# Pharmacokinetics 2

HIGH YIELD

Distribution : It involves the distribution of the substance throughout the body compartment

❑After absorption the drug is distributed through 3 body compartments:

- Vascular
- Vascular & interstitial
- 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-lonized 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)

## VOLUME OF DISTRIBUTION (Vd)

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

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

### 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.

### ❑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 (Vd).

### Importance of Vd:

Calculation of the loading dose of a drug

calculation of the corrective dose of a drug

treatment of a drug toxicity

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### 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.

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

**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.

**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.

### 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.

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.

❑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

لا تنسَ يا فَتى..
كُلّ مسارٍ يتّصل بالسّماء لا يخيب! كُلّ خطوةٍ تُستَمَدّ من الصّدق لا تَميل، كُلّ تَعَبٍ للأُمّة مهما زادَ يَهون، كُلّ لحظةٍ كانت لله لا تَضيع، فأبشر! رغم قلبك المهترئ.

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