BASIC PRINCIPLES IN PHARMACOLOGY

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PHARMACOLOGY

Pharmacology: is the study of drugs, their uses and how they affect organisms

- **Pharmacokinetics:** describes what the body does to a drug.

- **Pharmacodynamics:** describes what the drug does to the body.

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PHARMACOKINETICS

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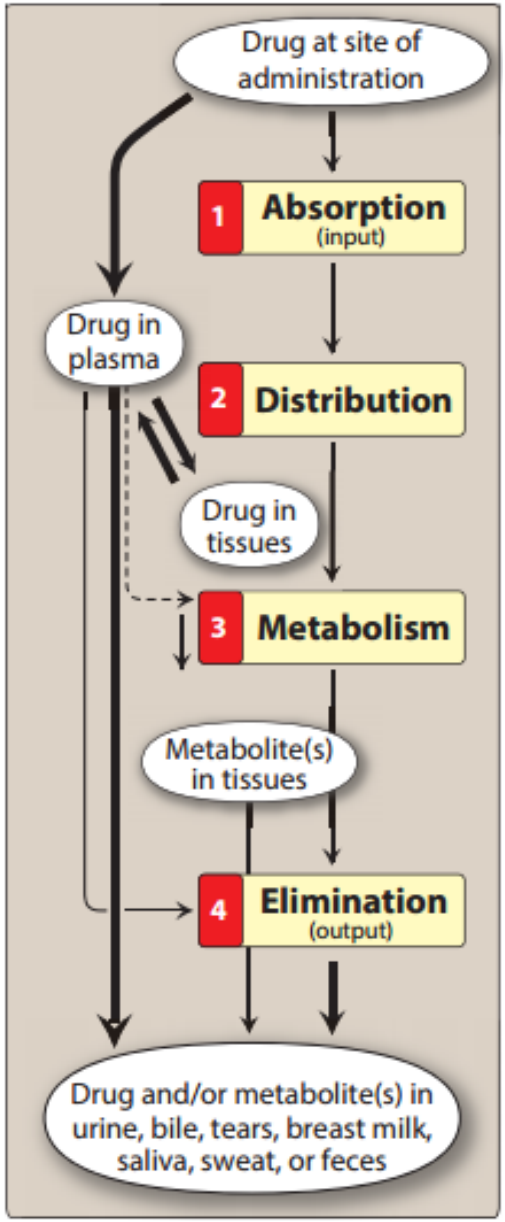
PHARMACOKINETICS

ADME

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

ADME determine:

- The speed of onset of drug action
- The intensity of the drug effect
- The duration of drug action



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ADME

Absorption: The drug absorption from the site of administration which permits the entry of the therapeutic agent into the plasma

Distribution: Reversible process, the drug leaves the bloodstream and distributes into the interstitial and intracellular fluids

Metabolism: Biotransformation of the drug into metabolites by the liver or other tissues

Elimination: The drug and its metabolites are eliminated into urine, bile or feces

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ROUTES OF DRUG ADMINISTRATION

Enteral

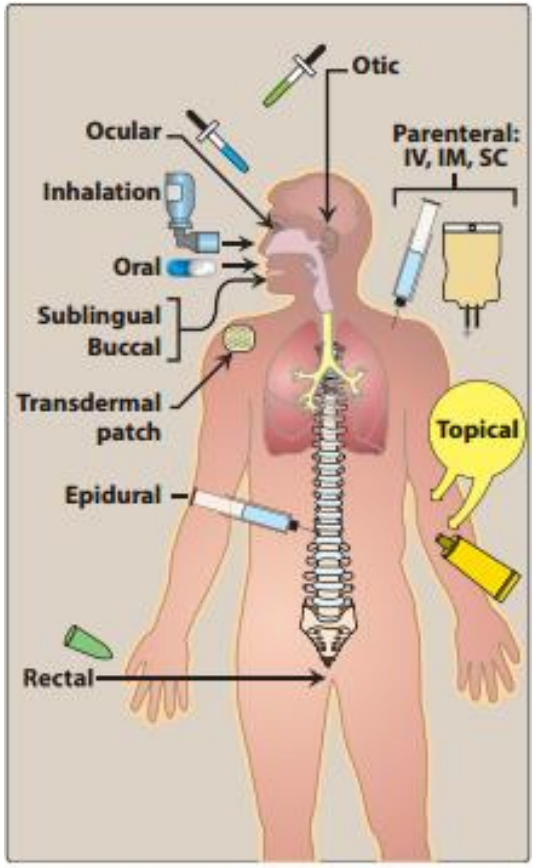
- Oral
- Sublingual

Parenteral

- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous (SC)

Other routes

- Inhalation
- Intrathecal/Intraventricular
- Topical
- Transdermal
- Rectal



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ROUTES OF ADMINISTRATION

Determined by

- Properties of the drug
  - Water or lipid solubility
  - Ionization

- Therapeutic objective
  - Rapid onset
  - Prolonged effect
  - Local effect

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ENTERAL ROUTE

Oral administration:

- Advantages
  - Easily self-administered
  - Low risk of systemic infections (compared to parenteral)
  - Easier to manage toxicity
- Disadvantages
  - Inactivation of drugs due to first pass effect or stomach acidity
- Enteric coated
  - To protect the stomach (e.g. Aspirin)
  - To protect the drug from stomach acidity
- Extended release
  - To control how fast the drug is released from the pill to the body

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ENTERAL ROUTE

Sublingual: Drug diffuses into the capillary network to the systemic circulation

- Advantages
  - Rapid absorption
  - Convenience
  - Low incidence of infection
  - Bypass GI
  - Bypass first pass effect

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PARENTERAL ROUTE

Direct administration of the drug across body barriers into the systemic circulation

- Used for: 1. Drugs with poor GI absorption (e.g. heparin)
  2. Drugs unstable in GI (e.g. insulin)
  3. Unconscious patients
  4. Rapid onset of action
  5. High bioavailability
- Advantage: no first pass metabolism
- Disadvantages: Risk of infection
- Can be irreversible

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PARENTERAL ROUTES

Intravenous (IV)

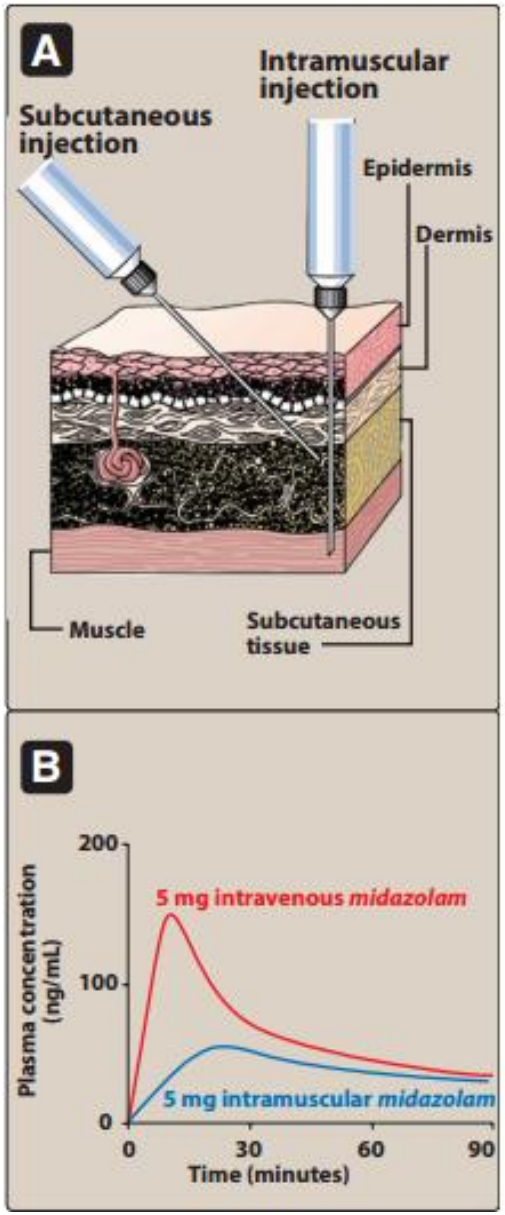
- Bolus: Immediate delivery of full amount
- Infusion: Delivery over a longer time

Intramuscular

- Aqueous solution (Rapid absorption)
- Depot preparation in nonaqueous vehicle

Subcutaneous

- Less risk of hemolysis
- May provide sustained slow effect



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ADDITIONAL ROUTES

Inhalation

- Oral or nasal
- Rapid delivery across the large surface area of mucous membranes

Intrathecal/intraventricular

- Direct injection into the cerebrospinal fluid
- Rapid delivery
- To avoid the blood brain barrier

Topical: application

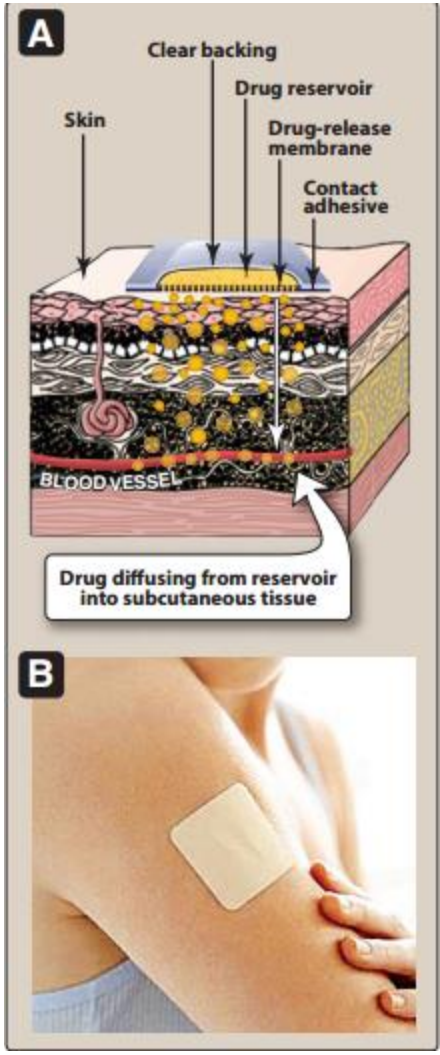
- Skin, for local effect.

Transdermal

- Sustained delivery of drugs (e.g. nicotine patches)

Rectal

- Avoids first pass metabolism
- Rapid delivery
- Used when oral administration is not possible (antiemetics)



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DRUG ABSORPTION

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ABSORPTION OF DRUGS

Absorption is the transfer of a drug from the site of administration to the bloodstream via one of several mechanisms

Rate and efficiency of absorption of a drug depend on:

- The environment where the drug is absorbed
- Chemical characteristics of the drug
- Route of administration

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Absorption Rate: how rapidly does the drug get from its site of administration to the general circulation ?

Absorption Extent: How much of the administered dose enters the general circulation ? (% bioavailability = F)

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BIOAVAILABILITY

Bioavailability: The fraction of administered drug that reaches the systemic circulation

Example 100 mg of a drug were administered orally, 70 mg of the drug were absorbed unchanged.

- The bioavailability of this drug is 0.7 or 70%

For IV drugs, absorption is complete

- (100% bioavailability)

Drug administration by other routes may result in partial absorption and lower bioavailability

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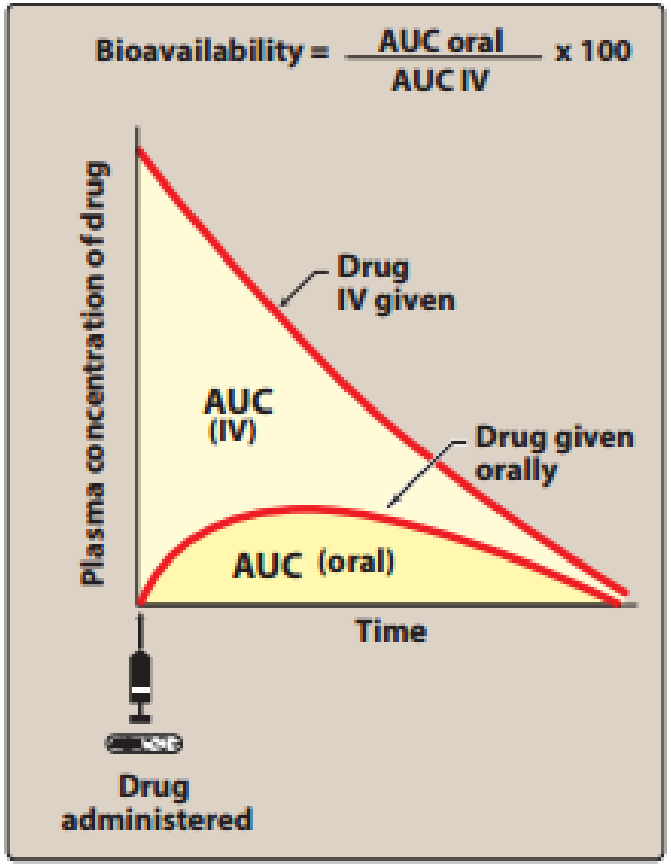
BIOAVAILABILITY



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Factors that influence oral bioavailability

- First-pass hepatic metabolism
- (Metabolism by liver enzymes prior to reaching the systemic circulation)
- Nature of the drug formulation
- Solubility of the drug
- Chemical instability
- Decomposition in acidic gastric juices
- Decomposition by hydrolytic gut enzymes (eg, proteases, lipases)
- Degradation by gut microorganisms
- Food in the gut may alter absorption rate and amount (eg. interact or form a complex)
- Metabolism by gut wall enzymes

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FIRST-PASS METABOLISM

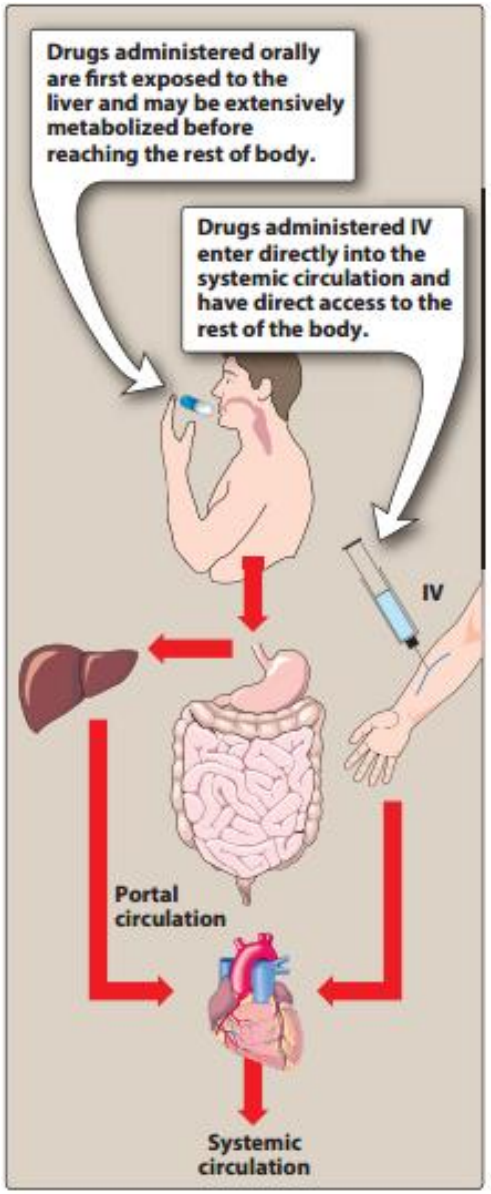
When an oral drug is absorbed across the GI tract, it first enters the portal circulation before the systemic circulation

If the drug is rapidly metabolized, less of the active ingredient will reach the systemic circulation

Example: nitroglycerine

(90% is cleared through passage through the liver)

- It is Given sublingually



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Solubility of the drug

- Very hydrophilic drugs can not cross lipid-rich cell membranes, and so they are poorly absorbed
- Extremely hydrophobic drugs are poorly absorbed because they're insoluble in aqueous body fluids
- For good absorption the drug needs to be hydrophobic with some water solubility
- Most drugs are weak acids or bases

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Chemical instability

- Insulin is destroyed in the stomach by degradative enzymes
- Penicillin G. is instable in gastric pH

Nature of the drug formulation

- Presence of excipients alter the rate of absorption

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MECHANISMS OF DRUG ABSORPTION FROM GI TRACT

Passive diffusion:

Facilitated diffusion

Active transport

Endocytosis and exocytosis

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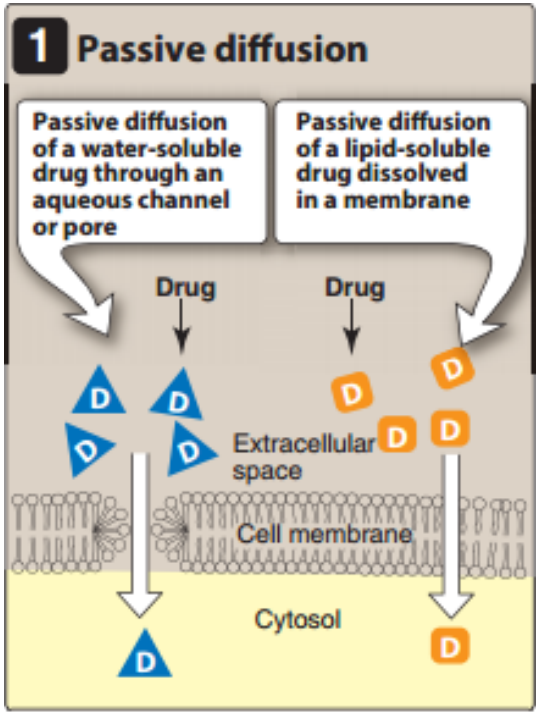
PASSIVE DIFFUSION

Movement of drug molecules across membranes from a region of high concentration to a region of lower concentration

Most drugs are absorbed through this mechanism

No carrier involved

Non saturable



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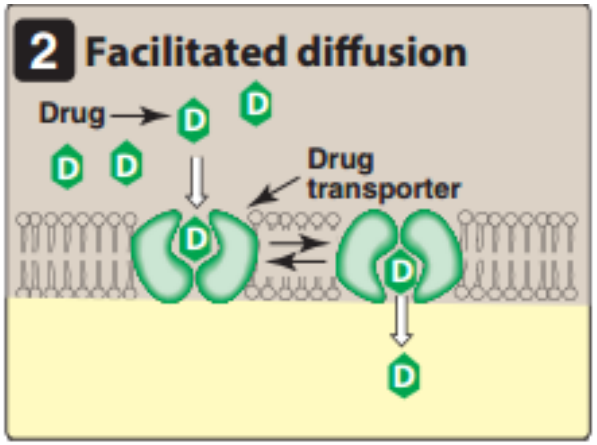
FACILITATED DIFFUSION

- Entry to the cell through specialized transmembrane carrier proteins
- Movement occurs from the area of the high concentration to the area of low concentration
- Does not require energy
- Can be saturated and inhibited by compounds that compete for the carrier



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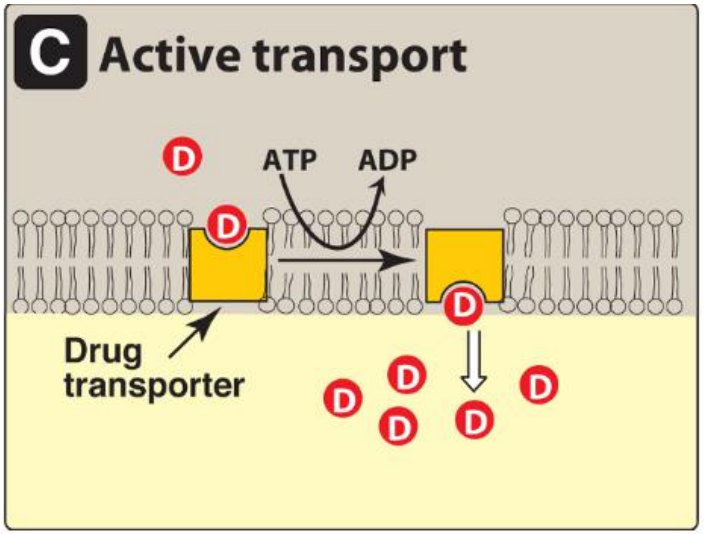
ACTIVE TRANSPORT



- Involves specific carrier proteins
- Requires energy
- Moves the drugs against the concentration gradient
  (from low concentration to high concentration regions)
- Selective
- Saturable, can be inhibited by cotransported substances

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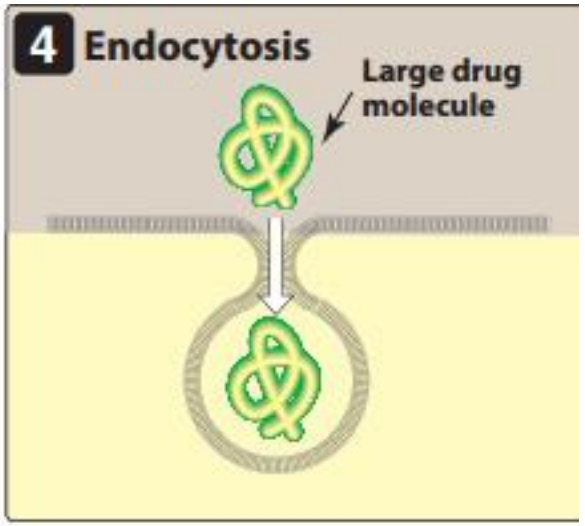
ENDOCYTOSIS AND EXOCYTOSIS

- Transport of exceptionally large drugs
- Endocytosis: engulfment of a molecule by the cell membrane
- Exocytosis: the reverse process that leads to the release of molecules
- Example: Vitamin B12 transport across the gut wall by endocytosis



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FACTORS INFLUENCING ABSORPTION

1. pH

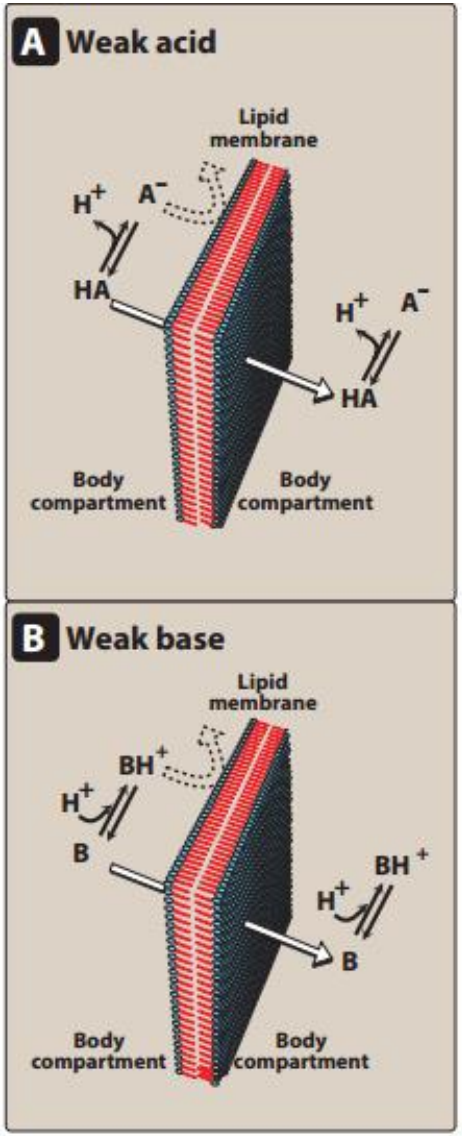
- Most drugs are weak acids or weak bases

$HA \rightleftharpoons H^+ + A^-$

$BH^+ \rightleftharpoons B + H^+$

- Drugs pass through membranes easier when uncharged

- $pH < pK_a$ protonated form predominates
- $pH > pK_a$ deprotonated form predominates



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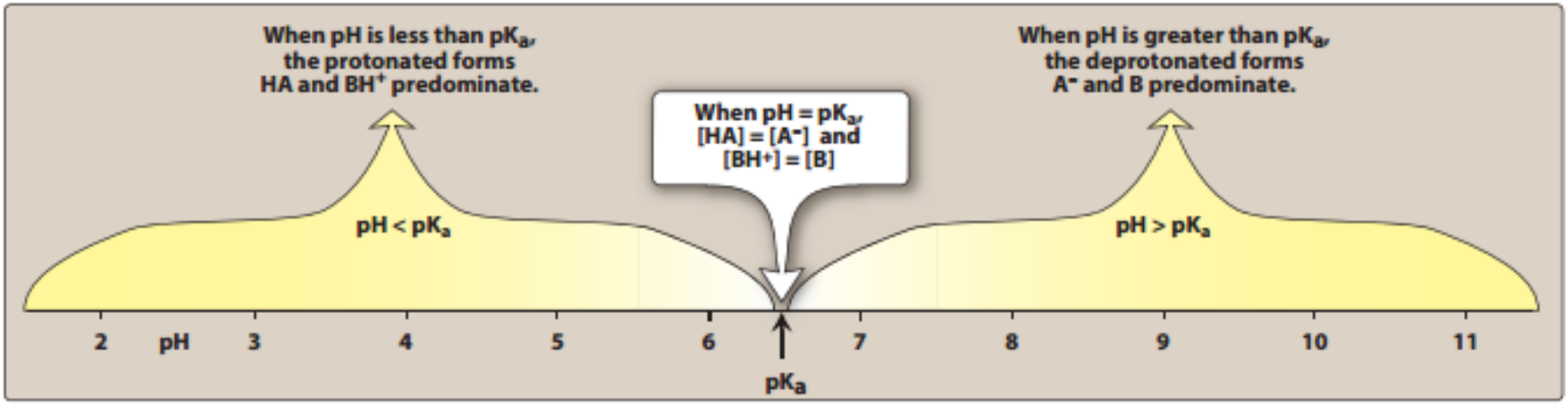

Figure 1.8

The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

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FACTORS INFLUENCING ABSORPTION

2. Blood flow to the absorption site
   - Because blood flow is much greater in the intestines than the stomach, absorption is greater in the intestines.

3. Total surface area available for absorption
   - Intestines have large surface area

4. Contact time at the absorption surface
   - Absorption is affected by changes in gastric motility (e.g. diarrhea)

5. Expression of P-glycoprotein
   - Drug transporter (reduces absorption)
   - In liver, kidney, brain, intestines

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P-GLYCOPROTEINS (P-GP)

It is expressed throughout the body, and its functions include:

- In the liver: transporting drugs into bile for elimination
- In kidneys: pumping drugs into urine for excretion
- In the placenta: transporting drugs back into maternal blood, thereby reducing fetal exposure to drugs
- In the intestines: transporting drugs into the intestinal lumen and reducing drug absorption into the blood
- In the brain capillaries: pumping drugs back into blood, limiting drug access to the brain

High expression of p-gp reduces absorption

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Bioequivalence

Two related drug preparations are bioequivalent if they show

- Comparable bioavailability
- Similar times to achieve peak blood concentrations.

Therapeutic equivalence

Two similar drug products are therapeutically equal if they are pharmaceutically equivalent with similar clinical and safety profiles

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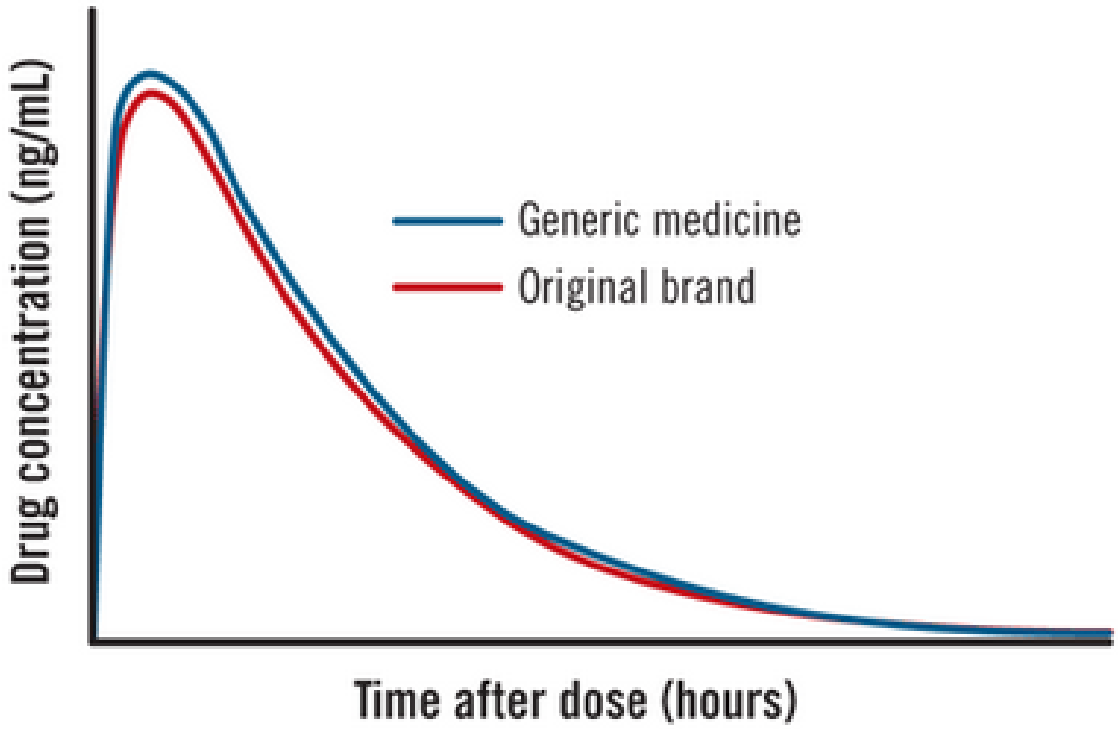
FIGURE

Bioequivalence analysis: *a hypothetical bioequivalence study*[6]



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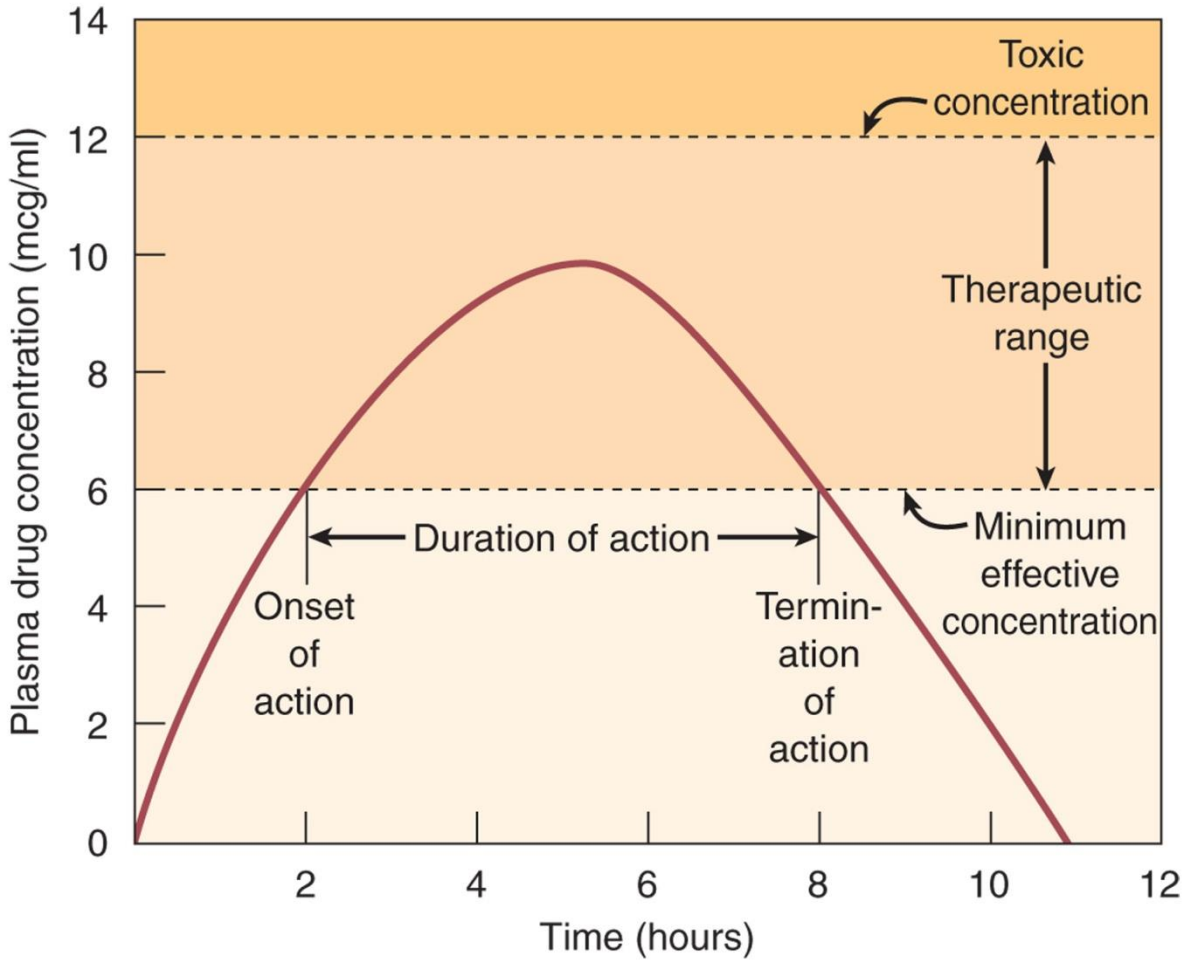

Adams et al. 2008

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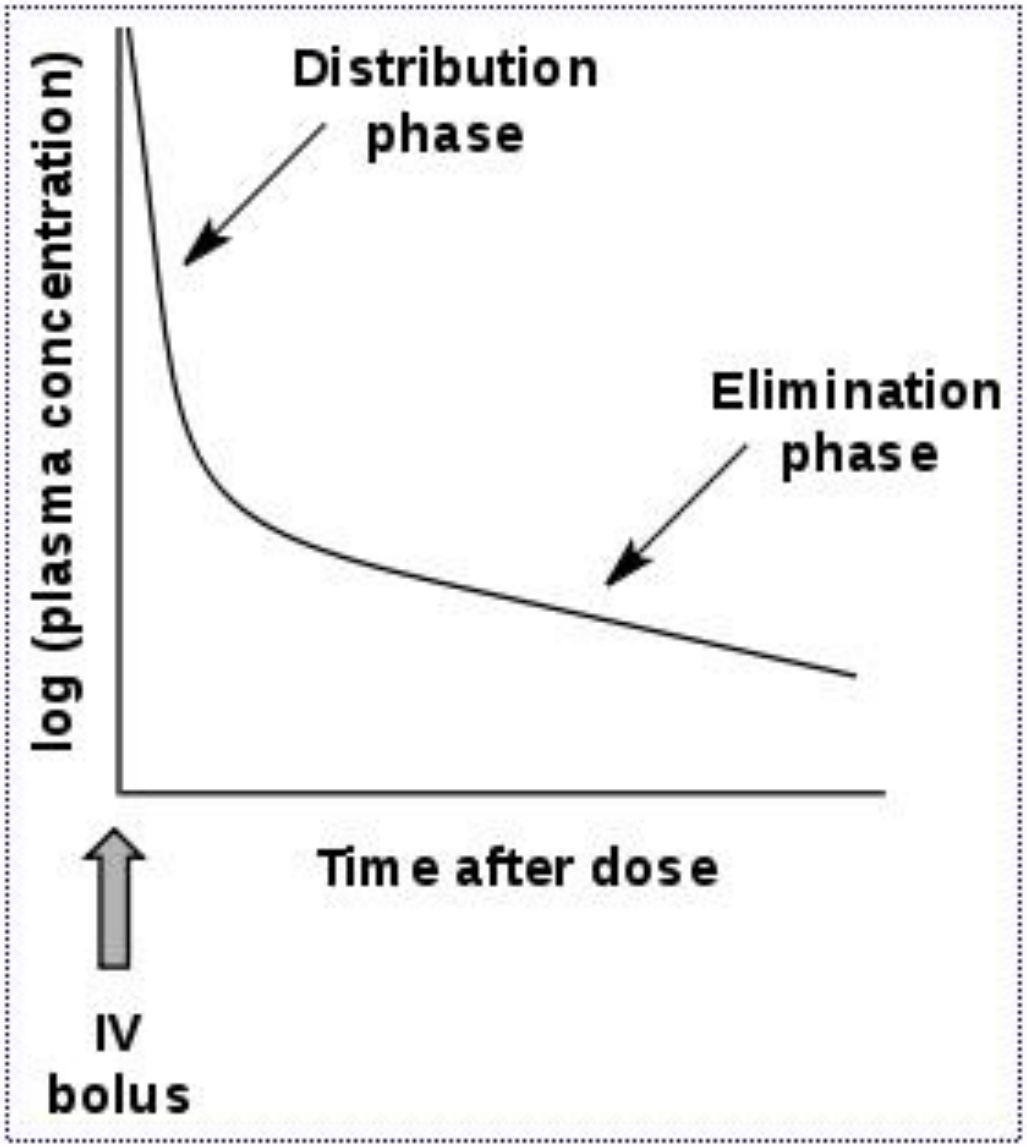

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DRUG DISTRIBUTION

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Distribution: the process by which a drug reversibly leaves the blood stream and enters the interstitium and then cells

For an IV drug; No absorption occurs

Distribution occurs immediately after administration

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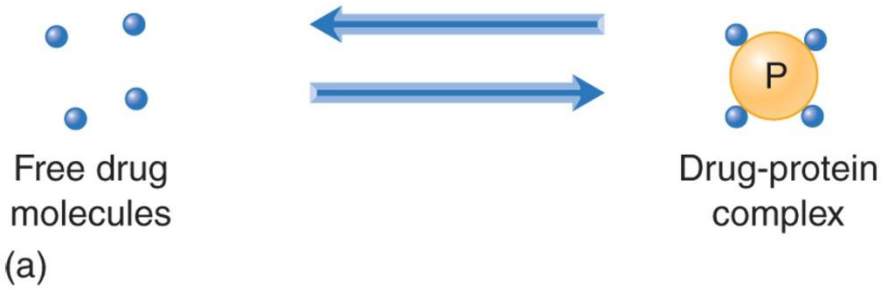
DRUG DISTRIBUTION

Distribution depends on

1. Cardiac output and regional blood flow
2. Capillary permeability
3. Tissue volume
4. Drug-protein binding in plasma and tissues
5. Hydrophobicity of the drug



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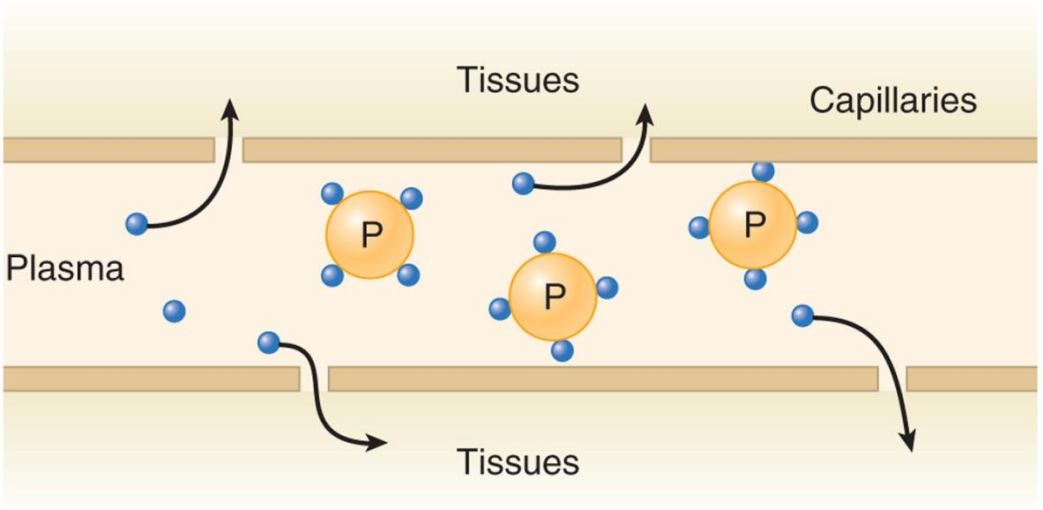

(b)

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1. BLOOD FLOW

Due to unequal distribution of cardiac output, the rate of blood flow to tissue capillaries is variable

Blood flow to the brain, liver and kidney is greater than that to skeletal muscles

Adipose tissue, skin and viscera have lower rates of blood flow

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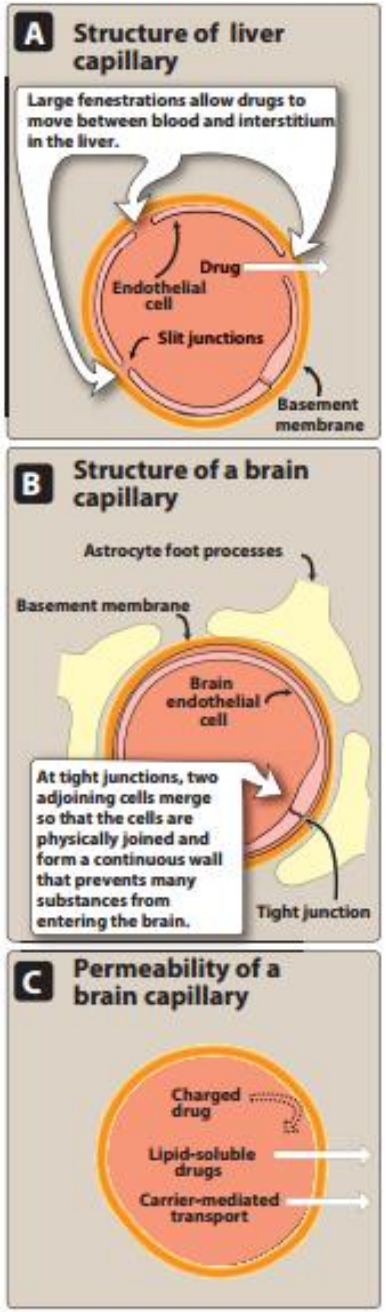
2. CAPILLARY PERMEABILITY

Depends on

- Capillary structure
- Chemical nature of the drug



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DRUG-PROTEIN BINDING

Binding to plasma proteins

Protein bound drug ⇌ Free drug → Distribution, Metabolism, Excretion

- Albumin

Binding to tissue proteins

- Drugs can accumulate in tissues due to tissue protein binding extending their effects or causing local toxicity

Hydrophobicity

- Hydrophobic drugs cross cell membranes
- Hydrophilic drugs need to pass through the slit junction

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VOLUME OF DISTRIBUTION

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Vd: Apparent volume of distribution

C0:Plasma concentration at time zero

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- Vd has no physiologic basis

  It can be used to compare the distribution of a drug in the water compartments of the body

  - Plasma (4L)

large molecular weight or highly protein bound drugs

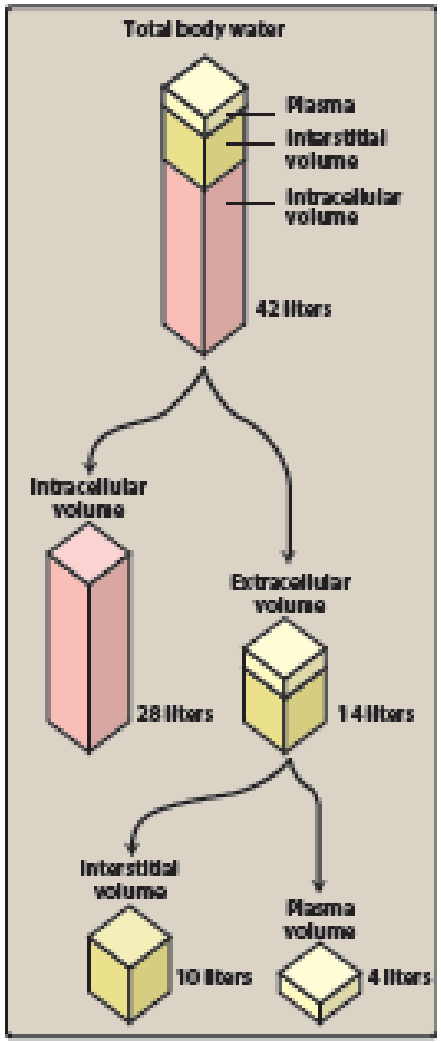
e.g. Heparin

  - Extracellular fluid (14L)

Low molecular weight but hydrophilic and can not cross cell membranes

  - Total body water (42 L)

Low molecular weight and hydrophobic



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Apparent volume of distribution (Vd)

- A drug rarely associates with one water compartment
- Usually drugs are bound to cellular compartments like
  - Proteins in plasma and cells
  - Lipids in adipocytes and cell membranes
  - Nucleic acids in nuclei of cells

Vd is useful for calculating the loading dose of a drug

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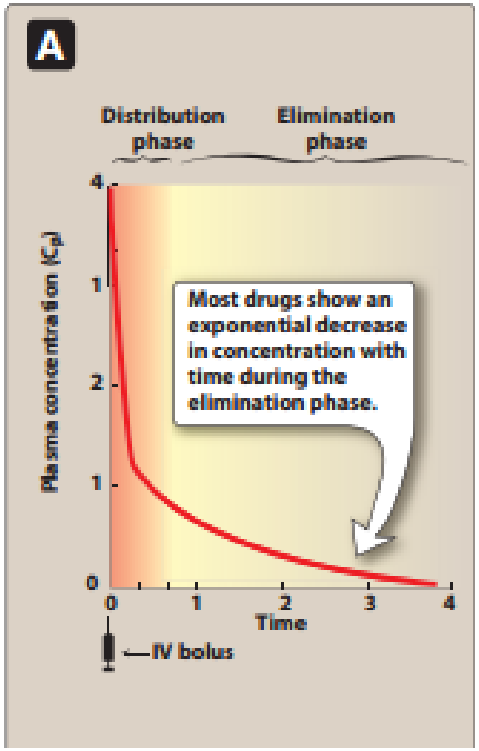
Example:

If 10 mg of a drug are injected and the plasma concentration is 1 mg/L what is Vd?

$$Vd = \frac{Dose}{C_0} = \frac{10}{1} = 10\ L$$



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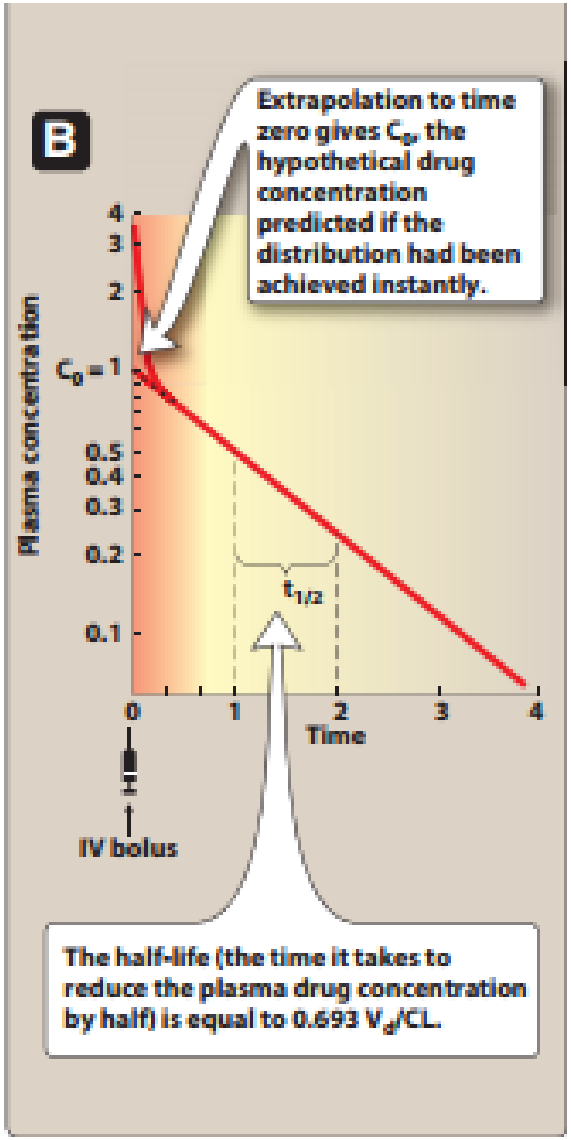
PLASMA HALF-LIFE ($T_{1/2}$) OF DRUGS

Length of time needed to decrease drug plasma concentration by one half

The greater the half-life of the drug, the longer it takes to excrete

Determines frequency and dosages



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Elimination depends on the amount of the drug delivered to the liver or the kidney per time unit

The greater the Vd the less drug that is available to the excretory organ

The greater the Vd the higher the half life of the drug, and the longer the duration of action

An exceptionally high Vd indicates the sequestration of the drug in tissues

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METABOLISM

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DRUG CLEARANCE THROUGH METABOLISM

Once the drug enters the body, elimination begins

Routes of elimination include:

1. Hepatic metabolism
2. Elimination in bile
3. Elimination in urine

Metabolism leads to products with increased polarity which allows drug elimination

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

- $CL = 0.693 \times Vd / t_{1/2}$

  $t_{1/2}$: elimination half life for the drug

  V_d: apparent volume of distribution

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METABOLISM KINETICS

1. First-order kinetics

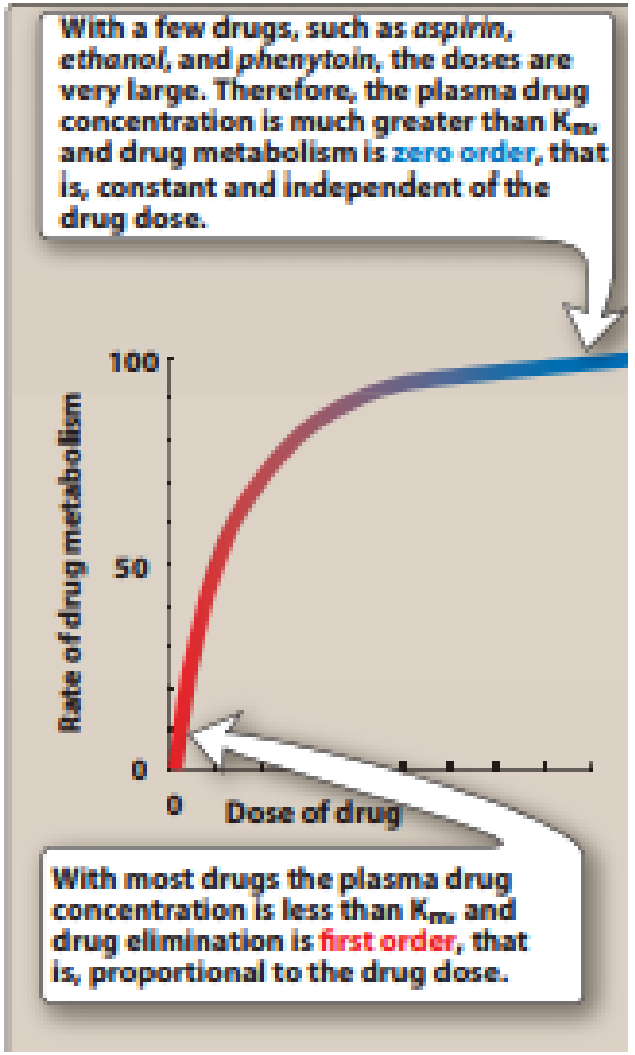
The rate of drug metabolism and elimination is directly proportional to the drug concentration

2. Zero-order kinetics

(nonlinear kinetics)

e.g. aspirin, ethanol, phenytoin

The rate of metabolism or elimination is constant and does not depend on drug concentration.



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Michaelis-Menten Enzyme Kinetics

$$V = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

- First-order kinetics (C is $<<<<K_m$)

$$V = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

- Zero-order kinetics ($C>>>>>K_m$)

$$V = \text{rate of drug metabolism} = V_{max}[C] = \frac{V_{max}}{[C]}$$

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REACTIONS OF DRUG METABOLISM

Kidney cannot efficiently eliminate lipophilic drugs as they get reabsorbed in distal convoluted tubules.

Lipid soluble agents must be metabolized into more polar (hydrophilic) substances in the liver

1. Phase I reactions

   Oxidation, Reduction, Hydrolysis

2. Phase II reactions

   Conjugation

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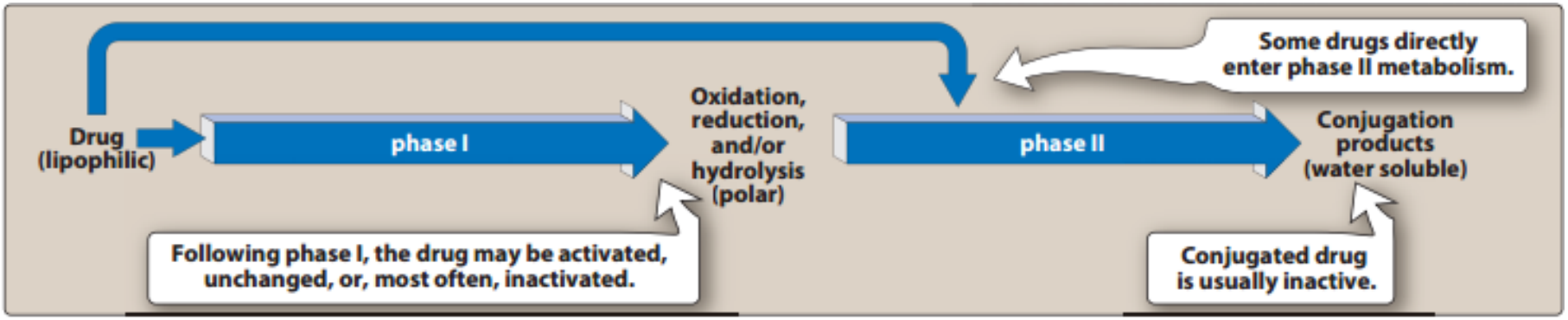

Not all drugs undergo Phase I and Phase II metabolism in that order, sometimes the order is reversed.

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PHASE I METABOLISM

Conversion of lipophilic molecules into more polar molecules by unmasking or adding a polar group like –OH or –NH2

- Involve P450 enzymes

(most frequent for Phase I drug metabolism)

- Not involving P450: e.g. Esterases and Hydrolysis

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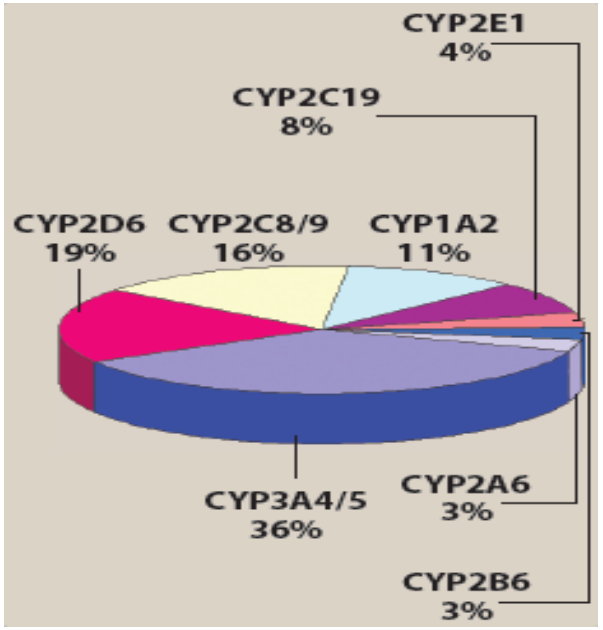
P450

Example: CYP3A4

Family — Isozyme

↓ Subfamily



Genetically variable

- Altered drug efficacy
- Altered toxicity risk
  - CYP2D6

Inducers (increase metabolism)

(Drug Interactions)

- Decrease plasma concentration
- Decrease therapeutic effect
- Decrease drug activity if metabolite is inactive
- Increase drug activity if metabolite is active

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	*Carbamazepine*
Cyclosporine	*Dexamethasone*
Erythromycin	*Phenobarbital*
Nifedipine	*Phenytoin*
Verapamil	*Rifampin*

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P450

Inhibitors:

- P450 inhibitors cause drug interactions
- Can cause adverse reactions
- Example: Grapefruit and its juice can inhibit CYP3A4 leading to increased levels of drugs metabolized by this enzyme causing higher therapeutic or toxic effects

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PHASE II METABOLISM

Conjugation reactions

If Phase I metabolite are still too lipophilic then they undergo conjugation reactions with endogenous substrates like:

- Glucuronic acid (most common)
- Sulfuric acid
- Acetic acid
- Amino acid

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EXCRETION

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DRUG EXCRETION BY THE KIDNEY

The most important route for drug removal from the body is through the kidney into the urine

Drugs need to be polar enough for efficient excretion

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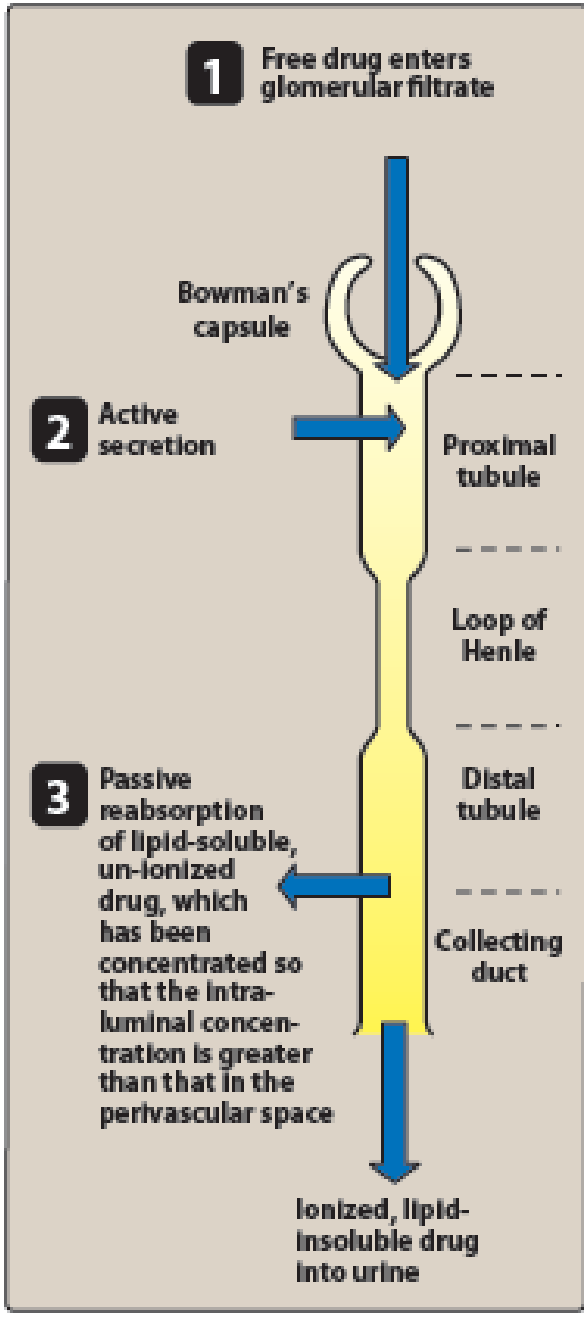
RENAL ELIMINATION

Elimination of drugs into the urine involves 3 processes:

1. Glomerular filtration
2. Proximal tubular secretion
3. Distal tubular reabsorption



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GLOMERULAR FILTRATION

Drugs enter the kidney through renal arteries which divide to form a glomerular capillary plexus

Free drug (non-protein bound) flows into Bowman's space as part of the glomerular filtrate

Glomerular filtration rate is 125mL/min

Lipid solubility and pH do not influence glomerular filtration rate

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PROXIMAL TUBULAR SECRETION

Secretion occurs in the proximal tubules by 2 energy requiring active transport systems

- One for anions (deprotonated forms of weak acids)
- One for cations (protonated forms of weak bases)

Competition between drugs on the transport systems can occur

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DISTAL TUBULAR REABSORPTION

As a drug moves toward DTC its concentration becomes higher than in the perivascular space

Uncharged drugs will diffuse out of the nephric lumen to the systemic circulation

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DISTAL TUBULE REABSORPTION

Increasing the ionized form of the drug in the lumen by changing the pH of the urine c
minimize the back-diffusion and increase clearance

{**Ion Trapping**}

- Elimination of weak acids can be increased by alkalinization of the urine
  - e.g. phenobarbital (weak acid) overdose

  Alkalinization of urine with bicarbonate keeps the drug ionized
- Elimination of weak bases can be enhanced by acidification of the urine
  - e.g. overdose of amphetamine (weak base)

  Acidification of urine with NH_4Cl causes the protonation of the drug and enhancement of its excretion

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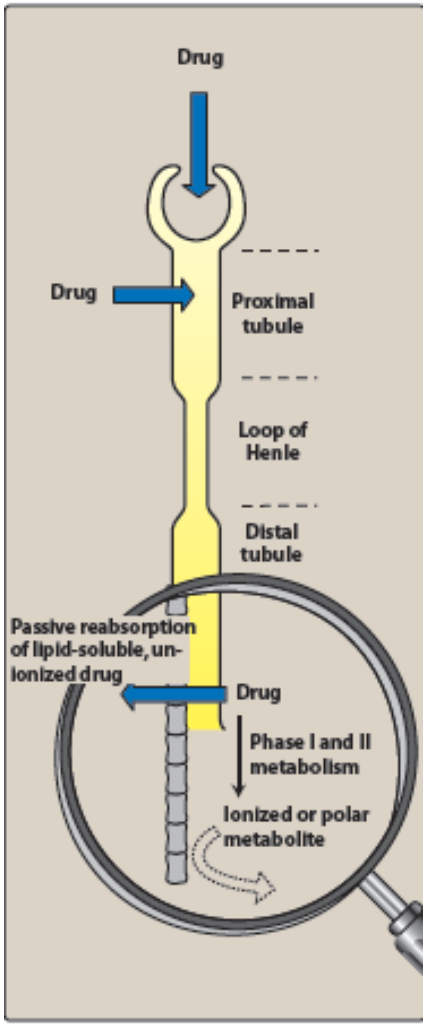
ROLE OF DRUG METABOLISM IN ELIMINATION

Most drugs are lipid soluble

Without chemical modification drugs would diffuse back from the kidney lumen when their concentration is higher there

To minimize reabsorption drugs are modified (mainly in liver) to more polar compounds



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CLEARANCE BY OTHER ROUTES

Liver

Intestine

Bile

Lungs

Milk in nursing mothers

To a small extent in sweat, tears saliva, hair and skin

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Liver

- contributes to drug loss through metabolism and/or excretion into the bile
- patients with renal failure may benefit from drugs excreted through this route

Feces

- Elimination of unabsorbed orally ingested drugs
- Elimination of drugs that are secreted directly into the intestines or bile

Lungs

- Elimination of anesthetic gases

Breast milk

- Source of undesired effects to the infant

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- Total body clearance

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

- t1/2 of drugs can be altered by
  - Diminished renal or hepatic flow (⇑ t1/2)
    (e.g. cardiogenic shock, heart failure, hemorrhage)
  - Decreased ability to extract drug from plasma (⇑ t1/2)
    (e.g. renal disease)
  - Decreased metabolism (⇑ t1/2)
  - Increased hepatic blood flow (⇓ t1/2)
  - Decreased protein binding (⇓ t1/2)
  - Increased metabolism (⇓ t1/2)

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DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

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To initiate drug therapy a dosage regimen is administered either by continuous infusion or in intervals of time and dose

The regimen depends on various drug and patient factors including how rapidly a steady state must be achieved

- Steady state: The state at which the rate of administration equals that of elimination

The regimen is refined to achieve maximum benefit with minimum adverse effects

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Drug administration

- Single dose
- Continuous administration
  - IV infusion
  - Fixed-dose/fixed time interval regimens

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DOSAGE REGIMENS

IV infusion or oral fixed-dose/fixed time interval regimens

The drug accumulates until a steady state occurs

At steady state the amount of drug administered equals the amount being eliminated

At steady state

- The plasma and tissue levels remain constant with IV infusion and fluctuate around a mean in oral fixed dosage

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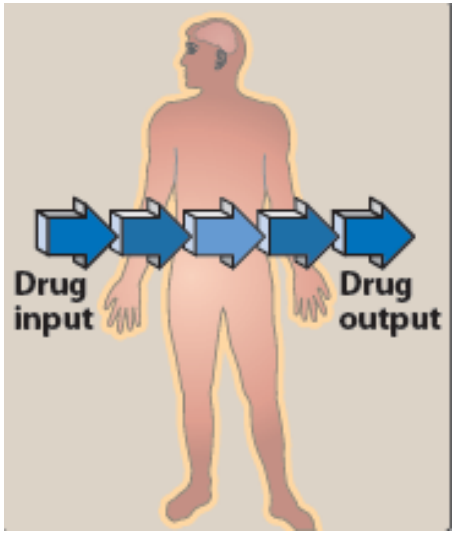
PLASMA CONCENTRATION OF A DRUG FOLLOWING IV INFUSION

- Following initiation of IV infusion the plasma concentration of drug rises until the rate of drug eliminated from the body balances the input rate



→ Steady state is achieved

(The plasma concentration of the drug remains constant)

Assuming the drug elimination is first order

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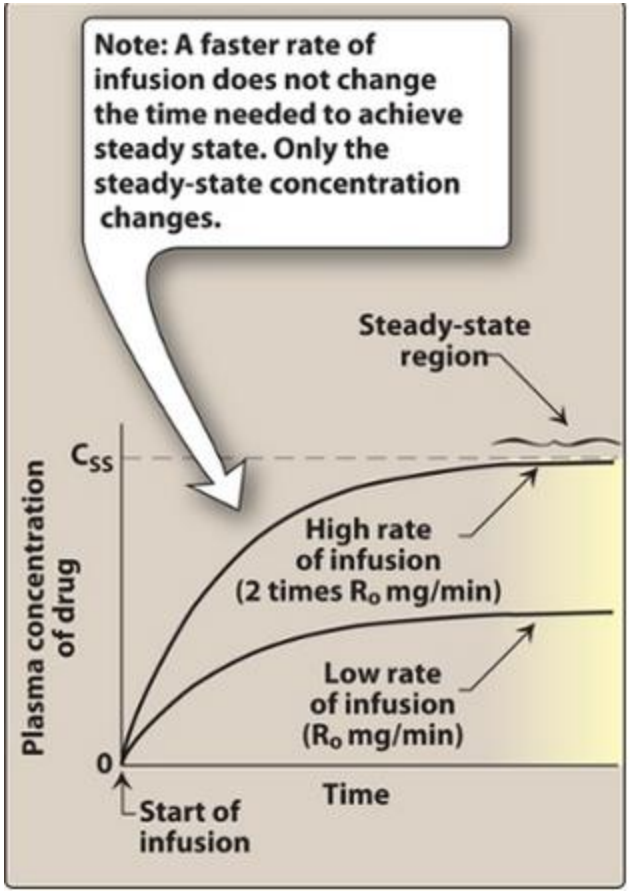
PLASMA CONCENTRATION OF A DRUG FOLLOWING IV INFUSION

The steady state plasma concentration is directly proportional to the infusion rate

The steady state concentration is inversely proportional to the clearance of the drug

- Hepatic or renal disease can increase Css
- Increased metabolism reduces Css



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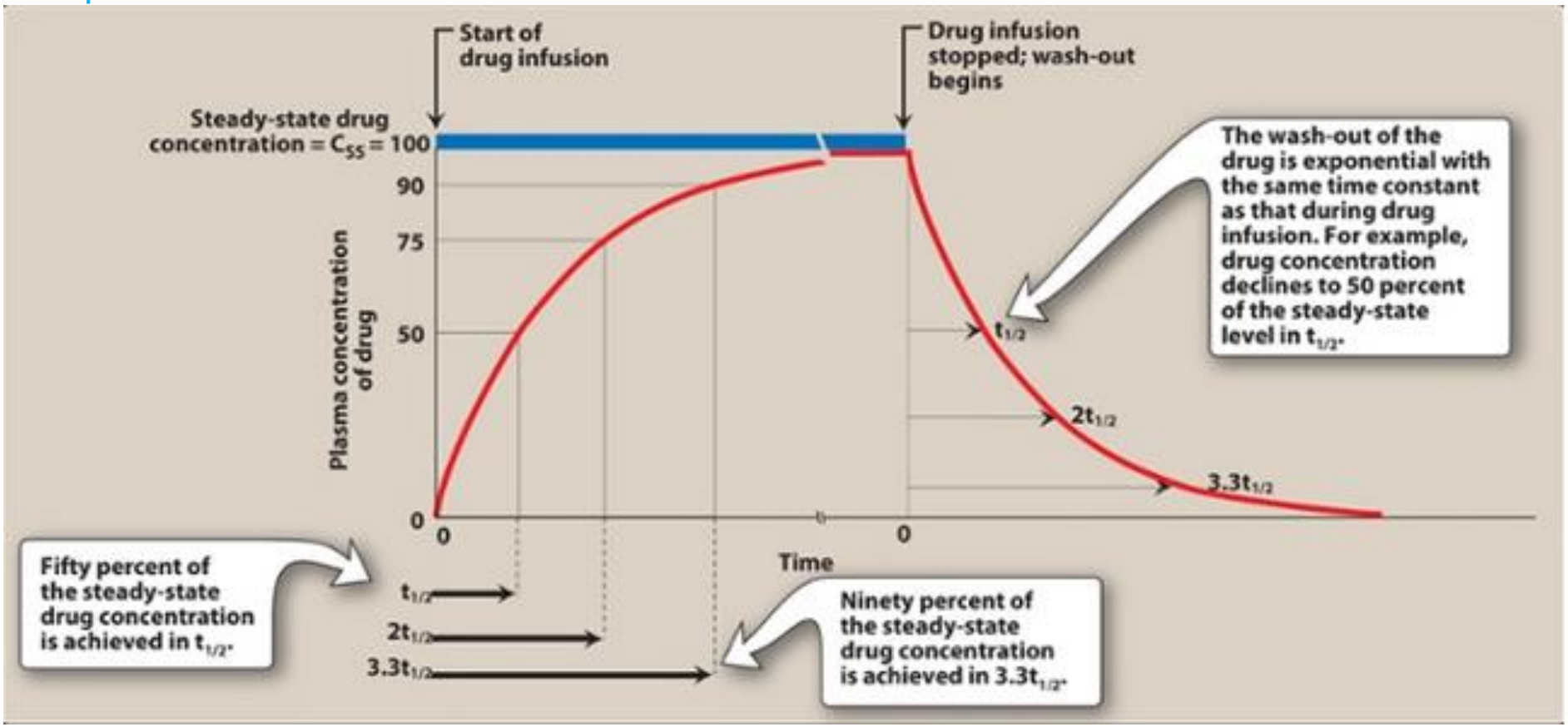
TIME REQUIRED TO REACH Css



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FIXED DOSE/FIXED TIME REGIMEN

Administration of drug by fixed doses is more convenient than continuous infusion

Fixed doses administered by fixed time intervals results in fluctuations in drug levels

Fixed dose regimens

- Multiple IV injections
- Multiple oral administrations

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MULTIPLE IV INJECTIONS

- Following administration of a drug at repeated intervals the plasma concentration increases until steady state is reached
- Using smaller doses at shorter intervals does not does not change the rate at which the steady state is approached or the Css
- 90% of steady state value is reached in $3.3t_{1/2}$

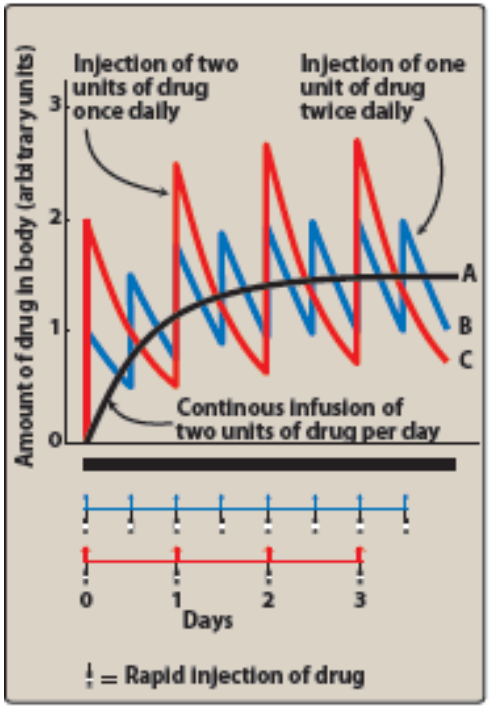

Figure 1.25
Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

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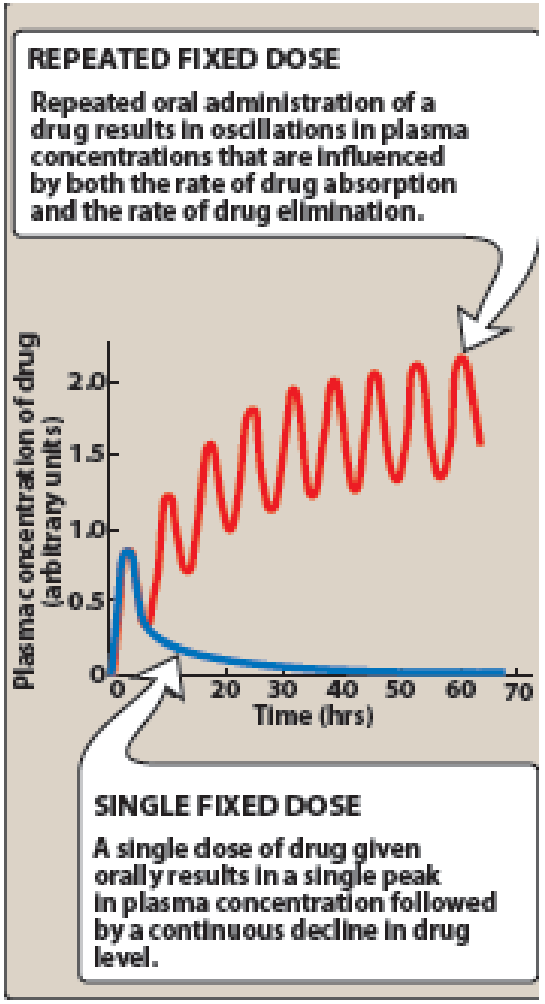
MULTIPLE ORAL ADMINISTRATION

Might be absorbed slowly

Plasma concentration is influenced by

- the rate of absorption
- the rate of elimination



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OPTIMIZATION OF DOSE

The goal of drug administration is to achieve and maintain therapeutic response with minimal toxicity or side effects

Loading dose: a higher dose or series of doses administered to achieve the desired plasma level rapidly.

Loading dose is followed by lower multiple doses

(Maintenance dose)

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Loading dose = (Vd)(desired Css)/F

For IV

Loading dose = (V_d)(desired Css)

Loading dose might be associated with risk of drug toxicity

Loading dose is useful for drugs eliminated from the body slowly, and hence require lower maintenance dose to keep the drug at a therapeutic concentration

Without an initial higher dose, it would take longer to reach Css

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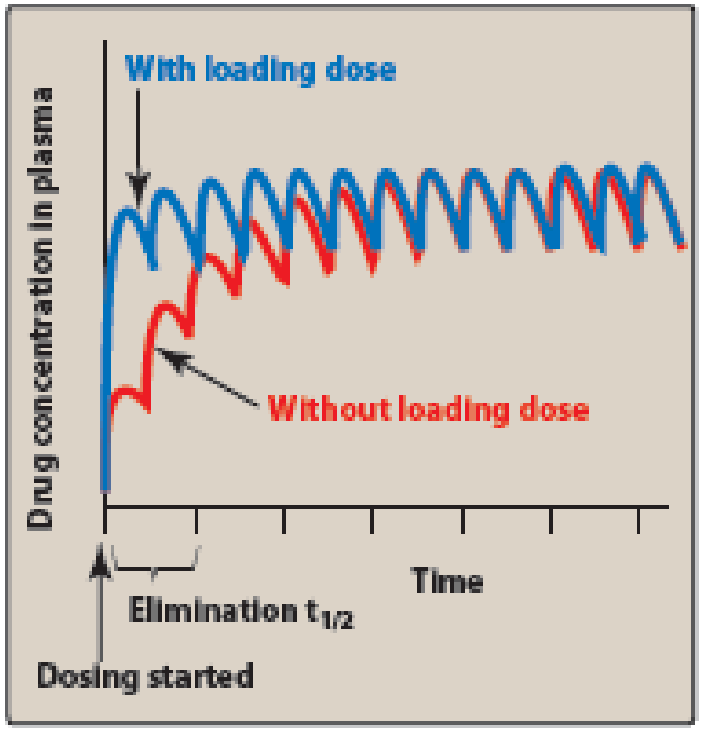

Figure 1.27
Accumulation of drug administered orally without a loading dose, and with a single oral loading dose administered at t=0.

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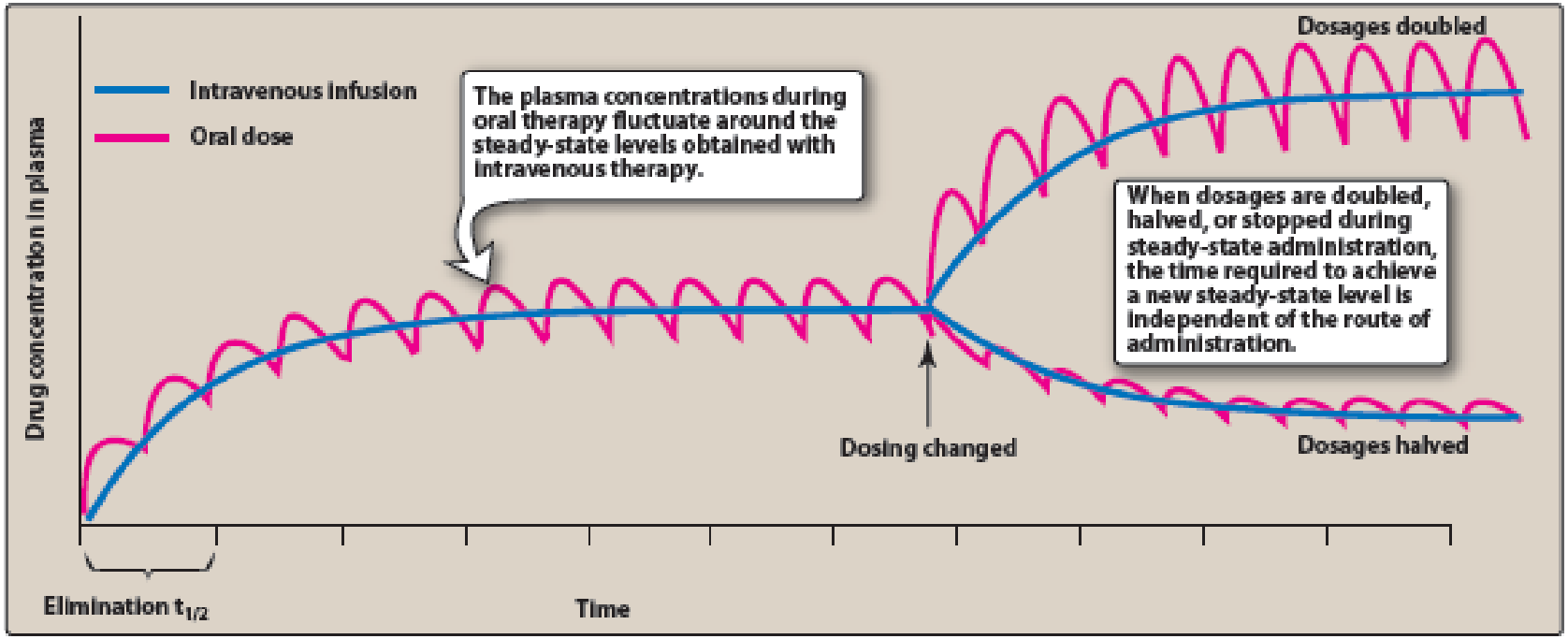

Figure 1.28
Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50 percent of $t_{1/2}$.

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DOSE ADJUSTMENT

The amount of drug administered is optimized for the patient taking into account:

- Interpatient variability
- Pharmacokinetic factors

Individualized therapy

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