Pharmacokinetic Principles

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ADME

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

Drug distribution

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

Factors affecting the drug distribution:

1. Blood flow

The rate of blood flow to the tissue capillaries varies widely. Blood flow to the “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow.

Drug distribution

Factors affecting the drug distribution:

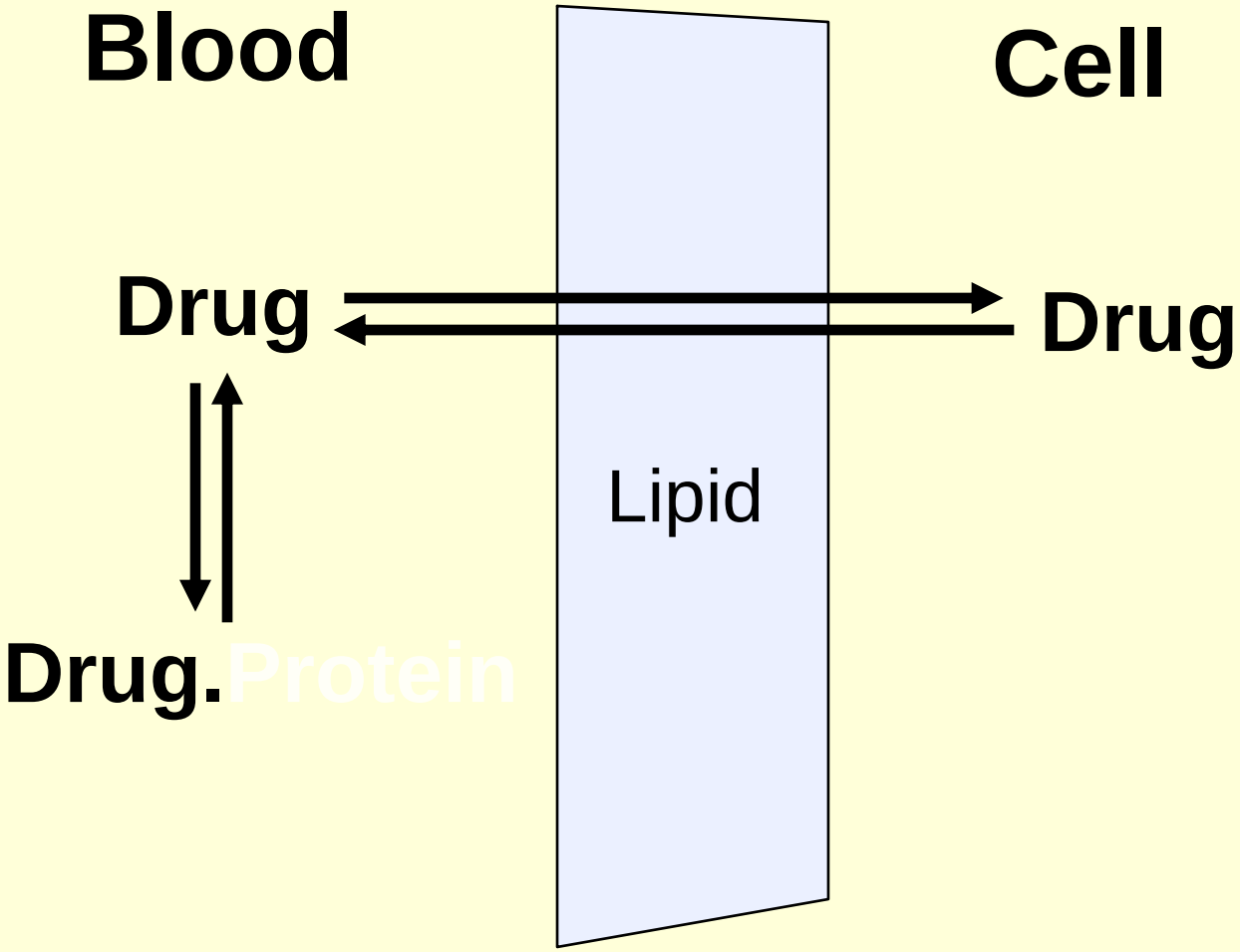
2. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

3. Binding of drugs to plasma proteins and tissues

a. **Binding to plasma proteins:** As the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein.
b. **Binding to tissue proteins:** Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids.

Plasma protein binding



Total drug conc. in blood greater than in cell

Plasma protein binding

- Most drugs circulate partly free in plasma and partly protein bound.
- The free fraction is the pharmacologically active and it is the one removed by metabolism, dialysis and excretion.
- Free and bound fractions are in equilibrium i.e. As the free drug is removed, it will be replaced by drug released from bound fraction.

Types of proteins available for drug binding

- Albumin: is the main binding protein with high capacity and low Affinity.
- Globulins: for hormones such as thyroxine and sex hormones
- Lipoproteins and α-acid glycoprotein: for basic drugs such as quinidine, imipramine and chlorpromazine

The significance of protein binding

- It is a source of drug interaction. Displacement may be important for drugs which are highly protein bound and at the same time having small Vd e.g. warfarin and NSAIDs ; the free fraction of warfarin is increased leading to bleeding

- In renal and liver failure The free fraction of drugs may increase and therefore, increase in response or toxicity.

Drug distribution

Factors affecting the drug distribution:

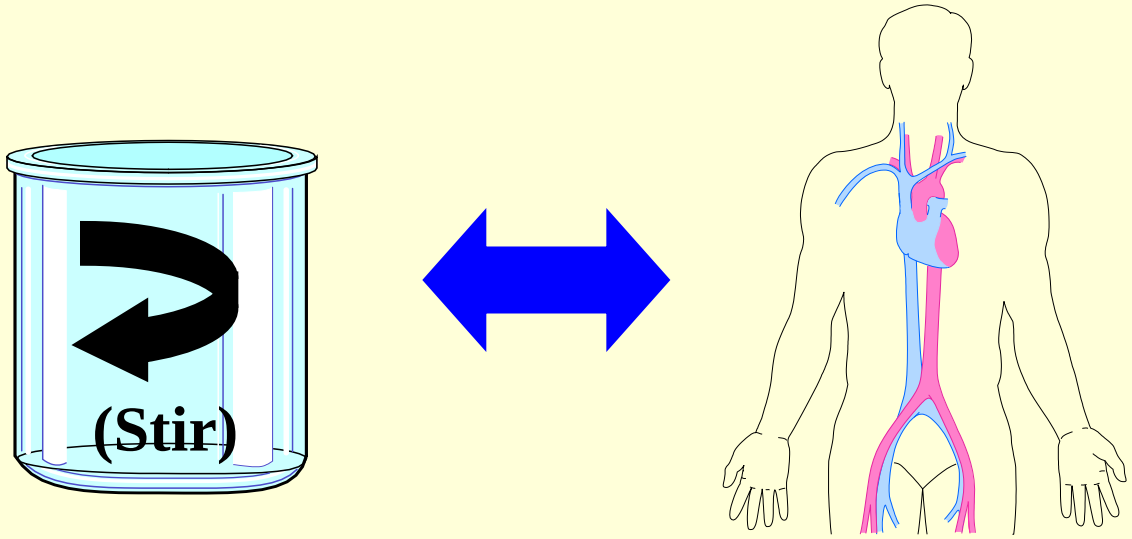
4. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes.

5. Volume of distribution

Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

VOLUME OF DISTRIBUTION (Vd) OF DRUGS



As a first approximation, the body behaves like a well-stirred beaker, i.e., chemicals are dispersed throughout the container (body) rather quickly.

VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF (Vd)

The **apparent** volume of distribution is the amount of fluid that would be required to contain the drug in the body at the same concentration as in the blood.

Vd is **NOT** a volume in the literal sense

Vd **IS**.... 1. a calculated value
2. a reproducible value
3. a clinically useful value

VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF (Vd)

It is a theoretical (apparent) volume of fluid in which the drug dose appears to distribute with a concentration equal to that in plasma.

$$Vd = \frac{Dose}{Co}$$

Co is the initial plasma concentration, i.e. At time zero

VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF (Vd)

Vd is **small**: if the drug remains mostly in plasma e.g. warfarin which is highly protein bound (also tolbutamide, salicylates)

Vd is **large**: if the drug is present mainly in the tissues e.g. Digoxin, pethidine, nortriptyline, chloroquine

VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF (Vd)

The significance of the Vd

1. In drug overdose ; removal of a drug by hemodialysis is appropriate for drugs with small Vd i.e. a major proportion of the dose is present in plasma

2. Drug interaction is likely to occur between those with small Vd e.g. Displacement from protein binding

Distribution into the water compartments in the body

a. Plasma compartment:

If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. Therefore, it has a low Vd. Example: **Heparin**.

b. Extracellular fluid:

If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into volume of the extracellular fluid (the sum of the plasma volume and the interstitial fluid), Example: **Aminoglycoside antibiotics**

Distribution into the water compartments in the body

c. <u>Total body water:</u>

If a drug has a low molecular weight and is lipophilic, it can move into the interstitium through the slit junctions and also pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight. Example: **Ethanol.**

Effect of Vd on drug half-life

Vd has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the organs where metabolism occurs per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of the drug in the plasma.

If a drug has a large Vd, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases Vd can increase the half-life and extend the duration of action of the drug.

DRUG CLEARANCE THROUGH METABOLISM

The three major routes of elimination are:

- hepatic metabolism
- biliary elimination.
- urinary elimination.

Most drugs are eliminated according to first-order kinetics, although some, such as aspirin in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated.

DRUG CLEARANCE (CL)

(CL) estimates the amount of drug cleared from the body per unit of time.

Total CL is calculated as follows: **$CL = 0.693 \times Vd / t_{1/2}$**

$t_{1/2}$ is the elimination half-life, Vd is the apparent volume of distribution and 0.693 is the natural log constant.

Kinetics of metabolism

1. **First-order kinetics:** the rate of metabolism and elimination is directly proportional to the concentration of free drug.

2. **Zero-order kinetics:** a constant amount of drug is metabolized per unit of time and the rate of metabolism and elimination does not depend on drug concentration.

Metabolism

Only few drugs excreted unchanged

Metabolism changes drugs in two major ways :

1. By reducing lipid solubility (increased elimination)
2. By altering biological activity which occurs in 3 possible ways :

a. Conversion of pharmacological active to an inactive substances (most drugs)

b. Conversion of active to another active substance. Example, codeine → morphine

c. Conversion of inactive (a pro-drug) to active
Example, levodopa → dopamine

Metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions called phase 1 and phase 2 reactions.

Sites of Metabolism

Organs :

- liver (most important)
- Kidney (e.g. vitamin D, insulin)
- gut mucosa (e.g. estrogen and progesterone)
- Gut flora (e.g. hepatic conjugates)
- lung (e.g. Serotonin and testesterone)
- skin (vitamin D activation and minoxidil)

Intracellular sites microsomal (mostly, mitochondria, cytoplasm, plasma)

Drug Metabolism occure in two phases

Phase 1: convert lipophilic drugs into more polar molecules by introducing a polar functional group, such as –OH or –NH2. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

a. **Phase I reactions utilizing the P450 system:** catalyzed by the cytochrome P450 system (also called microsomal mixed-function oxidases).
b. **Phase I reactions not involving the P450 system:** includes amine oxidation (e.g. oxidation of catecholamines or histamine), alcohol dehydrogenation (e.g. ethanol oxidation), esterases (e.g. metabolism of aspirin in the liver), and hydrolysis (e.g. of procaine).

Enzyme induction

An increase in enzyme amount and activity as a result of exposure to certain chemicals.

Non-microsomal enzvmes are not inducible

Examples of enzyme inducers: **barbiturates**, **rifampicin**, **phenytoin**; **carbamazepine**, **griseofulvin**, **smoking**, **chronic (not acute) alcohol** ingestion.

The importance of Enzyme induction

1. It can be responsible for clinically important interactions Examples

   a. contraceptive failure if potent inducers are taken at the same time

   b. Increased breakdown of vitamin D resulting in osteomalacia and hypocalcemia; and also in megaloblastic anemia due to folate deficiency.

   c. Failure of anticoagulant therapy due to reduction of warfarin level

The importance of Enzyme induction

2. Tolerance to certain drugs may occur e.g. anti-epileptic drugs can induce their own metabolism

3. May increase drug toxicity e.g. Hepatotoxicity in patients on rifampicin.

4. Enzyme inducers can alter liver function tests.

5. Enzyme induction can be used therapeutically e.g. phenobarbitone can stimulate fetal hepatic glucuronyl transferase and reduce severe hyperbilirubinemia in neonates.

Enzyme inhibition

An important mechanism for drug-drug interaction and can lead to drug accumulation and toxicity particularly with drugs of low therapeutic index

- General non-specific inhibition of microsomal enzymes e.g. cimetidine (inhibits metabolism of warfarin, diazepam, propranolol)

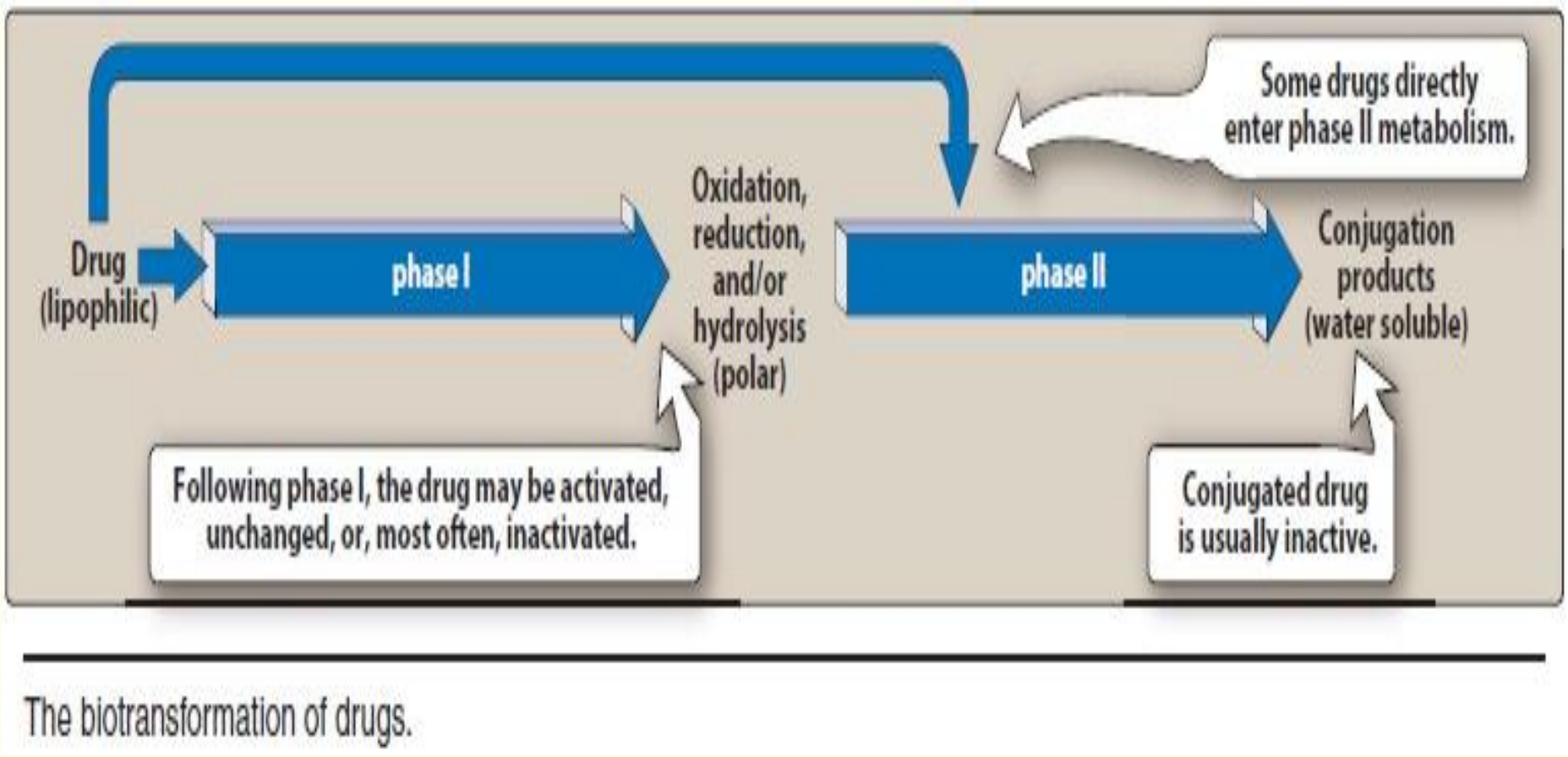
- Inhibition of specific enzymes could be a mechanism for therapeutic action of drugs e.g. captopril inhibits ACE, aspirin inhibits cyclooxygenase, and also, allopurinol inhibits xanthine oxidase.

Drug Metabolism

Phase II metabolism:

This phase consists of conjugation reactions. If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, water-soluble compounds that are often therapeutically inactive (exception is morphine-6-glucuronide, which is more potent than morphine). The highly polar drug conjugates are then excreted by the kidney or in bile.

The biotransformation of Drugs



The biotransformation of drugs.