PHARMACOKINETICS

Prepared by: Heba Ahmed Hassan
Assistant professor of clinical pharmacology
faculty of medicine, mutah university, JORDEN

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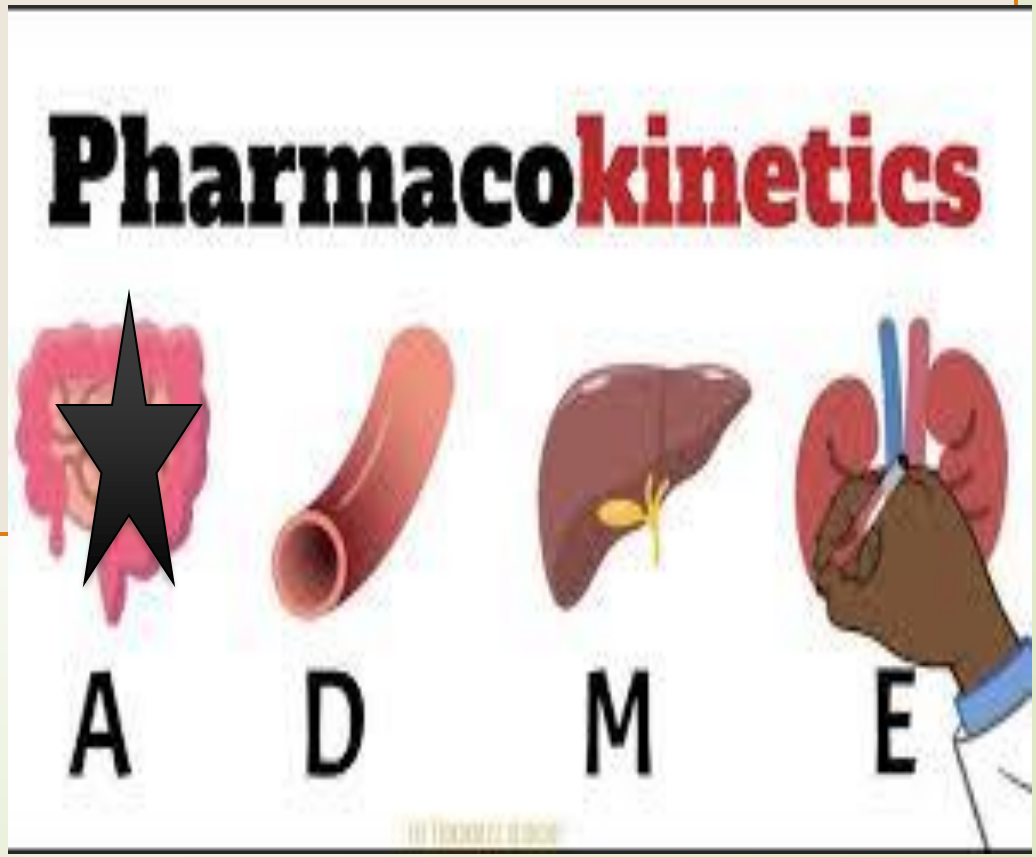
Pharmacokinetics

what the body does to the drug?

- **Absorption**
- Distribution
- Metabolism
- Excretion.



Distribution

↳ when drug distributed it depend on perfusion.

It involves the distribution of the substance throughout the body compartment] From the blood to tissue.

→ Highly prefused tissue.... Vital organs. [heart, brain, lung]

→ Lesser " " .... skin, skeletal muscle.

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

depending on perfusion.

1. **Vascular** .... in B.V just (in heavy drug ionized form) → in pH plasma.
2. **Vascular & interstitial**
3. **Vascular, interstitial and intracellular**

1. Vascular compartment:

→ in Drug of high MW , ionized in plasma ∴
→ The Drug will placed in B.V

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). → Highly MW → ionized.

2. Vascular and Interstitial compartments:

lesser ionization + ↓ MW → part in B.V, and part in interstitial fluid.

- 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

→ Low MW and lipophilic.

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).

The only type of drug is category A, B because no toxins in it.

Placental barrier:

every thing that the pregnant eat or drink is passed by placenta → Fetus.

For that → Not allowed for pregnant women to take drug

Drugs that pass placental barrier may cause: abortion.

- *During pregnancy* : Teratogenicity, embryotoxicity

  if the mother take it, it'll pass to fetus bone and tooth so he'll face a problem in development.

- *During labor:* Neonatal asphyxia ,neonatal jaundice

  (Kernicterus)

  Fetus poisoned.

⇒ During Labor :-

if the mother is an addicated on morphen, when it labor the baby → it'll appear as it was take on morphen (because of passage of drug through placenta to fetus) ; so you'll notice ↓ depression in RS and brain. (because baby doesn't have a complecate pharmakokinetic)

⇒ neonatle jaundice يرقان

↳ in first week, this case occur due to hemoglobin breakage, because it convert it from fetus to adult

↳ but if it occur from the 1st day, it'll be pathological =

↳ because mother take ↓ drug (pass placenta) reach to fetus, break albumin and pass to brain cause brain damage. (Kernicterus)

↳ strong BBB

Redistribution:

= Thiopental → Highly lipophilic.

- Occurs with highly lipid-soluble drugs as

→ intravenous anesthetic → short duration of anesthetic. 5–10 min)

thiopental. After initial distribution to CNS,

↳ Go for brain → Finishing it work → Redistribution.

thiopental redistributes to less perfused tissues

↳ and termination of its action.

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 (initial dose)

Calculation of the **corrective dose of a drug**

Treatment of drug toxicity:

❑ Calculation of the loading dose of a drug:

Then, we start to give Pt at a small level to keep it constant in blood, because a higher value → Toxis

Loading dose (initial does)

a large loading does that we give it to the patien fast.

to increase the Pc and rise Pt to desiropathic level

= target plasma concentration (Tc) x Vd2.

❑ Calculation of the **corrective dose of a drug**

desired plasma Css –achieved plasma level) X (V_d).

(2 - 1.3) x Vd

0.7 x Vd

2. **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

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.

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, 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%)