PHARMACOLOGY

Pharmacokinetics

Skye McKennon, PharmD.
BCPS, ACSM-GEI

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

DISCLOSURE

None

Use Statement

OBJECTIVES

1. Describe physiochemical factors that affect absorption of drugs.
2. Describe the factors that affect distribution of a drug to its site of action or other sites.
3. Describe how plasma proteins, tissues, and fat can act as reservoirs for drugs.
4. Describe the processes whereby drugs are excreted/reabsorbed by the kidney.
5. Explain the effects of altering urine pH on the excretion of weak acids and weak bases.
6. Describe phase I and phase II metabolism of drugs and how these reactions facilitate excretion of drugs.
7. Using specific examples, explain how drug interactions can occur with respect to the metabolism of drugs (emphasis on CYP P450 enzymes).
8. Define the first-pass effect.
9. Describe the relationships between volume of distribution (Vd), half-life (t1/2), and clearance (CL) and demonstrate calculations using these variables.
10. Calculate bioavailability, loading dose, and maintenance dose.

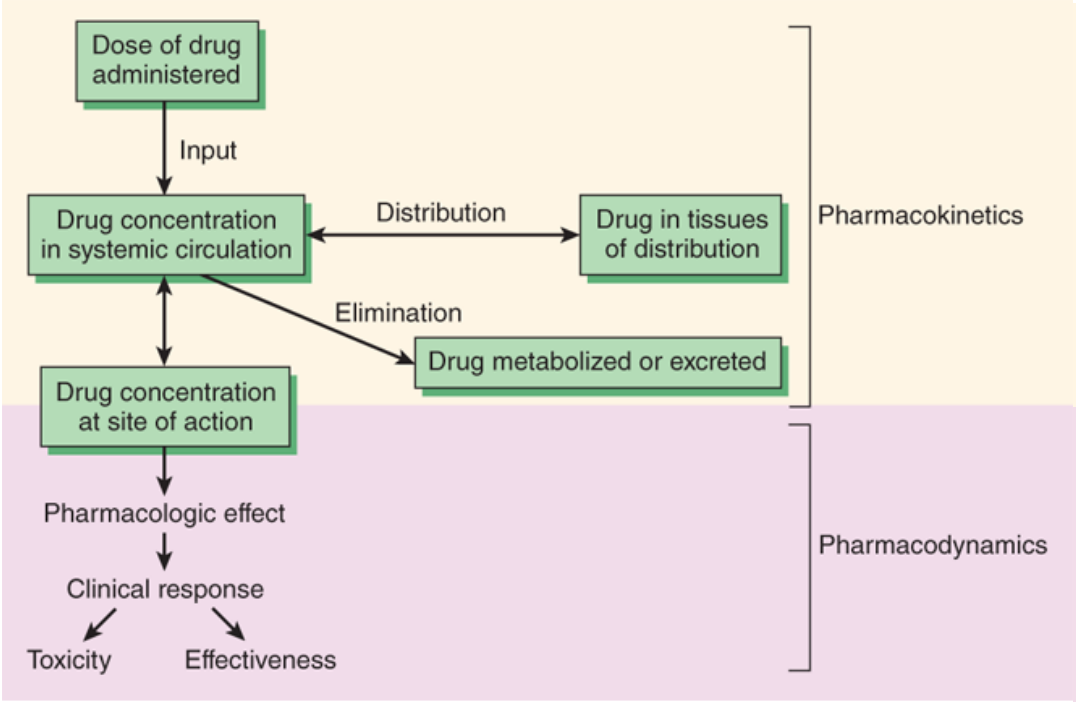
DRUG DEFINITION

Any substance that acts at the molecular level on a biological system that results in a functional change

A substance approved by the Food and Drug Administration for the treatment or prevention of disease

- Include inorganic ions, small peptides, proteins, nucleic acids, lipids, carbohydrates
- First isolated from plants and microorganisms
- Now many are partially or completely synthetic

COMPARISON



Study of the time course of drug absorption, distribution, metabolism, and excretion

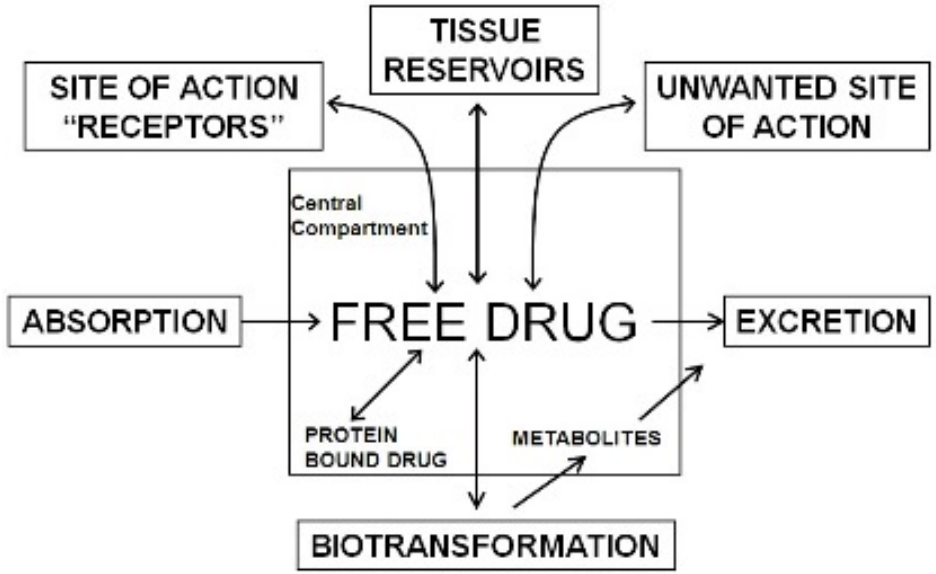
Study of the biochemical, cellular, and physiological effects of drugs and their mechanisms of action.

PHARMACOKINETIC BASICS - ADME

Absorption	Distribution	Metabolism	Elimination
• Process that brings drug from administration into systemic circulation • Bioavailability	• How a substance is spread throughout the body • Volume of distribution	• Processing of drug by body into subsequent compounds • Hepatic or other	• Process by which drug is eliminated from body • Clearance

FUNDAMENTAL HYPOTHESIS OF PK

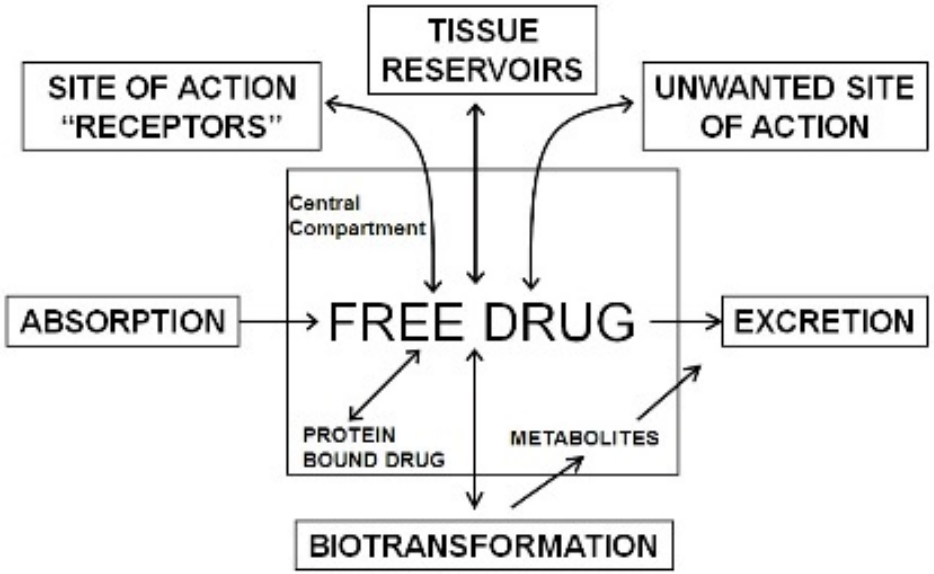
Relationship exists between pharmacologic (and toxic) effect of a drug and the concentration of the drug in the blood



FUNDAMENTAL HYPOTHESIS OF PK

Most drugs elicit effect at receptor sites

Concentration of free drug in body relates directly to the concentration of drug at receptors



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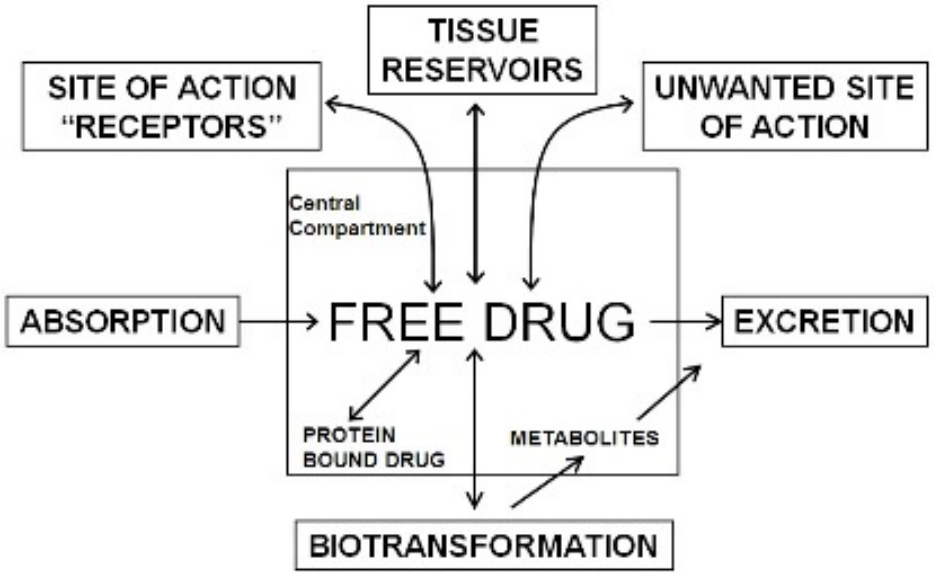


PK provides quantitative relationship between drug efficacy and drug dose

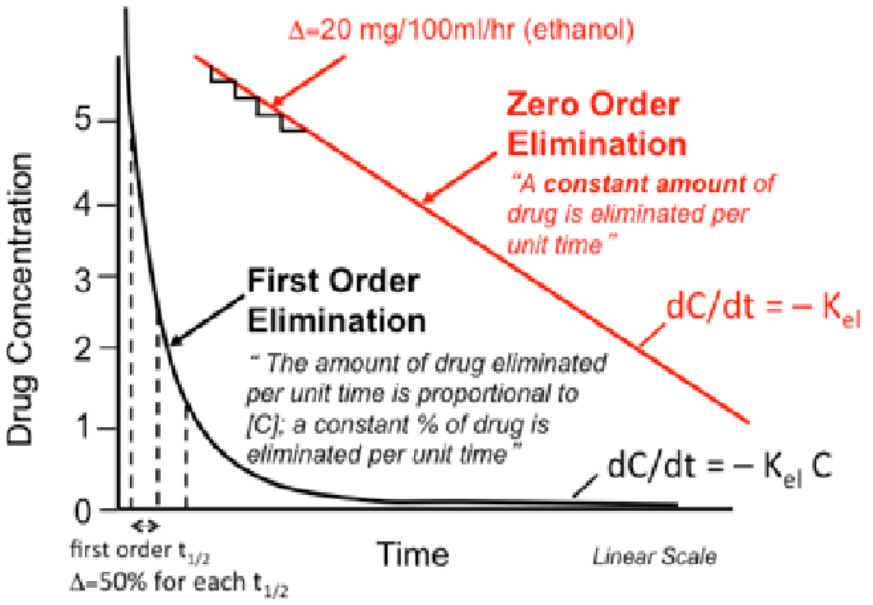
ZERO AND FIRST ORDER KINETICS

Zero Order

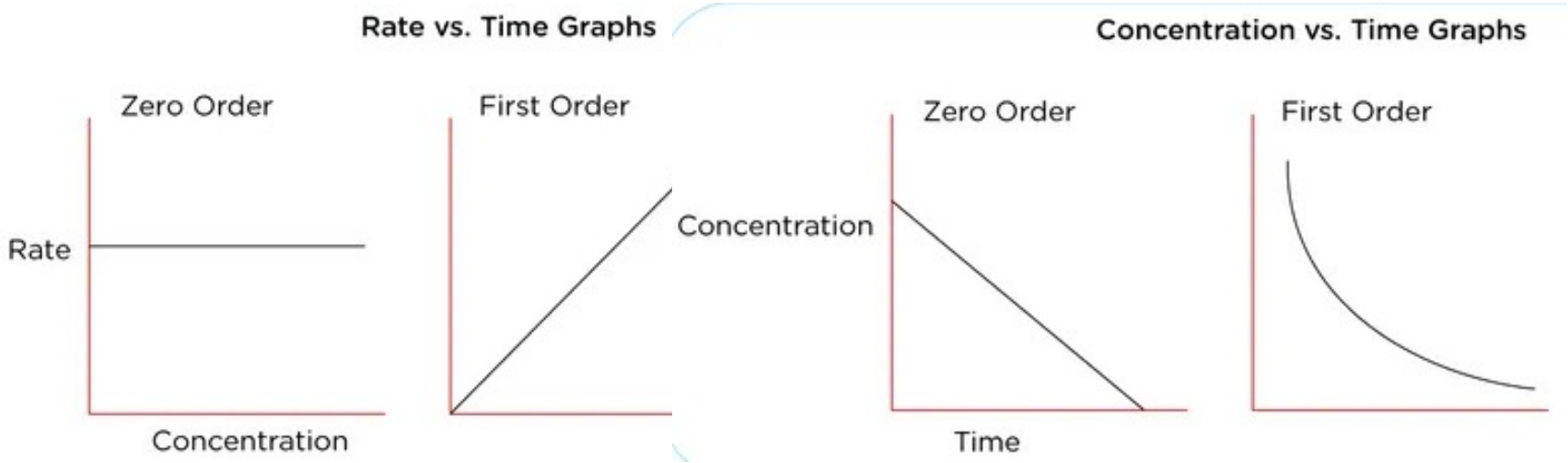
- Constant elimination regardless of the plasma concentration, following a linear elimination phase as the system becomes saturated
- Phenytoin, ethanol, aspirin (at high doses)

First Order

- Proportionally increases elimination as the plasma concentration increases, following an exponential elimination phase as the system never achieves saturation
- Most other drugs



ZERO AND FIRST ORDER KINETICS



TODAY'S ASSUMPTIONS OF PHARMACOKINETICS

1. First order kinetics

$$-\frac{dC}{dt} \propto k[C]$$

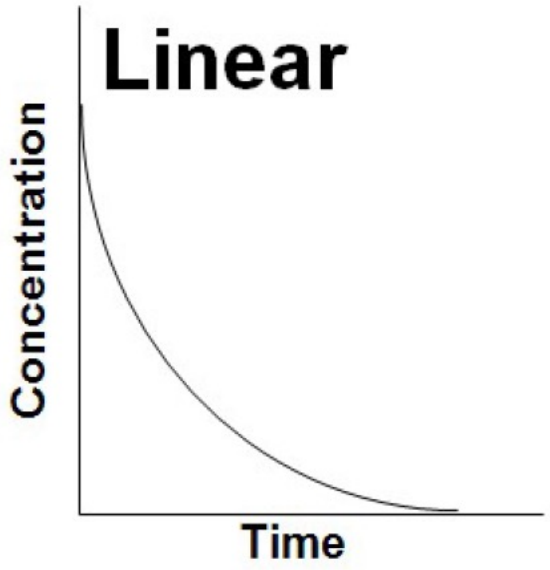
"Rate of ↓ of drug concentration"

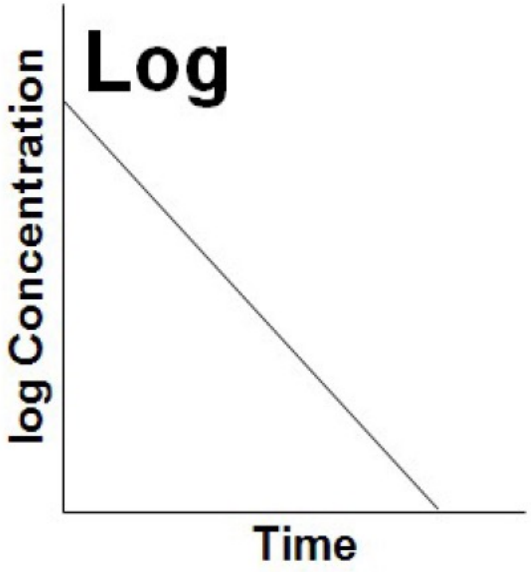
"concentration"

C = concentration of drug
t = time
k = proportionality constant (elimination rate constant)
Note: negative sign on the left side of proportionality indicates the drug concentration is decreasing

FIRST ORDER KINETICS

1. First order kinetics

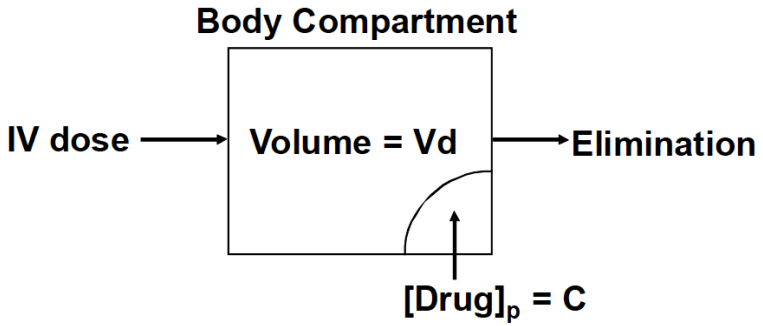




COMPARTMENT MODELS

One compartment model

- Treat the body as a single compartment
- After intravenous administration of drug into the body compartment, it distributes very rapidly
- Any elimination occurs from this same compartment
- We are able to measure the drug concentration in this compartment



TODAY'S ASSUMPTIONS OF PHARMACOKINETICS

1. First order kinetics
2. One compartment model

INTERACTIVE QUESTIONS

1. Summarize the two assumptions of pharmacokinetics we are using in our approach today.

a.

b.

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ABSORPTION

Pharmacokinetics

SELECTED ROUTES OF DRUG ADMINISTRATION

Route	Absorption Pattern	Advantages	Limitations
Enteral (related to the digestive system)			
Oral ingestion	Variable	Safest; most convenient; economical	Patient must be cooperative; bioavailability may be limited for several reasons
Sublingual	Across oral mucosa (e.g., nitroglycerin)	Bypasses liver; avoids first-pass effect	Only certain drugs, i.e., nonionic, high lipid solubility
Rectal	Across rectal mucosa	Less first-pass metabolism vs. oral; useful when oral ingestion is not possible	Bioavailability can be incomplete; irritating to rectal mucosa

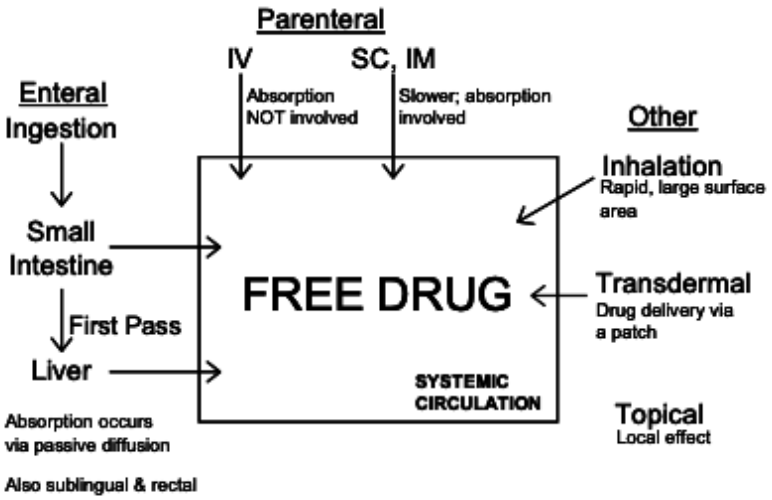
SELECTED ROUTES OF DRUG ADMINISTRATION

Route	Absorption Pattern	Advantages	Limitations
Parenteral (outside of the digestive system)			
Intravenous	Absorption circumvented; potentially immediate effects	Availability is rapid, extensive & predictable emergency use; irritating solutions can be administered	Asepsis must be maintained; injection site pain; difficult for self-medication; mistakes (once injected, no retreat)
Intramuscular	Aqueous drugs absorbed readily via diffusion, blood flow- dependent; Slow, constant absorption from repository preps	Good for moderate volumes, oily vehicles, some irritating substances	Precluded during anticoagulant therapy
Subcutaneous	Aqueous drugs absorbed readily via diffusion, blood flow- dependent; Slow, constant absorption from repository preps	Good for insoluble suspensions and implanting solid pellets	ONLY for drugs that are not irritating to tissues

SELECTED ROUTES OF DRUG ADMINISTRATION

Route	Absorption Pattern	Advantages	Limitations
Other routes			
Inhaled	Absorption through pulmonary endothelium & mucous membranes	Rapid absorption due to large surface area; gaseous and volatile drugs, e.g., anesthetics; topical application of drugs to treat pulmonary disease, e.g., asthma	Drugs should be nonirritating; important route of entry for drugs of abuse and environmental toxicants
Transnasal	Passive diffusion across respiratory endothelium directly into systemic circulation	Rapid absorption	Few products available
Transdermal	Varies based on dosage form	Effect can be local or systemic	Depends on dosage form – absorption can be variable

ABSORPTION



There are several useful routes of drug administration, but almost all require that the drug cross a biological membrane to reach its site of action

ABSORPTION

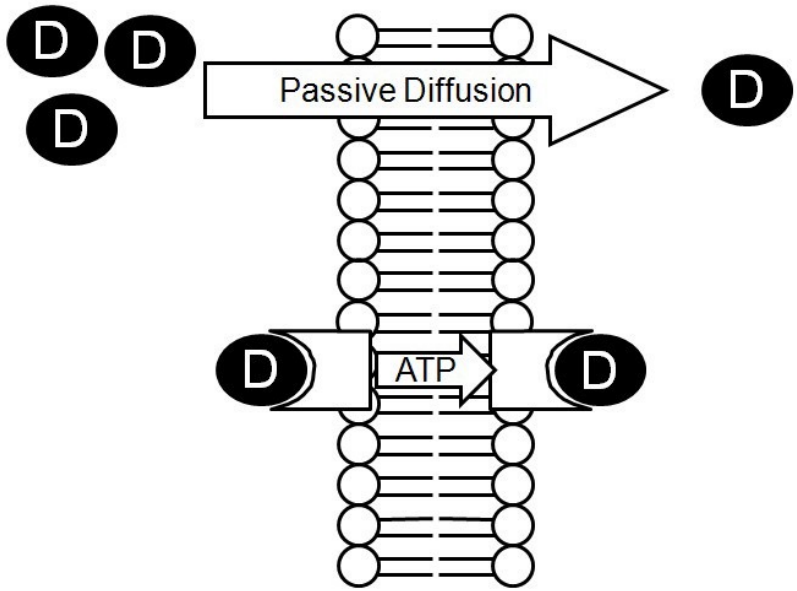
Almost all routes of administration require that the drug cross a biological membrane to reach its site of action

HOW DRUGS CROSS MEMBRANES

Drugs cross membranes primarily through

1. Passive diffusion
   - Requires a concentration gradient across a membrane
   - **Majority of drugs access their site of action by this method**
2. Active transport
   - Requires energy (ATP)

Note: Other methods exist



HOW DRUGS CROSS MEMBRANES

Drugs cross membranes primarily through

3. Aqueous diffusion
   - Occurs within larger aqueous compartments of body (interstitial space, cytosol, etc.)
4. Transporter proteins
   - Can mediate drug efflux
   - Liver, kidney, intestines
   - P-glycoprotein and multidrug-resistance type 1 (MDR1) transporter mediate efflux of drugs

Note: Other methods exist

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ABSORPTION: PHYSIOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

1. Molecular size
   - Determined by number and type of atoms in drug molecule
2. Partition coefficient
   - Measure of overall polarity
   - $PC = \frac{[Drug]_{fat/lipid}}{[Drug]_{water}}$
   - Like dissolves like
     - PC > 1 = lipophilic
     - PC < 1 = hydrophilic
3. Ionic character
   - Discuss further
4. pH effects

IONIC CHARACTER

A drug tends to cross membranes if it is uncharged (neutral, non-ionized)

Uncharged drugs are more lipid soluble than charged drugs

Most drugs are weak acids or weak bases

Neutral compounds neither donate nor accept protons

- Neutral, uncharged; e.g., alcohols (ROH), amides (RCONHR)
- Neutral, charged; e.g., quaternary ammonium salts (R4N+ X-)

Weak acids

- Proton donors: $HA \leftrightarrows H^+ + A^-$
- E.g., carboxylic acids (RCOOH), sulfonamides (RSO2NHR)

Weak bases

- Proton acceptors: $B: + H^+ \leftrightarrows BH^+$
- E.g., amines; primary (RNH2), secondary (R2NH), tertiary (R3N)

IONIC CHARACTER: WEAK ACIDS

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

pK is the equilibrium constant

- pH = pK, there are equal amounts of weak acid in the ionized and nonionized forms
- pH < pK (add more H^+), drive the equilibrium to the left and there is more protonated (nonionized) form
- pH > pK (take away H^+), drive the equilibrium to the right and there is more unprotonated (ionized) form

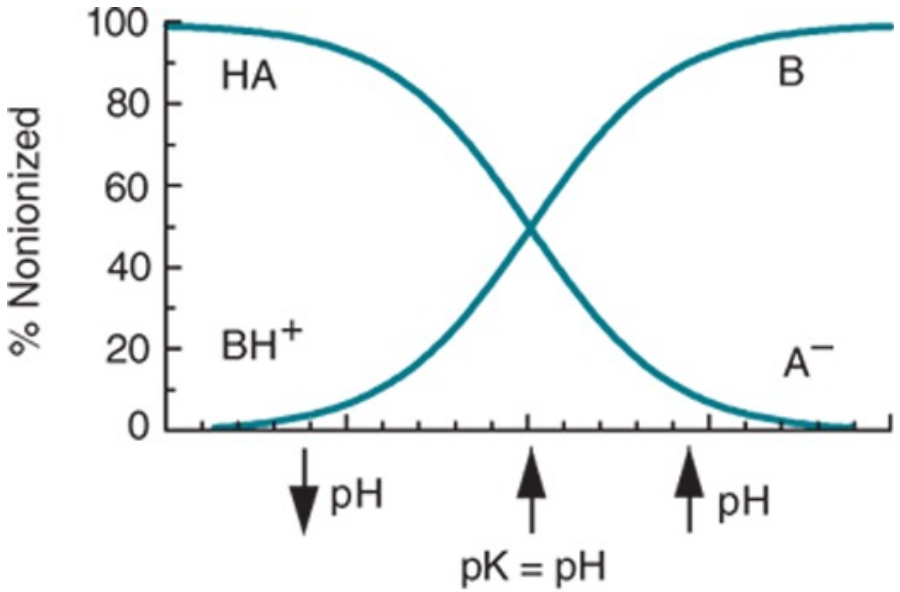
IONIC CHARACTER: WEAK BASES

- pH = pK, there are equal amounts of weak base in the ionized (protonated) and nonionized (unprotonated) forms
- pH < pK (add more H^+), drive the equilibrium to the right and there is more protonated (ionized) form
- pH > pK (take away H^+), drive the equilibrium to the left and there is more (unprotonated) nonionized form

Weak base is a hydrogen ion acceptor

- If a loose hydrogen ion seeks to join it, the base may accept it; if it accepts the hydrogen ion, then it becomes charged

IONIZATION OF WEAK ACIDS & BASES



Source: Janet L. Stringer: Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, Fifth Edition, www.accesspharmacy.com

INTERACTIVE QUESTIONS

2. In the intestine (pH 8.0), which will be better absorbed, a weak acid (pK 6.8) or a weak base (pK 7.1)?

INTERACTIVE QUESTIONS

Many drugs excreted in the urine

Altering urine pH can alter drug excretion

With that in mind,

3. If we alkalinize the urine to a pH of 7.8, will a lower or higher percentage of a weak acid (pK 7.1) be ionized, compared with when the urine pH was 7.2?

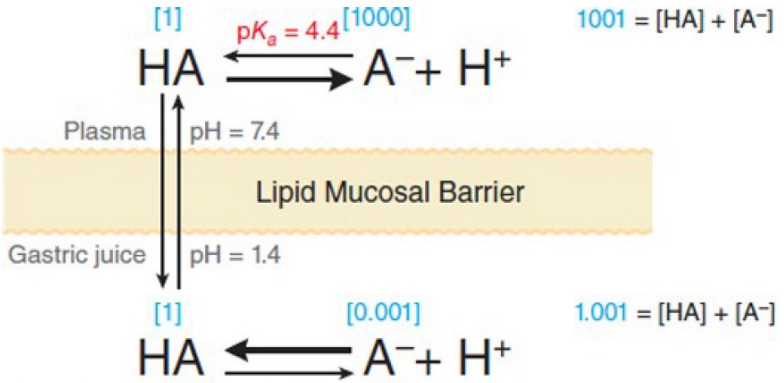
IONIZATION: ALTERING DRUG EXCRETION

As urine pH drops (as [H+] increases), weak acids (A–) and weak bases (B) will exist to a greater extent in their protonated forms (HA and BH+)

Reverse is true as pH rises, where A– and B will be favored

Alkaline urine favors excretion of weak acids

Acid urine favors excretion of weak bases.



BIOAVAILABILITY (F)

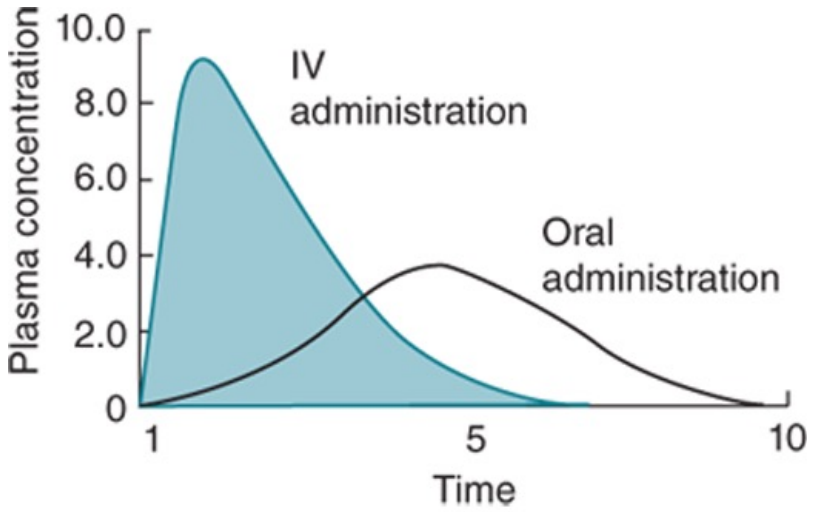
Amount of drug that is absorbed after administration by route X compared with the amount of drug that is absorbed after intravenous (IV) administration

- X is any route of drug administration other than IV

Fraction of unchanged drug that reaches systemic circulation

- Intravenous drug F = 1
- All other routes F ≤ 1

Can be calculated from area under the curve (AUC)



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BIOAVAILABILITY (F)

Bioavailability may be less than 1 (or 100%)

- Incomplete absorption (lack of absorption from the gut, metabolism of drug in gut wall)
- First-pass elimination

$$F = \frac{AUC_{oral} \times Dose_{iv}}{AUC_{iv} \times Dose_{oral}} = \frac{\frac{AUC_{oral}}{Dose_{oral}}}{\frac{AUC_{iv}}{Dose_{iv}}}$$

F = bioavailability

AUC = area under the curve

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4. The AUC after administration of an oral antibiotic tablet of 10 mg was 816 mg x hr/L. The AUC calculated after intravenous administration of 10 mg of the same antibiotic was 1,077 mg x h/L. What is the oral bioavailability of this drug?

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DISTRIBUTION

Pharmacokinetics

DISTRIBUTION

Drugs distribute into interstitial and intracellular fluids following absorption or systemic administration

Factors that Affect Distribution

- Drug physiochemical properties
- Blood flow rate to tissue capillaries
- Capillary structure
- Plasma protein binding
- Age, sex, disease state, body composition

DISTRIBUTION: DRUG RESERVOIRS

Many drugs accumulate in tissues at higher concentrations than those in extracellular fluids and blood
Reversible tissue binding (proteins, phospholipids, nuclear proteins)
Large fraction of drug may be found in this fashion and serve as reservoir that prolongs drug action through same tissue or distant site through circulation

Reservoir	Comments
Plasma proteins	Acidic drugs can bind to albumin; α1-glycoprotein is a carrier for basic drugs
Tissues	Tissue binding of drugs usually occurs reversibly with cellular constituents such as proteins, phospholipids, or nuclear proteins. A large fraction of drug in the body may be bound in this fashion and serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation
Fat	Many lipid-soluble drugs are stored by physical solution in the neutral fat. Thus, fat may serve as a reservoir for lipid-soluble drugs

VOLUME OF DISTRIBUTION (V_D)

Volume of distribution (V_D) is a calculation of the apparent volume in which a drug is dissolved

Volume of fluid a drug would occupy if total amount of drug in body were in solution at the same concentration as in plasma

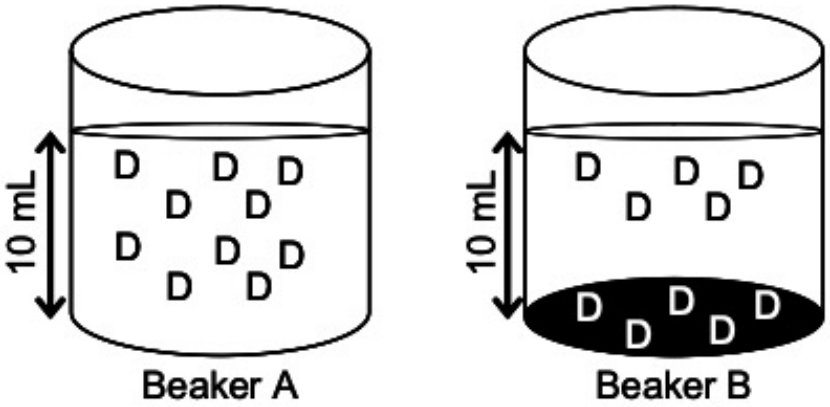
Assumes drug is evenly distributed and metabolism or elimination has not taken place

- In reality, it does not correspond to any real volume

Gives rough approximation of where a drug goes in the body

- Helps calculate dose of drug needed to achieve a desired plasma concentration

VOLUME OF DISTRIBUTION (V_D)



$$Vd = \frac{Dose \times F}{C_0}$$

Dose = amount of drug administered

F = bioavailability

C_0 = initial or maximum concentration of drug measured in the plasma soon after drug administration.

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5. What is the Vd for an antibiotic if the maximum concentration soon after intravenous administration of a 0.5 mg dose is 0.78 ng/ml?

$$Vd = \frac{(Dose \times F)}{C_0}$$

VOLUME OF DISTRIBUTION (V_D) APPLICABILITY

Drug with a ↑ Vd has propensity to leave the plasma and enter the extravascular compartments of the body

- ↑ dose required to achieve a given plasma concentration
- ↑ Vd → More distribution to other tissue

Drug with a ↓ Vd has propensity to remain in the plasma

- ↓ dose of a drug required to achieve a given plasma concentration
- ↓ Vd → Less distribution to other tissue

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ELIMINATION

Pharmacokinetics

ELIMINATION

Metabolism

Primarily
by liver

Excretion

Primarily
by kidneys

FIRST-PASS METABOLISM OR FIRST-PASS EFFECT

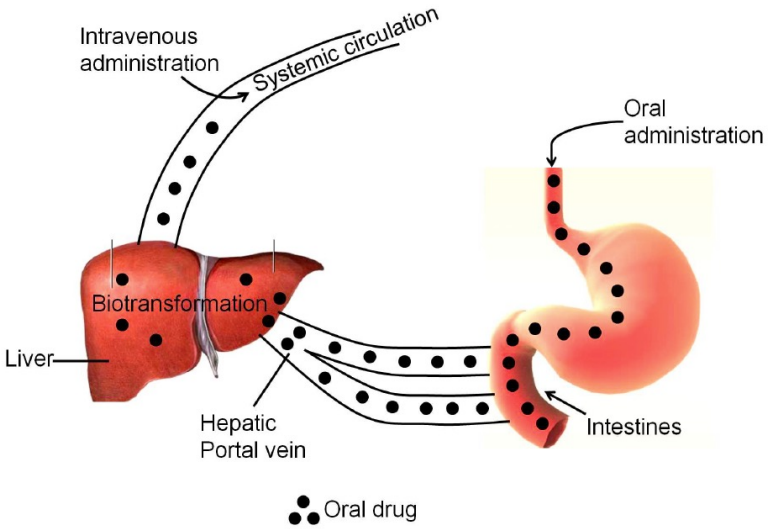
Drugs absorbed from GI tract can be biotransformed before reaching systemic circulation

Via enzymes in gut wall and liver

Inactivates and lowers degree of bioavailability

Drugs administered intravenously bypass the liver

- *Not subject to first-pass metabolism*



METABOLISM

Process by which **enzymes** in the body catalyze reactions that **change the chemical structure of a drug**

Principle site of metabolism is the liver

Goal of drug metabolism is to produce metabolites that are polar or charged

- Makes drugs easier to be excreted

Renal elimination of unchanged drugs plays a modest role in elimination (lipophilic drugs reabsorbed)

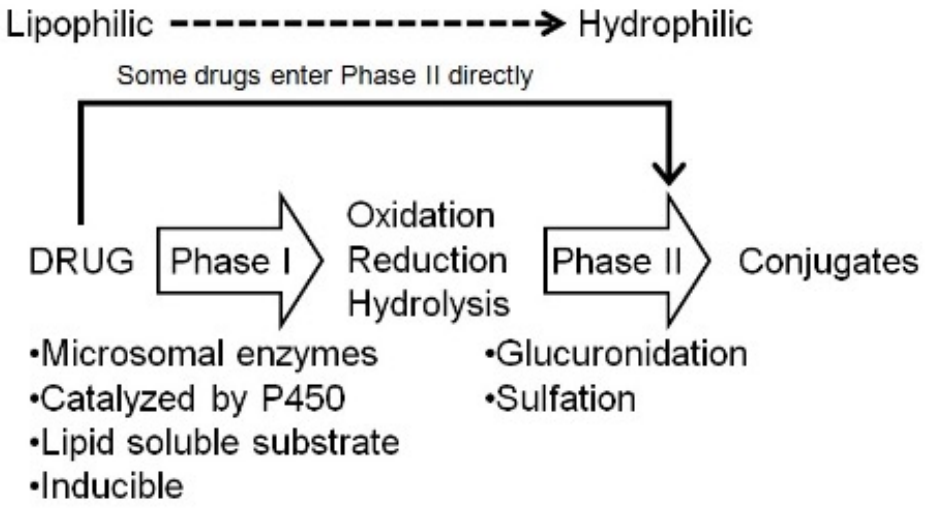
Metabolism of drugs into hydrophilic metabolites facilitates elimination of the active drug

- Enhanced excretion
- Termination of pharmacologic activity

METABOLISM

Drugs may be metabolized via phase I and/or phase II

- Mediated by different families of enzymes



METABOLISM: PHASE I REACTIONS

Lead to exposure/introduction of functional groups

- Render the drug more likely to undergo metabolism by a phase II enzyme that will increase polarity
- Minimal impact on water solubility

Most phase I reactions catalyzed by cytochrome P450 (CYPs or P450s) enzyme superfamily

- CYPs in families 1, 2, and 3 mediate Phase I metabolism of ~80% of drugs
- A single compound may be metabolized by multiple different CYPs

METABOLISM: PHASE II REACTIONS

Synthetic (conjugation) reactions that result in metabolite with increased molecular mass and substantially increased hydrophilicity

- Glucuronidation, sulfation, methylation, N-acetylation, glutathionylation

Catalyzed by

- Transferases (eg, glutathione-S-transferase, UDP-glucuronosyltransferases)

METABOLISM: PHASE I AND II COMPARISON

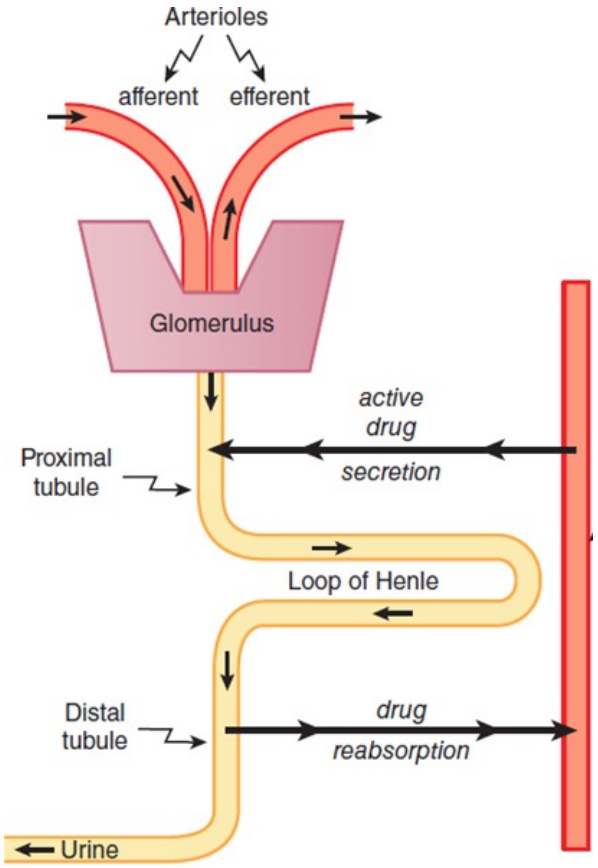
Phase I	Phase II
Frequently involve cytochrome (CYP) P-450 system	Conjugations (mostly with glucuronide)
Convert lipophilic molecules to more polar molecules	Convert drug to more polar molecule
Introduce or unmask a functional polar group such –OH or $–NH_2$	Combine a glucuronic acid, sulfuric, acetic, or amino acid with drug
Basis of many common drug interactions	Can cause drug interactions

RENAL EXCRETION

Kidney most important organ for drug excretion

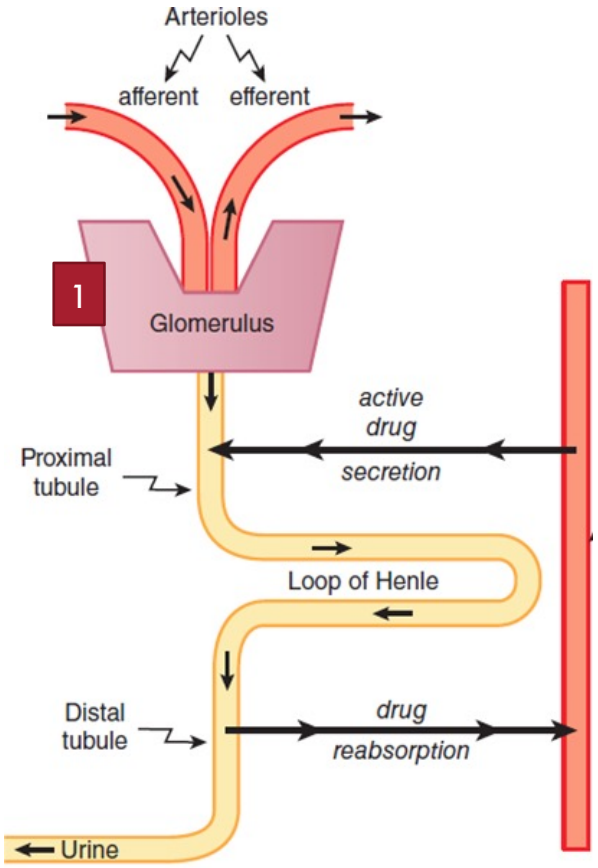
Drug excretion involves

1. Glomerular filtration
2. Active proximal tubular secretion
3. Passive distal tubular reabsorption



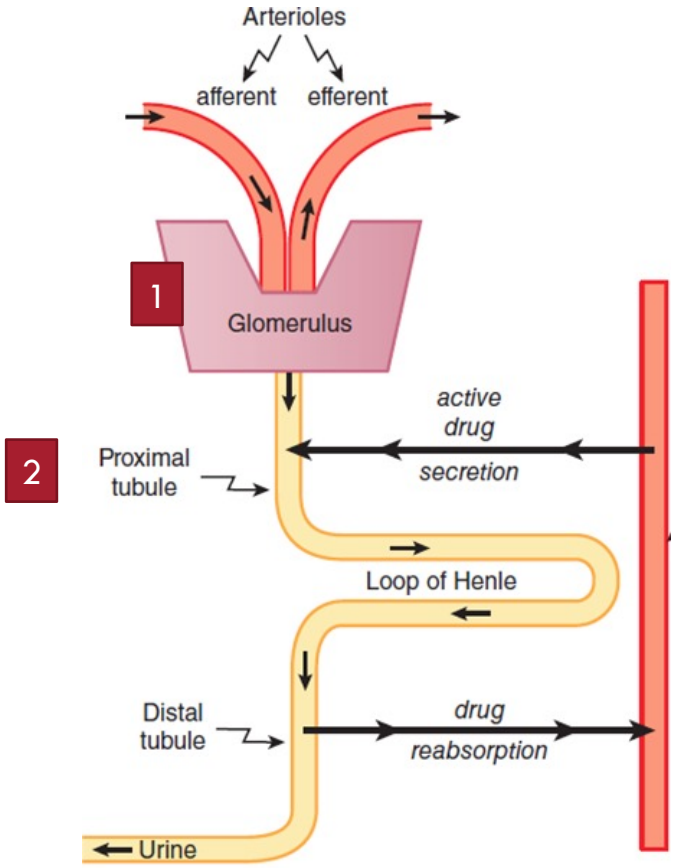
RENAL EXCRETION

1. Glomerular filtration: **Free drug** flows out of the body and into the urine-to-be as part of the glomerular filtrate
   - Molecular size is only limiting factor
     - Small-molecule (<60 kDa) drugs enters tubular lumen by passive filtration
   - Depends on the glomerular filtration rate (GFR) and plasma protein binding of the drug
   - Only unbound drug is filtered
   - Rate of filtration is not drug-specific but is the same for all filtered drugs in healthy adults



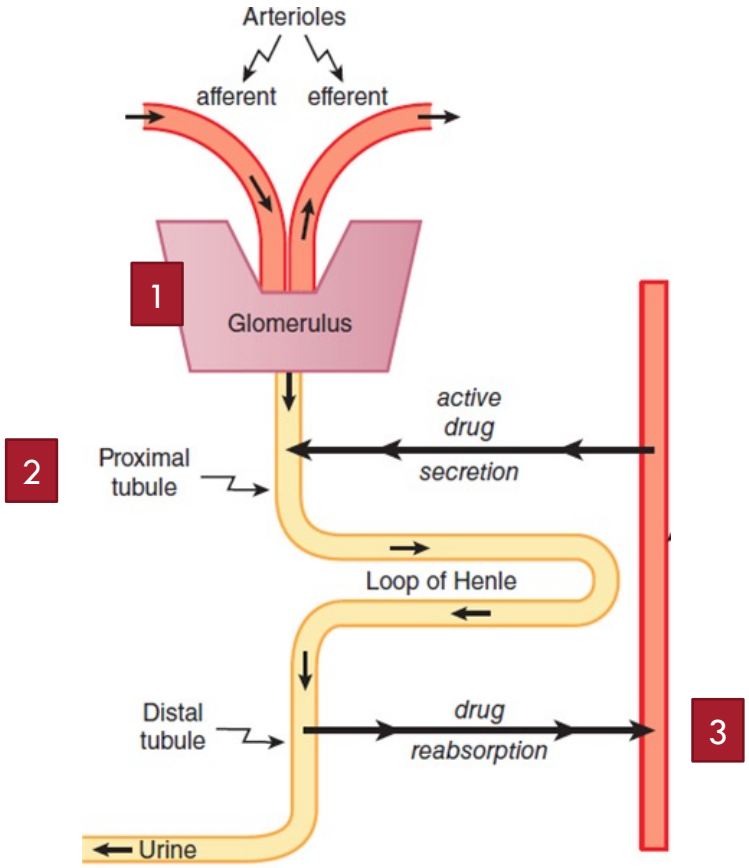
RENAL EXCRETION

2. Active proximal tubular secretion
   - In proximal renal tubules, active, carrier-mediated secretion can move drug from blood into urine
   - Membrane transporters (e.g., OAT, OCT, MDR1, and MRP2) mediate secretion of drug from blood into urine in the proximal tubule
   - **Only unbound drug** can be secreted



RENAL EXCRETION

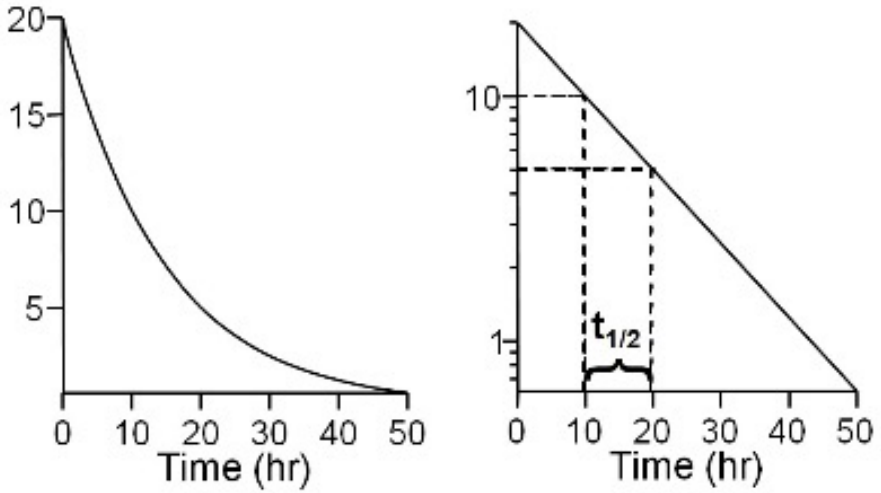
3. Distal tubular reabsorption
   - **Uncharged** drugs may diffuse out of the kidney and escape elimination
     - Manipulating urine pH may alter this process by changing the ionization of the weak acids and bases
   - **For a drug to be excreted, it needs to be charged so that it is trapped in the urine and can't cross the membrane to sneak back into the body**
   - Urine flow rate impacts reabsorption; ↑ flow rate ↓ time available for drug to move across cell membrane and back into blood



RELATED CALCULATION: ELIMINATION HALF-LIFE ($t_{1/2}$)

Time required for the concentration of the drug in the circulation to decrease by one-half

- $t_{1/2}$ for a drug is constant (remember we are assuming first order kinetics)

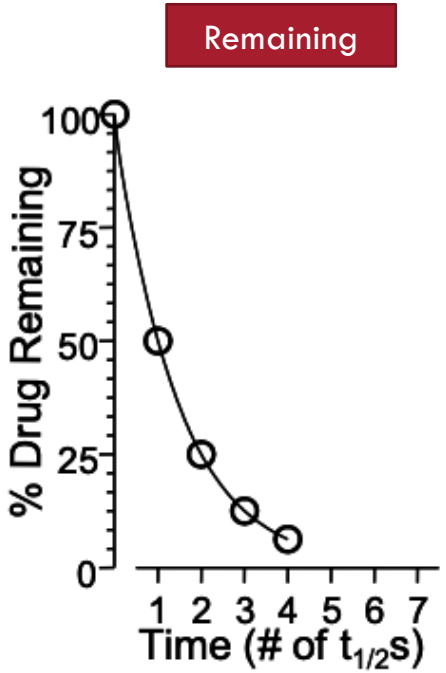


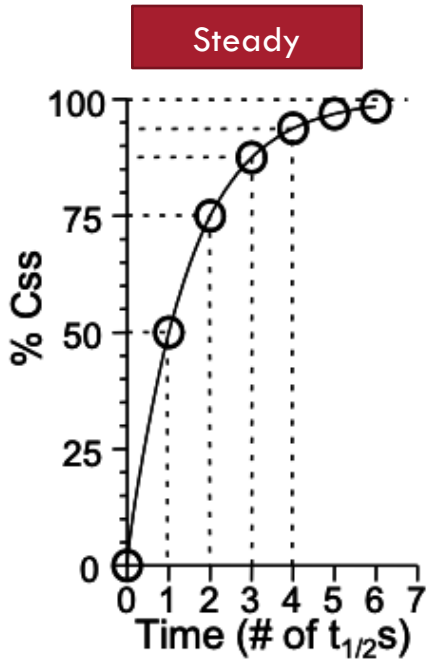
RELATED CALCULATION: ELIMINATION HALF-LIFE ($t_{1/2}$)

USEFULNESS: 4 – 5 half-life rule

$t_{1/2}$ allows prediction of how long a drug:

- Will remain in the body after administration
- Will take to reach steady state





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6. The half-life of a drug used to treat upper respiratory infections is 72 hours. This drug is taken as a single dose, one time only. Based on this, how long would you expect the drug to remain in the body after the last dose?

RELATED CALCULATION: CLEARANCE (CL)

Intrinsic ability of the body or its organs of elimination (usually the kidney and liver) to remove drug from the blood or plasma

Volume of plasma from which drug is completely removed per unit time

$$CL = \frac{rate\ of\ elimination\ of\ drug}{plasma\ concentration\ of\ drug} = Vd \times ke$$

RELATED CALCULATION: RELATIONSHIP BETWEEN $t_{1/2}$, V_D AND CL

$t_{1/2}$ of a drug is determined by the CL of the drug and the drug's V_d

$$t_{1/2} = \frac{0.693 \times Vd}{CL}$$ (for first-order kinetics)

All of the factors outlined that affect the V_d and CL of a drug also affect the $t_{1/2}$ of the drug

- A decrease in drug clearance or increase in volume of distribution tends to prolong the elimination half-life
  - Enhances the effect of the drug on the target organ
- $t_{1/2}$ must be carefully considered in designing any dosing regimen, as the effects from a drug with a long half-life may last for a number of days

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7. The plasma clearance of a drug is 630 mL/min and its volume of distribution is 32 L. What is the half-life of this drug? Hint: Be mindful of units!

HOW IS THIS RELEVANT?

Calculate doses!

$$Loading\ dose = \frac{C_p \times Vd}{F}$$

$$Maintenance\ dose = \frac{C_p \times CL \times \tau}{F}$$

C_p = plasma concentration (sometimes referred to as target concentration or TC)

V_d = volume of distribution

CL = clearance

τ = dosing interval

F = bioavailability

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8. If your desired plasma concentration of a drug is 3.5 mg/L, what intravenous loading dose should be administered if the drug has a volume of distribution of 35 L and a clearance rate of 70 ml/min?

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9. What would your maintenance dose of the same drug from the previous question be if it were administered every 8 hours?

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DRUG INTERACTIONS

DRUG INTERACTIONS

Differences in rate of metabolism of a drug can be due to drug interactions

- Two drugs co-administered and subjected to metabolism by the same enzyme

Drug interactions occur when one drug modifies the actions of another drug

DRUG INTERACTION TERMINOLOGY

Drug Effect	Definition	Example
Additive	The effect of two drugs given together is equal to the sum of the responses to the same doses given separately	Aspirin + acetaminophen ("2 + 2 = 4")
Antagonism	The effect of two drugs given together is less than the sum of the responses to the same doses given separately	Vitamin K given as antidote to warfarin ("2 + 2 < 4")
Synergism	The effect of two drugs given together is greater than the sum of the responses to the same doses given separately	Clopidogrel + aspirin ("2 + 2 > 4")

DRUG INTERACTIONS

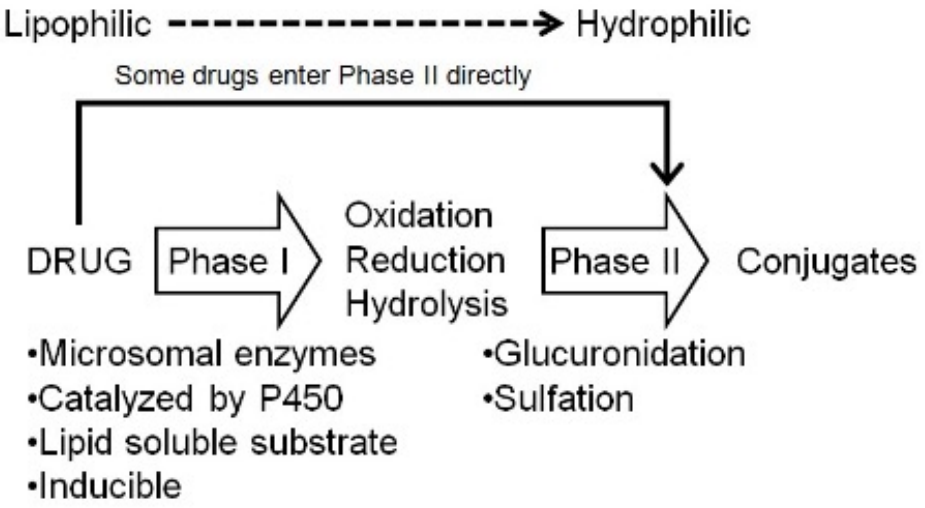
Focus on interactions based on metabolic clearance

Most drug interactions are due to phase I reactions (CYPs)

- Identify the CYP that metabolizes a particular drug

Increased risk

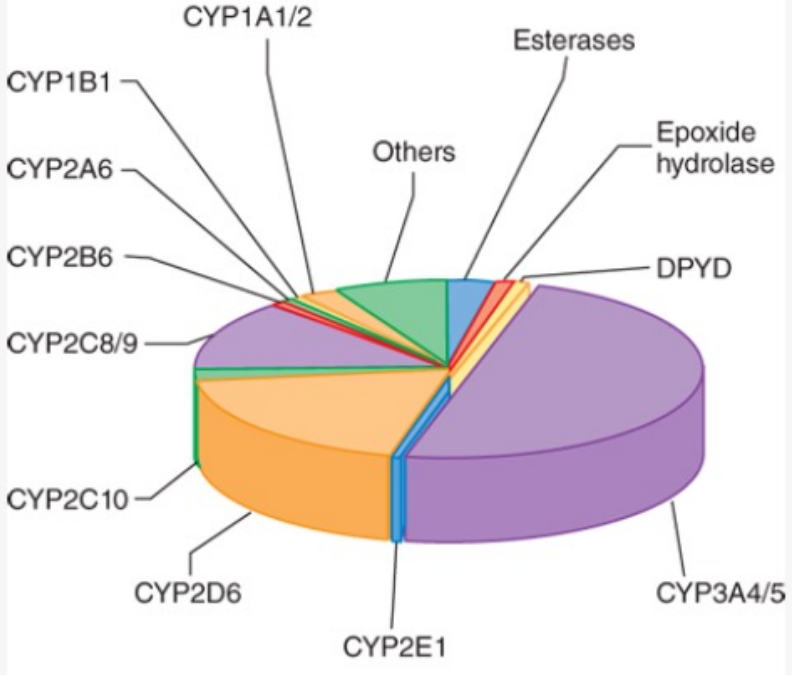
- Individuals using multiple drugs
- Older adults



PHASE I REACTIONS

Fraction of clinically used drugs metabolized by phase I enzymes

Sometimes more than a single enzyme is responsible for metabolism of a single drug



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10. Which two CYP enzymes metabolize the largest proportion of drugs?

DRUG INTERACTION TERMINOLOGY

Substrate	Drug or other substance metabolized by CYP450 enzymes
Inhibitor	Blocks the metabolic activity of CYP450 enzymes
Inducer	Enhances the metabolic activity of CYP450 enzymes

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11. Drug A is a substrate of CYP3A4, Drug B is an inhibitor of CYP3A4, and Drug C is an inducer of CYP3A4.

Compared to Drug A being administered alone, how would you expect the concentration of Drug A to change when administered with Drug B?

PLEASE ACCESS YOUR WORKSHEET

12. Drug A is a substrate of CYP3A4, Drug B is an inhibitor of CYP3A4, and Drug C is an inducer of CYP3A4.

Compared to Drug A being administered alone, how would you expect the concentration of Drug A to change when administered with Drug C?

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13. You have a patient using cyclosporine s/p solid organ transplant. Your patient presents with an infection and you are considering the use of the following antibiotics: azithromycin, clarithromycin, or erythromycin. If you were only considering the potential for drug interactions, which antibiotic would be most appropriate for your patient? Defend your answer.

CYP3A4

Enzyme	Substrate	Potent Inhibitors	Potent Inducers
CYP3A4	alprazolam (Xanax) amlodipine (Norvasc atorvastatin (Lipitor) cyclosporine (Sandimmune) diazepam (Valium) estradiol (Estrace) simvastatin (Zocor) sildenafil (Viagra) verapamil (Calan) zolpidem (Ambien)	clarithromycin (Biaxin) diltiazem (Cardizem) erythromycin grapefruit juice itraconazole (Sporanox) ketoconazole (Nizoral) nefazodone (Serzone‡) ritonavir telithromycin (Ketek) verapamil (Calan)	carbamazepine Hypericum perforatum (St. John's wort) phenobarbital phenytoin rifampin

CYP2D6

Enzyme	Substrate	Potent Inhibitors	Potent Inducers
CYP2D6	amitriptyline carvedilol (Coreg) codeine donepezil (Aricept) haloperidol (Haldol) metoprolol (Lopressor) paroxetine risperidone (Risperdal) tramadol (Ultram)	amiodarone (Pacerone) cimetidine (Tagamet) diphenhydramine (Benadryl) fluoxetine (Prozac) paroxetine (Paxil) quinidine ritonavir terbinafine (Lamisil)	Not very susceptible to enzyme induction

PRODRUGS

Compound with negligible, or lower, activity against a specified pharmacological target than one of its major metabolites

Biotransformed

- Esterification of a hydroxyl or amine group
- CYP450 enzymes

Purpose

- Improved bioavailability
- Decreased toxicity
- Delivering drug to specific cells or tissues

PRODRUG EXAMPLE

Loratadine (Claritin)

- Readily absorbed
- Undergoes extensive metabolism to descarboethoxyloratadine (principal pharmacologically active agent)
- CYP3A4 and CYP2D6 primarily responsible

PLEASE ACCESS YOUR WORKSHEET

14. Now consider Drug D, a substrate of CYP3A4. Drug D is prodrug that is metabolized to its active form. How would you expect the therapeutic effect of Drug D to be impacted if it were given with carbamazepine, a potent CYP3A4 inducer?

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

ANY QUESTIONS?

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College of Medicine

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