

Therapeutics

Drug Absorption, Distribution, and Elimination

Dose Determines Effect

Dose is crucial in determining the benefit and risk of a drug, affecting pharmacokinetics, clinical response, and pharmacokinetics.

- Bioavailability
- Volume of Distribution
- Clearance
- Half-life

Pharmacodynamics

Pharmacodynamics is what the drug will do in the body

- Benefit: Desired clinical response (efficacy)
- Risk: Undesired clinical response (toxicity)

Pharmacokinetics

Pharmacokinetics is what the body will do to the drug. It involves drug administration, absorption, distribution, metabolism, and excretion (ADME) to determine dosing. It is also used to determine how much and how often to administer it

- Depends on bioavailability, volume of distribution, clearance, and half-life

Administering the Dose

Drugs can have local or systemic actions based on their administration route.

- Local: administered near; limited tissue access, e.g., skin, lungs, nose, rectum
- Systemic: bloodstream; accesses many tissues, more potential for side effects e.g., oral

Absorption and Drug Properties

Absorption involves how drugs cross membranes, influenced by factors like pH (most are weak acids/bases), aqueous solubility, lipid solubility, and physicochemical properties (size, charge)

- Small (diffusion) vs. Large molecules (pinocytosis)

- Lipid solubility vs pH: acidic/basic drugs are charged/uncharged based on whether it is low/high pH, which impacts their lipid solubility
 - Most drugs are weak acid/bases
 - Uncharged = not lipid soluble = not well absorbed

Systemic Administration

- Oral administration: most common, absorption from the gastrointestinal tract
 - Dose forms: tablets, capsules, powders, solutions
 - pH of GI: stomach 1-3, duodenum 5, small intestine 5-7
 - Usually absorbed through the small intestine
 - Small intestine is superfolded, has villi, microvilli = very large SA
 - Limitations: need to be conscious, overdose, compliance, first pass metabolism
 - Saliva enzymes and gastrointestinal fluids: peptides susceptible e.g. insulin
 - Exposed to first pass metabolism
 - Absorbed across portion of GIT that is drained by veins in the hepatoportal system (first pass hepatic metabolism)
 - Nitrates susceptible e.g.
 - Can be used to generate active molecules
 - Prodrugs: e.g. nitrates
- Other routes (parenteral) are used to avoid first pass metabolism
 - Local administration: e.g. skin, lungs, nose, rectum
 - Injectable routes
 - subcutaneous (sc)
 - intramuscular (im)
 - Intradermal (id)
 - intravenous (iv): (need to find vein)
 - instant; exact amount of drug enter blood; no absorption required

Bioavailability and Distribution

Bioavailability (F) determines the proportion of active drugs entering circulation, while distribution involves drug spread in the body.

- Bioavailability affected by absorption (pH, size, lipid solubility), first pass metabolism, and enzyme activity
 - iv = 100% initially, everything else peak <100%
- Distribution is driven by circulation and influenced by molecular size, lipid solubility, **capillary structure**, and **plasma-protein binding** (only free drug has access to tissues)
 - Distribution rarely uniform
 - Once absorbed most drugs distribute rapidly and behave as if in a single compartment
 - Drugs are simultaneously distributing and being eliminated (distribution faster)
 - Reaches distribution equilibrium

Types of Capillaries

Capillaries play a crucial role in drug distribution and absorption in the body. There are three main types of capillaries:

- **Continuous Capillaries:** These have uninterrupted endothelial cells and are found in most tissues. They have intermediate drug accessibility.
 - Brain, eyes, and testes are particularly diffusionally tight, limiting drug entry
- **Fenestrated Capillaries:** Characterised by small pores (fenestrations) that allow for increased permeability, commonly found in the kidneys (drug filtration) and intestines (drug absorption)
- **Sinusoidal Capillaries:** These have larger openings and are found in the liver (drug metabolism) facilitating the exchange of larger molecules.

Binding of Drugs to Plasma Proteins

The binding of drugs to plasma proteins, such as the main one albumin, affects their distribution and elimination. Key factors influencing this binding include:

- Relative affinity of the drug for the protein.
- Amount of protein relative to the drug concentration.
- Drug-drug interactions that may alter binding dynamics.

Free drug access to tissues and elimination processes influence the amount of free drug available, which can be affected by age and disease state.

Specific Binding Proteins

Specific binding proteins exist for several hormones, including:

- Thyroxin binding globulin.
- Corticosteroid binding globulin.

Volume of Distribution

- The volume of distribution is the volume of body water in which a drug appears to be dissolved in after it has distributed throughout the body
- $V_d = \text{amount in body} / \text{plasma concentration } (c_p) = \text{dose given} / \text{initial concentration}$
 - $\text{Dose} = c_p \times V_d \times \text{weight}$
- Volume of distribution is an apparent volume that enables calculation of a starting dose for a drug
- Varies for different drugs based on their properties
 - Tends to be smaller for drugs that bind to plasma proteins; hydrophilic
 - greater concentration appears in plasma
 - Tends to be larger for drugs that distribute to tissues/taken up by cells; lipophilic