PHARMACOKINETICS

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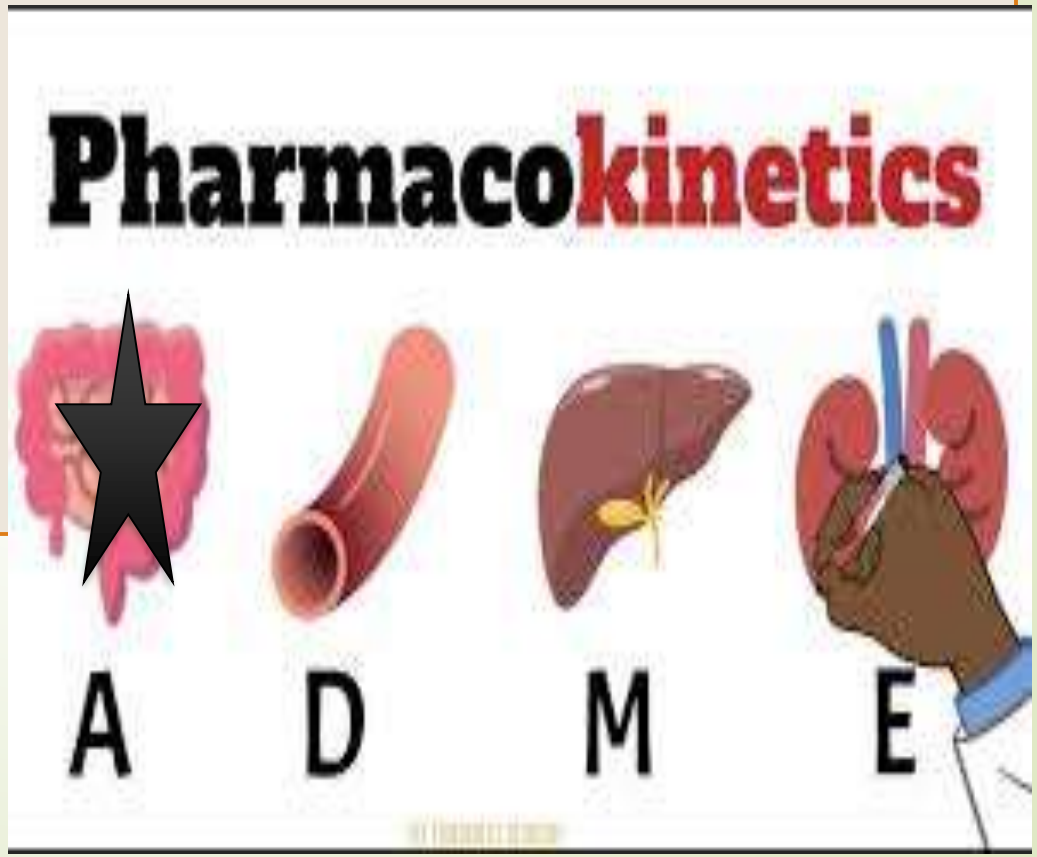
Pharmacokinetics

what the body does to the drug?

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



Distribution

It involves the distribution of the substance throughout the body compartment

- 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).

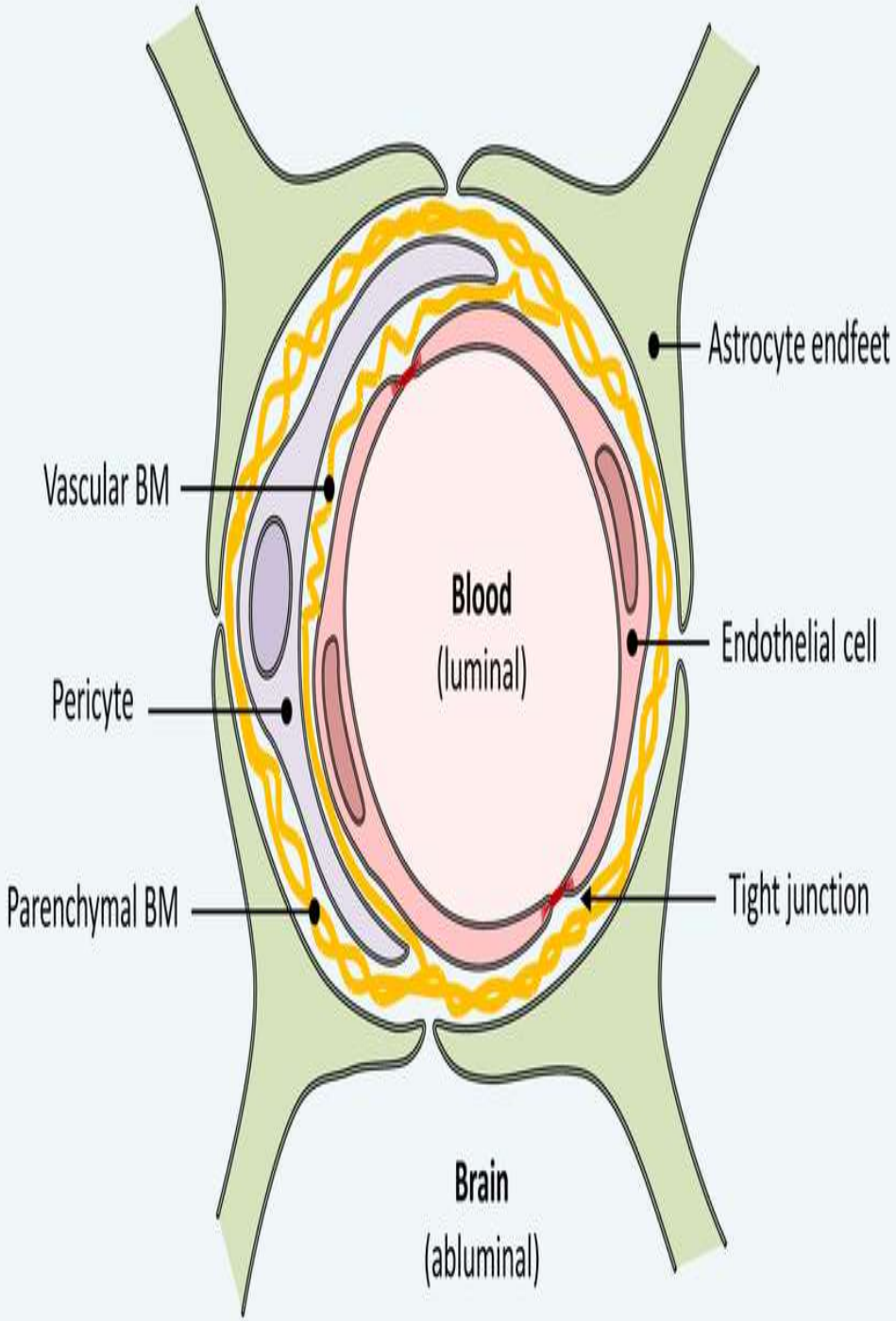
- Only lipid-soluble & non-ionized drugs can pass blood-brain barrier.
- Inflammation (meningitis) increases permeability of BBB (The concentration of penicillins & cephalosporins in the CSF of normal subjects is 0.5 -1 % of plasma level, this could increase up to 5% in case of meningitis).

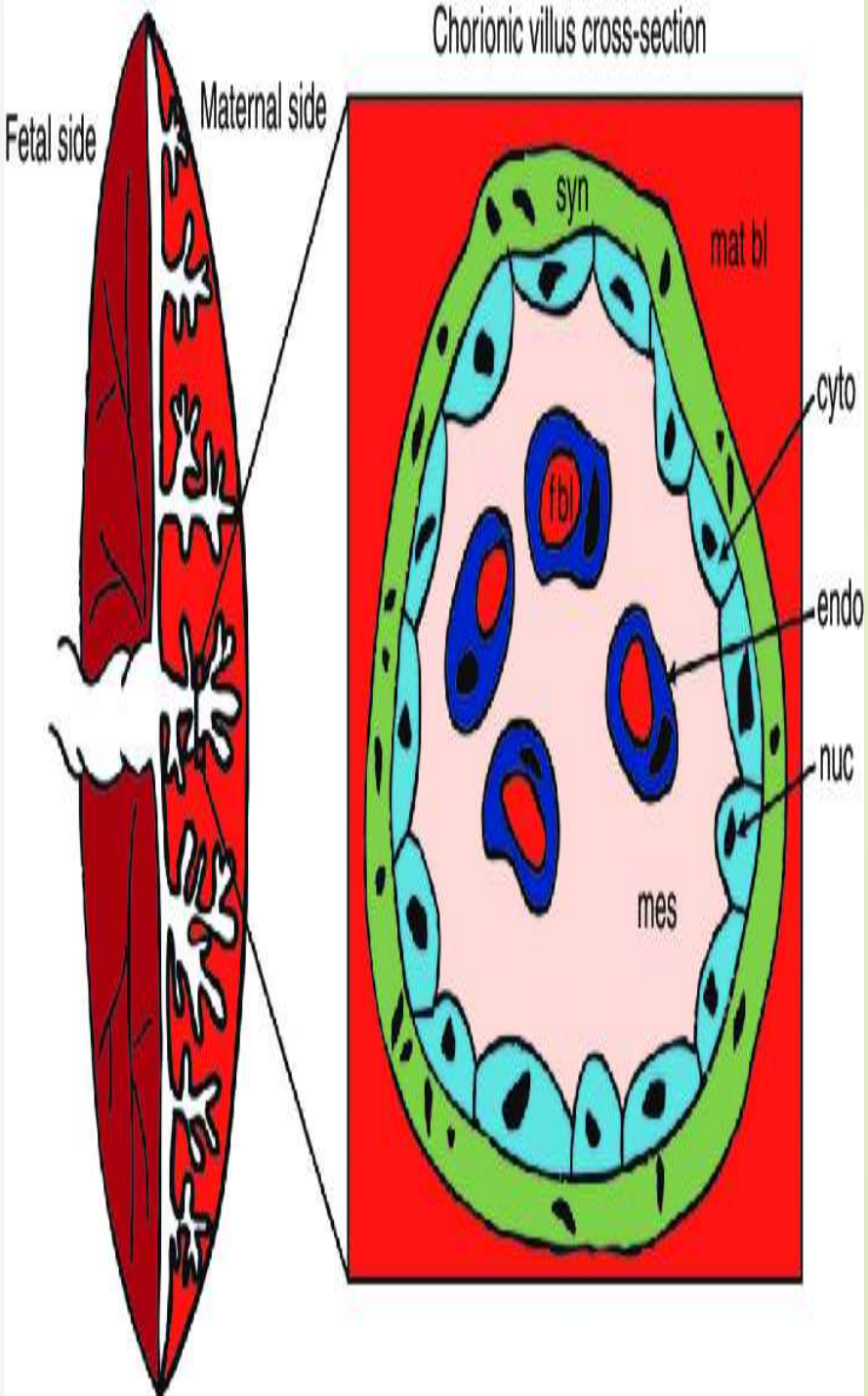
Placental barrier:

Drugs that pass placental barrier may cause:

- *During pregnancy* : Teratogenicity, embryotoxicity
- *During labor:* Neonatal asphyxia ,neonatal jaundice

(Kernicterus)


Astrocyte endfeet
Vascular BM
Blood
(luminal)
Endothelial cell
Pericyte
Parenchymal BM
Tight junction
Brain
(abluminal)


Chorionic villus cross-section
Fetal side
Maternal side
syn
mat bl
cyto
fbl
endo
nuc
mes

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:

- **Calculation of the loading dose of a drug:**

Loading dose

= target plasma concentration (Tc) x Vd2.

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

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

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%)

→ **bleeding**


TO BE
CONTINUED