Pharmacokinetics

- Pharmacokinetics focuses on what the body does to drugs after they are administered.
- What the body does to drugs
- Pharmaco means “medicines.”
- Kinetics means “movement.”

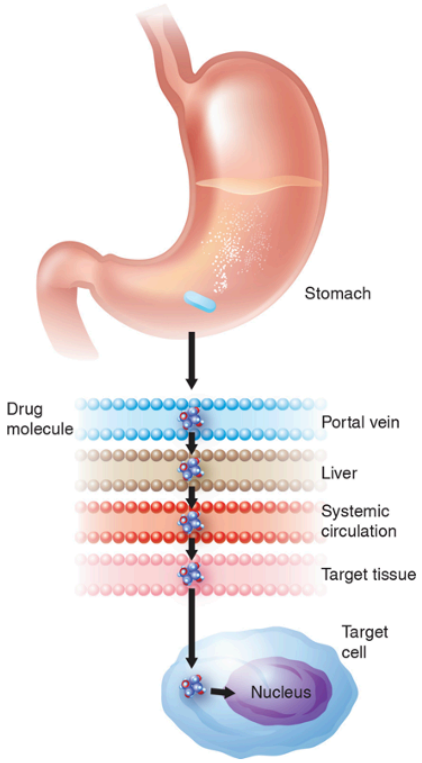
Barriers to drugs attempting to reach target cells

- Many membranes
- Physiological processes

Processes of pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion

Figure 3.1



Barriers that a drug administered by the oral route must cross before interacting with a target cell.

Drugs use diffusion and active transport to cross plasma membranes to reach their target cells.

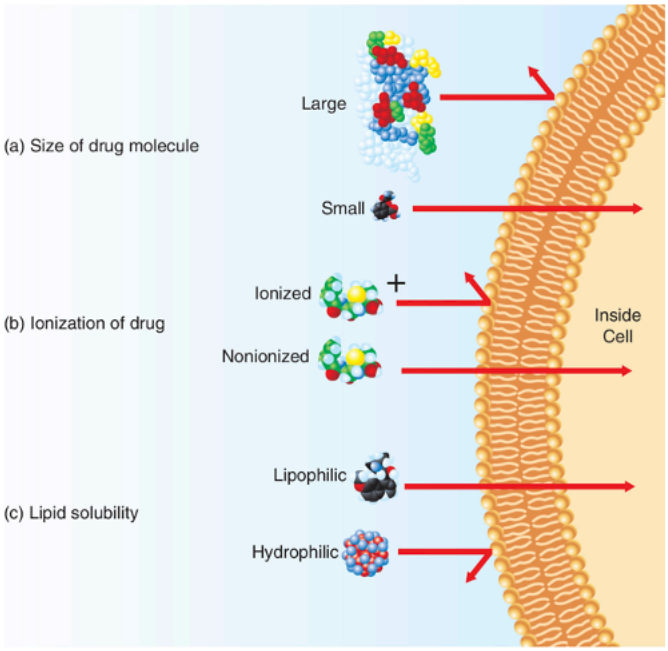
Diffusion

- Simple diffusion or passive transport
- Movement of a chemical from an area of higher concentration to an area of lower concentration
- Assumes chemical is able to cross plasma membrane freely
    - Not the case for all drugs

Factors affecting movement across plasma membranes

- Size of drug molecule
- Ionization of molecule
- Lipid solubility

Figure 3.3



Passage of drugs across plasma membranes: (a) Small drugs, (b) nonionized drugs, and (c) lipophilic

Facilitated diffusion

- Utilizes carrier proteins to cross membranes.
- Does not require energy from cell.
- Active transport pumps require cell energy.

Primary Processes of Pharmacokinetics

Absorption is the process of moving a drug from the site of administration to the bloodstream.

Absorption

- Movement from site of administration to bloodstream
- Primary factor for determining onset of drug action

Route of administration

- One of the most important variables affecting absorption
- Enteral route (GI tract)
    - First-pass effect
        - Drugs absorbed from the stomach and small intestine travel to liver, where they may be inactivated before reaching target organ(s)
- Topical route
    - Applied to skin, mucous membranes
    - Local effects
    - Some given for slow release
        - Systemic effects
    - Transdermal patches

        - Specified amount of medication
        - Rate of delivery can vary
    - Vaginal route
        - Local conditions or birth control
    - Rectal route
        - Local or systemic
- Parenteral route
    - Intradermal and subcutaneous administration
        - Major difference is depth of injection.
        - Dermis contains more blood vessels.
        - Subcutaneous route delivers drugs to deepest layers of skin.
            - Insulin, heparin, vitamins, vaccines
    - Intramuscular administration
        - Drugs directly into large muscles
        - Tissue can receive larger volume of drug
        - More rapid onset of action
    - Intravenous administration
        - Directly to bloodstream
        - Fastest onset but also most dangerous

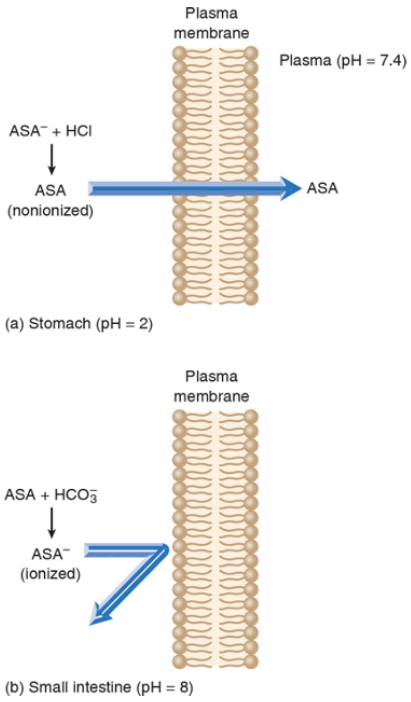
Drug concentration and dose
- Higher doses produce faster, greater response for most drugs
- Greater concentration gradient for diffusion

GI tract environment
- Most absorption in small intestine
- Digestive motility variable among patients
- Presence of food in stomach slows absorption
    - Few exceptions

Blood flow to the absorption site
- Drugs absorbed faster from areas of body where blood flow is high.
    - Diminished blood flow during heart failure or shock
- Blood flow can purposely be manipulated to slow absorption.
    - Vasoconstrictors
    - Ice packs

Drug ionization
- Depending on pH of surrounding fluid, most drugs in either charged or uncharged state
    - Acids are absorbed in acids because they are nonionized.
    - Bases are absorbed in bases because they are nonionized.

Figure 3.4



Effect of pH on drug absorption: (a) A weak acid such as aspirin (ASA) is in a nonionized form in an acidic environment and absorption occurs. (b) In a basic environment, aspirin is mostly in an ionized form and absorption is prevented.

Drug interactions
- Drug–drug and food–drug
- Can affect absorption
- High-fat meals slow stomach motility.

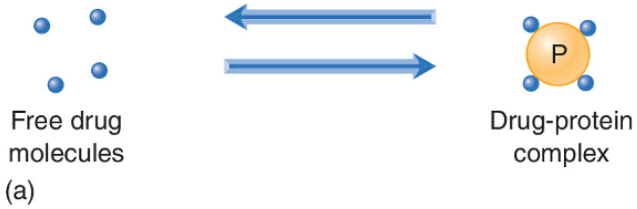
Surface area
- Drugs absorbed faster when applied to regions with a larger surface area.
  - Such as small intestine, lung

Distribution describes how drugs are transported throughout the body.

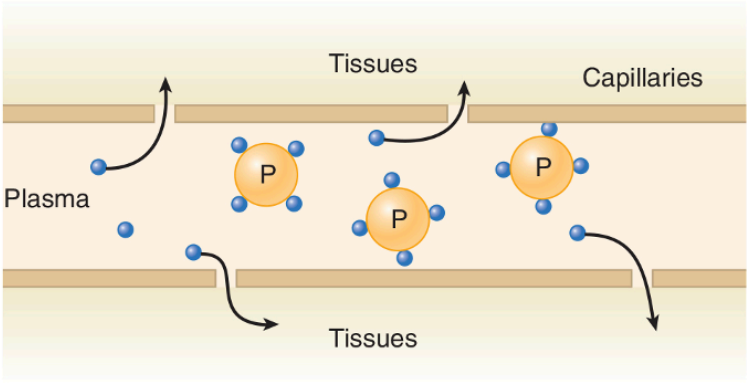
Distribution
- Transportation of drugs throughout body

Factors affecting distribution
- Blood flow to tissues
- Drug solubility
- Tissue storage
- Drug-protein binding

Figure 3.5



(a)



(b)

Plasma-protein binding and drug availability: (a) The drug exists in a free state or is bound to plasma protein. (b) Drug-protein complexes are too large to cross membranes.

Special barriers to drug distribution

- Blood–brain barrier
  - Possess special anatomic barriers
  - Protects brain from pathogens and toxins
  - Lipid-soluble drugs able to cross
  - Not fully developed in neonates
  - Inflammation can increase permeability.
- Fetal–placental barrier
  - Prevents harmful substances from passing from mother's blood stream to fetus
  - Inefficient
    - Substances such as alcohol, cocaine, caffeine, prescriptions can cross
- Question women of childbearing age prior to prescribing a drug.

Metabolism is a process that changes the activity of a drug and makes it more likely to be excreted.

Metabolism

- Alters structure and function of drugs, nutrients, vitamins, and minerals
- Primary site is liver.
- Changes to drug structure allow for excretion.
- Functional changes alter pharmacological activity.
- Metabolites may be more toxic.

Prodrugs

- Medications that require metabolism to produce therapeutic actions

- Have no pharmacological activity

Hepatic microsomal enzymes

- Cytochrome P450 (CYP450)
  - An enzyme that metabolizes many drugs
- Many isoenzyme systems within CYP
  - Determine speed at which drug is metabolized
  - Contribute largely to drug–drug interactions

CYP systems

- Drugs as substrates
  - Drugs metabolized by a CYP450 enzyme
- Drugs as enzyme inhibitors
  - Drug inhibits action of CYP450 isoenzymes.
  - Can contribute to toxic drug levels
- Drugs as enzyme inducers
  - Accelerate metabolism of specific isoenzymes
  - Drug level may decrease more rapidly.

Excretion processes remove drugs from the body.

- Rate of excretion determines drug blood level.
- Renal excretion
  - Primary site is kidney.
  - Some drugs undergo reabsorption after renal filtration
  - Drug excretion dependent on urine pH
  - Can manipulate pH of kidney filtrate
  - Dose reduction indicated in renal impairment
- Pulmonary excretion
  - Gases and volatile liquids
  - Most excreted unmetabolized
  - Respiratory rate and blood flow affect excretion.
- Glandular secretion
  - Saliva, sweat, breast milk
  - Taste and smell some drugs
  - Excretion of some drugs in breast milk.
- Fecal and biliary excretion
  - Feces, bile
  - Enterohepatic recirculation
    - May recirculate drugs, metabolites, and prolong action

Time–Response Relationships

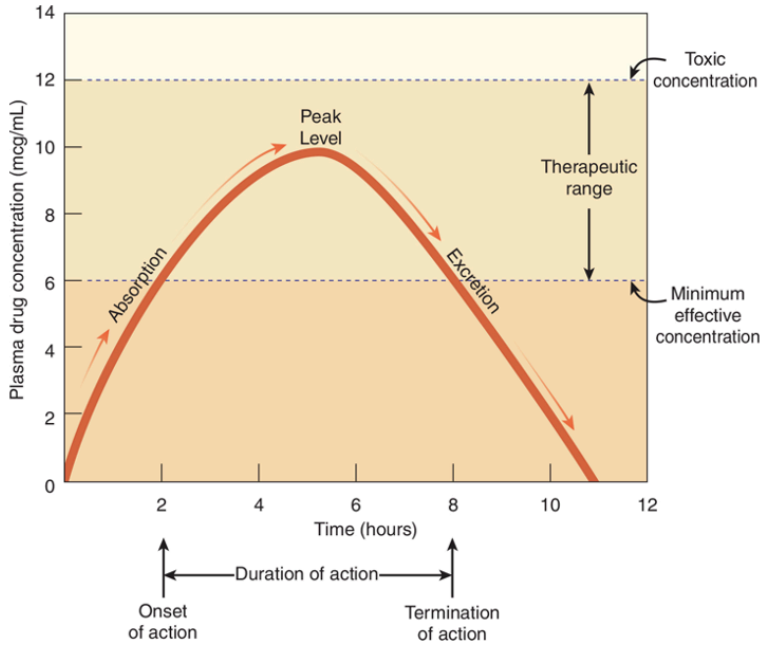
- The drug half-life estimates the duration of action for most medications**.**

Drug half-life

- Provides estimate of duration of action
- Plasma half-life ($t_{1/2}$)
  - Plasma concentration decreases by half.
  - Short half-life
    - Drug given more frequently
  - Long half-life
    - Drug given less frequently

- Approximately four half-lives until excretion

Figure 3.7

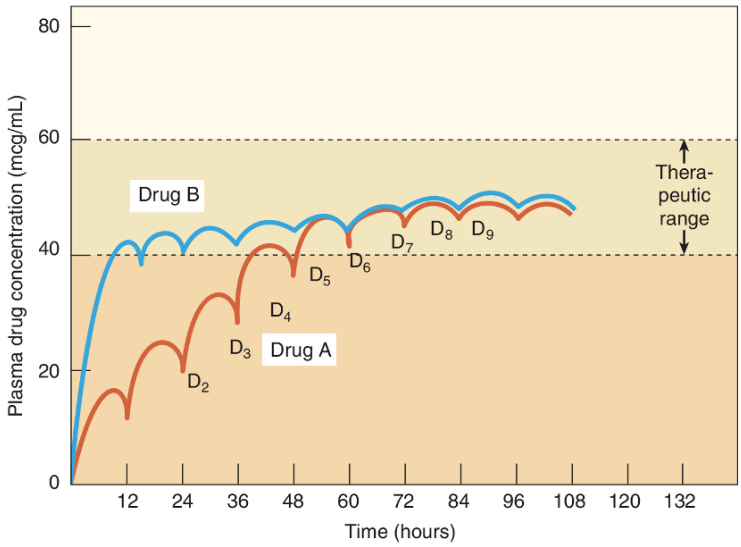


Single-dose drug administration. Pharmacokinetic values for this drug are as follows: onset of action = 2 hours; duration of action = 6 hours; termination of action = 8 hours after administration; peak plasma concentration = 10 mcg/mL; time to peak drug effect = 5 hours; $t_{1/2}$= 4 hours.

Time–Response Relationships

- Repeated dosing allows a plateau drug plasma level to be reached.

Figure 3.8



Multiple-dose drug administration. Drug A and drug B are administered every 12 hours. Drug B reaches the therapeutic range faster, because the first dose is a loading dose.