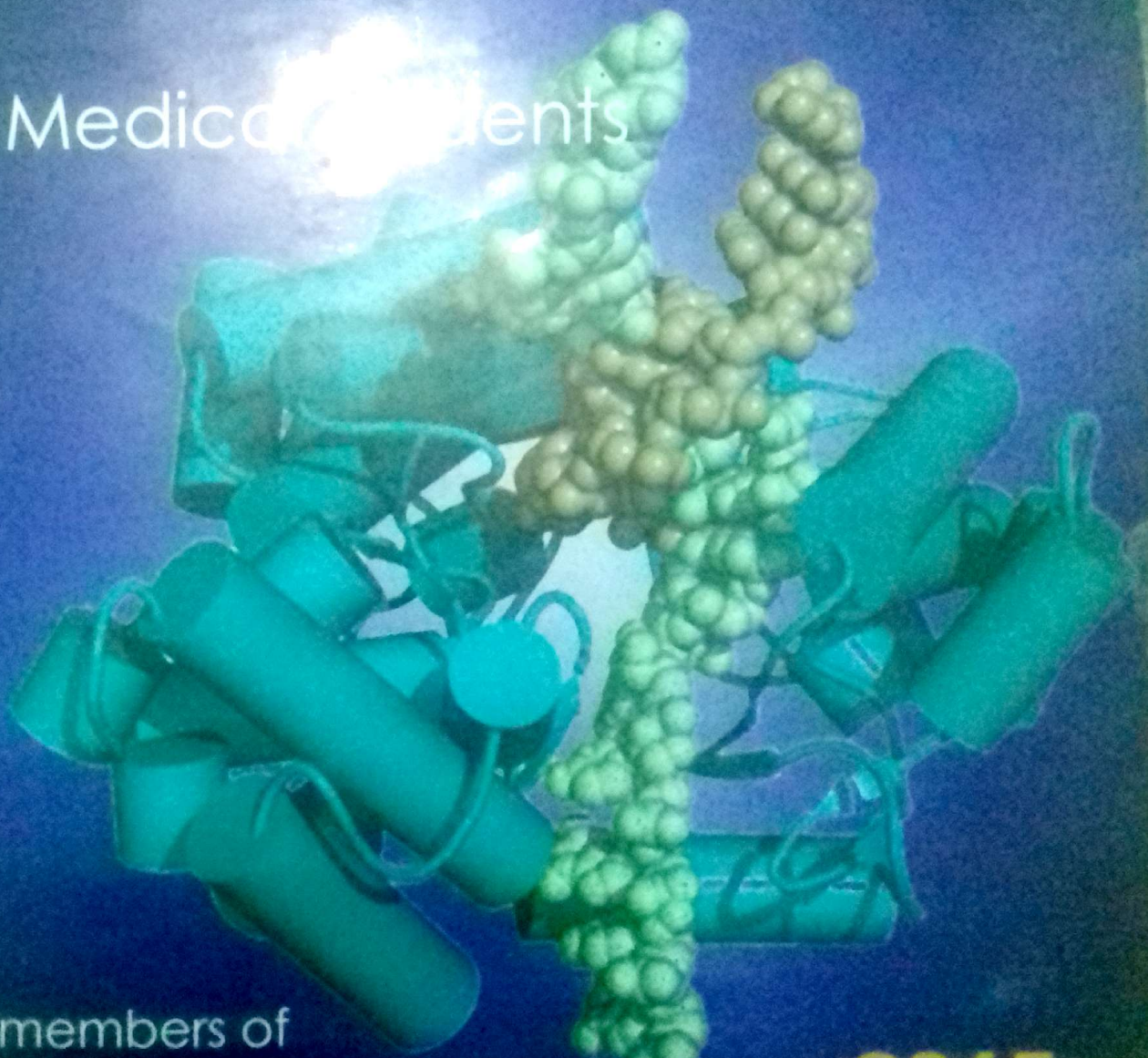
Mansoura Clinical Pharmacology

2015 Simplified approach

For Medical Students



By
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Clinical Pharmacology Department
Mansoura Faculty of Medicine

2015 update

Mansoura Clinical Pharmacology

For Medical Students

Volume 1

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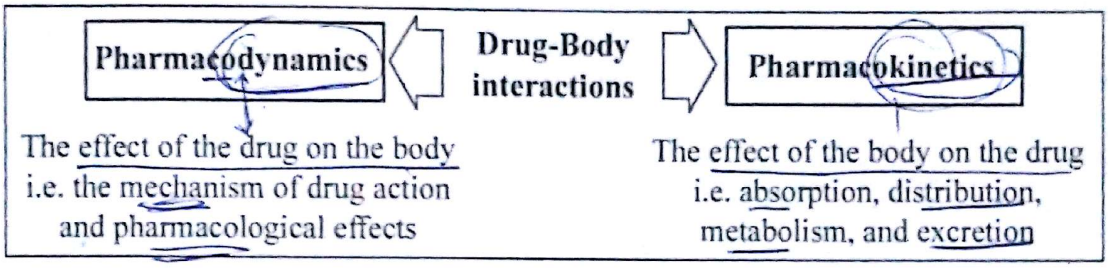
Chapter 1 General Principles

Medical pharmacology is the science dealing with small molecules used to prevent, diagnose, or treat diseases.

A drug is any small molecule can interact with body systems at the molecular level and produce effect.

Clinical pharmacology is the science concerned with the rational, safe and effective use of drugs in humans. It combines elements of classical pharmacology with clinical medicine in other words, it involves the complex interaction between the **patient** and the **drug**.

The drug-body interactions



Part 1: Pharmacodynamics (Mechanism of drug action)

A drug may produce its effects through interaction with:

1. **Body control systems** (regulatory proteins):
   - (a) Receptors
   - (b) Ion channels
   - (c) Enzymes
   - (d) Carrier molecules
2. Direct chemical or physical mechanisms.
3. Interaction with certain metabolic pathways.

Notes

Receptors

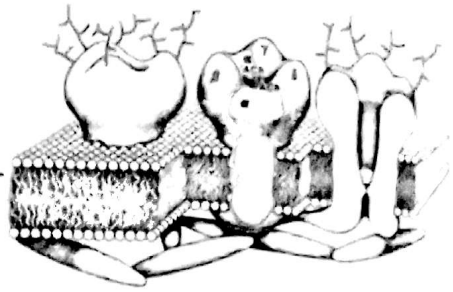
Receptors: they are protein macromolecules. When they combine with a drug, they may be activated or blocked.

Ligand: is any molecule that can combine with the receptors. A ligand that activates the receptor is called **agonist**. A ligand that blocks the receptor is called **antagonist.**

Affinity: it is the empathy of the receptor to the ligand. It determines the number of receptors occupied by the drug.

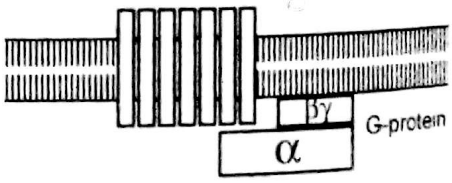
Types of receptors

- **Ion channel-linked receptors (direct ligand-gated ion channels):**

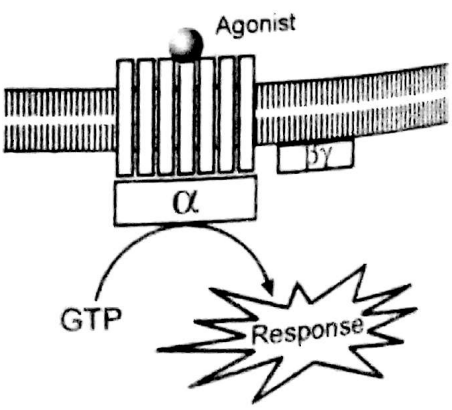


  - The receptor is an ion channel consists of 5 transmembrane subunits (α_1, α_2, β, γ, δ).
  - Binding of the agonist to the extracellular part of the receptor causes opening of the channel for a specific ion.
  - The response of these receptors is very fast and their duration is very short.
  - Examples:
    - *Nicotinic Ach receptors in the motor end-plate*, the ion channel opens for Na^+ ions in response to stimulation by Ach.
    - *The Gama aminobuteric acid (GABA) receptors in the brain*, the ion channel opens for Cl^- ions in response to stimulation by GABA.

- **G-protein-linked receptors:**
  - The receptor consists of 7 membrane subunits.
  - Binding of the agonist to the extracellular part of the receptor causes activation of intracellular G-protein which consists of 3 subunits (α, β, γ)



  - When the G-protein is activated, its α subunit binds to GTP to be phosphorylated and bring stimulatory or inhibitory response.
  - Their response is slower than ion channel receptors but their duration is longer.



  - **Stimulatory G-protein (Gs):** can lead to:
    - ↑ *adenyl cyclase enzyme* → ↑ cAMP → activation of specific proteins.

- ↑ *phospholipase C enzyme* → ↑ inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 causes ↑ free intracellular Ca^{2+} while DAG can activate protein kinase C.
- ↑ *phospholipase A_2 enzyme* → ↑ prostaglandin formation.
- Open ion channels.

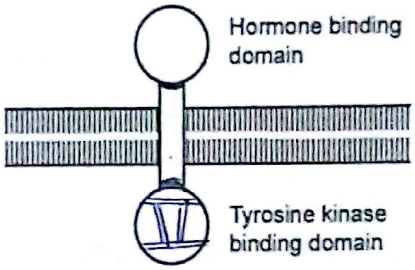
- **Inhibitory G-protein (Gi):** can lead to:
  - ↓ *adenyl cyclase enzyme* → ↓ cAMP → inhibition of specific proteins.
  - Regulation of K^+ and Ca^{2+} channels.

- Examples:
  - *Receptors linked to Gs:* e.g. β-adrenergic receptors.
  - *Receptors linked to Gi:* e.g. α_2-adrenergic receptors.

NB: there is a third type of G-protein receptors called **Gq**

▪ Tyrosine kinase (TK)-linked receptors:

- The receptor consists of 2 large domains: an extracellular hormone-binding domain and an intracellular TK-binding domain connected by a transmembrane segment.
- Binding of the agonist to the hormone-binding domain causes activation of the intracellular domain to activate TK enzyme → activation of several proteins known as *"signaling proteins"*.
- Examples: *insulin receptors.*



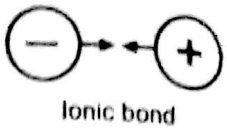
▪ Intracellular receptors:

- They are located inside the cell either in the cytoplasm or **directly on the DNA.**
- They regulate transcription of genes in the nucleus or the mitochondria.
- Their agonist must enter inside the cell to reach them.
- They have two important features:
  - Their response is **slow** (time is required for synthesis of new proteins).
  - Their effects persist for **long time** after the agonist is removed.
- Examples: receptors for ***corticosteroids***, *sex hormones*, *thyroxin*, *etc.*

Notes

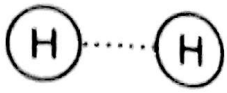
↑ adenyl cyclase → ↑ cAMP
↑ phospholipase C → ↑ IP3, DAG
↑ phospholipase A_2 → ↑ prostaglandin.
open ion channels

Types of drug-receptor bonds



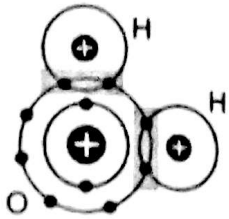
Ionic bond

- **The ionic bond:**
  It is strong but reversible.



Hydrogen bond

- **The hydrogen bond:**
  It is weak and reversible.



The covalent bond

- **The covalent bond:**
  Very strong and irreversible.
  If occurred between drug and receptor, the receptor becomes permanently blocked.

Biological response to drug-receptor binding

When a drug combines with a receptor, this may lead to one of the following:

- **Agonist effect:** means that the drug gives certain response.
- **Antagonist effect:** means that the drug gives **NO response** and prevents the receptor from binding to another agonist.
- **Partial agonist effect:** the drug acts like agonist & antagonist.

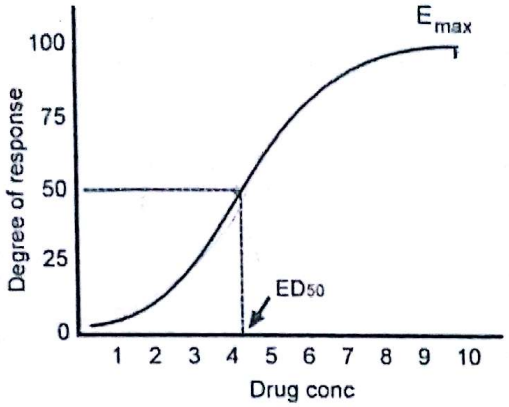
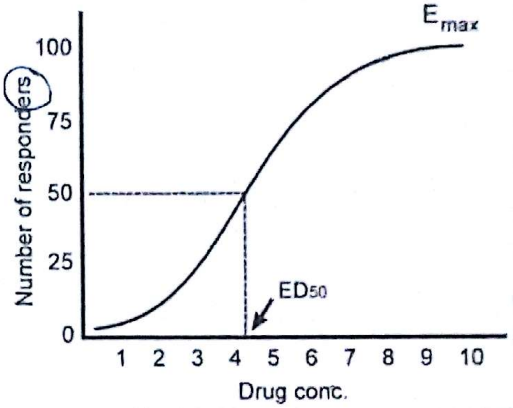
Agonist effect

- Agonist is the ligand that combines with the receptor and gives response.
- Response will never exceed a certain limit whatever the drug conc. This is termed *"the point of maximal response"* = the E_{max}.

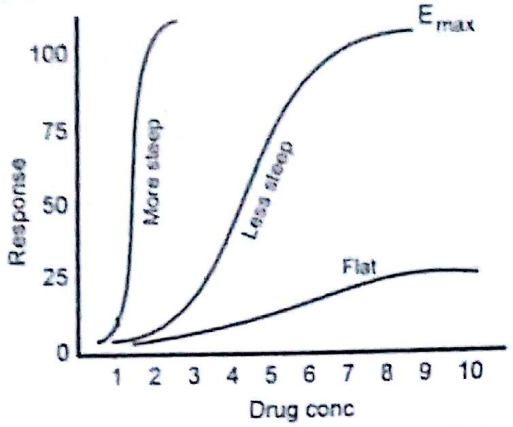
- There are 2 types of responses to drugs:

- **Graded response:** the response increases by increasing the agonist.
- **Quantal response:** the response is *all-or-none* effect.

Notes

Graded response	Quantal response
– It is the response to **most** drugs. – Could be tested in **one or more** animals. – Example: the response of the heart to adrenaline.	– It is response to **certain** drugs. – Could **not** be tested in one animal and must be tested in a **group** of animals. – Example: prevention of convulsions by antiepileptic drugs
	
Clinical significance:	**Clinical significance:**
1 Calculation of the ED_{50}: – ED_{50} is the dose that produces 50% of the maximal response in **one** animal. – Value of knowing the ED_{50}: ▪ Comparing the potencies of multiple drugs in one animal. ▪ Comparing the **equieffective doses** of multiple drugs in one animal.	**1 Calculation of ED_{50} and LD_{50}:** – ED_{50} is the dose that gives specific effect in 50% of **group** of animals. – LD_{50} is the dose that kills 50% of treated animals.
2 Calculation of drug efficacy: – Efficacy is the maximal response (E_{max}) obtained by a drug. – Value of knowing the E_{max}: ▪ Knowing the maximal respo-nding capacity of the organ. ▪ Differentiation between full agonists and partial agonists.	**2 Calculation of therapeutic index (TI):** – **TI** is the ratio between LD_{50} and ED_{50}. – It is rough index of drug safety. $$TI = \frac{LD_{50}}{ED_{50}}$$ (it must be **>1**) – The LD_{50} must be greater than the ED_{50} i.e. the ratio must be **>1**. The higher the ratio, the safer the drug.
3 Determination of the slope of the dose-response curve:	**3 Calculation of the protective index (PI):** – Protective index is similar in principle to TI but it measures the relation

- The slope varies for different drugs and different responses.
- A steep (sharp) dose-response curve means minimal changes of the dose may produce dramatic response.



between undesirable effects (not lethal) and desirable effects.

$$PI = \frac{LD_{50}\ \text{(undesirable effects)}}{ED_{50}\ \text{(desirable effects)}}$$

- The PI must be > 1.
- A drug with PI = 1 is useless since the dose that treats the patient causes an unacceptable degree of side effects

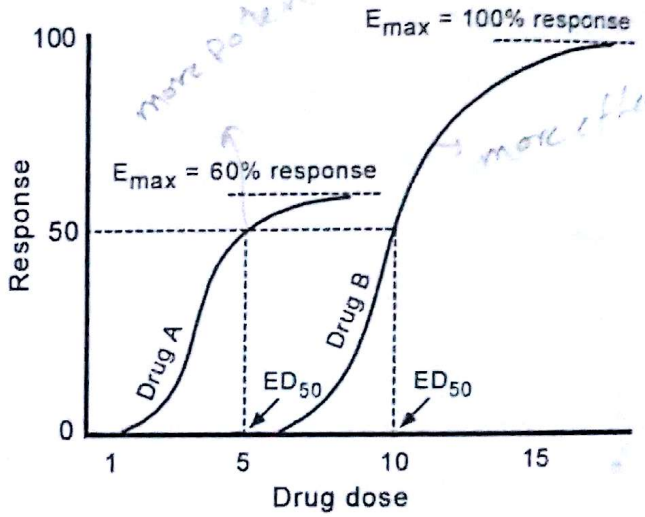
Potency versus efficacy

▶ **Potency:** *it is the effect of drug in relation to its dose.*

Potent drug means that the drug can give certain ED_{50} by a small dose, this does not necessarily mean that it can give high E_{max} by increasing its dose.

▶ **Efficacy:** *it is the ability of the drug to give certain E_{max}.*

Efficacious drug means that the drug can give high E_{max} by increasing its dose.



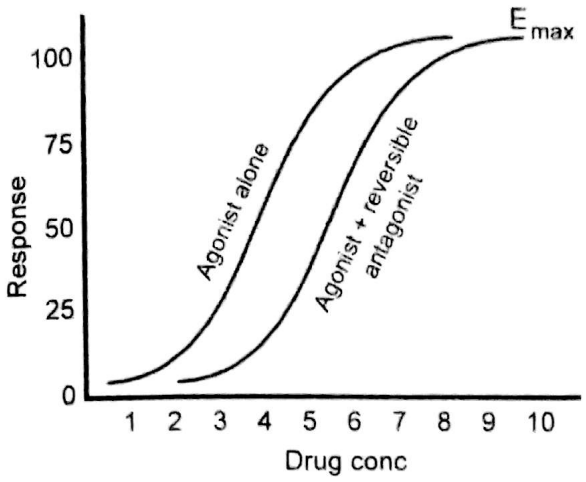
Efficacy is **more important** than potency because it is the major determinant of drug effectiveness while potency has **little clinical importance** because simply you can increase the dose of a less potent drug to obtain the effect of a more potent one (provided that it is not toxic).

Notes

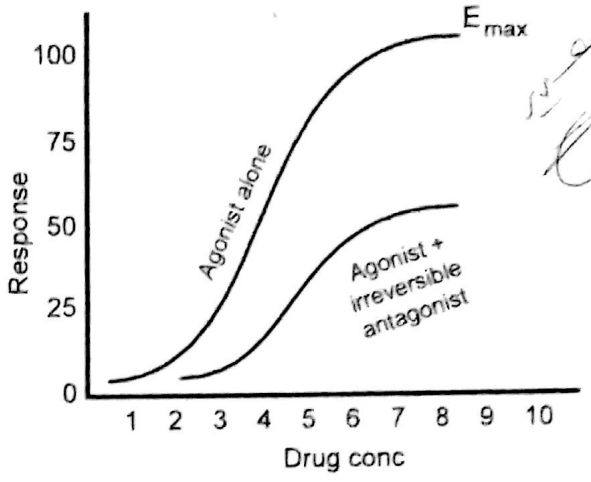
Potency
effect of the drug in relation to its dose
potent drug → can give ED_{50} by small dose

Efficacy

Antagonist effect



Reversible antagonism



Irreversible antagonism

- **Antagonist** is the ligand that combines with the receptor and **does not activate it**. It has no intrinsic activity, but may cause a pharmacological response by inhibiting the actions of endogenous substances or other drugs.
- If the antagonist binds to the same site of the agonist on the receptor, it is called **competitive antagonist**. If the antagonist binds to another site on the receptor, and prevented the action of the agonist, it is called **non-competitive antagonist** (non-competitive antagonist are produced experimentally but not clinically present).
- **Competitive antagonism** may be **reversible** or **irreversible**:
  - **Reversible antagonist** (equilibrium type) makes **weak** bond with the receptor so as you can overcome the inhibition by giving high doses of the agonist, and even you can get the maximal response in presence of the antagonist.
  - **Irreversible antagonist** (non-equilibrium) makes **covalent** bond with the receptor so as you cannot overcome the inhibition by increasing the dose of the agonist.

Other types of drug antagonism

- **Chemical antagonism:** e.g. one **acidic** drug when added to a **basic** drug can cause precipitation of each other's.
- **Physical antagonism:** antagonism between two drugs carrying opposite charges.

  Example: **protamine** is used for treatment of **heparin** toxicity because protamine carries **+ve** charge and heparin carries **–ve** charge.

- **Physiological antagonism:** antagonism between two drugs producing opposite effects by acting on different receptors.

  Example: **adrenaline** is the physiological antagonist of **histamine** because while histamine causes hypotension and bronchoconstriction through activation of histamine H_1 receptors, adrenaline causes hypertension and bronchodilatation through activation of adrenergic α & β receptors.

- **Pharmacokinetic antagonism:** (see drug interactions).

- One drug may **prevent absorption** of another drug e.g. antacids ↓ absorption of iron & aspirin.
- One drug may **increase metabolism** of another drug e.g. rifampicin induces hepatic enzymes and ↑ metabolism of contraceptive pills.
- One drug may ↑ **excretion** of another drug e.g. $NaHCO_3$ cause alkalinization of urine and ↑ excretion of acidic drugs like **aspirin**.

Ion channels

How drugs could modulate ion channels?

- Physical block: e.g. blocking of Na^+ channels by local anesthetics.
- The ion channel may be part of the receptor e.g. ion channel-linked receptors.
- The ion channel may be modulated by G-protein linked receptors.
- Ion channels may be modulated by intracellular ATP e.g. ATPase sensitive K^+ channels in the pancreatic β cells.

Enzymes

How drugs could affect enzymes?

- The drug may act as a competitive inhibitor of the enzyme e.g. neostigmine on cholinesterase enzyme.
- The drug may act as irreversible inhibitor of the enzyme e.g. organophosphates on cholinesterase enzyme.
- The drug may act as a false substrate for the enzyme e.g. α-methyldopa is a false substrate for *dopa decarboxylase*.
- The drug may induce or inhibit hepatic microsomal enzymes activity (see later).

Carrier molecules

- These are small protein molecules that carry organic molecules across the cell membrane when they are too large or too polar.
- Drugs could affect carrier molecules by blocking their recognition site.

Part 2: Factors affecting dose-response relationship

Factors related to the drug

Drug shape (stereoisomerism)

- Most drugs have multiple stereoisomers.
- The receptor site is usually sensitive for one stereoisomer and not suitable for another, like the hand and the glove. This means that one isomer may be hundred times more potent than the other. In other instances one isomer is beneficial while the other is toxic.
- This phenomenon may explain how a single drug could act as agonist and antagonist (partial agonist), because many drugs are present in *"racemic mixtures"* rather than as pure isomers.

Drug size (MW)

- Most drugs have MW between 100 and 1000 units. Drug particles larger than MW 1000 cannot be absorbed or distributed.
- Drug particles larger than MW 600 cannot cross placental barrier.

Time of drug administration (Chronopharmacology)

- Many body functions (e.g. liver metabolism, RBF, blood pressure, HR, gastric emptying time, etc.) have daily circadian rhythm. Some enzymes responsible for metabolism of drugs are active in the morning or evening.
- Also many diseases (e.g. asthma attacks, myocardial infarction, etc.) are circadian phase dependent.
- *Chronopharmacology* is the science dealing with tailoring drug medication according to the circadian rhythm of the body to get better response or to avoid possible side effects.
- Example:
  Episodes of acute bronchial asthma are common at night due to circadian variation of cortisol and other inflammatory mediators. So it is better to give the anti-asthmatic treatment in the evening.

Drug cumulation

- Cumulation occurs when the rate of drug administration exceeds the rate of its elimination (especially in patients with liver or renal disease).
- Cumulative drugs are those having slow excretion e.g. digitalis.

Drug combination

- Drug combination is very common in clinical practice. When two or more drugs are combined together, one of the following may occur:

- **Summation or addition:** 1+1=2
  Summation means that the combined effect of two drugs is *equal* to the sum of their individual effects. It usually occurs between drugs having the same mechanism.
  Example: the use of two simple analgesics together.

- **Synergism or potentiation:** 1+1>2
  It means that the combined effect of both drugs is *greater* than the sum of their individual effects.
  The two drugs usually have different mechanism of action.
  Examples:
  - *Phenobarbitone* has no analgesic action but it can potentiate the analgesic action of *aspirin*.
  - The use of *penicillin* with *aminoglycosides* to exert bactericidal effect.

- **Antagonism:** H1=0
  One drug abolishes the effect of the other e.g.:
  - Competitive and non-competitive antagonism (see before).
  - Chemical antagonism.
  - Physical antagonism.
  - Physiological antagonism.
  - Pharmacokinetic antagonism.

Factors related to the patient

Age, sex, and weight.

Pathological status

Liver or kidney diseases significantly alter the response to drugs due to altered metabolism. Also the failing heart is more sensitive to digitalis than the normal heart.

Notes

Pharmacogenetic factors (idiosyncrasy)

It is abnormal response to drugs due to genetic abnormality in drug metabolism. These are some examples:

Heritable conditions causing INCREASED or toxic drug response:

- **Pseudocholinestrase deficiency:**

Succinylcholine is a neuromuscular blocker metabolized by *pseudo-cholinestrase* enzyme. Some individuals have deficient PsChE, when they take succinylcholine, severe muscle paralysis occurs due to lack of succinylcholine metabolism, and may lead to death from respiratory paralysis (*succinylcholine apnea*).

- **Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency:**

G-6-PD is an important source of reduced NADPH which maintains glutathione in the RBCs in its reduced form. Reduced glutathione keeps Hb in the reduced (ferrous) form and prevent formation of methemoglobin and cell membrane injury (hemolysis) by oxidizing drugs.
Individuals with deficiency in G-6-PD enzyme may suffer acute hemolysis if they are exposed to oxidizing drugs e.g. nitrates, antimalarial drugs, and others.

- **Acetylator phenotypes:**

Many drugs are metabolized in the liver by acetylation e.g. **isoniazide**. People can be classified according to their rate of acetylation reaction into **rapid** and **slow** acetylators:

- In rapid acetylators: isoniazide causes *hepatocellular necrosis* due to accumulation of hepatotoxic metabolites.
- In slow acetylators: isoniazide causes *peripheral neuropathy* due to interference with pyridoxine metabolism, so pyridoxine "vit B6" is added to isoniazide to prevent neurotoxicity.

Notes

hydralazine in slow acetylators may lead to SLE-like syndrome.

hydralazine

Heritable conditions causing DECREASED drug response:

- **Resistance to coumarin (warfarin) anticoagulants:**

In normal individuals, warfarin anticoagulant acts by inhibiting the enzyme vit K *epoxide reductase* responsible for reduction of the oxidized vit K (inactive) to its reduced form (active).
Some individuals have another variant of this enzyme making them needing 20 times the usual dose of coumarin to get the response.

warfarin

- **Resistance to vit D (vit D-resistant rickets):**

Children with *vit D-resistant rickets* need huge doses of vit D to be treated.

- **Resistance to mydriatics:**

Dark eyes are genetically less responsive to the effect of mydriatics!

Hyporeactivity to drugs:
(Tolerance, tachyphylaxis, drug resistance)

Tolerance: progressive decrease in drug response on successive administration. The same response could be obtained by higher doses. It occurs over long period.

Tachyphylaxis: it is acute (rapid) tolerance occurs very rapidly.

Mechanism of tolerance:

- Change in the receptors (desensitization): due to slow conformational changes in the receptors.
- Receptor down-regulation: prolonged exposure to the **agonist** leads to decrease number of receptors due to endocytosis by the cells. It is a slow process and recovery takes several days.
- Exhaustion of mediators: e.g. depletion of catecholamines by amphetamine.
- Increased metabolic degradation: e.g. barbiturates can activate hepatic enzymes and accelerate its own metabolism and metabolism of other drugs.
- Physiological adaptation. (to diuretics)

Notes rifampcin + barbiturates activate hepatic enzymes

Hyperreactivity to drugs:
(Hypersusceptibility, overshot phenomenon, intolerance)

It is an exaggerated response occurs on sudden stopping of a drug taken for long time.

Mechanism: up-regulation means increase number of receptors due to prolonged exposure to the **antagonist** or prolonged deficiency of the natural agonist. When the antagonist is suddenly withdrawn, severe reaction occurs in the form of rebound or withdrawal effects

Examples: severe tachycardia & arrhythmia occurring after sudden stoppage of beta-blockers.

N.B. Some examples of drugs must not be stopped suddenly:

Drug		Sudden withdrawal can lead to:
▪ Beta-blockers	:	Severe tachycardia, arrhythmia, and even myocardial infarction.
▪ Clonidine	:	Severe hypertension (hypertensive crisis).
▪ Cimetidine	:	Severe hyperacidity and even peptic ulceration.
▪ Corticosteroids	:	Acute Addisonian crisis.
▪ Morphine	:	Withdrawal symptoms (see CNS).
▪ Warfarin		Thrombotic catastrophes

Drug dependence: (habituation and addiction)

Habituation (psychological)	Addiction (physical)
- Psychic craving of the drug	- Physical dependence of the drug
- Sudden withdrawal causes psychological troubles.	- Sudden withdrawal causes severe withdrawal symptoms.
- Example: coffee and smoking.	- Example: morphine and alcohol.

Notes

Part 3: Clinical pharmacokinetics

Definition: it is the journey of the drug inside the body. It includes 4 processes:

Absorption **D**istribution **M**etabolism **E**xcretion

Absorption of drugs

Definition: it is the passage of drug from the site of administration to the plasma.
The main routes of administration: oral, sublingual, rectal, inhalation, injection, etc.

Factors affecting drug absorption:

Factors related to the drug

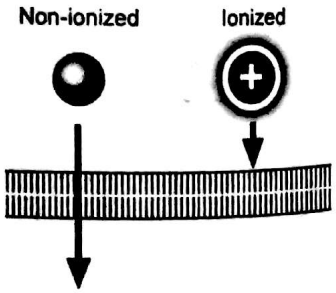
- Molecular size: small molecules are absorbed than large molecules.
- Dose: absorption increases with increasing the dose (up to limit).
- Drug formulations: e.g. sustained-release tablets are slow in absorption.
- Local effects of the drug: e.g. drugs producing VC ↓ their own absorption.
- Drug combination: e.g. vit C ↑ absorption of iron.
- Lipid solubility, drug ionization, and the pKa of the drug.

Factors related to the absorbing surface:

- Route of administration: i.v. route is the fastest while rectal is the slowest.
- Integrity of the absorbing surface: may ↑ or ↓ absorption.
- Local blood flow: ischemia ↓ absorption.
- Specific factors: e.g. apoferritin system for iron, etc.

The pKa and drug ionization

Principles



- Ionized (polar; charged) drugs are **poorly** absorbed, while unionized (non-polar, non-charged) drugs are **more** absorbed.
- Most drugs are weak acids or bases. They become ionized or non-ionized according to the **pH** around them.
- Acidic drugs (e.g. aspirin) are more ionized in alkaline pH and *vice versa*.
- Basic drugs (e.g. amphetamine) are more ionized in acidic pH and *vice versa*.
- **pKa of a drug: is the pH at which 50% of the drug is ionized and 50% is non-ionized.** *(Where p = inverse log; Ka = association/dissociation constant).*

Example of pH variation and drug kinetics

- Aspirin is an acidic drug; its pKa = **3.5**
- The pH of the stomach is **1.5**-------The pH of the intestine is **8.5**

▶When aspirin is put in the stomach:

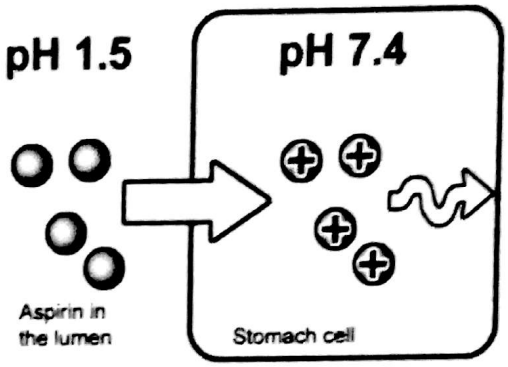
- Log (Unionized : Ionized) = pKa – pH = 3.5 – 1.5 = 2 (10^2).
- i.e. aspirin becomes 100 times unionized than ionized (i.e. **more** absorbable).

▶When aspirin is put in the intestine:

- Log (Unionized : Ionized) = pKa – pH = 3.5 – 8.5 = – 5 (10^{-5}).
- i.e. aspirin becomes 0.00001 times unionized than ionized (i.e. **less** absorbable).

▶Ion trapping of aspirin:

In the stomach, aspirin is more absorbable into stomach cells but once entered the cells, the pH changes from 1.5 outside to 7.4 inside the cell. So aspirin becomes ionized inside the cells and can't diffuse outside them again → gastric ulcer.

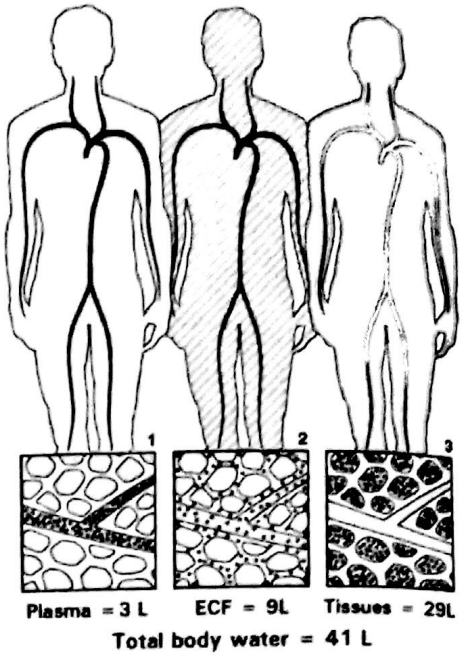


Clinical significance of pKa

- Knowing the site of drug absorption from the GIT (... mention the principles).
- Treatment of drug toxicity:
  - Toxicity with acidic drugs (e.g. aspirin) could be treated by alkalinization of urine, which renders this drug more ionized in urine and less reabsorbable.
  - Toxicity with basic drugs (e.g. amphetamine) could be treated by acidification of urine, which renders this drug more ionized in urine and less reabsorbable.
- Ion trapping in breast milk:
  - The pH of the breast milk is 7 i.e. it is considered acidic in relation to plasma (pH 7.4).
  - Basic drugs tend to be ionized in breast milk and thus, become trapped inside it.

Notes

Distribution of drugs



Sites of drug distribution

- Plasma: 3 liters
- Extracellular water: 9 liters
- Intracellular water: 29 liters

Volume of distribution (Vd)

Definition: The apparent volume of water into which the drug is distributed in the body after distribution equilibrium.

Calculation:

$$Vd = \frac{\text{Total amount of the drug in the body}}{\text{Plasma conc of the drug (after distribution equilibrium)}} \quad L$$

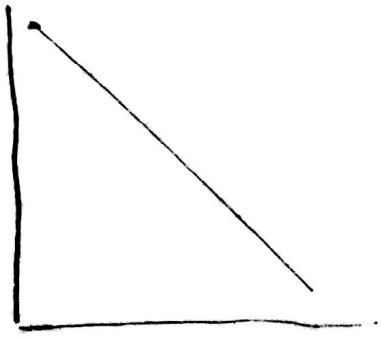
Clinical significance:

- Determination of the **site of drug distribution** e.g.:
  - A total Vd < 5 L: means that the drug is confined to the vascular compartment and can be removed by dialysis.
  - A total Vd 5-15 L: means that the drug is restricted to the ECF.
  - A total Vd > 41 L: means that the drug is highly bound to tissue proteins and cannot be removed by dialysis.
- Calculation of the **total amount of drug in the body** by single measurement of plasma concentration (from the equation).
- Calculation of the **loading dose** (LD) needed to attain a desired plasma concentration (Cp): LD = Vd x Cp.
- Calculation of **drug clearance:**

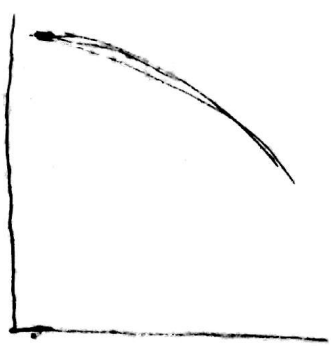
$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Notes

First order



Zero order



Binding of drugs to plasma proteins

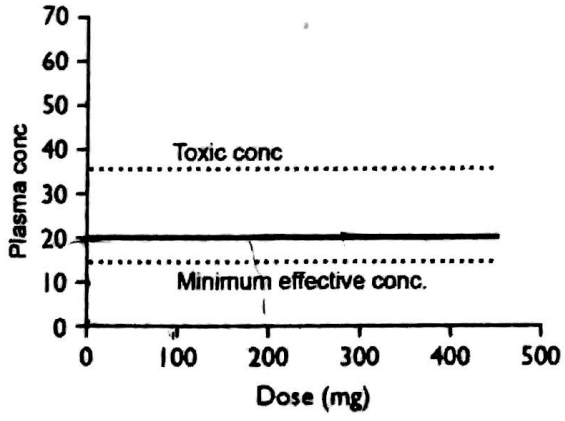
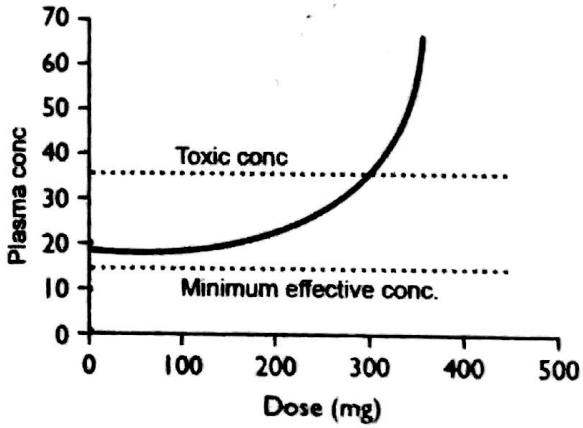
- Most drugs when introduced into the body are bound to plasma proteins.
- Albumin: the most important plasma protein and it can bind –ve or +ve charged drugs.

Clinical significance:

- The pharmacological effect of the drug is related only to its **free part** not to its bound part (the bound part acts only as a reservoir from which the drug is slowly released).
- Binding of drugs to plasma proteins **prolongs** their effects.
- When the drug has **high plasma protein binding** (e.g. 99% for warfarin), the free part that exerts the pharmacologic effect is 1%. Any small displacement of the bound part by another drug (say for example another1% is displaced) can lead to dramatic toxicity (doubles the amount of the free part in plasma).
- Many **disease states** (e.g. chronic liver disease, pregnancy, renal failure) can affect the level of albumin and the nature of plasma proteins, thus causing serious problems with some drugs.

Excretion and elimination of drugs

Elimination of drugs may follow one of 2 processes (orders):

First-order elimination	Zero-order elimination
	
- Occurs to **most** drugs. - The rate of elimination is **proportional** to plasma conc. i.e. constant **ratio (%)** of the drug is eliminated per unit time. - Elimination **does not** depend on **saturable enzyme** system.	- Occurs to **limited** number of drugs. - The rate of elimination is **not proportional** to plasma conc. i.e. constant **amount** of the drug is eliminated per unit time. - Elimination depends on **saturable enzyme** system.

- Has **linear** elimination curve i.e. plasma conc can be expected at any time. - The $t_{1/2}$ of the drug is constant.	- Has **non-linear** elimination curve i.e. plasma conc of the drug cannot be expected at any time. - The $t_{1/2}$ of the drug is not constant.

Examples of drugs eliminated by zero-order: prednisolone, theophylline.

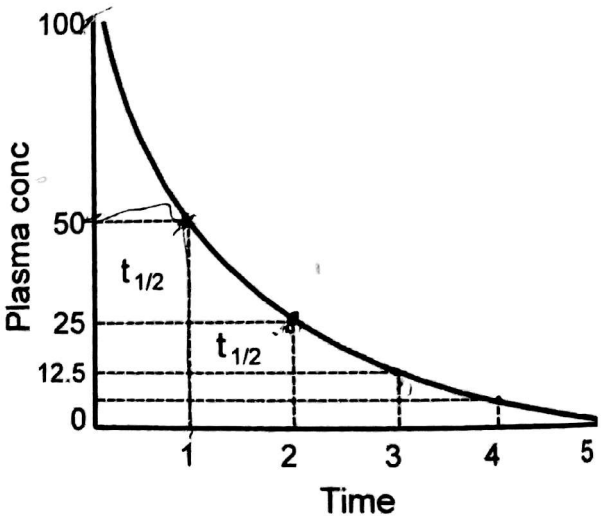
N.B. Some drugs are eliminated by first-order elimination in **low doses** and by zero-order elimination in **high doses** e.g. aspirin and phenytoin.

Clinical significance of zero-order elimination:

- Modest change in drug dose may produce unexpected toxicity.
- Elimination of drugs or attainment of Cpss takes long time.
- Changes in drug formulation may produce adverse effects.
- Drug cumulation and interactions are common.

Elimination half-life ($t_{1/2}$)

Definition: It is the time taken for the concentration of a drug in blood to fall half its original value.



Calculation:

- From the plasma concentration versus time curve.
- From the equation

$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Clinical significance:

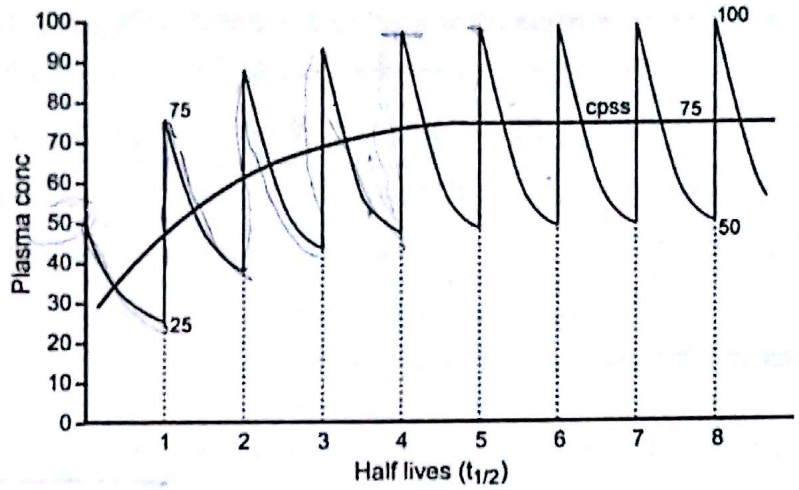
- Determination of **inter-dosage interval:** drugs are given every $t_{1/2}$ to avoid wide fluctuations of the **peak** level (the highest plasma concentration of the drug) and **trough** level (the lowest plasma concentration).
- **Time-course of drug accumulation:** if a drug is started as a constant infusion, the Cp will accumulate to approach steady-state after 4-5 $t_{1/2}$.
- **Time-course of drug elimination:** If a drug is stopped after an infusion, the Cp will decline to reach complete elimination after 4-5 t1/2.
- Drugs having long $t_{1/2}$ could be given **once daily** to improve patient **compliance.**

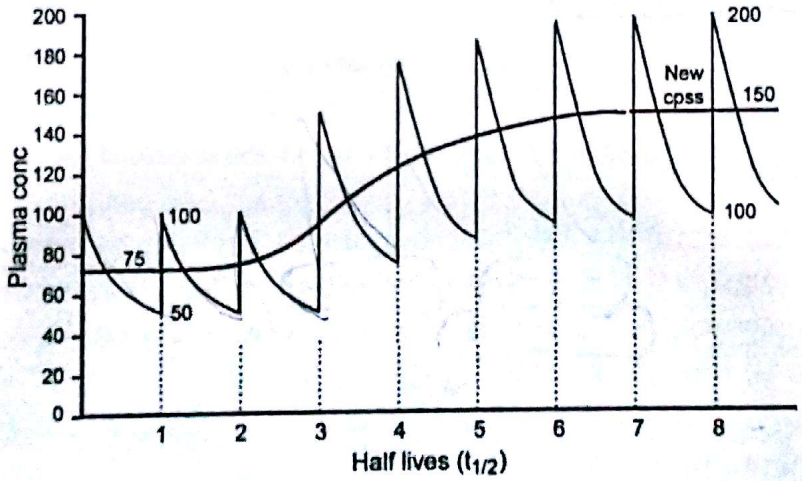
Steady-state plasma concentration (Cpss)

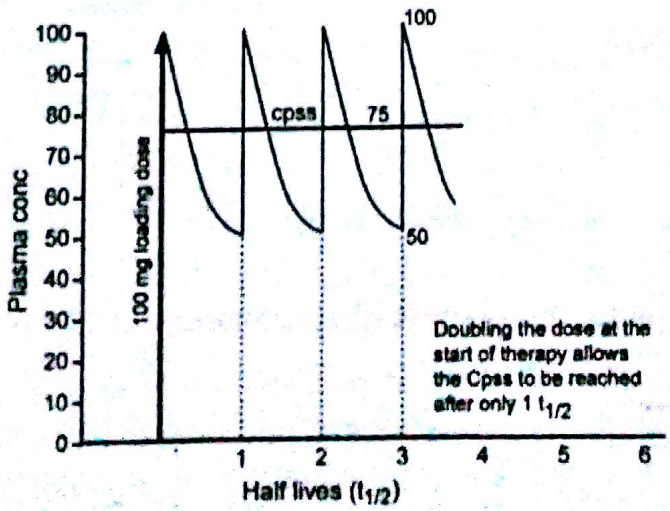
Definition: the steady level of drug in plasma achieved when the rate of administration equals the rate of elimination.

When is it reached? ►►the rule of 5:

- The Cpss is reached after 4-5 $t_{1/2}$.
- If we changed the dose, the new Cpss is reached after 4-5 $t_{1/2}$.
- If dosing stops, complete elimination of drug from plasma occurs after 4-5 $t_{1/2}$.







Therapeutic drug monitoring (TDM)

Definition: TDM describes the monitoring of concentrations of drugs in body fluids, usually plasma, for therapeutic purposes

- **Clinical significance:**
  - **Improvement in efficacy:**
    Drugs with pharmacokinetic problems (e.g. phenytoin and drugs with non-linear kinetics).
  - **Avoidance of toxicity:**
    - Drugs with a low 'therapeutic index' require individualized dosing.
    - Presence of disease states (especially liver or renal dysfunction).
  - **Differentiation between** drug resistance and non-compliance.
  - **Differentiation between** drug-induced from organic disease (e.g. coma caused by sedative overdose).

Clearance as a channel of elimination

Definition: plasma clearance of a substance means the amount of plasma cleared from this substance per minute.

Calculation:

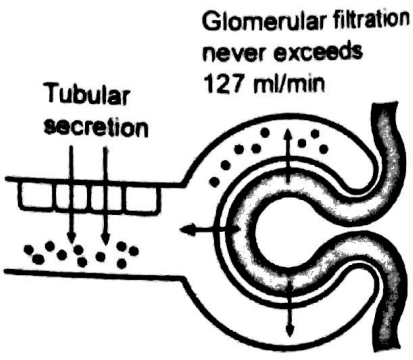
$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Clinical significance:

If the drug is cleared by the kidney, clearance can help to determine whether this drug is eliminated by renal **filtration** or **secretion**: a drug that is eliminated only by *filtration* cannot exceed 127 ml/min. If clearance > 127 ml/min → the drug is eliminated also by *tubular secretion*.

Routes of elimination:

- Kidney (the major route).
- Bile and liver.
- Intestine.
- Lungs.
- Milk, saliva and sweat.



Clinical importance of knowing the route of elimination:

- Help to adjust the dose to avoid cumulation.
- Avoid drugs eliminated by a diseased organ.
- Targeting therapy: e.g. drugs eliminated by the lung are used as expectorants.

Metabolism of drugs (biotransformation)

- The liver is the major site of drug metabolism but other organs can also metabolize drugs e.g. kidney, lungs, and adrenal glands.
- Many lipid soluble drugs must be converted into a water-soluble form (polar) to be excreted
- **Metabolism of drugs may lead to:**
  - Conversion of **active** drug into **inactive** metabolites → termination of drug effect.
  - Conversion of **active** drug into **active** metabolites → prolongation of drug effect:

Active drugs:	**Active metabolites:**
Codeine	→ Morphine

  - Conversion of **inactive** drug into **active** metabolites **(PRODRUGS):**

Inactive drugs:	**Active metabolites:**
Enalapril	→ Enalaprilat
L-dopa	→ Dopamine

  - Conversion of **non-toxic** drug into **toxic** metabolites (e.g. paracetamol).

Biochemical reactions involved in drug metabolism

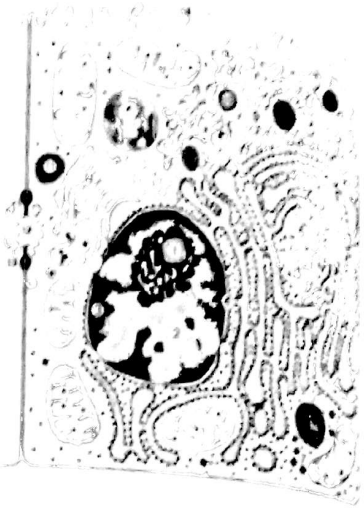
The drug must enter **phase I** of chemical reactions be excreted as water-soluble compound. If the drug is not liable to conversion into water-soluble compound by phase I, it must enter **phase II** to increase solubility and enhance elimination.

Notes

Phase I reactions (oxidation-reduction – hydrolysis)

Oxidation:

Microsomal oxidation:



- The smooth endoplasmic reticulum in the liver has membranous vesicles (*microsomes*) contain oxidizing enzymes (**cytochrome P_{450}**) that catalyze oxidation-reduction reactions (mixed function oxidases) of drugs and chemicals.
- Some drugs and environmental substances can (**induce** (increase) or (**inhibit** the microsomal enzyme activity and lead to undesirable drug interactions.

Clinical significance of microsomal enzyme induction:

- To accelerate degradation of other drugs e.g. phenobarbitone can be used for treatment of some drug toxicities.
- To accelerate degradation of bilirubin e.g. phenobarbitone can be used for treatment of physiological jaundice in neonates.

Clinical significance of microsomal enzyme inhibition:

- They ↓ rate of metabolism leading to accumulation (toxicity) of other drugs.

Some examples of interactions due to enzyme induction:

Drugs affected	Inducing drug	Clinical outcome
Oral contraceptives	Rifampicin	Failure of contraception.
Cyclosporine	Phenytoin	Graft rejection

Some examples of interactions due to enzyme inhibition:

Drug affected	Inhibiting drug	Clinical outcome
Oral anticoagulants	Ciprofloxacin	Risk of bleeding from ↑ anticoagulant levels
Theophylline	Erythromycin	Increased toxicity of theophylline

Non-microsomal oxidation: e.g.

- Xanthine oxidase: converts xanthine to uric acid.
- Monoamine oxidase (MAO): oxidizes catecholamines and serotonin.

Reduction: e.g. nitroreduction of chloramphenicol.

Hydrolysis: e.g. hydrolysis of acetylcholine by cholinesterase enzyme.

Phase II reactions (conjugation)

It involve coupling of a drug or its metabolite to water-soluble substrate (usually glucuronic acid) to form water-soluble conjugate.

Glucuronide conjugation:

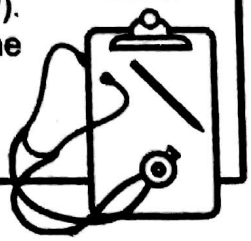
- It is most common conjugation reaction.
- It occurs frequently with phenols, alcohols, and carboxylic acids.
- Glucuronide conjugates secreted in bile can be hydrolyzed by intestinal bacteria and free drug can be reabsorbed again (*enterohepatic circulation*), this can extend the action of drugs.

Other non-glucurounide conjugation:

- Sulphate formation: (e.g. steroids).
- Glycine conjugation: (e.g. salicylic acid).
- Glutathione conjugation: (e.g. ethacrynic acid).
- Acetylation reaction.

N.B. Breakthrough pregnancy!!!

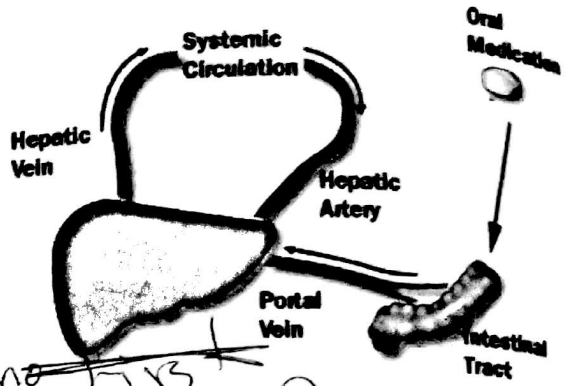
- Contraceptive pills contain estrogen, which is metabolized by glucuronide conjugation and excreted in bile as conjugate.
- Intestinal bacteria hydrolyze this conjugate to form free estrogen again which is reabsorbed and attain long duration of action (so contraceptive pills are given once daily).
- If the woman took contraceptive pills with broad-spectrum antibiotics (kills the intestinal bacteria), estrogen will lose its long duration of action and pregnancy can occur.



Notes

First-pass metabolism (pre-systemic elimination)

Definition: metabolism of drugs at the site of administration before reaching systemic circulation e.g. the liver after oral administration, the lung after inhalation, the skin after topical administration, etc.



Gut first-pass metabolism:

- Gastric acidity: benzyl penicillin.
- Digestive enzymes: e.g. insulin.
- Intestinal mucosa: e.g. tyramine.

Hepatic first-pass metabolism:

- Complete: sex hormones and lidocaine.
- Partial: propranolol, morphine, nitroglycerine
- None: atenolol and mononitrates

How to avoid?

- By increasing the dose of the drug.
- By giving the drug through other routes e.g. sublingual, inhalation, or i.v.

Bioavailability

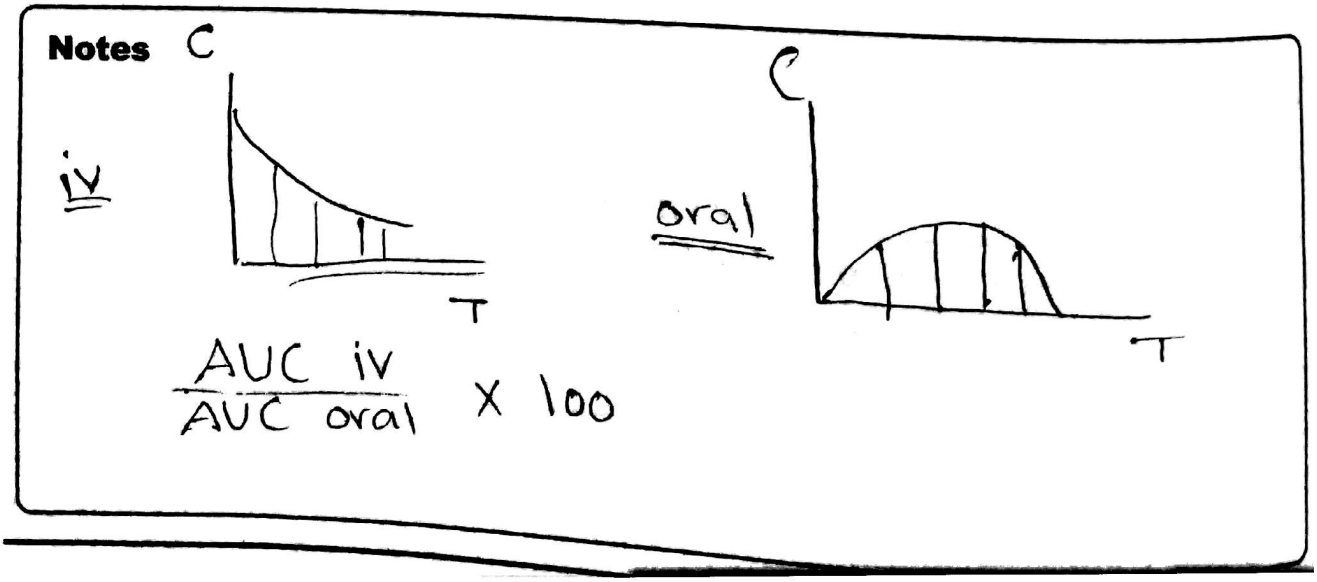
Definition: it is the fraction of the drug become available for systemic effect after administration. The bioavailability of drugs given i.v. is 100%.

at site of action

Factors affecting bioavailability include:

- Factors affecting absorption.
- Factors affecting metabolism.
- First-pass metabolism.

Notes



Part 4: Adverse drug reactions (ADR)

An ADR is any response to a drug which is noxious, unintended, and occurs at doses used in man for prophylaxis, diagnosis or therapy.

Predisposing factors:

- Multiple drug therapy.
- Extremes of age: due to age related changes in pharmacokinetics and dynamics.
- Associated disease: e.g. impaired renal or hepatic function.
- Genetics: can affect the pharmacokinetics.

Classification:

Type A (Augmented):

These reactions are predictable from the known pharmacology of the drug. They may result from an **exaggerated response** (e.g. hypotension from an antihypertensive) or **non-specificity** (e.g. anticholinergic effects with tricyclic antidepressants).

Prevention

- Take a careful history for predisposing factors.
- Use as small a dose as possible commensurate with desired effect.
- Adjust dosage to therapeutic end-points, e.g. BP or INR.
- Adjust dosage to optimum plasma concentrations, e.g. digoxin.
- Adjust dosage in relation to renal function, hepatic function, or other drugs.

Type B (Bizarre):

These are less common, less predictable, and may be severe. **Examples are:**

- Immunologic: penicillin allergy
- Genetic: haemolysis in G6PD deficiency
- Disease: amoxycillin rash in glandular fever
- Idiosyncratic: malignant hyperpyrexia in anesthesia.

Prevention

- Take a careful drug history, especially of allergies
- Family history a allergies and genetic disease
- Avoid drugs susceptible to ADRs in particular disease states, e.g. clozapine in bone marrow depression.

Type A (Augmented)	Type B (Bizarre)
- Predictable	- Unpredictable
- Dose-dependent	- Dose-independent
- High incidence.	- Low incidence
- May respond to dose adjustment	- Generally need to stop the drug

Drugs and pregnancy

Three factors determine the risk of teratogenicity: **dose** of the drug; **duration** of administration; and **stage** of pregnancy.

Mechanism of teratogenicity:

Indirect effects

- **On the placenta:** e.g. vit A → villous atrophy.
- **On the uterus:** e.g. ergot alkaloids → uterine contractions.
- **On the mother's hormonal balance:** e.g. sex hormones.
- **On the father's sperm:** e.g. cancer chemotherapy → sterility.

Direct effects

- **Before implantation: (0-14 day):** The effect is *all-or-none* i.e. either death of the embryo or no effect.
- **Early pregnancy: (3-10 weeks):**
  - It is the most dangerous period because it is period of organogenesis,
  - Selective interference can produce characteristic anatomical abnormality e.g. thalidomide causes *phocomelia* (absent upper limbs).
  - Drugs known to be teratogenic: *cytotoxic drugs*, *warfarin*, and *vit A*.
- **Late pregnancy:**
  - Gross anatomical abnormalities are less liable to occur.
  - Functional defects rather than anatomical abnormalities can occur especially in organs having delayed formation e.g. brain, testes, and bone.

Notes

The FDA pregnancy categories:

Category	Definition	Animal	Human
A	Adequate studies in animal and human did not show a risk to the fetus either in the first or in the late trimesters.	✓	✓
B	Animal studies did not show risk to the fetus but there are no adequate studies in human. **or:** Animal studies showed a fetal risk, but adequate studies in human did not show a risk to the fetus.	✓ ×	? ✓
C	Animal studies showed a risk to the fetus but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may by acceptable despite its potential risks.	×	? **Benefit > Risk**
D	There is evidence of human fetal risk, but the potential benefit of the drug may outweigh its potential risk.	×	× **Benefit > Risk**
X	Studies in animals and humans showed evidence of fetal risk. The potential risk of use in pregnant women clearly outweighs any potential benefit.	⊗	⊗ **Risk > Benefit**

Recommendations

- Avoid all drugs if possible, including social drugs (e.g. smoking, and alcohol).
- Avoid drugs in the first trimester.
- Choose drugs of proven safety or least toxicity.
- Use short courses and the smallest doses.

Notes

Part 5: Principles of drug-drug interactions

Classification:

- **Pharmacokinetics interactions.**
- **Pharmacodynamic interactions.**

in vitro

Pharmacokinetic interactions

Drug interactions *in vitro*:

e.g. Benzylpenicillin and aminoglycosides form complexes with heparin solutions.

Drug interactions *in vivo*:

Absorption

Formation of complexes:

- Tetracycline forms complexes with Ca^{2+}, Mg^{2+} and Al^{3+}
- Cholestyramine forms complexes with digitalis and thyroxin.

Absorption can be blocked:

- Adrenaline ↓ absorption of local anesthetics due to VC.
- Colchicine ↓ absorption of vitamin B12

Change in intestinal motility:

- Anticholinergic drugs ↓ intestinal motility → ↑ absorption of some drugs.
- Prokinetic drugs ↑ intestinal motility → ↓ absorption of some drugs.

Changes in gastric pH:

- Antacids ↓ absorption of salicylates.
- Ketoconazole is poorly absorbed in absence of gastric acidity.

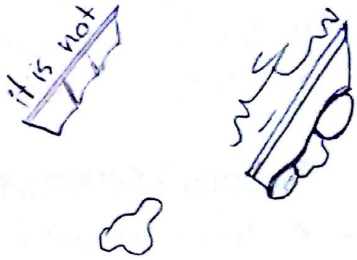
Notes

Distribution

- Sulfonamides displace bilirubin from pl pr in premature infants → kernicterus.
- Phenylbutazone displaces warfarin → excessive bleeding.

Metabolism

- **Inhibition or induction of microsomal metabolism.**
- **Inhibition of non-microsomal enzymes:**
  - MAO inhibitors ↓ metabolism of some drugs e.g. barbiturates, benzodiazepines, serotonin and norepinephrine.
  - Disulfiram inhibits acetaldehyde dehydrogenase enzyme → ↓ metabolism of acetaldehyde → accumulation of acetaldehyde causes flushing, nausea, vomiting, and tachycardia.



Excretion

- **Reduction in urinary elimination:**
  - Probenecid ↓ excretion of penicillin.
  - Aspirin ↓ excretion of methotrexate.
- **Changes in urinary pH:**
  - Alkalinization of urine (e.g. sodium bicarbonate) ↑ excretion of weak acids
  - Acidification of urine (e.g. ammonium chloride) ↑ excretion of weak bases.
- **Changes in urinary volume:**
  Diuretics can reduce the renal toxicity of drugs by reducing the tubular concentration of the toxin e.g. mannitol reduces cisplatin toxicity.
- **Stimulation of biliary excretion:**
  Phenobarbital ↑ biliary excretion of many drugs by increasing both bile flow and the synthesis of conjugating proteins.

Pharmacodynamic interactions

- **Antagonism:** competitive, non-competitive, chemical, physical, etc.
- **Synergism:** e.g. MAO inhibitors can cause toxic synergism with TCA.
- **Potentiation:** e.g. ethanol can enhance CNS depression caused by opioids
- **Changes in the intracellular or extracellular environment:** e.g. diuretic-induced hypokalemia can ↑ digitalis toxicity.

Review questions

Define the following pharmacokinetic parameters:

- Volume of distribution
- pKa of drugs
- Elimination half life
- First-pass metabolism
- Bioavailability

Mention the clinical significance of each of the following:

- Volume of distribution
- pKa of drugs
- Plasma protein binding of drugs
- Elimination half-life
- Zero-order elimination
- Microsomal enzyme induction
- Hepatic conjugation of drugs

Mention 3 differences between:

- Reversible and irreversible antagonism.
- Graded response and quantal response.
- First order elimination and zero order elimination of drugs.
- Potency and efficacy.
- Physical and physiological antagonism.
- Habituation and addiction.
- Oxidation and conjugation of drugs.

Discuss 2 pharmacogenetic conditions associated with toxic drug response

Discuss 2 pharmacogenetic conditions associated with reduced drug response

Write short account on antagonism between drugs