General Pharmacology

- Pharmacokinetics
- Pharmacodynamics
- Drug-drug interactions

Passive diffusion:

- The most important means by which drugs are absorbed from sites of administration & distributed within the body.
- It depends mainly on: * Lipid solubility * Non-ionization of drugs
- **Ionization of the drug:**
  - The charge of ionized drug attracts water with formation of water-soluble [lipid-insoluble] complex. *The unionized drug is lipid soluble*.
  - A very large percentage of the drugs in use are weak acids or weak bases.
  - Weak acids are unionized when protonated [bind hydrogen] while weak bases are unionized when unprotonated

$HA \longleftrightarrow A + H^+$ **<u>while</u>** **$B + H^+ \longleftrightarrow BH^+$**

For weak acid or weak bases**: log protonated/unprotonated = pKa –pH**

The pK_a is that pH at which the concentrations of the ionized and unionized forms are equal. pK_a is specific for each drug and can be obtained from pharmacokinetic tables.

- The lower the pH relative to the pK_a, the greater will be fraction of drug in the protonated form so, weak acid are unionized while weak bases are ionized.

- So, more weak acid will be unionized and in the lipid-soluble form at acid pH, where as more basic drug will be unionized and in the lipid-soluble form at alkaline pH.

Examples:

- **Aspirin** [acid] has pKa=3.5 and pH in the stomach=2.5

pKa - pH =log protonated/unprotonated. So 3.5-2.5=1=log10/1

So aspirin is more protonated [unionized] and more lipid-soluble in the stomach.

- Pyrimethamine [base] has pKa=7 and pH of small intestine=8

pKa - pH =log protonated/unprotonated. So, 7-8= -1=log1/10

So Pyrimethamine is more unprotonated, unionized and more lipid-soluble in small intestine

Clinical importance of pKa:

1. **GIT:**

- Aspirin (acid drug) is mostly non-ionized in the empty stomach crosses the cell membrane of gastric mucosal cells. In gastric mucosal cells the pH is alkaline, so aspirin becomes ionized (lipid insoluble)and cannot cross the cell membrane → Aspirin is trapped in gastric mucosal cell → death of these cells inducing "peptic ulceration"

2. **Kidney**:

- In drug poisoning, renal drug elimination can be enhanced by changing urinary pH to increase ionization of the drug and decrease lipid solubility and inhibit tubular reabsorption.
- Alkalininzation of urine (to increase urine pH above drug pKa) is useful in acidic drug poisioning e.g. aspirin and phenobarbital.
- Acidification of urine (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine.

In conclusion:

- Absorption of drugs is mostly by simple diffusion through lipid membranes.
- Ionized form of the drug is water-soluble and cannot pass lipid membranes except through water filled pores which is too narrow to allow large molecules to pass.
- Non-ionized form of the drug is lipophilic and can easily cross lipid membranes.

Bioavailability

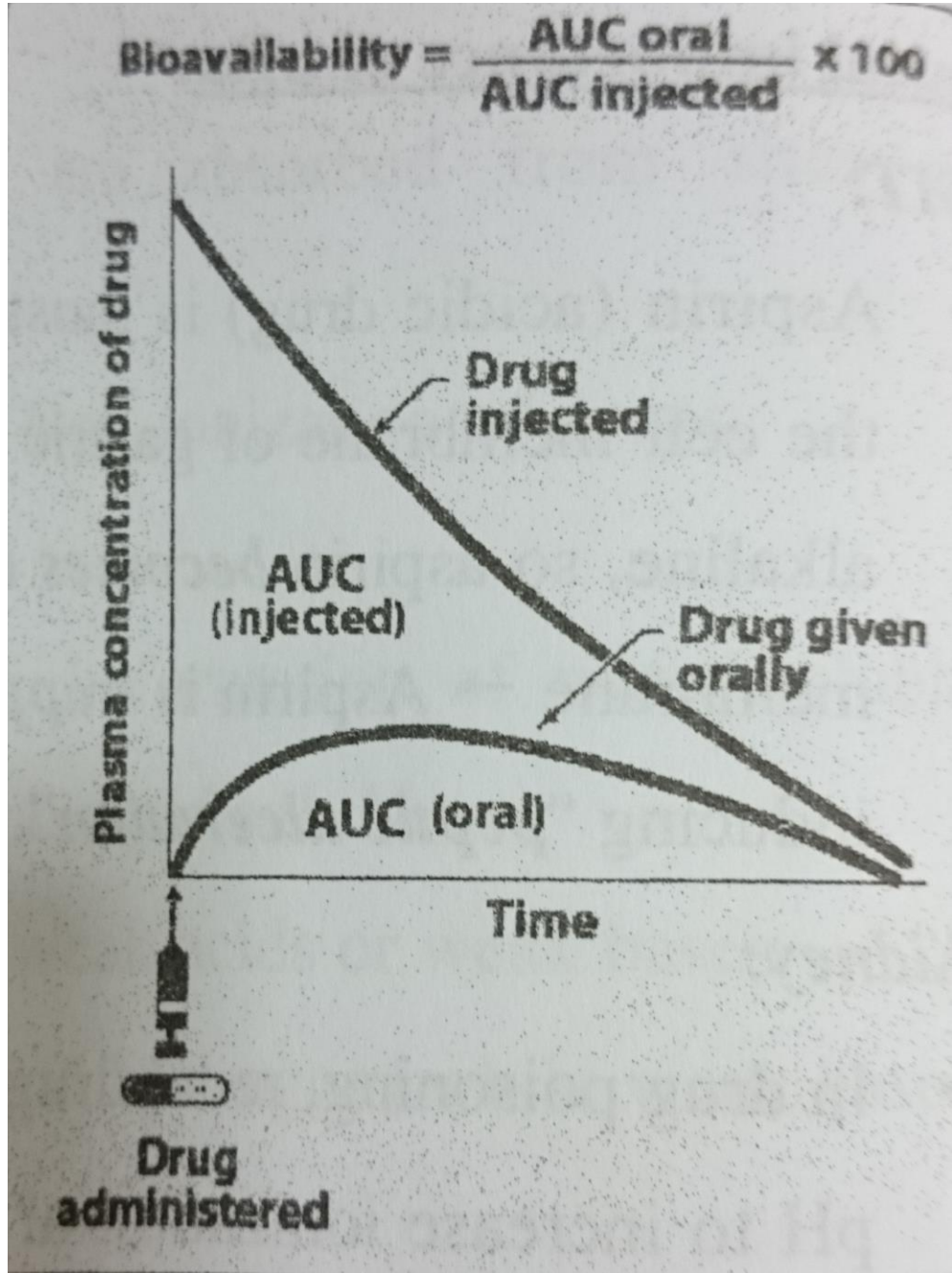
It is the percentage of drug that reaches the systemic circulation and becomes available for biological effect.

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

Factors affecting bioavailability:

1. **The extent of drug absorption.**
2. **1st pass effect(1st pass metabolism):**

- It is the metabolism of some drugs in a single passage through gut wall, liver or lungs before reaching systemic circulation.



A. **Hepatic 1st pass effect:**

- Nitroglycerin and propranolol pass from GIT to liver where they are extensively metabolized in their 1st pass through liver before reaching systemic circulation.

B. **Intestinal 1st pass effect:**

- Estrogens are extensively metabolized in their 1st pass through intestinal wall.

C. **Pulmonary metabolism:**

- After inhalation, nicotine is partially metabolized in the lung.

DRUG DISTRIBUTION

After absorption the drug is distributed through 3 body compartments:

A. **Vascular compartment = small volume of distribution** (4 litres in 70 kg person): drugs distributed in this compartment are ***hydrophilic*** (lipid/water partition coefficient is low), and most of the drug is ionized at the plasma pH e.g. heparin.

B. **Vascular and interstitial compartments =Moderate volume of distribution** (14 Litres in 70 kg person): drugs distributed in these compartments are ***hydrophilic*** (lipid/water partition coefficient is low), with lesser degree of ionization at plasma pH e.g. neostigmine.

C. **Vascular and interstitial and intracellular compartments =Large volume of distribution** (Total body water about 40-42 Litres in 70 kg person): drugs distributed in these compartments are ***non-ionized and lipophilic*** (lipid/water partition coefficient is high) 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)

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.

- *Importance*: repeated administration ➞ Tissue saturation ➞ CNS accumulation ➞ Toxicity.

VOLUME OF DISTRIBUTION (Vd)

- It is a theoretical expression, defined as the apparent volume that would accommodate the entire amount of the drug in the body in a concentration equal to that of plasma.

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

Factors affecting distribution of drugs:

1. Blood flow (perfusion): Amount of drug delivered to particular organ depends on the blood flow to that organ (Blood flow distribution)
2. Lipophilicity (diffusion): The ability of the drug to diffuse across cell membranes depends on its lipophilicity (⬆ lipophilicity ➡ ⬆ distribution)

Characteristic of Lipophilic drug:

1. Well- absorbed orally.
2. Usually subjected to hepatic 1st pass effect.
3. Eliminated mainly by liver (hepatic elimination).
4. Crosses blood-brain, and placental barriers.

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.
- 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 which bind to albumin can displace each other leading to clinically significant interactions.

- Aspirin and other drugs (e.g. amiodarone) displace warfarin from its PP binding sites. Since warfarin has a small free fraction (1%) and highly PP bound fraction(99%),the displaced portion may be dangerous (if 1% is displaced, the active part of the drug increased 100%)

4. Binding to tissue constituents (Tissues affinity): It is due to affinity of drugs to some cellular constituents.

- Chloroquine is concentrated in liver.
- Iodides are concentrated in thyroid and salivary glands.

Importance of V_d:

- Calculation of the ***loading dose of a drug = (desired plasma Css) X (V_d).***
- Calculation of the **corrective dose of a drug =**
  (desired plasma Css –achieved plasma level) X (V_d).

- **In both circumstances, if the drug is not given by IV route the value should be divided by the bioavailability of the drug by the given route.**

3. In treatment of drug toxicity:

- **Dialysis is not useful for drugs with high V_d (most of the drug is in the tissues).**
- **Hemodialysis is useful for drugs with low V_d (most of the drug is in the blood).**
- **Peritoneal dialysis is useful for drugs with moderate V_d**
- **V_d of a drug is directly proportionate to half life of the drug: $t_{1/2}$= 0.693 V_d/Cis**

(Cls= *Drug Clearance*, **Css=** *drug steady state plasma concentration*)

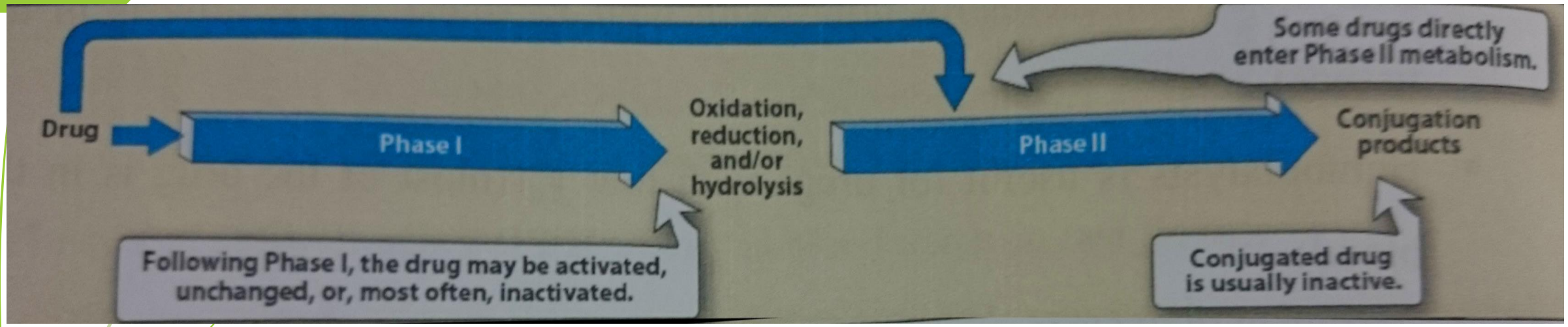
BIOTRANSFORMATION (METABOLISM)

- These are changes that occur to drugs after absorption until excretion.
- Drug metabolism occurs mainly in the *liver*.
- The aim of drug metabolism is the conversion of ionized drugs to non-ionized, water-soluble metabolite which is *easily excreted*

Consequences of drug metabolism:

1. Convert ***active*** drug to ***inactive*** metabolite (most drug).
2. Convert ***inactive prodrug*** into ***active drug*** e.g. enalapril enalaprilat (active) & prednisone prednisolone (active).
3. Convert ***active*** drug to ***inactive*** metabolite e.g. codeine morphine.
4. Convert drug to **toxic** metabolites e.g. halothane & paracetamol toxic epoxides which are conjugated with glutathione. Glutathione deficiency may precipitate paracetamol or halothane hepatotoxicity.

Types of biotransformation reactions:



Phase I (functionalization) reactions:

- Phase I reaction include: oxidation, reduction and hydrolysis.
- **The** most important reaction is oxidation by cytochrome p_{450} (CYP) oxidases.
- **Phase** I reaction result in conversion of active drug to inactive metabolite (some times convert the prodrug to active drug). If the metabolite is water-soluble it is excereted, if not, it enters phase II.

- **Phase II (biosynthetic "conjugation") reactions:**
- An endogenous substrate (e.g. glucronic acid, sulfate, glutathione, amino acids, or acetate.) is conjugated with the parent drug or its phase I metabolite.
- This result in formation of non-toxic, highly polar (ionized), water-soluble and rapidly eliminated conjugates.

Metabolizing enzymes:

A. Microsomal enzymes e.g.
   - Cytochrome P_{450} oxidases and their family $^{O}_{1}$ & subfamily $^{O}_{2}$ (CYP $^{O}_{2}$ $^{O}_{1}$ C9 $^{O}_{2}$).
   - Glucuronyl transferases for conjugation.

B. Non-microsomal enzymes e.g. dehydrogenase, esterases (plasma) & xanthine oxidases (cytoplasm).

Factors affecting biotransformation:

1. Physiological changes (age & sex).
2. Pathological factors (liver cell failure).
3. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators.
4. Enzyme induction & enzyme inhibition.

Enzyme induction:

- Many drugs are able to include (increase activity) of microsomal enzymes resulting in **increased rate of metabolism of** the inducing drug as well as other drugs metabolized by microsomal enzymes.
- **Some inducing drugs:**

- Phenobarbitone
- Phenytoin
- Carbamazepine
- Rifampicin
- Nicotine