACH on B.P.

• **Synergism:**

- Both drugs are biologically active, but when combined, the net effect is more than the sum of their individual effects
- e.g. sulphonamide and trimethoprim.

• **Potentiation**

- This occurs when one drug has no apparent action on one system but increase the effect of another drug on that system.
- e.g. barbiturates potentiate the analgesic effect of salicylates.

• **Antagonism:**

- This occurs when drugs with opposing actions are given simultaneously

Types of antagonism:

• **Physiological antagonism:**

- Drugs with opposing actions act on 2 different receptors on the same physiological system
- e.g. histamine and adrenaline.

• **Chemical antagonism:**

- one drug reacts chemically with an active drug to form an inactive compound
- e.g. neutralization (acid + base)

• **Pharmacological antagonism:**

- Competitive & non competitive

QUIZ

Q.A woman is taking oral contraceptives (OCs). Which of the following drugs is unlikely to reduce the effectiveness of the OCs?

- a. Phenytoin.
- b. Cimetidine.
- c. Phenobarbital.
- d. Rifampin.

Q.Drugs that are highly bound to albumin:

- a. Effectively cross the BBB.
- b. Are easily filtered at the glomerulus.
- c. Have a large Vd.
- d. Can undergo competition with other drugs for albumin binding sites.

Q.A competitive antagonist is a substance that:

- a. Interacts with receptors and produces submaximal effect.
- b. Binds to the same receptor site and progressively inhibits the agonist response.
- c. Binds to the nonspecific sites of tissue.
- d. Binds to one receptor subtype as an agonist and to another as an antagonist.

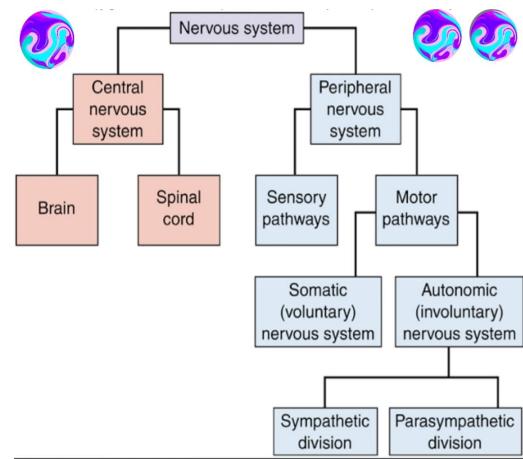
sympathomimetices

Autonomic nervous system

It regulates involuntary functions of the body which are:

- 1-Cardiovascular system(CVS)
- 2-Smooth muscles fibres(SMF)
- 3-Exocrine glands

Autonomic nervous system includes : Sympathetic - Parasympathetic



	Sympathetic	Parasympathetic action
Heart	Increase all cardiac properties	Decrease all cardiac properties except atrial conduction
Blood vessels	VC of skin and mm VD of skeletal and coronary blood vessels	Non innervated
Blood pressure	Hypertension	Hypotension
<u>SMF</u> Eye	Active mydriasis	Miosis
Bronchi	Bronchodilatation	Bronchcnstriction
GIT	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Urinary tract	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Sex organ	Ejaculation in males Relax uterine wall in female	Erection in male
Exocrine glands Salivary glands Sweet glands	Thick viscid secretion Increase	Profuse watery secretion No effect

Sympathetic

****Chemical transmitter**

****Types of adrenergic receptors:** α – β

****Mechanism of actions of adrenergic receptors:**

They are G protein coupled receptors

1-Alpha 1: Gq proteins: stimulate

Phospholipase C → ↑ IP₃ and DAG → ↑ intracellular Ca²⁺

2-Alpha 2: Gi proteins: decrease adenylcyclase → ↓ cAMP

3-Beta receptors: Gs proteins: stimulate adenylcyclase → ↑ cAMP

Beta 1

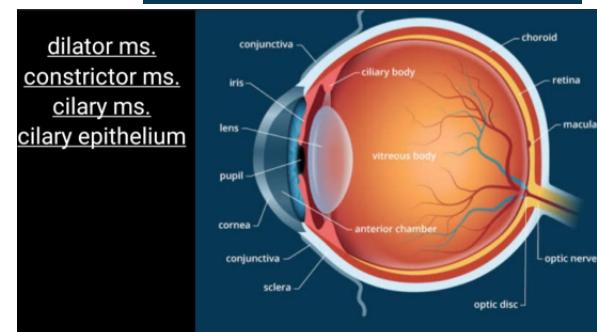
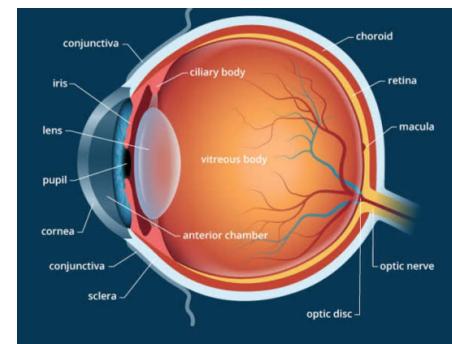
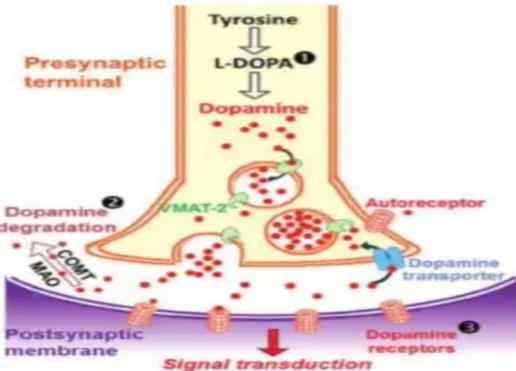
1-CVS: Heart: Increase all cardiac properties (Contractility-Conductivity-Excitability-Heart rate) and C.O.P -O₂ consumption

2-SMF: - Eye: Ciliary epithelium → ↑ aqueous secretion (↑ IOP)

3-Other actions:

-Kidney: Renin secretion

-CNS: ↑ sympathetic outflow



Beta 2

1-CVS: VD of skeletal and coronary blood vessels

2-SMF: - Eye: Ciliary epithelium → ↑ aqueous secretion (↑ IOP)

-Bronchi: relaxation

-GIT and urinary wall : relaxation

-Uterus: relaxation

3-Other actions:

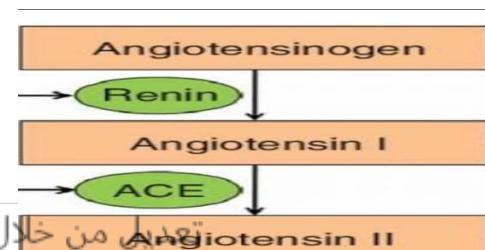
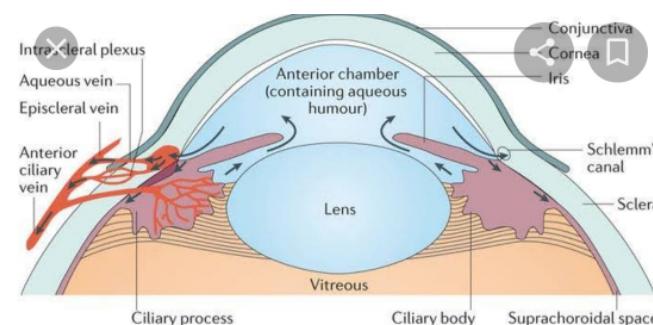
-Liver: Glycogenolysis → ↑ glucose

-Skeletal muscles: - Muscles tremors

- ↑ uptake of K by skeletal muscles → Hypokalemia

Beta 3

Fat cells: ↑ lipolysis



1a

1-CVS:V.C of skin and mm membrane blood vessels

2-SMF: - Eye : Iris ms(dilator pupillae→mydriasis)

3-Salivary glands

2a

(inhibitory)

1-CNS: inhibit sympathetic centres→ ↓ sympathetic outflow

2-Presynaptic → It decrease NA release

Sympathomimetics

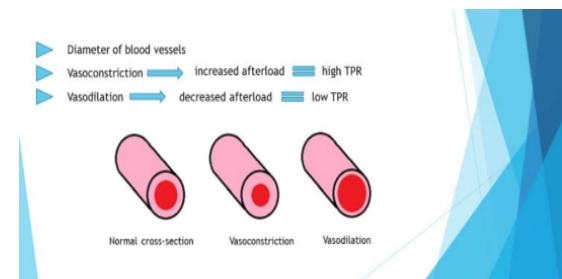
Drugs that produce actions similar to sympathetic nerve stimulation.

Classifications:

1-*According to Chemistry:*

2. *According to Mechanism of Action:*

► Diameter of blood vessels
 ► Vasoconstriction → increased afterload ► high TPR
 ► Vasodilation → decreased afterload ► low TPR



Catecholamines	Non-catecholamine
- Contain catechol nucleus	-Don't contain catechol nucleus
- Not absorbed orally	-Well absorbed orally
-Rapid onset, short duration	-Slow onset, long duration
- can not pass BBB	can pass BBB
- Metabolized by MAO and COMT.	- Not metabolized by MAO or COMT
-Adrenaline, noradrenaline Dopamine, Isoprenaline, Dobutamine.	- Ephedrine, Amphetamine

Direct	Indirect	Dual
-Direct stimulation of the receptor include:	Release Nor-adrenaline from vesicles	- Dual mechanism
Effect increased after Sympathectomy (supersensitivity) - No Tachyphylaxis	Absent Present	Present Present
Adrenaline, Noradrenaline Isoprenaline Dopamine Dobutamine	Amphe tamine Tyramine	Ephidrine

Catecholamine

Adrenaline - Noradrenaline - Dopamine - Isoprenaline Dobutamine.

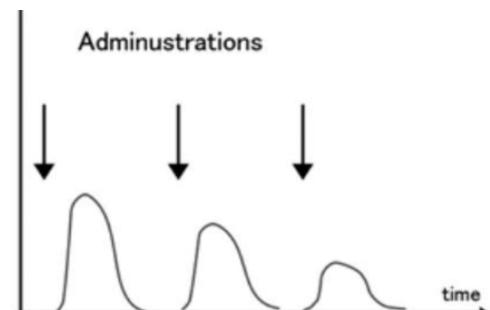
Adrenaline=Epinephrine (α+β)

Routes of administration

local on eye- inhalation- intracardiac- SC- not oral

Pharmacological actions:

Systemic effects - local effects:



- Systemic effects:

- Cardiovascular system:

-heart: adrenaline increase all properties of the cardiac muscle through action on (B 1).

Increase (↑) heart rate - (↑) contractility- (↑) conductivity (↑) excitability and automaticity of the heart - (↑) cardiac output (C.O.P.) and cardiac work

-Blood vessels: VC of blood vessels of skin, mucous membrane (α1) VD of coronary and skeletal blood vessels (B2)

- Blood pressure (BP):

-adrenaline increase C.O.P, so increase systolic BP with slight variation in diastolic BP

Adrenaline reversal phenomenon:

the hypertensive effect of adrenaline is reversed to hypotension after alpha blocker is given because of vasodilatation effects (B2 action) of adrenaline are unmasked -----> fall of B.P. (*adrenaline reversal*)

2- Eye:

A- pupil size: mydriasis(α1) and decongestion

B- intraocular pressure (IOP) : decrease IOP (in open angle glaucoma)

3-Respiratory system:

Bronchodilation:B2

Decongestion due to α1 stimulation of mucous membrane blood vessels

4-GIT

Relax wall (B2) - Contraction of sphincters (α1)

5-Urinary

Relax wall (B2)- Contraction of sphincters (α1)

6-Sex organs

Males : ejaculation (α1)

Females: relaxation of pregnant human uterus (B2).

7-Other actions:

- 1-Kidney: Renin secretion ↑ (B1)
- 2-Liver: Glycogenlysis → ↑ glucose (B2)
- 3-Sk. ms: -Muscles tremor(B2)
 - ↑ uptake of K by sk.ms (B2)
 - Facilitate NM(neuromuscular) Transmission (α1)
- 4-Fat cells: Lipolysis(B3)
- 5-CNS: affect sympathetic flow

8- antiallergic action:

Adrenaline is the physiological antagonist of histamine.

- local effects:

- 1- Vasoconstriction (VC) of cutaneous blood vessels (α1) :used to prolong action of local anesthetics
- 2- VC of mucous membrane blood vessels of the nose (α1) : used as nasal pack for hemostasis in epistaxis
- 3- VC of conjunctival blood vessels (α1)
- 4- VC of mucous membrane blood vessels of the bronchi (α1) and bronchodilator (B2) :inhalation in acute bronchial asthma

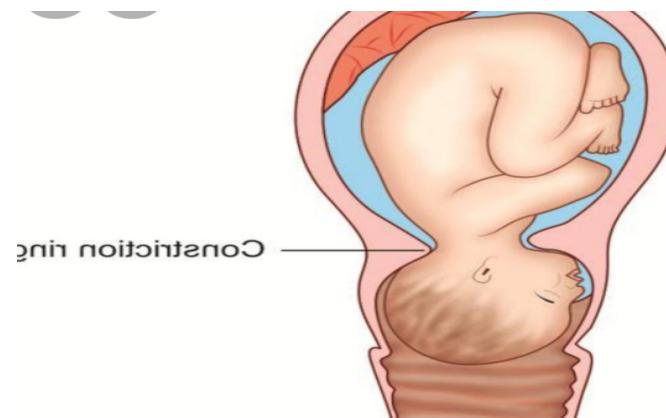
Therapeutic use:

A- local uses:

- 1- With local anaestheticsto prolong its effect.
- 2- local hemostatic in epistaxisand bleeding surfaces
- 3- Decongestion of m.mof nose and eye
- 4- acute bronchial asthma :inhalation

B- systemic uses:

- 1-Cardiac resuscitation: intracardiac.
- 2-Acute attack of bronchial asthma: SC .
- 3-Contriction ring during labourto relax the uterus
- 4- Allergic reactions e.g. anaphylactic shock.
- 5- Hypoglycemic coma (SC)



Side effects	Contraindications
Tachycardia, palpitation arrhythmia.	Ischemic heart disease - (angina) Arrhythmia
Hypertension and cerebral haemorrhage	Hypertension
If used with local anaesthesia in region of end arteries (Finger, toe, penis) → gangrene.	with local anaesthesia in region of end arteries (Finger, toe, penis)
If used with general anaesthesia → ventricular fibrillation	with general anaesthesia

Noradrenaline (NA)=Norepinephrine

(α+weak B1+No β 2)

Routes of administration: Iv infusion only

Pharmacological actions:

C.V.S:

A-blood vessels: sever VC of cutaneous, splanchnic, renal blood vessels (α₁effect) lead to increase of PR.

B-blood pressure: it increase systolic and diastolic ↑ (peripheral resistance),this effect is abolished after alpha blocker

C- Heart: Reflex bradycardia Bb ↑ → vagal stimulation → bradycardia

Therapeutic uses: it is used to elevate Bb in hypotensive states (as in spinal anaesthesia)

Side effect:

1- Hypotension

2- Bradycardia

Isoprenaline (Beta only)

_SL- IV infusion- inhalation

:Routes of administration

Pharmacological actions:

1- Cardiovascular system:

-Heart: increase all properties of the cardiac muscle through action on (B 1).

-Blood vessels: VD of coronary and skeletal blood vessels (B2)

- Blood pressure (BP): hypotension

2-SMF:- Eye, Bronchi, urinary, uterus

3-Other actions:- Liver - Sk. ms- Fat cells



Therapeuticuses:

1-Heart block 2-Bronchial asthma

Side effects	Contraindications
Tachycardia, palpitation arrhythmia.	Arrhythmia
If used with general anaesthesia → ventricular fibrillation	with general anaesthesia

Dopamine

(Dopaminergic receptors+B1+a)

Routes of administration: IV infusionPharmacological actions: according to rate of infusion:

- 1- At low doses it stimulates dopaminergic receptors causing VD of renal, coronary, mesenteric and cerebral blood vessels.
- 2-At moderate doses it stimulate beta 1 receptors leading to increase all cardiac properties (mainly contractility) and increase of C.O.P and systolic blood pressure.
- 3- At high dose it stimulates alpha1 receptors leading to VC of peripheral blood vessels and rise of diastolic BP

Therapeuticuses:

1-Different types of shock (Cardiogenic, hemorrhagic & Septic shock) due to: *

VD of renal blood vessels → ↑ renal blood flow

* increase of C.O.P and systolic blood pressure.

2-Heart failure, hypotension

Side effects:

1-Tachcardia ,ventricular arrhythmia2-Nausea and vomiting

Dobutamine

(Selective β_1 + weak α)

Routes of administration : IV infusion

Pharmacological actions:

It stimulate beta 1 receptors leading to increase all cardiac properties (mainly contractility) and increase of C.O.P and systolic blood pressure.

Therapeutic uses:

1-Cardiogenic shock due to: increase of C.O.P and systolic blood pressure.

2- Heart failure, hypotension

Side effect

Tachcardia,ventricular arrhythmia



Sympathomimetics (part 2)

•Non Catecholamines

- *CNS stimulant: as Ephedrine – Amphetamine.
- *Anorexigenics: as Fenfluramine- Phenmetrazine.
- *Vasopressors as Methoxamine - Midodrine -Metaraminol- Phenyl ephrine (weaker than NA)
- *Nasal decongestants Old group: as Phenylephrine – Pseudoephedrine.
- *Recent group: as Naphazoline – Xylometazoline.
- *Vasodilators and uterine relaxants as Isoxsuprine- Ritodrine.
- *Bronchodilators as Salbutamol- Terbutaline- Salmeterol.

•Ephedrine(α+β)

-Non catecholamines.

-Dual mechanism.

-Repeated administration cause tolerance and tachyphylaxis.

-Weak base → renal acidification of urine increase excretion.

-Routes of administration: oral- injection.

-Pharmacological actions: as adrenaline but weaker (especially β) + no adrenaline reversal + CNS actions which include:

1- Stimulate RC + VMC especially when depressed.

2-Stimulate cerebral cortex and reticular formation → anxiety and insomnia.

-Therapeutic uses: as adrenaline +

1-Nocturnal enuresis.

2-Narcolepsy.

3-Morphine toxicity.

4-Myasthenia gravis (a effect on muscle).

-Side effects: as adrenaline +

1-Tolerance and tachyphylaxis.

2-Retention of urine in male patient with enlarged prostate.

3-CNS: insomnia and anxiety.

-Contraindication: as adrenaline + old prostatic patient.

•Amphetamine (x+B)

- Non catecholamines -Indirect mechanism.
- Repeated administration cause tolerance, tachyphylaxis and addiction.
- Weak base → renal acidification of urine increase excretion.

-Routes of administration: oral- injection.

-Pharmacological actions: as ephedrine + marked CNS action which include:

- 1-Psychic: euphoria- alterness- delay fatigue-schizophrenia - convulsion .
- 2- Anorexia (-- feeding centres of hypothalmous) .
- 3- ++ RC, VMC .

-Therapeutic uses: (rarely used now)

1-Nocturnal enuresis. 2-Narcolepsy. 3-Obesity.

4-Calm hyperkinetice syndrome in children (ADHD).

-Side effects: as ephedrine +

1- CNS: anxiety - tremors- schizophrenia.

2-Prolonged use: addiction.

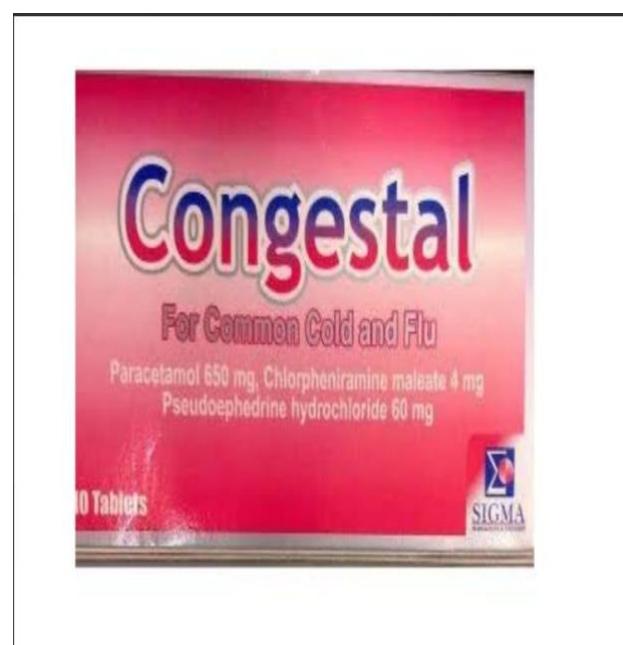
•Nasal decongestant (α 1)

-Old group: as Phenylephirine – Pseudoephedrine.

-Recent group: as Naphazoline – Xylometazoline.

-Routes of administration: oral- drops – spray.

-Therapeutic uses: common cold -rhinitis -sinisiuti.



- Side effects:

- 1-Rebound congestion after stopping (irritant).
- 2-Long use >>atrophy of cilia.
- 3-Oily solution, if inhaled lead to lipoid pneumonia.

-Contraindications: in hypertensive patient and angina patient Vasodilators and uterine relaxants (B2).

- **Vasodilators and uterine relaxants (B2)**

-Eg: Ritodrine

-Therapeutic uses:

1-Vasodilators: in peripheral vascular disease.

2-Uterine relaxants:

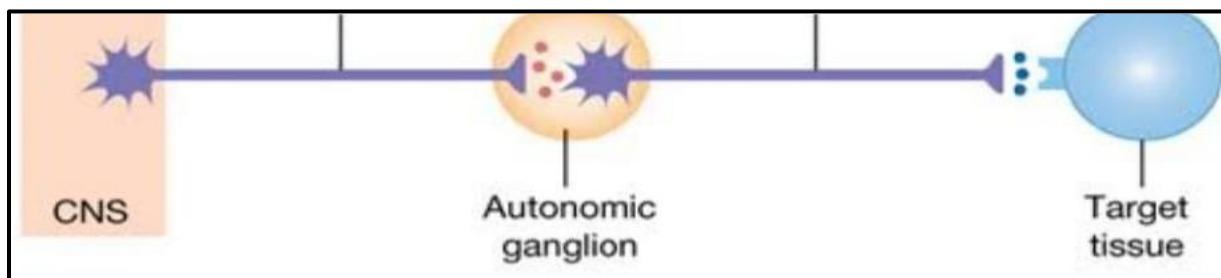
-contraction ring of uterus.

-premature labour.

ADRENERGIC PHARMACOLOGY

❖ Sympatholytics:

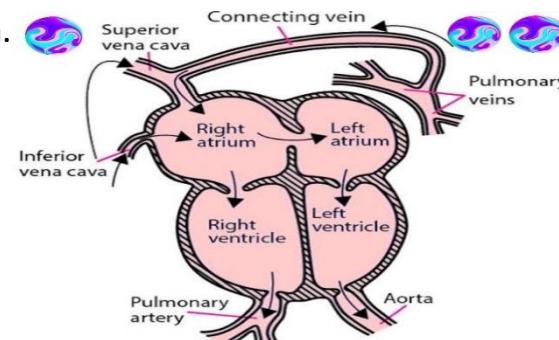
1. Adrenergic receptor blockers: **α -blockers**, **β -blockers**, **α & β -blockers**.
2. Adrenergic neuron blockers: which interfere with:
 - Noradrenaline release: **guanethidine**.
 - Noradrenaline storage: **reserpine**.
 - Noradrenaline synthesis: **α methyl dopa**.
3. Ganglion blockers: block transmission in ganglion as **Trimethaphan**
4. Centrally acting drugs:
 - α_2 -agonist (**clonidine**, **guanafacine**, **guanabenz** and **α -methyl dopa**).
 - Imidazoline receptors: **Reboxetine**.



α - blockers:

Classification:

1. Selective α_1 blockers: as **prazosin**, **terazosin**, **tamsulosin**.
2. Selective α_2 blockers: **yohimbine**.
3. Nonselective α blockers (block both α_1 and α_2):
 - Ergot alkaloids: as **ergotamine**, **ergotoxine**.
 - Imidazoline derivatives: **tolazoline**, **phentolamine**.
 - β -Haloalkylamines: **phenoxybenzamine**- **dibenamine**.
4. α_1 and β receptors blockers: **labetalol**, **carvedilol**.



Sites of α_1 receptors:

1-CVS: V.C of blood vessels \rightarrow arteries \rightarrow ↑ TPR \rightarrow veins \rightarrow ↑ VR.

2-SMF:

- Eye : Iris ms (dilator pupillae \rightarrow mydriasis).
- GIT and UB sphincter \rightarrow constriction and increase tone.
- Male sex organ \rightarrow ejaculation .

α_2 (inhibitory effect):

1-CNS: inhibit sympathetic centers \rightarrow ↓ sympathetic outflow .

2-Presynaptic \rightarrow It decreases NA release.

Prazosin (Selective α_1 -blocker):

Actions:

1. VD on veins $\rightarrow \downarrow$ VR(venous return).
2. VD on arteries \rightarrow congestion and \downarrow TPR(total peripheral resistance).
3. \downarrow tone of UB sphincter .
4. No reflex tachycardia???
5. Failure of ejaculation.

Mechanism of VD:

1- α_1 blocking (no blocking of presynaptic α_2 so no increase in sympathetic outflow or NE release)

2- \uparrow cAMP, cGMP through inhibition of phosphodiesterase enzyme

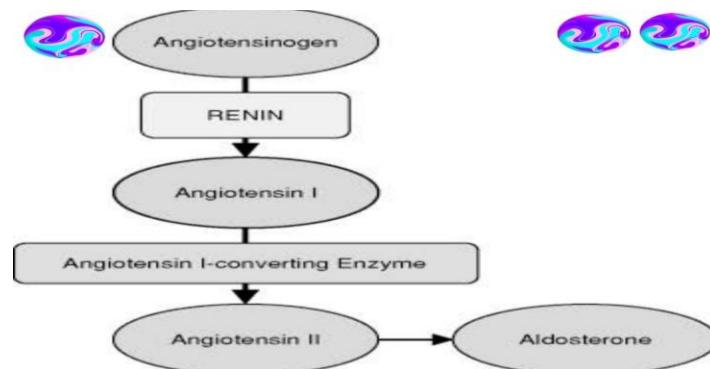
- cAMP: increase HR(heart rate) - CGMP:decrease HR
- net result: **constant**

Therapeutic uses:

1. Hypertension (1ry-2ry)
2. PVD (peripheral vascular disease)
3. Benign prostatic hypertrophy
4. Heart failure

Side effects:

1. Orthostatic (Postural) hypotension (1st dose).
2. Nasal stuffiness.
3. Headache and drowsiness.
4. Sexual dysfunction.
5. Oedema (chronic therapy).



❖ Nonselective α blockers

Phenoxybenzamine:

Very powerful non-selective α blocker - prodrug- **Irreversible and non-competitive blocker** (only α blocker) \rightarrow delayed onset and prolonged Duration

Actions:

- non-selective α blocker.
- Block histaminic, cholinergic, and serotonergic receptors as well.
- Antishock :due to:
 - a- α blocking effect: \rightarrow VD (improve tissue perfusion)
 - b- \downarrow excess release of ADH \rightarrow VD

Therapeutic uses:

1. Hypertension(2ry to pheochromocytoma).
2. PVD.
3. Benign prostatic hypertrophy.
4. Shock.

Side Effects:

1. Postural hypotension and tachycardia.
2. Nasal stuffiness.
3. Sedation.
4. Sexual dysfunction.

- **Phentolamine:**

• Non selective α blocker • competitive.

It has histamine like action (VD-bronchospasm- \uparrow GIT secretion).

Therapeutic uses:

1. Hypertension (2ry to pheochromocytoma).
2. PVD.
3. Benign prostatic hypertrophy.

- **Tamsulosin:**

The most commonly used in treatment of **benign prostatic hyperplasia** because it has high affinity for $\alpha 1A$ subtypes responsible for mediating smooth muscle fibres contraction in prostatic tissue.

- **Pheochromocytoma:**

Tumor of adrenal medulla secrete Noradrenaline (90%) – Adrenaline (10%)

Diagnosis:

Treatment of pheochromocytoma:

- | | |
|--|-----------------------------|
| 1. Surgical | 3. BB (propranol) not alone |
| 2. α blocker (Phenoxybenzamine) not alone | 4. Labetalol |

- **Labetalol (Block $\alpha 1$ and B receptor):**

- Produce quick drop in Bp.
- No tachycardia.
- Used in treatment of hypertension (emergency).
- Used in hypertension due to pheochromocytoma.

QUIZ.... 

1-.....is a selective alpha 1A receptor blocker used in treatment of benign prostatic hyperplasia

- | | |
|----------------------|-----------------|
| a) Alpha methyl dopa | c) Phentolamine |
| b) Tamsulosin | d) Pindolol |

2- Phenoxybenzamine is a

- | |
|---|
| a) Reversible competitive alpha 1 blocker |
| b) Irreversible non competitive alpha 1 blocker |
| c) Reversible competitive non selective alpha blocker |
| d) Irreversible non competitive non selective alpha blocker |

sympatholytics2

Adrenergic receptor blockers: Beta blockers

Reversibly and competitively bind to B receptors preventing effects of catecholamines.

Classification:

According to selectivity:

*Non selective :Propranolol - Nadolol- Pindolol- Timolol(eye) *Selective β blockers (block $\beta_1 > \beta_2$):Atenolol -Metoprolol- Esmolol- Celiprolol

* β_2 blockers:Butoxamine(for academic interest)

* $\alpha_1 + \beta$ blockers:Labetalol- Carvediolol

According to generation:

1st generation:: non-selective beta blockers

2nd generation: cardioselective beta1 blockers

3rd generation: vasodilator beta blockers: they either have

a- B2 Agonistic activity : celiprolol

b- direct VD and alpha blocking effect: **carvedilol,,bucindolol**



According to lipid solubility:

	Lipophilic	Hydrophilic
Absorption	Well absorbed oral	Less
Distribution	Pass BBB	Not pass
Metabolism and excretion	Hepatic metabolism (short half life)	Pass unchanged to urine (long half life)
Examples	Propranolol- Metoprolol	Atenolol- Nadolol

Propranolol (Non selective)

Pharmacokinetics: lipophylicBB extensively metabolized in liver (1st pass metabolism) having bioavailability about 30%.

Pharmacological actions:

CNS: decrease sympathetic flow (lipid soluble)

CVS:

1-Heart:

-Decrease all cardiac properties, decrease myocardial work and O₂ requirements.

-Antiarrhythmic action through:

- B blocking effect decreasing AVN conduction
- increase refractory period (RP) in SAN
- Membrane stabilizing action (Na channel blocking).

2-Bl. vessels: prevent B2 mediated VD decrease blood flow to most of tissue

3-Blood pressure: hypotension . how?

↓ sympathetic flow (inhibition of central and presynaptic B2)

- ↓ COP-

↓ renin release

-increase prostacyclin (VD)

Respiration: produce bronchospasm

Eye: ↓ IOP (Timolol) (decrease synthesis of aquashumor)

Metabolism: - ↓ glucose: as it inhibit B in liver → -- glycogenolysis → hypoglycemia

- ↓ renin - ↑ plasma k (hyperkalemia)



Therapeutic uses:

1-Antianxiety

2- IHD .ischemic heart disease (angina - myocardial infarction)

used in angina due to coronary atherosclerosis not due to spasm in coronary (not in variant angina) through :

a- decrease cardiac work and O₂ demand.

b- bradycardia so ↑ diastolic time ↑ coronary filling.

3- Arrhythmias (supraventricular tachcardia) **how?**

4-Hypertension (1ry – 2ry to pheochromocytoma)

5- Glaucoma (by timolol).

6-Thyrotoxicosis through (improve tremors,, tachycardia and prevent conversion of T4 to t3-)

7- Treatment of esophageal varices due to liver cirrhosis as it decrease COP so decrease blood flow to splanchnic area

Side effects:

1-Sedation –depression

2-Heart block and bradycardia treated by atropine

3-Cold extremities-numbness-tingling

4-Hypotension

5-Bronchospasm

6-Hypoglycemia (in patient receive insulin or oral hypoglycemic drugs) and mask sympathetic symptoms of hypoglycemia)

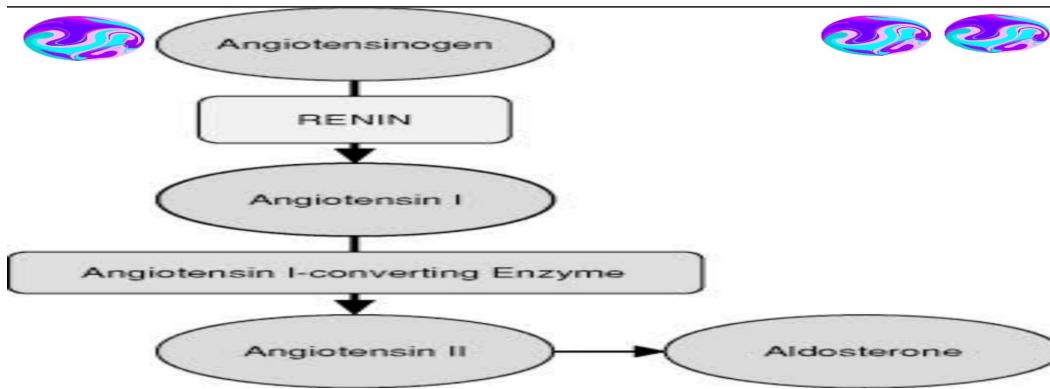
7-Hyperkalemia

8-Sudden discontinuation leads to sympathetic overactivity due to upregulation of receptors



Contraindications:

- 1-Severe depression
- 2- Angina due to spasm in coronary (variant angina) because it will block B receptors leaving the unopposed supersensitive Alphareceptors.
- 3-Bradycardia and heart block.
- 4-Peripheral vascular disease (use selective B blockers).
- 5-Hypotension
- 6-Bronchial asthma (use selective BB)
- 7- care in Patient receive insulin or oral hypoglycemic drugs (EXPLAIN)



Propranolol can be used for treatment of

Myocardial infarction

Heart block

Bronchial asthma

Hypertension

B blockers are unlikely to produce

Hyperglycemia

Hyperkalemia

- Enumerate 4 uses and 4 side effects of B blockers.

- Explain on pharmacological basis why BB are used in treatment of hypertension



Parasympathomimetics

- Parasympathomimetics or cholinergic drugs are drugs that produce parasympathetic like actions

Actions of parasympathomimetics:

A) Actions related to stimulation muscarinic receptors:



1- Decrease in heart rate and cardiac output.

2- Decrease in blood pressure: By indirect mechanism of action.

Acetylcholine activates **M₃ receptors** found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide which causes vasodilation and lowering of blood pressure.



1-stimulating ciliary muscle contraction: accommodation for near vision. 2-constriction of the pupillae muscle causing miosis (marked constriction of the pupil).

3-stimulate tears.

4-Reduction of intraocular pressure (IOP).



Bronchi: bronchoconstriction.



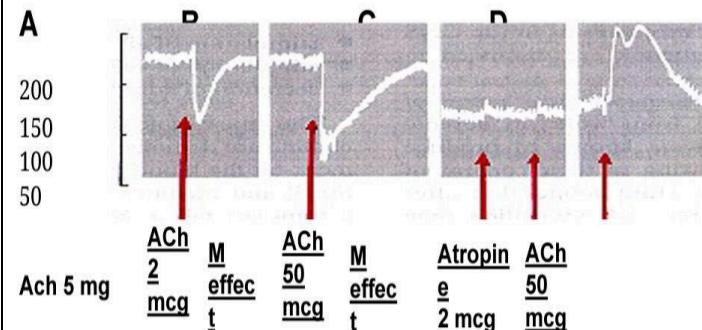
increases salivary and gastric secretions and stimulates intestinal secretions and motility.



B) Actions related to stimulation nicotinic receptors:

- ++ of Nm in skeletal muscle: twitches.

- ++ of Nn in autonomic ganglia & adrenal gland: **large dose** of Ach release of adrenaline &NA so hypertension in **atropinized** dogs (Ach reversal).



 In the genitourinary tract:

increased the tone causing expulsion of urine.

Cholinergic agents adverse effects:

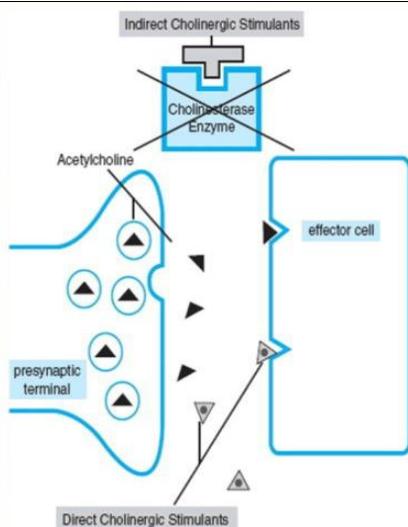
- Bradycardia and hypotension.
- Miosis, lacrimation, salivation, sweating.
- Urgency and spontaneous micturition Bronchospasm and increased bronchial secretion.
- Colic, vomiting, diarrhea, hyperacidity & peptic ulcer.

General contraindication of parasympathomimetics:

- ✓ Bradychardia, heart failure, heart block.
- ✓ Bronchial asthma.
- ✓ Peptic ulcer.
- ✓ Parkinsonism.
- ✓ Mechanical obstruction of the GIT and urinary bladder.

Parasympathomimetics are classified according to the mechanism of action into:

Direct parasympathomimetics	Indirect parasympathomimetics (Anticholinesterases)
Alkaloids	<ul style="list-style-type: none"> ➤ Reversible. ➤ Irreversible.
 They stimulate the cholinergic receptors directly.	 They inhibit cholinesterase enzyme leading to accumulation of endogenous acetylcholine at both muscarinic and nicotinic receptors classified into reversible and irreversible.



Choline esters:

	Acetyl choline	methacholine	bethanecol	carbachol
GIT Absorption	NO	Partial	complete	complete
fate	By true and pseudo ch E	By true only	not	not
duration	transient	long	longer	longer
Actions:	+ 1) muscarinic	+ 2) nicotinic:	+ 3) selectivity:	+ Eye, GIT, urinary
1) muscarinic				
2) nicotinic:	+	-	-	+
3) selectivity:	Not selective	heart	GIT, urinary	Eye, GIT, urinary
Uses	Not used	-proxysmal tachycardia. -peripheral vascular disease.	-post operative. -urine retention. -paralytic ileus	-miotic eye drop glaucoma. -post operative urine retention -paralytic ileus
Administration	IV	S.C	S.C, oral, eye drop	S.C, oral, eye drop



Pilocarpine:

- ✓ The alkaloid pilocarpine is a tertiary amine.
- ✓ Not hydrolyzed by cholinesterase Long duration.

Action:

- ✓ Muscarinic only: mainly eye (miosis, decrease IOP) & increase secretion (salivary & sweat).

Used in:

- ✓ Glaucoma: Pilocarpine is the drug of choice in the emergency lowering of intraocular pressure Counteract action of mydriatic.
- ✓ To stimulate salivationin dry mouth.

Indirect parasympathomimetic (anticholinesterases):

	Reversible	Irreversible
Binding to enzyme	loose	Firm
Enzyme activity	Can be regained	Can not
Action duration	short	Long
Examples	<ul style="list-style-type: none"> ✓ Physostigmine, ✓ neostigmine, ✓ edrophonium 	<ul style="list-style-type: none"> ✓ Organophosphorus compounds ✓ Ecothiopate (antiglaucoma drug) ✓ Malathion, parathion (antiscabes, insecticides) ✓ Metrifonate(antihelminthic)



Reversible anticholinesterase:

	phyostigmine	neostigmine
source	natural	synthetic
chemistry	Tertiary amine	Quaternary amine (does not pass BBB)
kinetics	Well	poor
dynamics	M: mainly on eye Muscle twitches. CNS: stimulation	N: M: GIT, urinary Muscle twitches +direct stimulation on SK MS CNS: no
uses	<ul style="list-style-type: none"> ✓ Glaucoma ✓ Counteract action of mydriatic ✓ Alternative with mydriatic to cut recent adhesion between iris & lens ✓ ttt of Alzheimer disease ✓ Antidote to atropine toxicity 	<ul style="list-style-type: none"> ✓ Post operative urine retention ✓ paralytic ileus ✓ Myasthenia gravis ✓ Antidote to curare toxicity
toxicity	<p>M:bradycardia,hypotension, bronchospasm, miosis, diarrhea , ++secretions.</p> <p>N: muscle twitches: eye lid and face.</p> <p>CNS: convulsion, coma</p>	<p>M:bradycardia,hypotension, bronchospasm, miosis, diarrhea , ++secretions</p> <p>N: muscle twitches: eye lid and face.</p> <p>NO CNS manifestations</p>
TTT of toxicity	<p>Stomach wash, anticonvulsant, oxygen, atropine is an antidote</p>	<p>Stomach wash, anticonvulsant, oxygen, atropine is an antidote</p>

Irreversible anticholinesterase:

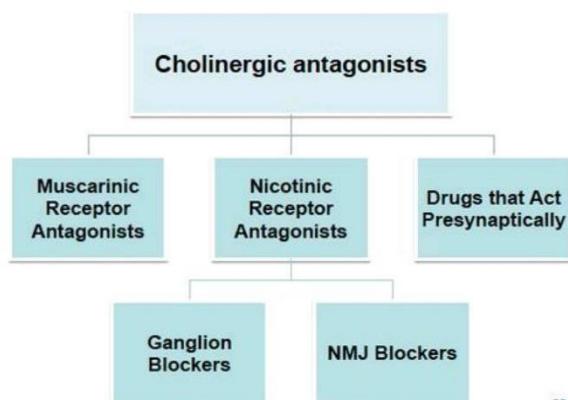
- Organophosphorus compounds: synthetic compounds have the capacity to bind covalently to acetylcholinesterase.
- The result is a long-lasting increase in acetylcholine at all sites where it is released.
- Many of these drugs are extremely toxic.

أحب قول عمر بن عبد العزيز :
"لو أن الناس كلها استصعبوا أمراً تركوه
ماقام للناس دنيا ولا دين .."

Parasympathetic Depressants

(Anti-cholinergic drugs, Parasympatholytic drugs or Anti-muscarinic drugs)

- Para-sympatholytic drugs that **block M receptors** → inhibition of all parasympathetic functions.
- In addition, they **block the few exceptional sympathetic neurons** that are cholinergic (sweat glands).
- They do **not block nicotinic receptors**, have no action at the neuromuscular junction



❖ Classification

Natural (Belladonna alkaloids)	Synthetic (Atropine substitute)
They are of plant origin	synthetic
1- Atropine. 2- Hyoscine (Scopolamine)	1. Mydriatic. 2. Anti-secretory & anti-spasmodics. 3. For urinary incontinence. 4. Anti-asthmatics 5. Anti-parkinsonians

Atropine

❖ Source and chemistry

- Natural belladonna alkaloids
- It is an ester of tropic acid and tropine base
- It is a tertiary amine

❖ Pharmacokinetic:

- Absorption:** from all sites except intact skin
- Distribution:** pass BBB
- Metabolism:** in the liver
- Excretion:** in urine (1/3 is excreted as such). acidification of urine increases its excretion.

❖ Pharmacodynamics

▪ Para-sympatholytic action:

Atropine blocks the muscarinic receptors by competition with Ach.

1. Cardiovascular system

- Heart
- Blood vessels
- Blood pressure



2. Smooth muscle fibers

- Eye
- Respiratory system
- Gastrointestinal system
- Urinary system

3. Secretions

- Local anesthetic action
- CNS (central nervous system) action

1. Cardiovascular system

- **Heart:** tachycardia due to blockage of the vagal tone to S.A. node. But if **injected I.V.** produce transient bradycardia followed by tachycardia. This bradycardia is due to stimulation of CIC

• **Blood vessels:**

- **Therapeutic dose:** no effect
- **Large dose** especially in children leads to atropine flush (due to histamine release)

• **Blood pressure**

- No significant action
- **Reverse hypotension** of Ach, carbachol, and neostigmine
(has a muscarinic and nicotinic effect)
- **Abolish hypotension** of methacholine, bethanechol, and pilocarpine
(has muscarinic effect only).

2. Smooth muscle fibers

- **Eye:** by local or systemic administration- duration of action 7-10 days

1. Paralysis of ciliary muscle (cycloplegia)

- **Loss of accommodation to near vision**
- Closure of canal of schlemm and spaces of fontana and increased intraocular pressure (\uparrow IOP)

2. Paralysis of constrictor pupillae muscle leads to **passive mydriasis** with **loss of light reflex**

3. Decrease lacrimation

Respiratory system:

1. Bronchodilatation

2. Decrease bronchial secretion (Thick viscid, difficult to expel)

Gastrointestinal system (GIT):

1. Relax the wall (antispasmodic) and constrict the sphincters

2. Reduced secretions (antisecretory) lead to constipation.

• **Urinary system:**

1. Relax the wall and constrict the sphincter of the bladder (urine retention)

2. Relax ureter

3. Secretions:

- Reduce all secretions (except milk, bile, and urine)

- Decrease salivary, lacrimal, bronchial, and gastric secretions

- **Toxic doses:** decrease sweat gland and increase body temperature (**atropine fever**)

• **Local anesthetic action:**

- ✓ Has mild local anesthetic action
- ✓ Sometimes added to irritant plaster or ointment

• **Action on CNS (stimulant and depressant but mainly stimulant)**

❖ **Stimulatory actions:**

- ✓ **Therapeutic dose:** stimulate cardio-inhibitory center (C.I.C) leading to initial bradycardia when it is given I.V

- ✓ **Large doses:** stimulate respiratory center (R.C.) leading to tachypnea

- ✓ **Toxic doses:** cause restlessness, hallucination, and delirium followed by depression and coma

❖ **Inhibitory actions:**

- ✓ **Inhibition of basal ganglia:** treatment of rigidity and tremors in parkinsonism.

- ✓ **Inhibit vomiting center** (antiemetic effect)

- ✓ **Counteract central effect of organophosphorus compound**

- ✓ **Decrease electric activity in the brain** so used in the treatment of epilepsy

❖ Uses

1. Parasympatholytic uses (general):

a. Preanesthetic medications:

- I. Counteract excess vagal tone during operations
- II. Counteract inhibitory effect of morphine on R.C.
- III. Decrease salivary secretion (prevent bronchopneumonia) and decrease bronchial secretion (prevent lung collapse)

b. Vagotonia (↑vagal tone)

c. Treatment of physostigmine and organophosphorus compound toxicity.

2. Parasympatholytic uses (systems):

- a. **CVS:** Heart block (in B.B., digitalis, infarction)
- b. **Eye:** Fundus examination and in iritis to prevent adhesion-cut recent adhesion alternatively with miotics
- c. **Respiration:** Bronchial asthma - **not preferred** (due to viscid secretion difficult to expel)
- d. **GIT:** Intestinal colic, anti-emetics, antidiarrheal and peptic ulcer
- e. **Urinary:** Renal colic and nocturnal enuresis.
- f. **Secretion:** Hyperhidrosis (excess sweating)
- g. **CNS:** Anti-parkinsonian

❖ Toxicity (side effects). Datura toxicity

1. Exaggerated parasympathetic effects:

- a. **CVS:** Tachycardia
- b. **Eye:** mydriasis, blurred vision with ↑ IOP (may precipitate glaucoma)
- c. **GIT:** constipation
- d. **Urinary:** urine retention especially in prostatic patient
- e. **Secretion:** dry mouth and dry skin (atropine fever and flush)

2. **CNS:** excitation, hallucination, convulsions followed by coma and inhibit respiratory center (cause of death).

❖ Treatment of atropine toxicity

1. Gastric lavage with tannic acid
2. O2 inhalation and artificial respiration
3. Cold fomentation with ice bags or alcohol
4. Sedatives as diazepam-paraldehyde
5. Neostigmine 0.5-1 mg S.C./ 3 hours –
physostigmine is dangerous (why?)



❖ Contraindication

1. Heart: arrhythmia
2. Eye: glaucoma
3. GIT: Constipation, paralytic ileus
4. Urinary: senile enlargement of prostate
5. Fever

Hyoscine (scopolamine)

	Atropine	Hyoscine					
Duration of action	Long (4-7 days)	Short (4-7 hours)					
Dominant PS action	CVS, GIT, Urinary	Eye, secretions (no tachycardia)					
CNS	Both stimulant and depressant but mainly stimulant	Both stimulant and depressant but mainly depressant	<table border="1"> <thead> <tr> <th><u>Depressant</u></th> <th><u>Stimulant</u></th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> ▪ Sedative, hypnosis & amnesia to recent events ▪ Anti-parkinsonian & antiepileptic ▪ Strong antiemetic (anti-motion sickness) </td> <td> <ul style="list-style-type: none"> ▪ Excitation & hallucination with over dose ▪ Strong R.C stimulation </td> </tr> </tbody> </table>	<u>Depressant</u>	<u>Stimulant</u>	<ul style="list-style-type: none"> ▪ Sedative, hypnosis & amnesia to recent events ▪ Anti-parkinsonian & antiepileptic ▪ Strong antiemetic (anti-motion sickness) 	<ul style="list-style-type: none"> ▪ Excitation & hallucination with over dose ▪ Strong R.C stimulation
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Local anesthetic	present	Absent					

❖ Uses of hyoscine

- Parasympatholytic (general)

pre-anesthetic medication is better than atropine because:

- a. No tachycardia
- b. Strong anti-secretory
- c. More CNS depressant & amnesia
- d. Strong stimulation of R.C

- CNS:

1. Parkinsonism
2. Motion sickness prophylaxis
3. Menieres disease
4. Mania as a sedative drug



❖ Side effects and contraindication: as atropine

❖ Atropine substitutes

- Mydriatics
- Antisecretory antispasmodic
- Antiasthmatic
- Atropine substitutes used in urinary incontinence
- Anti-parkinsonian

Mydriatic atropine substitutes

	Atropine	Homatropine	Tropicamide and cyclopentolate	Eucatropine
Duration	7-10 days	24 hours	6 hours	4 hours
Cycloplegia	++++	++	+	No
Uses: a-iritis	Used		Not	
b-fundus examination	Not used		Used	

❖ Antisecretory antispasmodic atropine substitutes

- Hyoscine butyl bromide (Buscopan) is a quaternary ammonium used to treat **spasms of GIT, bile duct, and urinary tract**. It is more potent and less CNS side effects than atropine.
- Darifenacin: **M3-specific blocker** used in the treatment of renal and intestinal colic
- Pirenzepine and telenzepine: It is a **selective M1 receptor antagonist**. It is used orally in the **treatment of peptic ulcer**. It blocks gastric HCl secretion(blocking M1) with little effect on gastrointestinal motility (no blockade on M3 receptors).

❖ Anti-asthmatic atropine substitute

- Ipratropium is preferred than atropine in the treatment of bronchial asthma because:
 - ✓ It has a bronchodilator effect
 - ✓ It does not cause dryness of bronchial secretion
 - ✓ No CNS effect, less anticholinergic side effect
- Given by inhalation

Atropine substitute used in urinary incontinence

- Emepronium and Oxybutynin
- Relieve bladder spasms after urological surgery

Anti-parkinsonian atropine substitute:

- Trihexphenidyl and Benztropine

Quiz

- Explain on a pharmacological basis
- Pirenzepene is preferred over atropine in the treatment of peptic ulcer
- Tachycardia induced by atropine
- List the manifestations of atropine toxicity
- Enumerate different types of atropine substitutes



ونكمّل ..

@nasser_junior

Ocular pharmacology

Anatomy and Physiology of the Eye

- The eye is composed of 3 layers; [an outer protective, a middle vasculomuscular and an inner neural layer].
- The lens and its zonular ligaments divide the eye into two cavities,
 - ¶ a small anterior one which contains the aqueous
 - ¶ a larger posterior one filled with the vitreous.

The anterior cavity is further subdivided by the iris into anterior and posterior chambers.

- **The outer protective layer** consists of the cornea and the sclera.

The conjunctiva is covering part of the sclera and the inner surface of the eyelids.

The sensory nerve fibers supplying the cornea and conjunctiva are derived from the trigeminal (V cranial) nerve.

- **The middle layer** is the uveal tract comprising the Iris, ciliary body and the choroid.

a- The Iris:

- It is a thin circular disc with a central opening; the pupil. The iris regulates the amount of light entering the eye by two muscles:

1-The constrictor or sphincter pupillae muscle with its fibers arranged Concentrically around the pupil. It is supplied by **parasympathetic** fibers along the oculomotor (III cranial) nerve. Contraction of this muscle results in constriction of the pupil or myosis.

2-The dilator pupillae muscle with its fibers arranged radially. It is supplied by **adrenergic sympathetic** fibers along the ciliary nerve. Contraction of this muscle results in dilatation of the pupil or mydriasis.

Both muscles of the iris are under continuous autonomic tone; a parasympathetic to the constrictor and a sympathetic to the dilator papillae muscles. **However**, the parasympathetic tone to the constrictor muscle predominates its sympathetic counterpart to the dilator muscle.

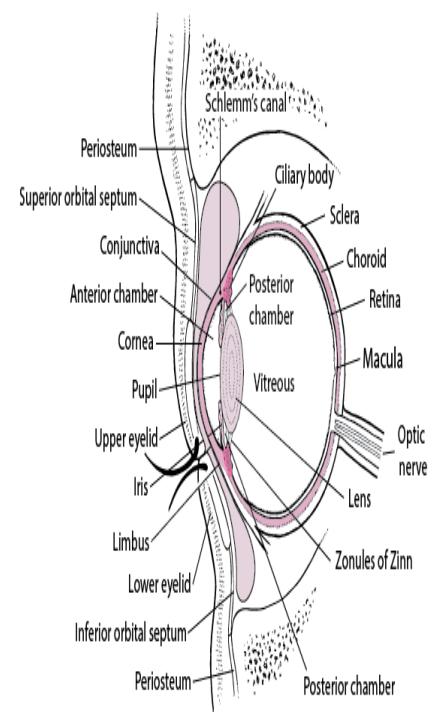
B- The ciliary body is triangular in shape with the iris attached to the **middle** of its base. The lens zonules are also attached to its base behind the attachment of the iris.

The ciliary muscles are composed of longitudinal, radial and circular fibers and are innervated by **parasympathetic** fibers (mainly) along the oculomotor nerve.

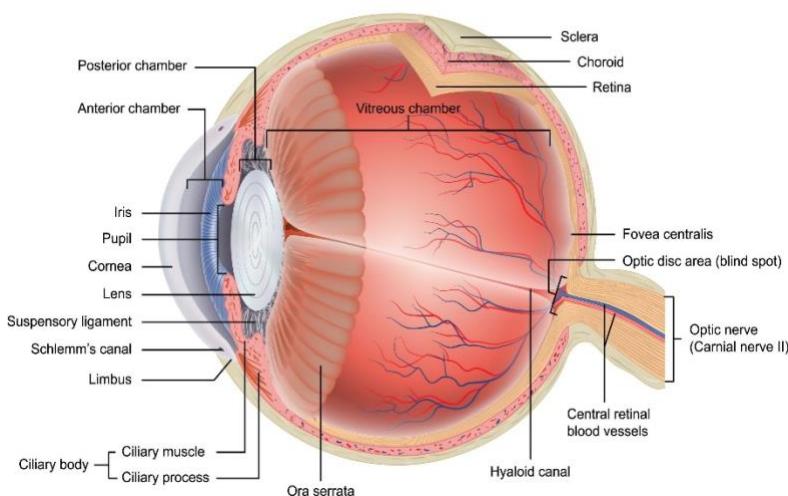
The ciliary body controls the accommodation of the lens to near and far objects.

The inner layer is formed of the retina which contains the end organs of vision; the rods & cones

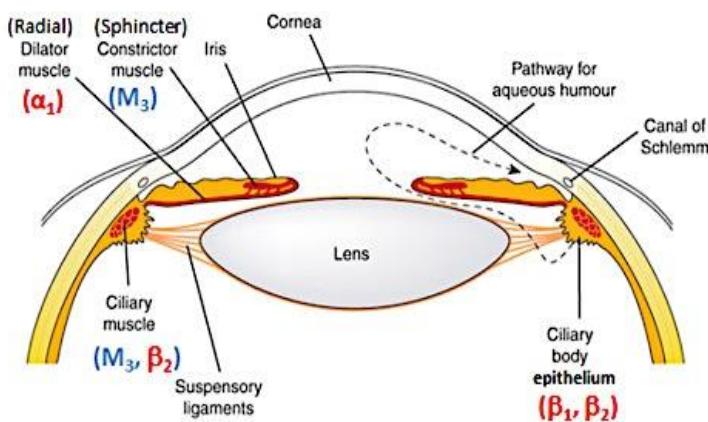
The nerve fibers of the optic nerve originate in the retina, the two optic nerves decussate and then fibers travel to the brain via the optic tract.



Anatomy of the Eye



Autonomic receptors in the eye



Formation and circulation of aqueous & the I.O.P.

The intraocular pressure (I.O.P.) is determined by the pressure of the aqueous. For the maintenance of the I.O.P. within the normal range (15-22mm Hg), the rate of formation of aqueous must be equal to the rate of its drainage

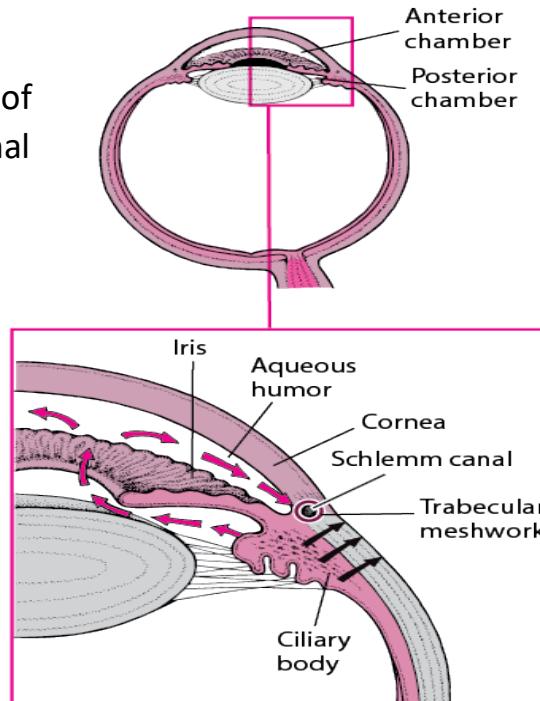
The aqueous is actively secreted by the ciliary processes into the posterior chamber then it passes through the pupil to the anterior chamber where it is drained through its angle

Encircling the eye at the angle of the anterior chamber is a sieve like Tayer with fine pores called the "**trabecular meshwork**" or the "**spaces of Fontana**". Through the pores of this meshwork the aqueous is filtered to reach the "canal of Schlemm" which lies within the inner surface of the sclera at the limbus (**corneo-scleral junction**),

The ciliary body, not only secretes the aqueous (by the ciliary processes) but it also helps in its drainage. Thus contraction of the longitudinal (meridional) muscle fibers causes traction on the postero-lateral wall of the canal of Schlemm (scleral spur) leading to opening of this canal which facilitates aqueous drainage. From the canal of Schlemm, aqueous passes to the aqueous veins then to the episcleral veins to the general circulation.

Factors affecting drainage of aqueous

(1) State of the pupil: Mydriasis leads to cobbling of the iris tissue at the angle of the anterior chamber thus obliterating the spaces of Fontana which hinders aqueous drainage. Myosis on the other hand leads to widening of the angle which gives clear way for the aqueous to reach the spaces of Fontana.



(2) State of the ciliary body: Contraction of the ciliary body will pull on the scleral spur leading to opening of Schlemm's canal which facilitates aqueous drainage. Paralysis of the ciliary body (cycloplegia), however, has the opposite effect.

Reflexes of the eye

(1) Accommodation reflex: The reflex is initiated by blurring of the retinal image on looking to near object. Impulses travel from the retina to the optic nerve, optic tract then to the cortex. The efferent pathway starts in the cortex to Edinger-Westphal (III nerve) nucleus to ciliary ganglia leading to contraction of the ciliary muscle and relaxation of the suspensory ligaments with increasing convexity of the lens. Accommodation to near object is accompanied by constriction of the pupils and convergence of the eyes.

(2) Pupillary light reflex: Exposure of one eye to light produces constriction of the exposed (same) eye (direct reaction) and of the other eye (consensual reaction).

Afferent pathway starts from the retina to optic nerve, optic tract then to preoptic nucleus. Efferent impulses travel from Edinger-Westphal nucleus to ciliary ganglia to the short ciliary nerves leading to contraction of the sphincter pupillae muscles.

(3) Corneal or Conjunctival reflex: Touching of the cornea or the conjunctiva causes blinking of the eye. The afferent pathway is along the trigeminal nerve and the efferent is along the facial nerve to the orbicularis muscle.

A- Drugs affecting size of the pupil

(1) Myotics: These are drugs which produce constriction of the pupil by:

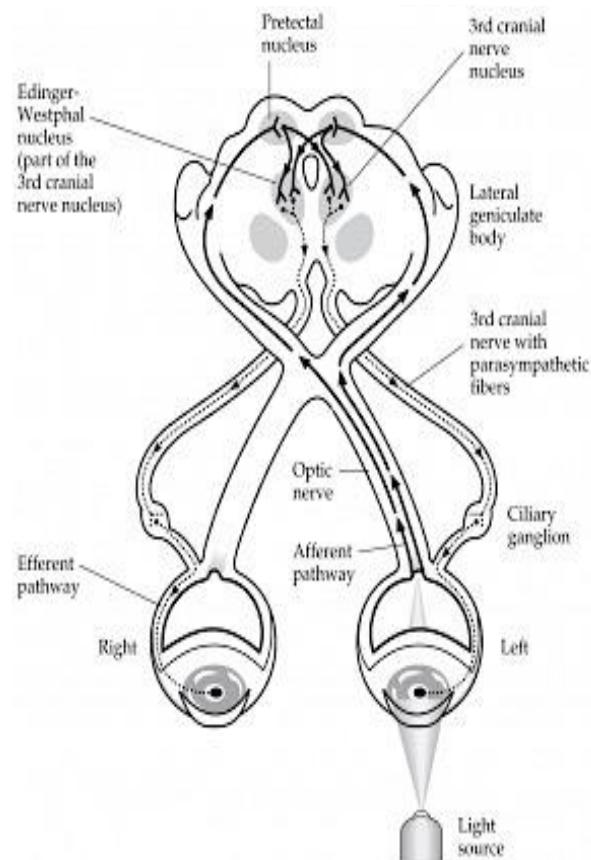
1-Stimulating the peripheral cholinergic (muscarinic) receptors in the constrictor pupillae muscle. They include:

- Choline esters e.g. bethanechol which stimulate muscarinic receptors only
- Reversible anticholinesterases e.g. eserine (locally and systemically) and neostigmine systemically.
- Irreversible anticholinesterases e.g. echothiopate.
- Cholinomimetic alkaloids that simulate muscarinic receptors e.g. pilocarpine.

2-Sympathetic blockers :

- Adrenergic neuronal blocker (Guanethidine).
- MAO inhibitors.

3- Stimulation of 3rd nerve nucleus by opiates.



Therapeutic uses of myotics:

1-Treatment of glaucoma .Pilocarpine is used as eye drops in treatment of both acute angle closure and chronic wide angle glaucoma. Because miosis facilitates aqueous drainage by opening canal of Schlemm.

2-Counteracting the effect of mydriatics .

Ocular side effects of myotics :

1-Headache due to excessive contraction of ciliary body.

2-Blurring of far vision (artificial myopia) due to excessive accommodation.



(2) Mydriatics

These are drugs which produce dilatation of the pupil.

Active mydriasis:

is a term applied when dilatation of the pupil IS due to stimulation of the dilatator pupillae muscle (light reflex is intact). Intraocular pressure is not usually affected or may be decreased due to decrease ocular blood flow. It could be produced by:

- a- Sympathomimetics as ephedrine which stimulates alpha adrenergic receptors on the dilator pupillae muscle
- b- Cocaine (a local anesthetic) producing mydriasis and vasoconstriction of conjunctival vessels by increasing the concentration of noradrenaline at the adrenergic receptors through inhibiting the enzyme MAO and blocking noradrenaline uptake.

Therapeutic uses of active mydriatics:

1-Examination of fundus (internal structures)of the eye because they produce mydriasis with no effect on intraocular pressure.

2-Treatment of allergic conjunctivitis because they produce vasoconstriction of conjunctival blood vessels due to their sympathomimetic effect.

3-Diagnosis of Horner's syndrome (Sympathetic denervation of the head due to dysfunction of cervical sympathetic chain by trauma ,tumor or degenerative conditions e.g. diabetes) .

Normally , sympathomimetics do not cause mydriasis on local application due to hydrolysis by lysosomes in tears .They produce mydriasis on local application in cases of Horner 's syndrome due to denervation hypersensitivity.

Passive mydriasis:

It is due to paralysis of the constrictor pupillae muscle thus giving the upper hand to the dilator pupillae muscle. Passive mydriasis are associated with:

- Loss of light reflex due to blockade of parasympathetic supply to constrictor pupillae muscle.
- Loss of accommodation due to paralysis of ciliary muscles.
- Increase intraocular pressure and may precipitate acute glaucoma in susceptible persons due to decrease aqueous drainage by closure of canal of Schlemm.

Preparations of passive mydriatics:

- 1- parasympatholytic e.g.. atropine, homatropine and tropicamide produce mydriasis and cycloplegia .Eucatropine, produces only mydriasis with no cycloplegia.
- 2- Ganglion blockers .They block parasympathetic ganglia in the eye (ciliary ganglion) on systemic administration.

Therapeutic uses of passive mydriatics:

- 1-Eye examination in person not susceptible to increase intraocular pressure.
- 2-Estimation of dioptic power of the eye after paralysis of accommodation .It is used in correction of errors of refractions by glasses.
- 3-Treatment of squint in children not tolerating glasses.
- 4-Prevention of postoperative intraocular adhesions.
- 5-Treatment of intraocular inflammation e.g. iridocyclitis and keratitis .They prevent intraocular adhesions.

Ocular side effects of passive mydriatics:

- 1-Blurring of vision in bright light due to mydriasis and loss of light reflex.
- 2-Blurring of near vision due to loss of accommodation.
- 3-Increase intraocular pressure in susceptible persons.
- 4-Decrease tear secretion which may promote inflammation after long term use due to loss of antiseptic effect of tears.

B- Drugs affecting reflexes of the eye:

- 1- **Parasympathomimetics:** These drugs in addition to its myotic effect produce contraction of the ciliary muscle which affect the accommodation reflex. Thus the eye would be accommodated for near object due to contraction of the ciliary muscles. The light reflex although present but it is weak due to spasm of the constrictor pupillae.
- 2- **Cycloplegics:** These are drugs which produce paralysis of the ciliary muscles thus impairing the accommodation reflex (loss of accommodation to near objects) They include the parasympatholytic group of drugs as atropine, homatropine and cyclopentolate. In addition to their cycloplegic effect, parasympathetics produce paralysis of the constrictor papillae muscle with the consequent loss of the light reflex.
- 3- **Local anesthetics:** These drugs block the sensory nerve endings of the trigeminal nerve thus abolishing both corneal and conjunctival reflexes. Examples of local anesthetics are cocaine, tetracaine

C- Drugs affecting intraocular pressure:

1-Drugs lowering intraocular pressure:

- 1-Parasympathomimetics as eserine and pilocarpine which produce myosis (widening of the angle) and contraction of ciliary muscles (opening the canal of Schlemm) help in lowering the LO.P.



2-Adrenaline decreases intraocular pressure in patients with glaucoma due to decrease aqueous formation as a result of decreasing ocular blood flow.

3-B blockers decreases aqueous formation

4-Adrenergic neuronal blockers e.g. guanethidine increasing aqueous drainage by producing miosis through relaxation of dilator pupillae

5-Osmotic diuretics withdraw fluids from the eye by dehydrating effect

6-Carbonic anhydrase inhibitors e.g. acetazolamide decreases formation of aqueous humor

2-Drugs tending to increase the I.O.P. (Drugs contraindicated in glaucoma):

1-Parasympatholytics: They decrease aqueous drainage by producing mydriasis and cycloplegia which lead to closure of Schlemm's canal.

2-Vasodilators e.g. nitrates , dopamine which increases ocular blood pressure by increasing aqueous formation.

3-Succinylcholine by producing spasm of extraocular muscles which exert pressure on the globe

4-Glucocorticoids causes salt and water retention and they increase intraocular pressure in some persons with defective aqueous drainage.

5-Adrenaline in normal person due to increase aqueous formation via stimulation of B2 receptors.

Treatment of glaucoma

a-Narrow Angle Glaucoma:

1-Miotic eye drops: Pilocarpine (1 - 2%) + Physostigmine (0.5%) . They promote drainage of aqueous humor, organophosphorus compounds are not indicated.

2- Carbonic anhydrase inhibitors : They inhibit synthesis of aqueous humor . Oral . Acetazolamide or Dichlorphenamide (Like acetazolamide but without a diuretic effect) .

3- Osmotic agents: Useful in acute congestive glaucoma mannitol I.V infusion and Glycerol orally.

b-Wide (open) angle glaucoma:

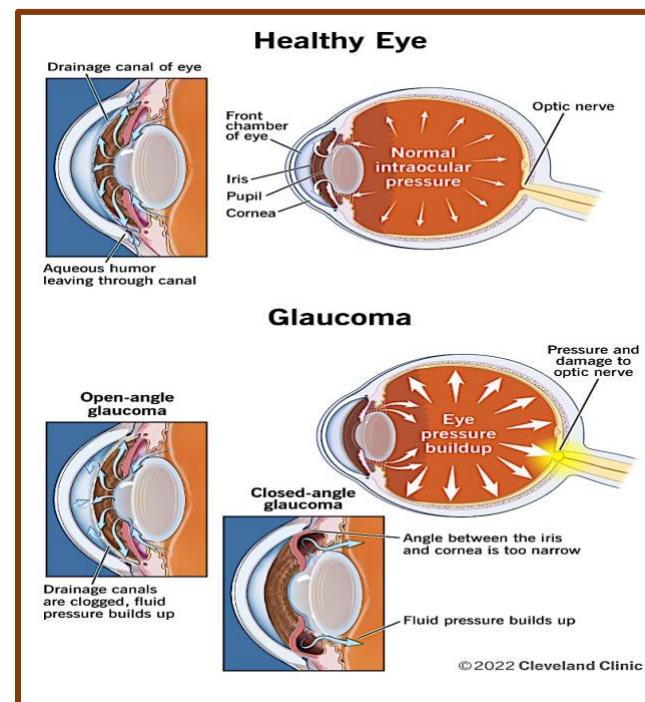
1- Miotic eye drops : Short acting : pilocarpine, physostigmine. Long acting: Echothiophate.

2- Carbonic anhydrase inhibitors : Acetazolamide (Diamox).

3- Sympathomimetics eye drops :Adrenaline (1-2%) or Dipivalyl Adrenaline 0.1 % (Lipophilic analogue of adrenaline).

4-Guanethidine 10% eye drops.

5- B blockers: Timolol (Timoptic) 0.25 – 0.5 eye drops .



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MECHANISM OF ACTION & TOXICITY OF SOME CHEMOTHERAPEUTIC AGENTS

- **Chemotherapy:** Drugs used to eliminate microorganisms e.g: Bacteria, virus, fungi, helminthes (worms) and malignant tumors.
- **Chemotherapeutic agent:** is any chemical substance which kills the organism or inhibits its growth e.g.: Sulphonamides.
- **Antibiotic:** is a substance produced by living micro-organisms to inhibit or kill another living micro-organisms e.g.: Penicillin.
- **Selective toxicity:** means that the drug, if used in a concentration tolerated by the body, is harmful to a parasite without being harmful to the host.
 - **Selective toxicity** may be due to **the presence of specific receptors for the drug attachment** or may be **dependent on inhibition of biochemical events** that is essential for the parasite but not for the host.

A-Classification of antimicrobial agents according to their mode of action:

Bactericidal:

- Kill microorganisms by direct effect e.g. **B-lactam antibiotics, Quinolones.**
- Effective in immunosuppressed host.

Bacteriostatic:

- Inhibit growth of microorganism. e.g. **Sulphonamides , chloramphenicol.**
- Not effective in immunosuppressed host.

Bacteriostatic and cidal: according to concentration e.g: **Erythromycin.**

B-Classification of antimicrobial agents according to the spectrum:

Broad spectrum:

- Effective against **multiple gram +ve & -ve** organisms e.g: **quinolones.**
- Used as initial empirical treatment till culture and sensitivity results appear.

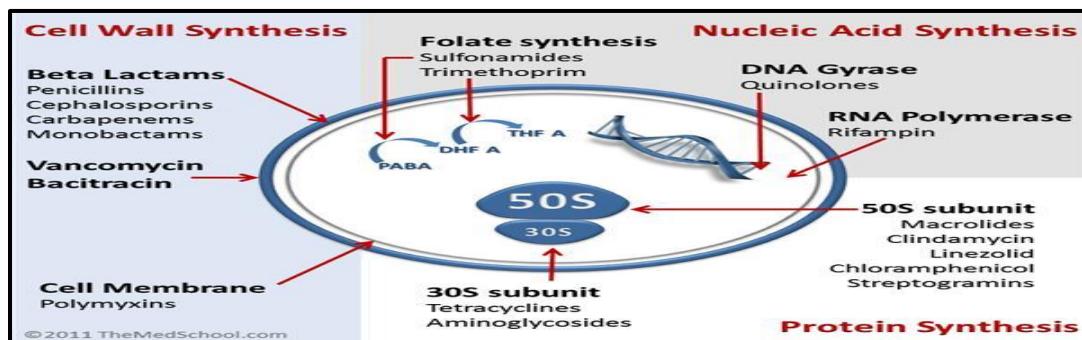
Narrow spectrum:

Effective against specific organisms e.g.:

- Antimicrobial against **gram +ve** bacteria: **Penicillin G.**
- Antimicrobial against **gram -ve** bacteria: **aminoglycosides.**
- Used in treatment of susceptible organisms based on culture and sensitivity results.

Moderate spectrum: e.g.: **Macrolides (erythromycin).**

C-Classification of antimicrobial agents according to mechanism of action:



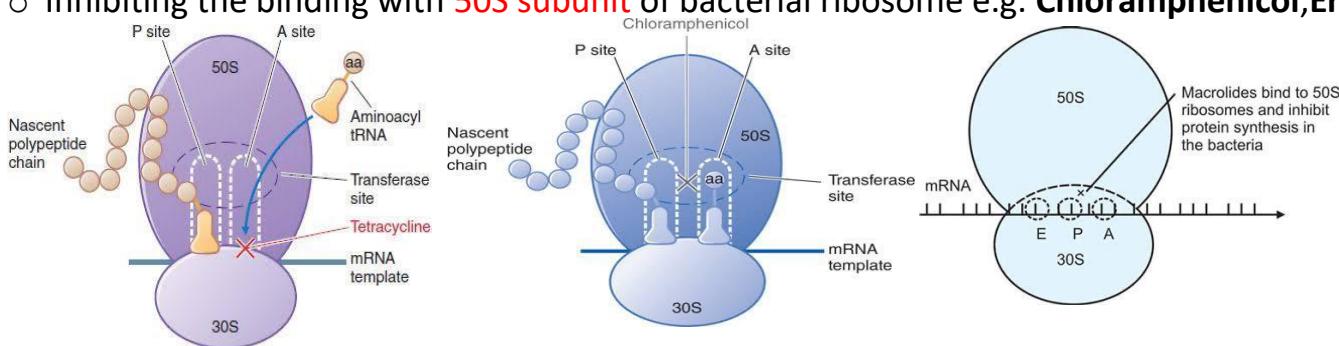
1-Cell Wall Synthesis Inhibitors: They include

- A. Beta-lactam antibiotics (**penicillins & cephalosporins**): inhibit the last step of bacterial cell wall synthesis (Inhibit transpeptidase E, responsible for cross linking of the long peptidoglycans).
- B. Vancomycin : inhibit the intermediate step of cell wall synthesis (Inhibition of the elongation of peptidoglycan).
- C. Cycloserine : inhibit the 1 st step of cell wall synthesis (Inhibition of the formation of di-d-alanine).

2- Increasing Permeability of Cytoplasmic Membrane leading to cell damage: e.g. **Polymyxins** .

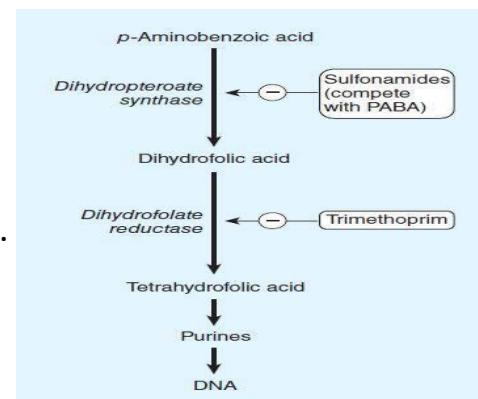
3- Inhibiting Protein Synthesis:

- Inhibition of the **formation of mRNA** (inhibition of RNA polymerase) e.g. **Rifampicin**.
- Inhibiting the binding with **30S subunit** of bacterial ribosome, e.g. **tetracyclines, Aminoglycosides**.
- Inhibiting the binding with **50S subunit** of bacterial ribosome e.g. **Chloramphenicol, Erythromycin**.



4- Inhibiting Nucleic Acid Metabolism:

- **Directly on DNA:**
 - **Metronidazole** •**Antiviral & Cancer chemotherapy.**
 - Quinolones** (inhibit DNA gyrase)
- **Directly on RNA:** **Rifampicin** (inhibits RNA polymerase enzyme).
- **Indirectly (Folate inhibitors) :**
 - Compete with PABA e.g: **Sulphonamide**.
 - Inhibit Dihydrofolate Reductase e.g. **Trimethoprim**.



Main Side Effects of Chemotherapeutic Agents & Antibiotics:

Hypersensitivity: fever, skin rash, arthralgia, cholestatic jaundice, hemolytic anemia, hemolysis, agranulocytosis, bone marrow aplasia, and anaphylactic reactions.

Hepatic toxicity:

- Hepatocellular (**INH&sulphonamides**)
- Cholestatic jaundice (**erythromycin** & **rifampicin**).

Renal toxicity :

- Tubular necrosis (**Cephaloredine**, & outdated **tetracyclines**)
- Interstitial nephritis (**methicillin** & **sulphonamides**)

Digestive system:

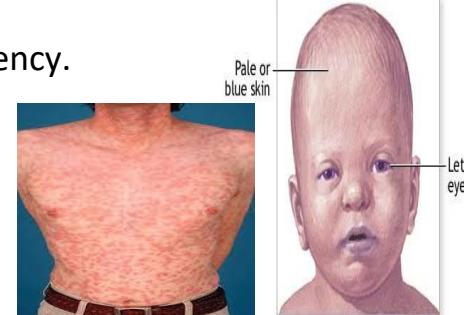
Pseudomembranous colitis occur with long term use of broad spectrum antibiotics as (**tetracyclines**, **clindamycin** , **chloramphenicol**, **lincomycin**, & **ampicillin**) .

In this condition:

- stop the drug
- eradicate cl. difficile, the causative agent, give **vancomycin** & **metronidazole**.

Specific toxicity:

- **Sulphonamides**: Crystalluria, Hemolytic anemias in G-6-PD deficiency.
- **Penicillins**: Allergy, Herxheimer reaction.
- **Cephalosporins**: Allergy, nephrotoxic.
- **Erythromycin**: Nausea, vomiting, diarrhoea, cholestatic jaundice.
- **Chloramphenicol**: Bone marrow depression, Grey baby syndrome.
- **Streptomycin(aminoglycosides)**: Deafness & vertigo (8th nerve affection), Curare-like action.
- **Tetracyclines** : Teratogenic & G.I.T. irritation (nausea, vomiting) Teeth (enamel hypoplasia, yellow discolouration).
- **INH**: Peripheral neuropathy.



Assessment:

According to mechanism which of the following act by inhibit 30s subunit of ribosome :

- | | |
|-----------------|---------------|
| a) Erythromycin | c) pencilline |
| b) Tetracycline | d) Quinolons |

Grey baby syndrome is mostly characteristic toxicity with:

- | | |
|-----------------|--------------------|
| a) Penicillin | c) Chlormphenichol |
| b) Sulphonamide | d) sterptomycin |

Cell wall synthesis inhibitors

- ❖ **Cell Wall Synthesis Inhibitors:** They include
- **Cycloserine :** inhibit the 1 st step of cell wall synthesis (Inhibition of the formation of di-d-alanine).
- **Vancomycin :** inhibit the intermediate step of cell wall synthesis (Inhibition of the elongation of peptidoglycan).
- **B-lactam antibiotics (penicillins & cephalosporins):** inhibit the last step of bacterial cell wall synthesis (Inhibit transpeptidase E, responsible for cross linking of the long peptidoglycans).

➤ **β-lactam Antibiotics**

The chemical structure of this group includes a β-lactam ring which is essential for their action.

- ✓ Penicillins. ✓ Monobactam.
- ✓ Cephalosporins. ✓ Carbapenems.

■ **Pencillins**

Mechanism of Action:

- ✓ Interfere with cell wall synthesis by binding to penicillin-binding proteins (PBPs) which are located in bacterial cell walls.
- ✓ Inhibition of PBPs leads to inhibition of peptidoglycan synthesis.
- ✓ Activation of autolysin (destruct cell wall)
.-They are bactericidal

NB: human cells don't contain peptidoglycan, so they don't affected by penicillin.

Mechanisms of Resistance

- ✓ Production of beta-lactamase enzyme is the most important and most common. It hydrolyzes beta-lactam ring causing inactivation.
- ✓ Alteration in PBPs leading to decreased binding affinity.
- ✓ Alteration of outer membrane leading to decreased penetration.

Pharmacokinetics

- ✓ Canot penetrate normal BBB but can penetrate it in case of meningitis.
- ✓ Cross placenta but not teratogenic (fetal cells not include transpeptidase enzymes).

Classifications

- ✓ Narrow spectrum penicillins: Penicillin G, penicillin V
- ✓ Beta-lactamase resistant penicillins: Methicillin, flucloxacillin.
- ✓ Broad spectrum penicillins: Ampicillins, amoxicillin, carbinicillin
NB: add betalactamase blocker (sulbactame, clavulanic acid) to Beta-lactamase sensitive penicillins.
- ✓ Antipsuedomonal penicillin: Carbinicillin & ticarcillin & piperacillin

- **Pro-ampicillin:** pivampicillin, bacampicillin & talampicillin are prodrugs, so they produce no effect on intestinal flora, good absorption & high bioavailability.
- NB: Antipsuedomonal drugs: penicillins as (Carbinicillin & ticarcillin & piperacillin), aminoglycosides, ceftazidime, cefperazone and quinolones.**

Uses of penicillins:

- ✓ Respiratory tract infections.
- ✓ Benzathine penicillin 1.2 MU/ month for prophylaxis in rheumatic fever for 5 years or up to 20 years.
- ✓ Procaine penicillin 600,000 U 2-3 h given before dental procedures to protect against subacute bacterial endocarditis in patient with rheumatic fever or prosthetic cardiac valves.
- ✓ Syphilis & gonorrhea.
- ✓ Cellulitis.
- ✓ Meningitis caused by pneumococci and meningococci.
- ✓ Amoxicillin in combination therapy for h. pylori eradication.
- ✓ Benzylpenicillin eye drop to protect against gonorrhreal neonatal ophthalmia.

Adverse effects

1. hypersensitivity (5-10%) (metabolic drugs of penicillins)

- Rashes (common), urticaria & erythema.
- Anaphylaxis (rare): circulatory failure, bronchospasm & laryngeal edema.

Treatment of anaphylaxis: adrenaline i.m, hydrocortisone i.v & antihistamine i.v.

2. Serum sickness: after 2-12 days, fever, malaise, arthralgia, angioedema & Steven-Johnson syndrome.

3. Neurotoxicity: in cases of high doses especially intrathecal injection, it gives rise to convulsions.

4. Diarrhea & thrush due to superinfection by fungi.

5. Hepatotoxic.

■ Cephalosporins:

Chemistry: contain B lactame ring

Mechanism of action:

Interfere with cell wall synthesis (inhibit the last step of bacterial cell wall synthesis (Inhibit transpeptidase E, responsible for cross linking of the long peptidoglycans).

Generations

generation	spectrum
1 st generation . • Cephalexin . • Cephradine.	Broad spectrum: • Mainly G+ve • Beta lactamase resistant • Not pass BBB • Betalactame sensitive Ex :renal • cross allergy with penicillin
2 nd generation • Cefaclor	Spectrum Similar to 1st generation but: • Less active against G +ve. • More active against G-ve except Pseudomonas. • Not pass BBB except cefuroxime. • Betalactame sensitive • cross allergy with penicillin Ex:renal.
3 rd generation • Cefixime(suprax). • ceftaixone	spectrum Similar to 2nd generation but: • More active against G-ve • Cefoperazone & Ceftazidime are active against Pseudomonas. • Pass BBB except cefpazole. • Betalactame resistant. • No cross allergywith penicillinEx : mainly billary
4 th generation • Cefepime .	Spectrum Similar to 3rd generation but: • more resistant to beta-lactamase. • Pass BBB. • Betalactame resistant. • No cross allergywith penicillin. Ex : mainly billary.

Uses

1. Infection resistant to penicillin e.g. Staph. & Gonorrhea.
2. Pseudomonas infection: cefoperazone & ceftazidime.
3. Meningitis (cefotaxime).
4. Anaerobic infection (cefoxitin).
5. Typhoid fever (3rd generation)
6. Respiratory and urinary tract infections.

Side effects:

- Allergy and 10% cross allergy with penicillin.
- Thrombophlebitis after i.v and painful after i.m injections.
- Nephrotoxicity especially with cephaloridine. The toxicity increased by furosemide and gentamycin.
- Cefoperazone have anti vitamin K effect & inhibit platelet function so they may produce bleeding.
- GIT upset and superinfections.(stop drug. Give metronidazole , vancomycine).

■ Monobactam

Aztreonam

- Aztreonam bind preferentially to PBP 3 of gram-negative aerobes including Pseudomonas.
- No effect on G+ve or anaerobes.
- Low risk of cross allergy with penicillin.
- Resistant to betalactamase enzyme.



Carbapenems

1. Imipenem

- The broadest spectrum antibiotic.
- **Used by** i.v in serious hospital acquired infections (nosocomial pneumonia and septicemia) add cilastatin(inhibit dihydropeptidase)

2. Meropenem:

- It is similar to imipenem, but not metabolized by dihydropeptidase in the kidney.
- It passes the BBB.
- Not associated with nausea or convulsion.

■ Vancomycin

It is a glycopeptide

Uses:

- Pseudomembranous colitis (orally).
- With aminoglycoside in streptococcal endocarditis in patients allergic to benzyl penicillin.
- Serious infections with multiply-resistant staphylococci.

S/E:

- Auditory damage, but tinnitus and deafness may improve if vancomycin is stopped.
- Nephrotoxicity.
- Allergic reactions and rapid i.v may cause red person syndrome due to histamine release.

Protein synthesis inhibitors

Include:

1-AMINOGLYCOSIDES

2- Tetracycline

3- Macrolide

4- Chloramphenicol

1-Aminoglycosides

• Members:

- The aminoglycoside include gentamycin, amikacin(least resistance), kanamycin, tobramycin, neomycin and streptomycin.
- These drugs resemble each other in their mechanism of action, , kinetics, therapeutics and toxic properties. . They only differ in their range antibacterial activity.
- Cross resistance is variable.

• Kinetics:

- These drugs are water soluble, poorly absorbed from GIT and must be given parenterally for systemic use.
- They distributed mainly into the extracellular fluids.
- They don't pass the BBB even if it is inflamed. (cross placenta)
- Safe during lactation(not absorbed orally)
- Excreted mainly in kidney (UTI increase their secretion ??

• Mechanism of action:

- They are bactericidal drugs.
- They inhibit protein synthesis by binding the 30S bacterial ribosome subunit.

Spectrum:

- They are active against G-ve bacteria (-ve charge on outer membrane so attract aminoglycoside with positive charge).
- e.g. Enterobacter, Ecoli, Proteus & Pseudomonas.
- G+ve e.g. some Staph. & Strept. • T.B.
- Combination of aminoglycosides with a B-lactam antibiotic is synergistic and extends the spectrum to include Gr+ve Bacteria.

Uses:

Streptomycin: Gram negative infections (**chest infection, urinary tract infection and septicemia**)

TB ,Brucellosis.

Gentamycin: In bacterial endocarditis (part of combination therapy).

Neomycin: it is too toxic for systemic use, but used orally for topical gut sterilization before colon operations and in pre-hepatic Coma (kill intestinal flora which produce ammonia).

Paromomycin: orally for intestinal amebiasis and hepatic coma.(only attach 30 s of protozoa)

Adverse effects:3N

- Ototoxicity , cochlear and vestibular affection of the **8th nerve** , more with long term, high dose and in old age .
- **Nephrotoxicity**, tubular damage which is reversible.
- **Neuromuscular blockade** especially with anaesthetics and muscle relaxants.
- Skin hypersensitivity.

Contraindications:

- | | | |
|---------------------|-------------------------------------|--------|
| 1- Renal impairment | 2- auditory disease | 3- M G |
| 4- with curare | 5- with penicillin in same solution | |

2- MACROLIDES:(Erythromycin , Clarithromycin , Azithromycin and Spiramycin)

-Erythromycin

• Kinetics:

- Erythromycin is poorly absorbed orally, affected by food **The active erythromycin diffuses readily into most tissues**, eliminated in hepatic bile and feces (90%).

- Poor distribution to BBB
- Cross placenta but not teratogenic.
- Concentrate inside neutrophil so have long biological half life (one per day)

• Mechanism of action:

- Bacteriostatic in low concentrations and bactericidal in high concentration.
- It is also claimed to be bacteriostatic in some organisms; bactericidal in others.
- It **acts on 50S** bacterial ribosomal subunit, inhibiting bacterial protein synthesis.

• Spectrum:

- It is similar to penicillin, but not identical.
- It is more active against G+ve than G -ve organisms because G +ve organisms accumulate the drug more efficiently.
- It is also active against chlamydia, mycoplasma, legionella, spirochetes, and toxoplasmosis.

• Resistance: modification of site on 50S.

Uses:

- Chest infections (especially chlamydia, mycoplasma & legionella ,intracellular atypical organisms).
- Treatment of **toxoplasmosis** (Spiramycin).
- Eradication of H. pylori in peptic ulcer (Clarithromycin).
- Streptococcal (Rheumatic fever) or pneumococcal infection in penicillin allergic patients.(gram positive).
- Diabetic gastroparesis and other GI motility disorders via motilin receptor activation.

- **Adverse effects:**

- cholestatic hepatitis (store in liver .enterohepatic circulation)
- Acute cholecystitis or pancreatitis (allergic reaction)
- Photosensitization, headache, vertigo, G.I.T. upset (diarrhea and nausea).
- Prolong QT interval.

- **NB: Erythromycin estolate is Contraindicated in liver diseases**

- **Interactions (all macrolides)**

- **Enzyme inhibitors:** they inhibit the metabolism of: Warfarin, carbamazepine, theophylline & disopyramide, so increasing their effect.

- Not add to penicillin (antagonism) cidal +static.

-Clarithromycin

- It is like erythromycin, affecting mainly G+ve organisms, but more active against the G-ve bacilli H. influenza & H. pylori.
- It causes fewer GIT disturbances than erythromycin
- Used in H. pylori eradication (in combination therapy).

- Azithromycin

- It is active against some important G-ve organisms e.g. H. influenza, N. gonorrhoea and also against chlamydia.
- Azithromycin is **lesser active** than erythromycin against G+ve organisms
- It is largely **unmetabolized and excreted in the bile and stool.**
- It is used in **chest infections and sexually transmitted diseases especially genital chlamydia infections.**

- **Adverse effects:** nausea, diarrhea, abdominal pain

- Contraindicated in liver disease

3-TETRACYCLINES

- Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.

- **Classifications:**

1. Short acting tetracyclines (250- 500 mg / 6h) as oxytetracycline, chlortetracycline and tetracycline.
2. Intermediate acting tetracyclines: as demeclocycline.
3. Long acting tetracyclines: (50 – 100 mg / 24 h) as doxycycline and minocycline.

- **Kinetics:**

- Partially absorbed from GIT. (affect by food especially contain calcium)
- Distributed throughout the body and crosses the placental barrier.
- Excreted unchanged in the urine except doxycycline and minocycline (more lipid soluble), which are eliminated by non-renal route, so are allowed in renal failure.
- teratogenic

- **Mechanism of action:**

- They act on 30S bacterial ribosomal subunit, inhibiting protein synthesis.

- **Bacteriostatic even in high concentration**

- **Spectrum:**

- Some G+ve & G-ve bacteria (except typhoid), rickettsiae, cholera, protozoa, chlamydia and treponema pallidum.

- **Uses:**

- Atypical pneumonia (Mycoplasma).
- Non gonococcal urethritis.
- Prophylaxis against meningococcal meningitis.
- Cholera, treatment & prophylaxis.
- Brucellosis & shigellosis.
- Topically in skin and eye infections.
- Acne.
- Syndrome of Inappropriate ADH secretion (SIADH): Demeclocycline.

NB: tetracycline uses have been declined due to increasing bacterial resistance

- **Adverse effects**

- 1- GIT upset 2- superinfection
- 3- enamel dysplasia , yellowish discoloration of teeth
- 4- Cholestatic jaundice , liver cell failure
- 5-Minocycline may cause dizziness, vomiting & vertigo.
- 6-Expired tetracyclines lead to Fanconi syndrome (vomiting, polyuria, polydipsia, proteinuria, glycosuria, and acidosis).
- 7- photosensitivity.

NB. Tetracyclines shouldn't be given to pregnant females, children below age of 8 or if outdated.

4-CHLORAMPHENICOL

- **Spectrum:**

- It is a broad-spectrum bacteriostatic antibiotic affecting G+ve & G -ve bacteria .
- It may be bactericidal against H. influenza, N. meningitidis and streptococcus pneumoniae.

- **Kinetics:**

- Administered orally in capsules to avoid its bitter taste, it is also given by i.m & i.v routes.
- Widely distributed allover the body and passes the BBB.
- Inactivated by glucuronidation in the liver and excreted in urine and milk.

- **Mechanism of action:**

- Binding to 50S bacterial ribosomal subunit, inhibiting protein synthesis.

• **Uses:**

- Typhoid & paratyphoid.
- Urinary & respiratory tract infections.
- Meningitis & brain abscess (superseded by cefotaxime& ceftriaxone). Pass BBB in normal and inflamed meninges .
- Mixed aerobic & anaerobic infections.
- Food poisoning.
- Topical in eye & ear infections.

• **Adverse effects:**

- Reversible bone marrow depression (dose-dependent).
- Irreversible and fatal aplastic anemia, (Idiosyncrasy, i.e. genetically dependent.(dose independent)
- G.I.T upset & superinfection.
- Grey Baby Syndrome: The liver of the premature neonates fails to metabolize chloramphenicol leading to vomiting, hypothermia, flaccidity, circulatory collapse, and gray skin.(not contain gluconyl enzyme).

بتسأل ليه
يا قلقس؟



بتعرف تعوم
يا زغلو؟



أصل احنا تقريبا
كده بنفرق في
بحر المنهج



Nucleic Acid synthesis Inhibitors

❖ QUINOLONES (Fluoroquinolones) FQs

- FQs are novel group of synthetic antibiotics Developed in response to growing resistance
- They derivatives of **nalidixic acid**

❖ Generations :

	Gram negative	Gram positive	Atypical	Aerobes
1st Nalidixic acid	+	-	-	-
2nd Norfloxacin Ciprofloxacin	+	+	+	-
3rd Levofloxacin	+	+	++	-
4th Gatifloxacin Moxifloxacin	+	+	++	+

❖ Kinetics:

- Well absorbed orally,
- food delays peak concentration(esp metal Chelat them),
- distributed allover the body with penetration of the BBB, eliminated by renal And hepatic routes
- Pass placenta and in milk so Contraindicated in pregnancy and lactation
- Excrete renal mainly except moxifloxacin

❖ Mechanism of action:

FQs are **bactericidal**. They **inhibit DNA replication**

Through:

1. Inhibition of DNA gyrase (Topoisomerase I), which is Responsible for removal of excess Positive supercoiling in The DNA helix. (relax helix)
2. Inhibition of topoisomerase IV which is essential for Separation of interlinked daughter DNA molecules.

✓NB: generally the DNA gyrase (Topoisomerase II) is the primary target in gram-negative Bacteria while topoisomerase IV is the :

- primary target in gram-positive bacteria.
- FQs display concentration-dependent Bactericidal activity
- Human DNA gyrase is not sensitive to quinolones

❖ Uses:

- Urinary tract infection
- Prostatitis.
- Gonorrhea.
- Typhoid fever & peritonitis.
- Multi-drug resistant T.B.
- Respiratory tract infection.
- Osteomyelitis and skin infections.

❖ Adverse effects:

- Nausea, vomiting & abdominal discomfort.
- Headache & dizziness.
- Photosensitivity.
- Arthropathy & damage of growing cartilage In children
- Can inhibit GABA -> seizures, insomnia, Nightmares.

❖ Contraindications:

- Pregnancy, lactation & prepubertal children.
- Epilepsy and with NSAIDs which potentiate This effect.
- Sparfloxacin & moxifloxacin prolong QT Interval, so not used in patient with Predisposed Arrhythmia or taking Antiarrhythmic drugs

