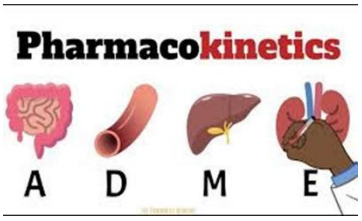
Pharmacokinetic I

Pharmacokinetics



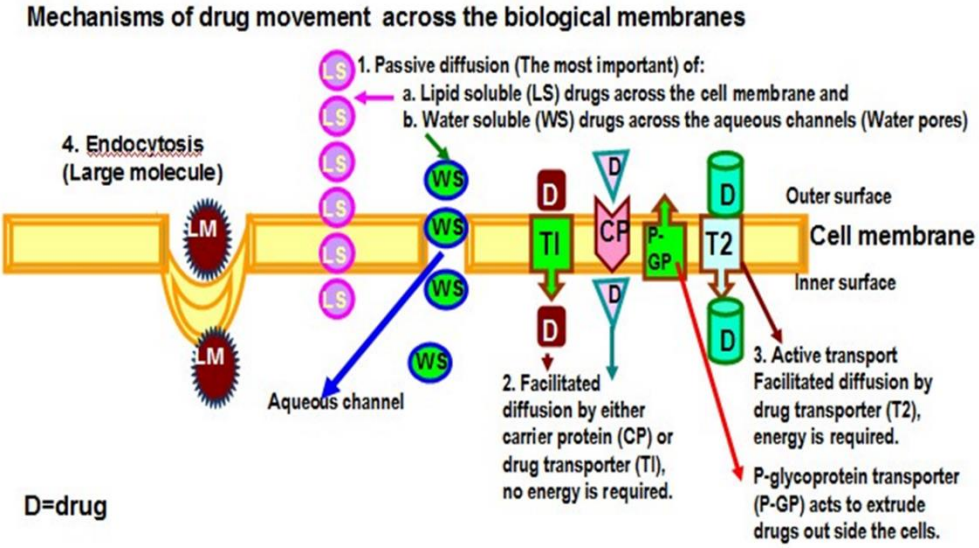
What the body does to the drug?

Absorption, Distribution, Metabolism, Excretion.

Absorption: refers to the process of drug movement from the site of administration into the systemic circulation. Several factors and mechanisms influence drug absorption, including:

Mechanisms of Absorption:

1. **Passive Diffusion:** Lipid-soluble drugs move rapidly across cell membranes. Water-soluble drugs move across aqueous channels (water pores) without requiring energy, following the concentration gradient.
2. **Facilitated Diffusion:** Drugs are transported into the cell via carriers or transporters, also without energy, following the concentration gradient.
3. **Active Transport:** Drug molecules move against the concentration gradient with the help of carriers or transporters, requiring energy.
4. **Endocytosis:** For drugs with high molecular weight, the drug binds to the cell membrane, becomes enveloped by it, and is absorbed into the cell.



Factors Affecting Absorption:

- **Route of Administration:** Intravenous (IV) and inhalation provide the fastest absorption, followed by intramuscular (IM), subcutaneous (SC), oral, and topical routes.
- **Absorbing Surface:** Larger and more vascularized surfaces (e.g., alveoli) provide better absorption. Pathological conditions like (diarrhea) decrease oral absorption.
- **Co-administration of Food/Drugs:** Some foods and drugs can either increase or decrease absorption. For instance, calcium in milk reduces oral absorption of tetracyclines. **S.C. adrenaline (added to local anesthetics) make V.C. so decrease absorption of local anesthetics make the duration of action of local anesthetics longer.**
- Systemic circulation: **Shock decrease absorption; oral and subcutaneous routes are not suitable.**
- Specific factors: **Intrinsic factor is essential for vitamin B12 absorption**
- **Solubility:** Lipid-soluble drugs are absorbed more efficiently than water-soluble drugs. Non-ionized (uncharged) drugs have better absorption.
- **Pharmaceutical Preparation:** Solutions are absorbed more quickly than suspensions, tablets, or other solid forms.
- **pH and Ionization:** Weak acids are absorbed better in acidic environments, while weak bases are absorbed better in alkaline environments. The degree of ionization (pKa) plays a critical role in absorption.

  Pka: the pH at which the concentrations of the ionized and unionized form of the drug are equal.

  1- GIT: Aspirin (acidic drug) has low pKa : Drug molecules become unionized in the empty stomach (low pH) and can enter gastric mucosal cells. In gastric mucosal cells (high pH) aspirin becomes ionized and trapped in gastric mucosal cell "peptic ulceration"

  2- Kidney: In drug poisoning:**(important)**

  -Alkalinization of urine by sodium bicarbonate (to increase urine pH above drug pKa) is useful in acidic drug poisoning e.g. Aspirin and phenobarbital.

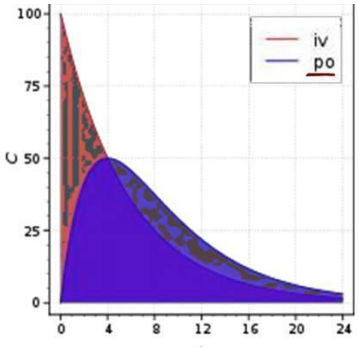
  -Acidification of urine by ascorbic acid (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine.

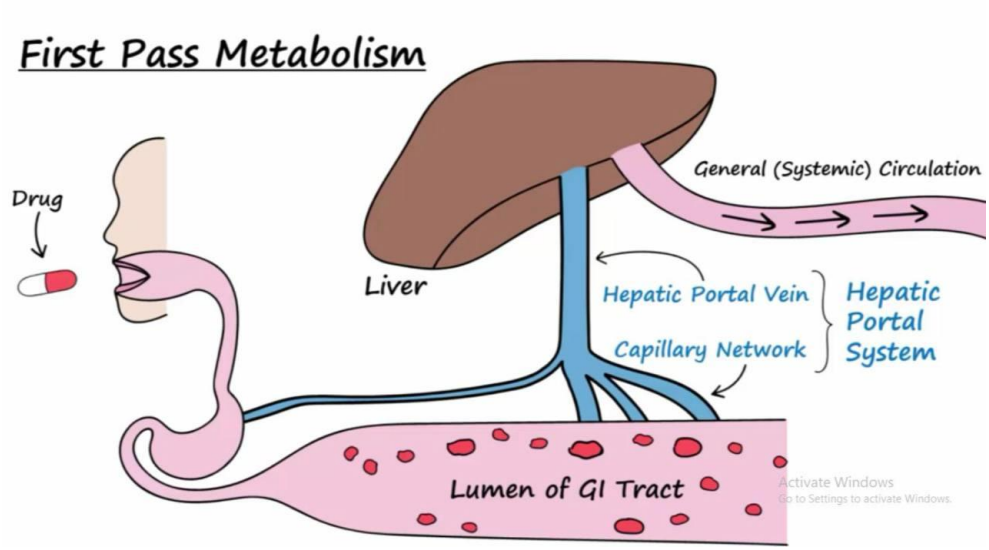
Absorption Modifiers:

- **Bioavailability:** This refers to the percentage of the drug that reaches systemic circulation. Drugs with poor oral bioavailability often undergo first-pass metabolism, where they are metabolized by the liver or gut wall or lung before reaching systemic circulation. Examples include nitroglycerin and propranolol

Bioavailability =

$$\frac{\text{Area under the curve (AUC) after oral route}}{\text{Area under the curve (AUC) after L.V. route}} \times 100$$



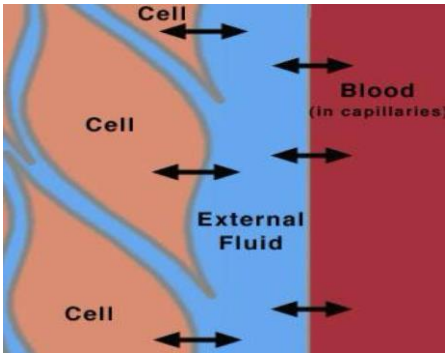


Done by: Dr. Maya Mashal – NOVA

Pharmacokinetic II

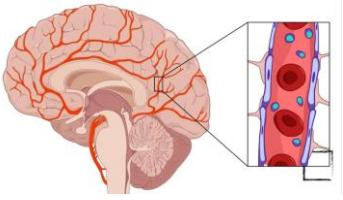
Distribution in pharmacokinetics refers to the process by which a drug is dispersed throughout the body compartments after absorption. It involves several factors, mechanisms, and considerations:

Body Compartments for Distribution:



1. **Vascular Compartment**: Small volume of distribution (around 4 liters in a 70 kg person). Drugs here are hydrophilic, ionized at plasma pH, and have high molecular weight (e.g., Heparin).
2. **Vascular and Interstitial Compartment**: Moderate volume of distribution (around 14 liters in a 70 kg person). Drugs are hydrophilic, have smaller molecular weight, and are less ionized at plasma pH (e.g., Neostigmine).
3. **Vascular, Interstitial, and Intracellular Compartment**: Large volume of distribution (around 40-42 liters in a 70 kg person). Drugs are non-ionized and lipophilic (e.g., Barbiturates).

Key Factors Influencing Distribution:



1. **Blood-Brain Barrier (BBB)**: Only lipid-soluble and non-ionized drugs can pass through the BBB. Inflammation (e.g., meningitis) can increase the permeability of the BBB, allowing drugs like penicillins and cephalosporins to reach higher concentrations in cerebrospinal fluid (CSF).
2. **Placental Barrier**: Drugs that cross the placental barrier can cause teratogenic effects during pregnancy or neonatal issues such as asphyxia or jaundice during labor.
3. **Redistribution**: Highly lipid-soluble drugs, such as thiopental, initially distribute to the central nervous system (CNS) but then redistribute to less perfused tissues (e.g., skeletal muscle and fat), which ends their action.

Volume of Distribution (Vd):

- **Theoretical Concept**: Vd relates the amount of drug in the body to its plasma concentration. It's used to:

1. Calculate the loading dose.

   Loading dose= target plasma concentration (Tc) x Vd2

2. Calculate the corrective dose.

   desired plasma Css-achieved plasma level) X (Vd)

3. Treat drug toxicity.

- **Effect on Dialysis:** Hemodialysis is useful for drugs with low Vd (mostly in the blood), but less useful for drugs with high Vd (mostly in tissues). Peritoneal dialysis can be useful for drugs with moderate Vd.

Factors Influencing Distribution:

1. **Lipophilicity (Diffusion):** Lipophilic drugs diffuse more easily across cell membranes.
2. **Tissue Binding (Tissue Affinity):** Some drugs concentrate in specific tissues due to affinity. For example:
   - Chloroquine is concentrated in the liver.
   - Iodides are concentrated in the thyroid.
3. **Plasma Protein Binding (PPB):**
   - Drugs in the blood exist as a **bound form** (inactive, non-diffusible, can't be metabolized or excreted) and a **free form** (active, diffusible, can be metabolized or excreted).
   - The bound form acts as a reservoir. When the free form is metabolized or excreted, more drug is released from the bound form to maintain equilibrium.
   - Displacement from PPB can be clinically significant, especially for drugs with high PPB capacity and small Vd, as small changes in the free form can lead to toxicity. For example, aspirin can displace warfarin, leading to an increased free concentration of warfarin, which may cause bleeding.

Done by: Dr. Maya Mashal – NOVA

Drug metabolism (biotransformation) -lec.5

It is the conversion of unionized drugs to ionized (water soluble) metabolite which Is easily excreted.

The **liver** is the main organ of metabolism but can occur in other organs like lung, kidney and intestine.

Consequences of drug metabolism:

- Convert active drug to inactive metabolite

(most drugs)

- Convert active drug to active metabolite

e.g. codeine to morphine.

- Convert inactive prodrug into active drug

e.g. enalapril to enalaprilat (active)

- Convert drugs to toxic metabolites

e.g.:Halothane & Paracetamol to hepatotoxic epoxides.

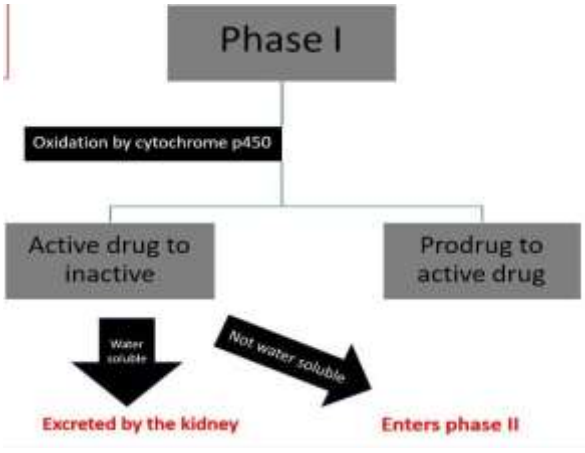
PHAS E 1 : **Oxidation**(the most important) or **reduction** or **hydrolysis**

Consequences of phase 1:

1- Active drug to inactive –and if the inactive form water soluble: Excreted by the kidney if not Enters phase II

2- Prodrug to active drug

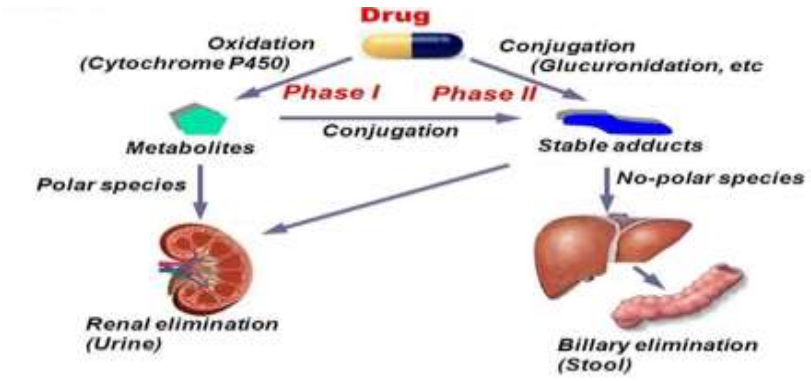
Most common CYP450 : CYP3A4 , CYP2D6



PHASE 2 : Biosynthetic reactions "**conjugation**"

An endogenous substrate e.g. glucuronic acid, sulfate, glutathione amino acids, or acetate is conjugated with the parent drug or its phase I metabolite.

This result in formation of water soluble and rapidly eliminated conjugates.



Factors affecting biotransformation:

- Physiological factors :

-age (CYP450 enzyme is low in infants, reaches its peak in adults, and then decreases with age in the elderly)

-Sex

- Pathological factors :liver cell failure.
- Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators. (if CYP3A4 genetically absent ,50% of drugs will not be metabolized)
- Enzyme induction & enzyme inhibition.

Enzyme induction: Many drugs are able to induce (increase activity and number) of microsomal enzymes resulting in increased rate of metabolism of the inducing drug as well as other drugs metabolized by the same microsomal enzymes.

-Some <u>inducing</u> drugs : IMPORTANT!

Phenobarbitone, Phenytoin, Carbamazepine, Nicotine, Rifampicin.

<u>Consequences of enzyme inducers:</u>

-Increase metabolism of the inducing drugs. This leads to tolerance e.g. phenobarbitone.

-Drug interactions:

1- Rifampicin enhances metabolism of warfarin.
2- Antiepileptics increase the metabolism of each other.

-Prolonged use of enzyme inducers may produce rickets or osteomalacia due to increased metabolism of vitamin D.

. Enzyme induction is reversible, it occurs over few days and passes off over 2 - 3 weeks after withdrawal of inducer.

<u>Enzyme inhibition:</u> Many drugs inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.e. potentiate their pharmacological actions.

-Some enzyme Inhibitor drugs: **IMPORTANT!**

Erythromycin ,Clarithromycin, Cimetidine, Contraceptive pills

<u>Consequences of enzyme inhibition :</u>

-Exaggerated pharmacological actions.

-Exaggerated adverse effects.

-Drug interactions.

Good luck 😊

Created by : Dr. Farah breik

Excretion of drugs - lec.6

Kidney: is the most important organ for excretion

➢ Excretion occurs through:

1-Glomerular filtration: All free drug molecules whose size is less than the glomerular pores are filtered into Bowman's capsule.

2-Proximal convoluted tubules (PCT):

Active secretion occurs either through :

-Acid carrier .e.g. for penicillin, probenicid, salicylic acid.

-Basic carrier for amphetamine and quinine.

3- Distal convoluted tubules (DCT)

- Lipophilic drugs may be reabsorbed back to systemic circulation.

-Alkalinization of urine keeps acidic drugs ionized and increases their excretion.

-Acidification of urine keeps basic drugs ionized and increases their excretion.

Other sites of excretion:

Bile: e.g. Doxycycline, Azithromycin.

Lungs e.g. Volatile anesthetics.

Saliva e.g. Iodides.

Sweat e.g Rifampicin.

Milk: this is important in lactating mothers (Nalbuphine(an opiod) during breastfeeding leading to prolonged sleep, lethargy, or reduced alertness in the infant)

Parameters of elimination:

Kinetics orders

Elimination half life (t1/2)

Systemic clearance (CLs)

Kinetics orders:

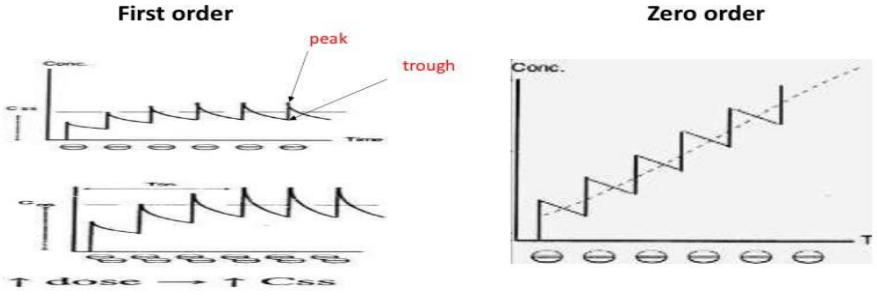
1-FIRST ORDER KINETICS: very important!

- Rate of elimination is directly proportionate to the blood concentration of drugs (constant percentage of the drug is eliminated per unit of time) (Constant "t1/2“)
- Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination.
- Steady state plasma concentration (Css)can be reached after 4-5 t1/2.
- Css is directly proportionate to the dose.

2-ZERO ORDER KINETICS: very important!

Ex: (phenytoin ,alcohol , Salicylates)

- Rate of drug elimination is constant i.e. constant amount of drug is eliminated per unit of time. "t1/2" (half life) is not constant.
- No Css is reached by repeated dosing.
- Any change of the dose may cause toxicity.
- Some drugs follow 1st order kinetics in small dose and zero order kinetic at large doses i.e. the elimination mechanism is said to be saturated (saturation kinetics).

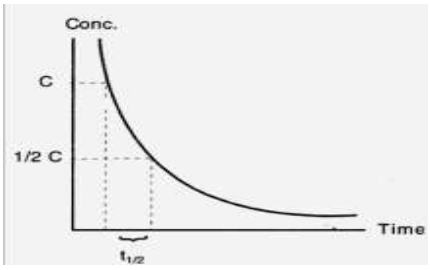


The **therapeutic range** is the interval between the **peak concentration (Cmax)**, which is the highest level of the drug in the bloodstream after administration, and the **trough concentration (Cmin)**, which is the lowest level just before the next dose

Characteristic	First-Order Kinetics	Zero-Order Kinetics
Rate of Elimination	Proportional to the drug concentration	Constant amount eliminated per unit time
Percentage or Amount	Percentage of drug eliminated remains constant (e.g., 50% of remaining drug)	Fixed amount eliminated (e.g., 10 mg/hour)
Half-Life	Constant half-life regardless of concentration	Half-life varies based on drug concentration
Reach Steady-State Concentration (Css) ?	YES	NO
Toxicity Risk	NO	YES

Elimination half life: the time required for drug concentration to be changed by 50%).

- T1/2 = 0.7 * Vd /CLs
- The therapeutic effect is not achieved after the first half- life; it occurs after 4 to 5 half-lives of continuous dosing.



Importance of elimination half life:

- It determines the dosage interval (T).
- It indicates time required to attain Css (about 4-5 t1/2):
- If "t1/2“ is very short (minutes), the drug should be given by IV infusion [dopamine].
- If "t1/2“ is long [digoxin], the drug should be administered in loading dose followed by maintenance dose.

Factors affecting elimination (t1/2):

• State of eliminating organs i.e. liver & kidney function.

• Delivery of drugs to the eliminating organs affected by:

1-plasma protein binding : Highly bound drugs are typically eliminated more slowly, while drugs with low binding are cleared more rapidly.

2-Vd of the drug : Drugs with a high volume of distribution may take longer to eliminate, while those with a low volume of distribution are usually cleared more quickly

Systemic clearance:

It is the volume of fluid cleared from the drug per unit of time.

• Systemic CLs = Renal clearance (CLr) + non-renal clearance (CLnr)

Significance of clearance: Calculation of the maintenance dose.

- **Loading dose**: The dose required to achieve a desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose.
- **Loading dose** = Vd×TC
- **Maintenance dose**: The dose given to maintain the desired Css.
- **Maintenance dose** = CLs×TC (Target concentration).

Created by : Dr.Farah Breik

Good luck 😊