Pharmacokinetics 1

MEDEMIA ACADEMY

Principles of Drug Therapy

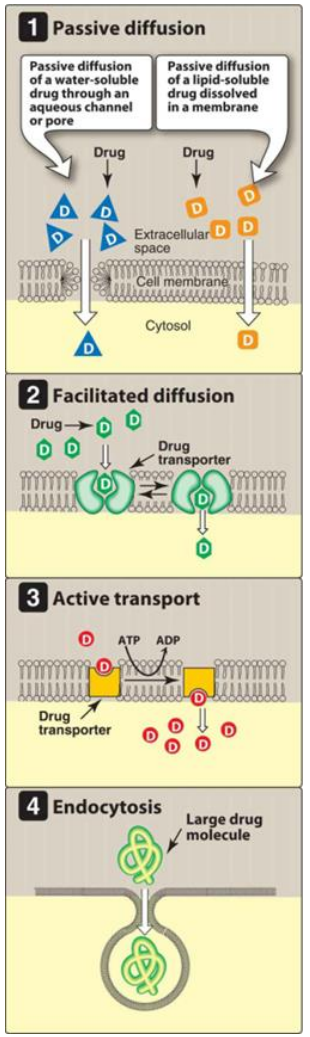
Pharmacokinetics	Pharmacodynamics
↓	↓
The effects of the body on the drug	The effects of the drug on the body
↓	↓
Absorption → **D**istribution → **M**etabolism → **E**limination	• Drug mechanism of action • Drug pharmacologic action • Adverse effects of drugs

Absorption

❖**Definition**: Passage of drug from site of administration to systemic circulation

❖**Mechanisms of absorption of drugs (from the GI tract)**

Passive diffusion	• Rapid movement of lipid soluble drugs across the cell membrane. • Movement of the water soluble drugs across the aqueous channels (water pores). • No energy needed and with concentration gradient.
Facilitated diffusion	• The drugs are carried into inside the cell by carrier or transporter • No energy is required and according to the concentration gradient
Active transport	• The drug movement may be against the concentration gradient by drug carrier or transporter. • Energy is required
Endocytosis	Drugs of high molecular weight, the drug binds to the cell membrane, dips in and enveloped by the cell membrane



Factors influencing absorption – Patient factors

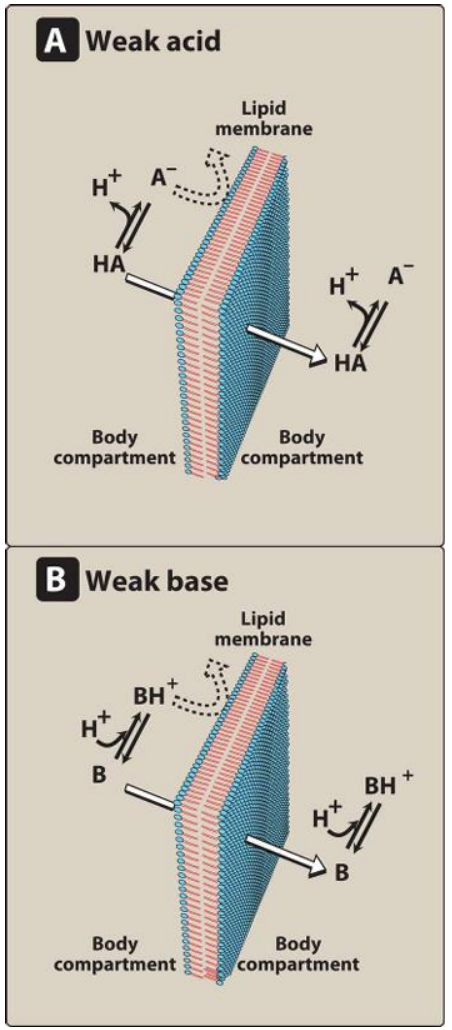
Route of Administration	I.V. and inhalation (Faster) > I.M. > S.C. > Oral >Topical (slower)
Absorbing surface	• **Vascularity**: (Alveoli > S.C. tissue) • **Surface area**: (Alveoli > Intestine > Stomach) • **Pathological conditions**: Diarrhea decrease oral absorption
Systemic circulation	Shock decrease absorption thus oral and subcutaneous routes are not suitable
Specific factors	Intrinsic factor is essential for vitamin B12 absorption
Co-administration of other drugs and/or food	• S.C. adrenaline (added to local anesthetics) → V.C. absorption of local anesthetics → longer duration of action of local anesthetics • Ca^{+2} (e.g. in milk) ↓ the oral absorption of tetracyclines (antibiotics)

Factors influencing absorption – Drug factors

Water and lipid solubility	• Completely water-soluble compounds are not absorbed (e.g. barium chloride). • Increase lipid solubility lead to increase absorption (lipid/water partition coefficient)
Pharmaceutical preparation	• Dosage form: Solution > Suspension > tablet • Shape, size of particles and rate of dissolution of tablets • Excipient (filler) containing Ca+2 decreases oral absorption of tetracyclines
Ionization of the drug	• Ionization decreases lipid solubility and absorption of drugs • Non-ionized (uncharged) → better absorption • Depends on pKa of the drug and pH of the medium • Quaternary ammonium compounds → ionized poor absorption • Streptomycin has high pKa → always ionized not absorbed orally

The effect of pH on drug absorption

- **When drugs bind hydrogen (low pH)**
  - Weak acids become unionized ($A^- + H^+ = HA$)
  - Weak bases become ionized ($B + H^+ = BH^+$)
- **Thus**
  - At low pH weak acids become unionized while the weak bases become ionized
  - At high pH weak base drugs become unionized while weak acids become ionized
- **Accordingly**
  - Weak acid are more absorbed in acidic media
  - Weak bases are more absorbed in alkaline media

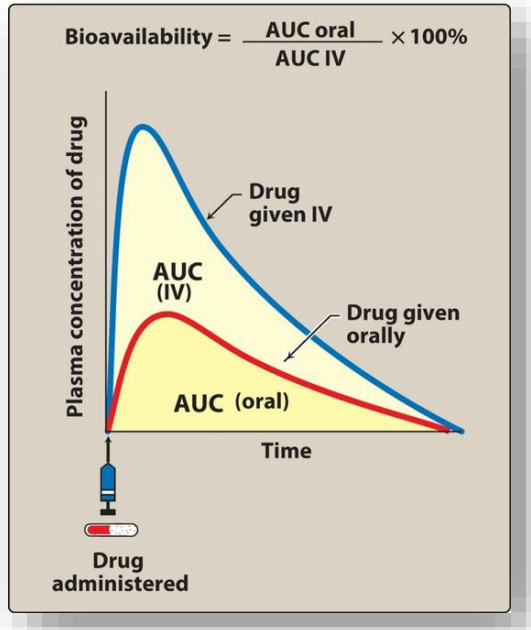


pKa

- **pKa** is the pH at which the concentrations of the ionized and unionized forms of the drug are equal (Each drug has its own pKa)
- **Clinical importance of pKa**
  - **GIT**: Aspirin (acidic drug) has low pKa
    - Drug molecules become unionized in the empty stomach (low pH) and can enter gastric mucosal cells. In gastric mucosal cells (high pH) aspirin becomes ionized and trapped in gastric mucosal cell “peptic ulceration”
  - **Kidney**:
    - **In drug poisoning** renal elimination could be enhanced by changing urinary pH to increase ionization of drug and inhibit tubular reabsorption of the drug
    - **Alkalinization of urine** by sodium bicarbonate (to increase urine pH above drug pKa) is useful in acidic drug poisoning e.g. Aspirin and phenobarbital
    - **Acidification of urine** by ascorbic acid (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine

Bioavailability

- **Definition**: the percentage of drug that reaches the systemic circulation and becomes available for biological effect
- **Bioavailability** = $\frac{Area\ under\ the\ curve\ (AUC)\ after\ oral\ route}{Area\ under\ the\ curve\ (AUC)\ after\ IV\ route} \times 100$
- **Factors affecting bioavailability**
  1. The extent of drug absorption
  2. 1st pass effect (1st pass metabolism)



1st pass metabolism

- **Definition**: the metabolism of some drugs in a single passage through gut wall, liver or lungs before reaching systemic circulation
- **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
- **Intestinal 1st pass effect**
  - Estrogens are extensively metabolized in their 1st pass through intestinal wall
- **Pulmonary metabolism**
  - After inhalation, nicotine is partially metabolized in the lung