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**Pharmacology**
**Med – Lecture 4**

# Pharmacokinetics II

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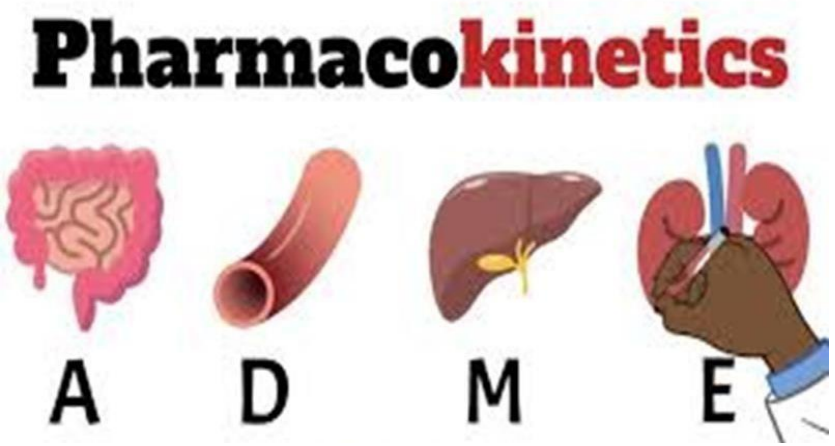
Original Slides for Dr. Heba Hassan

# Pharmacokinetics




**What the body does to the drug?**

- Absorption
- Distribution
  - ➢ It involves the distribution of the substance throughout the body compartment
- Metabolism
- Excretion

# Drug Distribution

Extra Notes

- Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

- After absorption the drug is distributed through **3** body compartments:

1. • **Vascular**
2. • **Vascular & interstitial**
3. • **Vascular, interstitial and intracellular**

# 1. Vascular compartment:

- Small volume of distribution (4 Litres in 70 kg person)
- Drugs distributed in this compartment are **hydrophilic**, and most drugs are **ionized** at the plasma pH (e.g. Heparin).

# 2. Vascular and interstitial compartments:

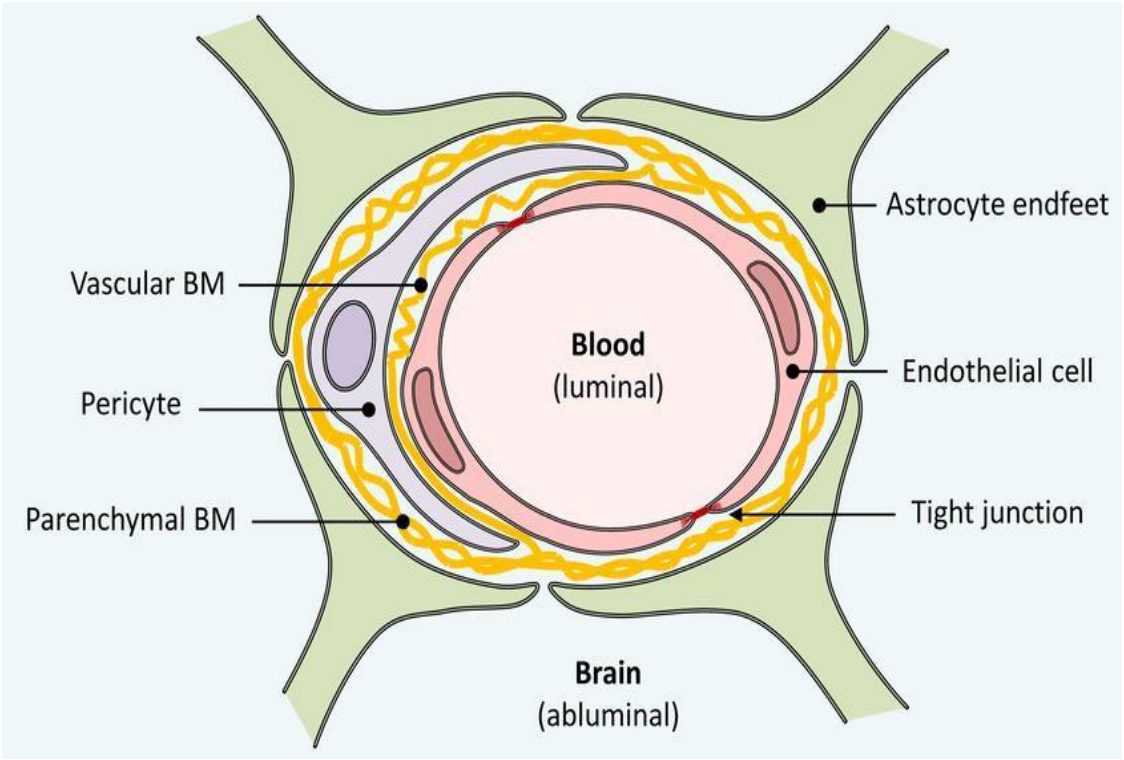
- Moderate volume of distribution (14 Litres in 70 kg person)
- Drugs distributed in these compartments are hydrophilic, with small molecular weight and lesser degree of ionization at plasma pH (e.g.neostigmine).

# 3. Vascular, interstitial and intracellular compartments:

- Large volume of distribution (40-42 litres in 70 kg person)
- Drugs distributed in these compartments are non-Ionized and lipophilic .e.g. barbiturates

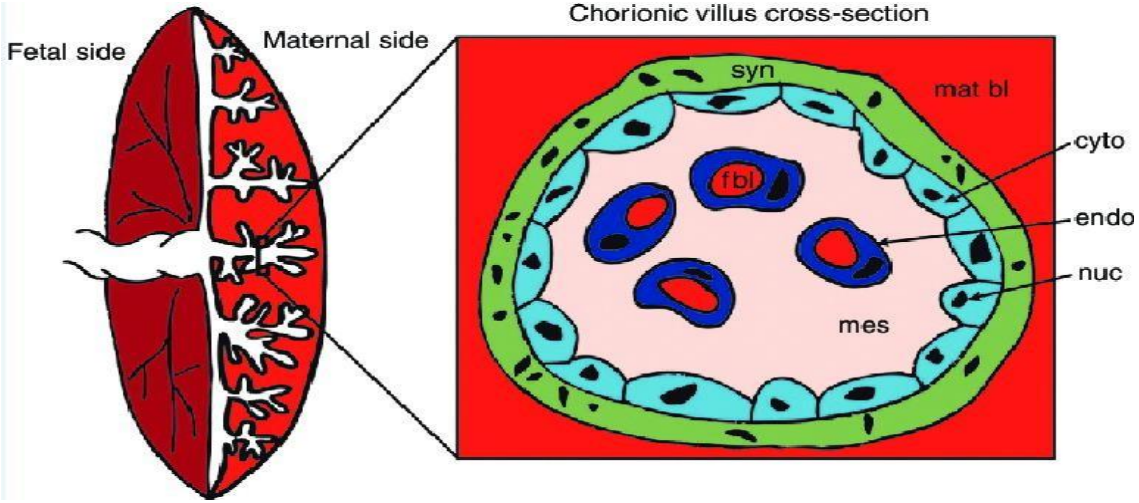
# Blood –brain barrier (BBB):

- Brain capillary endothelium with tight inter-cellular pores & adjacent glial tissues).
- Only **lipid-soluble** & **non-ionized** drugs can pass blood-brain barrier.
- Inflammation (meningitis) increases permeability of BBB (The concentration of penicillins & cephalosporins in the CSF of normal subjects is 0.5 -1 % of plasma level, this could increase up to 5% in case of meningitis).



# Placental barrier:

- Drugs that pass placental barrier may cause:
- **During pregnancy:** Teratogenicity (Congenital malformation), embryotoxicity (Kill the fetus)
- **During labor:** Neonatal asphyxia (Morphine) ,neonatal jaundice (Kernicterus) physiological jaundice caused by the destruction of HB into bilirubin which result in jaundice, but in case of pathological jaundice due to Iso-immunization which leads to kernicterus if it pass to Brain.



# Redistribution:

- Occurs with highly lipid-soluble drugs as thiopental.
- After initial distribution to CNS, thiopental redistributes to less perfused tissues e.g. skeletal muscle and fat, ending its action.

## ✓ Volume of distribution *(vd)*

- It is a theoretical expression, relates the entire amount of the drug in the body to its concentration in plasma.

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

## ✓ Importance of *Vd*:

- **Calculation of the loading dose of a drug**
- Calculation of the **corrective dose of a drug**
- **Treatment of drug toxicity**

# 1. Calculation of the loading dose of a drug:

**Loading dose** =target plasma concentration (Tc) x Vd2.

- Loading dose is an initial, larger dose of a drug that is administered to quickly achieve a therapeutic or target plasma concentration (Ct) of the drug, Loading doses are often used for drugs that have a prolonged time to reach steady-state concentrations in the body (such as drugs with a long half-life) or when an immediate therapeutic effect is needed.
- The loading dose is determined by the target plasma concentration (Ct) and the Vd of the drug.
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# 2. Calculation of the corrective dose of a drug

- **The corrective dose** is used to adjust a patient's drug dosage to maintain the desired therapeutic plasma concentration ($C_{ss}$) after the loading dose has been administered. The volume of distribution (Vd) also plays a role in determining the corrective dose
- **Calculation of Corrective Dose**: to maintain a steady-state concentration ($C_{ss}$) of a drug in the body, which is necessary for continuous therapeutic effect, After the administration of a loading dose, the concentration of the drug in the body will rise and eventually reach a plateau, representing the desired steady-state concentration.

**Corrective dose** = (desired plasma Css –achieved plasma level) X ($V_d$).

- **Corrective Dose:** The additional dose to maintain the desired concentration
- **C:** The current achieved plasma concentration.
- **Css:** The desired steady-state plasma concentration.
- **Vd:** The volume of distribution.

# 3. Treatment of drug toxicity:

- Hemodialysis is **not** useful for drugs with **high Vd** (most of the drug is in the tissues).
- Hemodialysis is useful for drugs with **low Vd** (most of the drug is in the blood)
- Peritoneal dialysis is useful for drugs with **moderate Vd (like 15,12)**

# Factors affecting drug distribution.

**1. Lipophilicity (Diffusion):** The ability of the drug to diffuse across cell membranes depends **on its lipophilicity.**

**2. Binding to tissue constituents (Tissue affinity):**

It is due to affinity of drugs to some cellular constituent.

- Chloroquine is concentrated in the liver
- Iodides are concentrated in the thyroid.

# Factors affecting drug distribution.

## 3- Plasma protein binding (PPB):

Drug in blood exists in **two forms:**

- **PP bound form:** inactive, non diffusible and cannot be metabolized or excreted.
- **Free Form:** active(biological effect), diffusible and can be metabolized or excreted.

**N.B** The two forms exist in **equilibrium**, when fraction of the free form is metabolized or excreted similar fraction is released from plasma protein binding sites.

# Characteristics of drug with high PP binding:

- PP bound fraction cannot be eliminated and acts as **reservoir**.
- Because the plasma protein binding sites are limited, drugs can displace each other clinically significant interactions.

- Displacement from PP is clinically important when the drug has high PPB capacity & small Vd (most of the drug is present in the circulation). So, minimal displacement → **large** increase in the free part → **toxicity**, Example: aspirin displaces warfarin (PPB: 99%)


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