KAPLAN medical

2006–2007 Edition

USMLE™ Step 1

Lecture Notes

Pharmacology

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USMLE·Step 1

Pharmacology Lecture Notes

2006-2007 Edition

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Author

Lionel P. Rayman, Pharm.D., Ph.D.
Department of Pathology
Forensic Toxicology Laboratory
University of Miami School of Medicine
Miami, FL

Contributing Authors

Craig Davis, Ph.D.
Associate Professor
University of South Carolina School of Medicine
Department of Pharmacology, Physiology, and Neuroscience
Columbia, SC

Maris Victor Nora, Pharm.D., Ph.D.
Associate Professor
Rush Medical College
Chicago.Tl.

Anthony Trevor, Ph.D.
Professor Emeritus
Department of Cellular and Molecular Pharmacology
University of California
San Francisco, CA

Steven R. Harris, Ph.D.
Associate Dean for Basic Sciences
Associate Professor of Pharmacology
Pikeville College School of Osteopathic Medicine
Pikeville, KY

Contributor

Kenneth H. Ibsen, Ph.D.
Director of Academic Development
Kaplan Medical
Professor Emeritus Biochemistry
University of California-Irvine
Irvine, CA

Director of Medical Curriculum
Sonia Reichert, M.D.

Editorial Director
Kathlyn McGreevy

Production Manager
Michael Wolff

Production Editor
William Ng

Cover Design
Joanna Myllo

Cover Art
Christine Schaar

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Preface

These seven volumes of Lecture Notes represent a yearlong effort on the part of the Kaplan Medical faculty to update our curriculum to reflect the most-likely-to-be-tested material on the current USMLE Step 1 exam. Please note that these are Lecture Notes, not review books. The Notes were designed to be accompanied by faculty lectures-live, on video, or on the web. Reading these Notes without accessing the accompanying lectures is not an effective way to review for the USMLE.

To maximize the effectiveness of these Notes, annotate them as you listen to lectures. To facilitate this process, we've created wide, blank margins. While these margins are occasionally punctuated by faculty high-yield "margin notes," they are, for the most part, left blank for your notations.

Many students find that previewing the Notes prior to the lecture is a very effective way to prepare for class. This allows you to anticipate the areas where you'll need to pay particular attention. It also affords you the opportunity to map out how the information is going to be presented and what sorts of study aids (charts, diagrams, etc.) you might want to add. This strategy works regardless of whether you're attending a live lecture or watching one on video or the web.

Finally, we want to hear what you think. What do you like about the notes? What do you think could be improved? Please share your feedback by E-mailingusatmedfeedback@kaplan.com.

Thank you for joining Kaplan Medical, and best of luck on your Step 1 exam!

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SECTION I

General Principles

Pharmacokinetics

1

Pharmacokinetic characteristics of drug molecules concern the processes of absorption, distribution, metabolism, and excretion. The biodisposition of a drug involves its permeation across cellular membrane barriers.

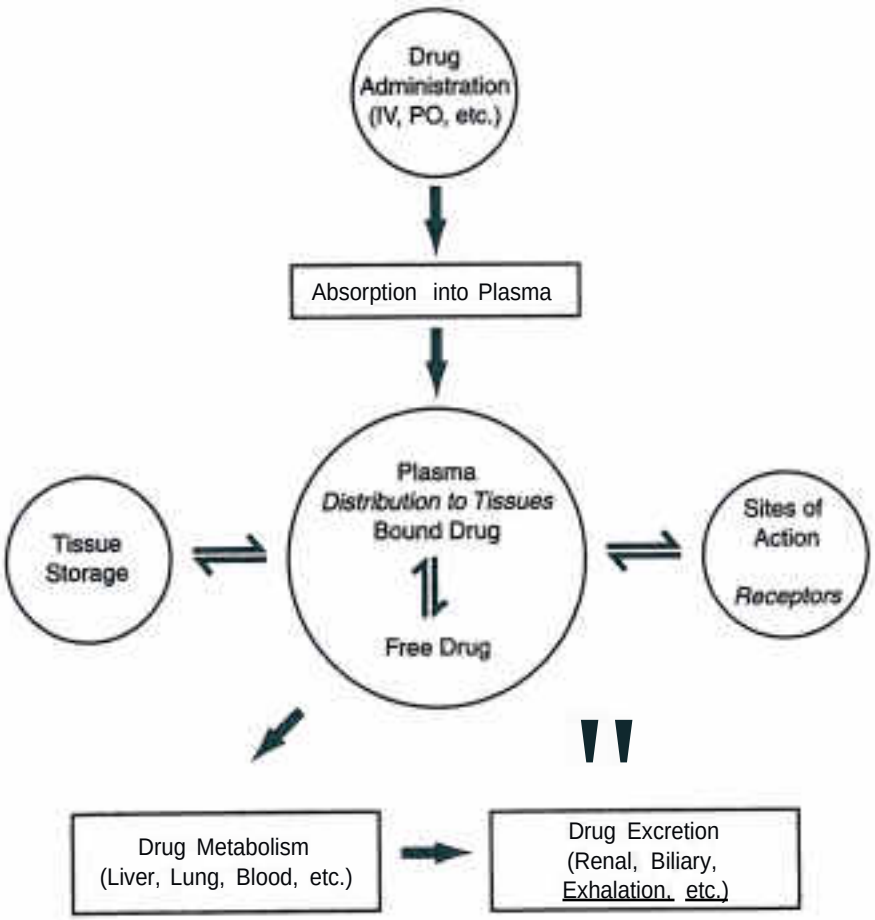


Figure 1-1-1. Drug Blodlsposltion

PERMEATION

- Drug permeation is dependent on:
  - Solubility. Ability to diffuse through lipid bilayers (lipid solubility) is important for most drugs; however, water solubility Can influence permeation through aqueous phases.
  - Concentration gradient. Diffusion down a concentration gradient--only, free, unionized drug forms contribute to the concentration gradient.
  - Surface area and vascularity. Important with regard to absorption of drugs into the systemic circulation. The larger the surface area and the greater the vascularity, the better is the absorption of the drug.
- Ionization
  - Many drugs are weak acids or weak bases and can exist in either nonionized or ionized forms in an equilibrium, depending on the pH of the environment and the pKa (the pH at which the molecule is 50% ionized and 50% nonionized)
  - Only the nonionized (uncharged) form of a drug crosses biomembranes.
  - The ionized form is better renally excreted because it is water soluble.

In A Nutshell

For Weak Acids and Weak Bases

Ionized = Water soluble

Nonionized = Lipid soluble

Weak Acid	R-COOH (crosses membranes)	⇌	R-COO-+H+ (better cleared)
Weak Base	R-NH~ (better cleared)	⇌	$R\text{-}NH_2$+H+ (crosses membranes)

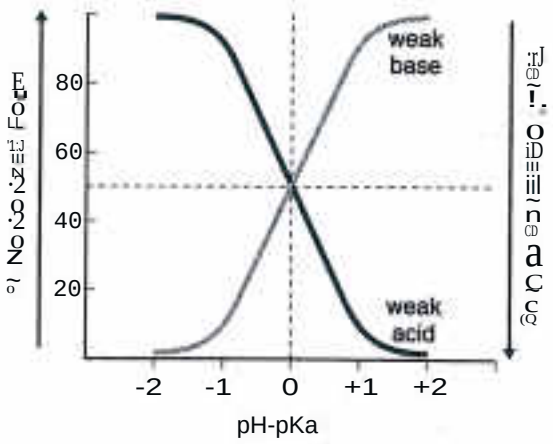


Figure 1·1·2. Degree of Ionization and Clearance Versus pH Deviation from pKa

Ionization Increases Renal Clearance of Drugs

- Only free, unbound drug is filtered.
- Both ionized and nonionized forms of a drug are filtered.
- Only nonionized forms undergo active secretion and active or passive reabsorption.
- Ionized forms of drugs are "trapped" in the filtrate.
- Acidification of urine ~ increases ionization of weak bases ~ increases renal elimination.
- Alkalinization of urine ~ increases ionization of weak adds ~ increases renal elimination.

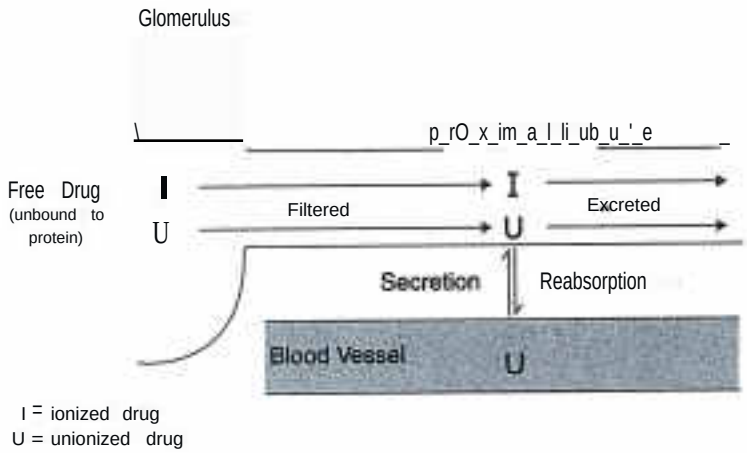


Figure 1-1-3. Renal Clearance of Drug

Modes of Drug Transport Across a Membrane

Table 1-1-1. The Three Basic Modes of Drug Transport Across a Membrane

Mechanism	Direction	Energy Required	Carrier	Saturable
Passive diffusion	Down gradient	No	No	No
Facilitated diffusion	Down gradient	No	Yes	Yes
Active transport	Against gradient (concentration!. electrical)	Yes	Yes	Yes

Clinical Correlate

To Change Urinary pH

- Acidify: NH_4C1,vitamin C, cranberry juice
- Alkalinize: $NaHCO_y$ aceta-zolamide (historically)
- See Aspirin Overdose and Management in Section VI.

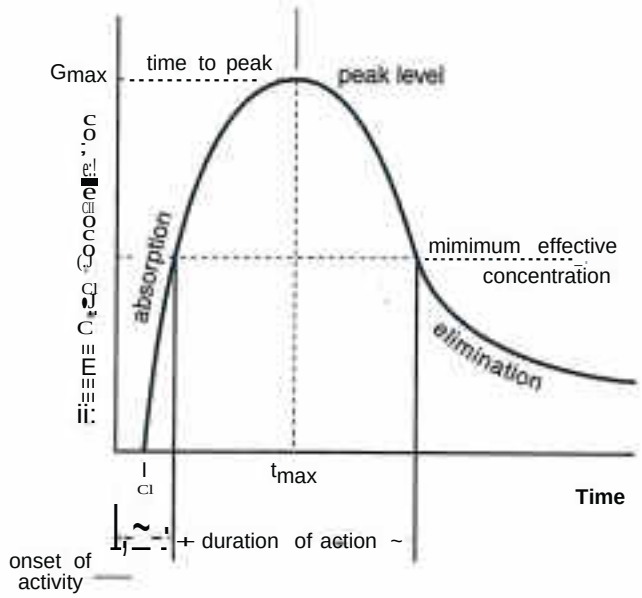
Bridge to Physiology

Ion and molecolar transport mechanisms are discussed in greater detail in Section I of Physiology.

ABSORPTION

- Concerns the processes of entry of a drug into the systemic circulation from the site of its administration.
- The determinants of absorption are those described for drug permeation.
- Intravascular administration (e.g., IV) does not involve absorption, and there is no loss of drug. Bioavailability = 100%
- With extravascular administration (e.g., per os [PO; oral], intramuscular [1M], subcutaneous [sq], inhalation), less than 100% of a dose may reach the systemic circulation because of variations in bioavailability.

Plasma Level Curves



G_{max} = maximal drug level obtained with the dose.
t_{max} = time at which G_{max} occurs.
Lag time = time from administration to appearance in blood.
Onset of activity = time from administration to blood level reaching minimal effective concentration (MEG).
Duration of action = time plasma concentration remains greater than MEG.
Time to peak = time from administration to G_{max}.

Figure 1-1-4. Plot of Plasma Concentration Versus Time

Bioavailability (f)

Measure of the fraction of a dose that reaches the systemic circulation. By definition, intravascular doses have 100% bioavailability, f = 1.

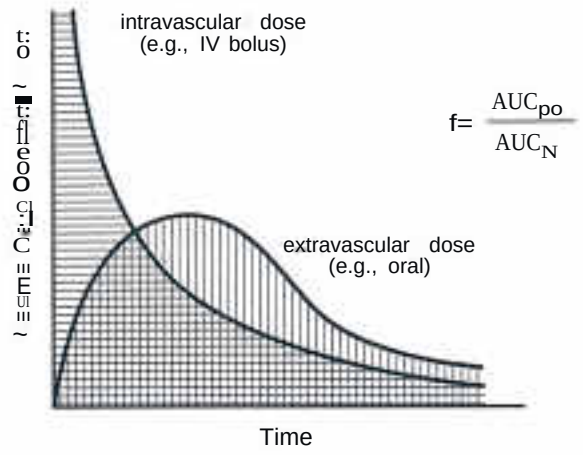


Figure 1-1-5. Area Under the Curve for an IV Bolus and Extravascular Doses

First-Pass Effect

With oral administration, drugs are absorbed into the portal circulation and initially distributed to the liver. For some drugs, their rapid hepatic metabolism decreases bioavailability-the "first-pass" effect.

Examples:

- Lidocaine (IV vs. PO)
- Nitroglycerin (sublingual)

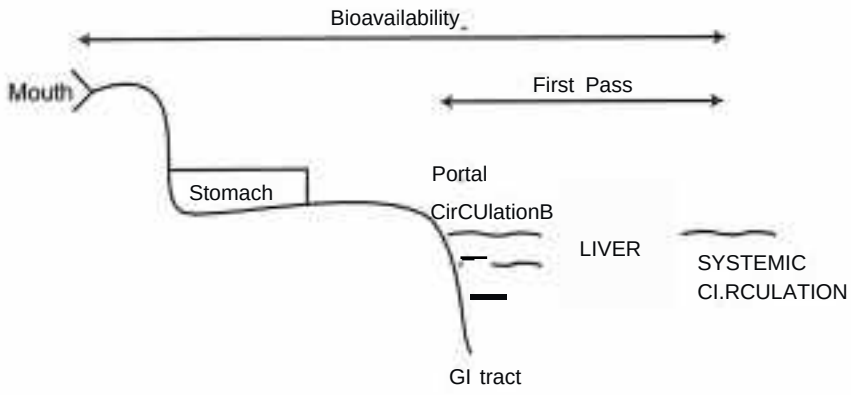


Figure 1-1-6.Bioavailability and First-Pass Metabolism

Abbreviations

AUC: area under the curve

po: oral

IV: intravenous bolus

AUC\v: horizontally striped area

AUC_{po}: vertically striped area

Bioequivalence

For bioequivalence to occur between two formulations of the same compound, they must have:

- the same bioavailability
- the same rate of absorption

Figure Legend

Figure 1-1-7 illustrates an example of bioinequivalence. The two formulations differ in rate of absorption. Brand B is more slowly absorbed than is brand A.

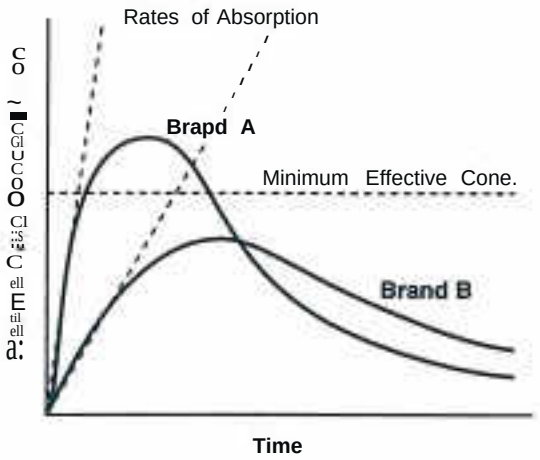


Figure 1-1-7. Effect of Rate of Absorption on Plasma Concentration

C_{max} and t_{max} are rate dependent. The faster the rate of absorption, the smaller the t_{max} and the larger the C_{max} and vice versa.

DISTRIBUTION

- The processes of distribution of a drug from the systemic circulation to organs and tissue.
- Conditions affecting distribution include:
  - Under normal conditions, protein-binding capacity is much larger than is drug concentration. Consequently, the free fraction is generally constant.
  - Many drugs bind to plasma proteins, including albumin, with an equilibrium between bound and free molecules (recall that only unbound drugs cross biomembranes).

Drug + Protein ~ Drug-Protein Complex
(Active, free) (Inactive, bound)

  - Competition between drugs for plasma protein-binding sites may increase the "free fraction," possibly enhancing the effects of the drug displaced. Example: sulfonamides and bilirubin in a neonate

Special Barriers to Distribution

- Placental-most small molecular weight drugs cross the placental barrier, although fetal blood levels are usually lower than maternal. Example: propylthiouracil (PTU) versus methimazole
- Blood-brain-permeable only to lipid-soluble drugs or those of very low molecular weight. Example: levodopa versus dopamine

Apparent Volume of Distribution (Vd)

A kinetic parameter of a drug that correlates dose with plasma level at zero time.

$$V_d = \frac{\text{Dose}}{C_0}$$ where C_0 = [plasma] at zero time

- This relationship can be used for calculating Vd by using the *dose* only if one knows C_0.
- Vd is needed to calculate a loading dose in the clinical setting *(see* Pharmacokinetic Calculation section, Equation 6).
- Vd is low when a high percentage of a drug is bound to plasma proteins.
- Vd is high when a high percentage of a drug is being sequestered in tissues. This raises the possibility of displacement by other agents; examples: verapamil and quinidine can displace digoxin from tissue-binding sites.

Redistribution

In addition to crossing the blood-brain barrier (BBB), lipid-soluble drugs redistribute into fat tissues prior to elimination.

In the case of eNS drugs, the duration of action of an initial dose may depend more on the redistribution rate than on the half-life. With a second dose, the blood/fat is less; therefore, the rate of redistribution is less and the second dose has a longer duration of action.

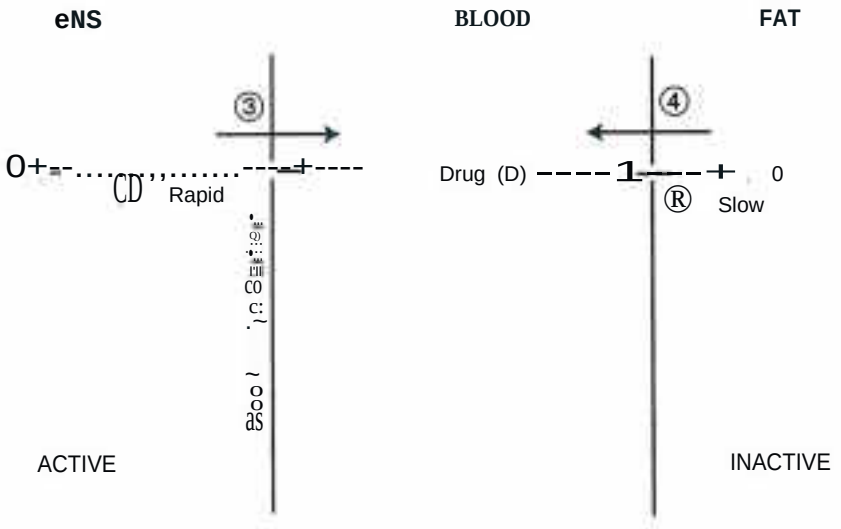


Figure 1-1-8. Redistribution

!~,~0 Physiology

Approximate Vd Values (weight 70 kg)

- plasma volume (3 L)
- blood volume (5 L)
- extracellular fluid (ECF 12-14 L)
- total body water (rBW 40-42 L)

BIOTRANSFORMATION

- The general principle of biotransformation is the metabolic conversion of drug molecules to more water-soluble metabolites that are more readily excreted.
- In many cases, metabolism of a drug results in its conversion to compounds that have little or no pharmacologic activity.
- In other cases, biotransformation of an active compound may lead to the formation of metabolites that also have pharmacologic actions.
- A few compounds (prodrugs) have no activity until they undergo metabolic activation.

Clinical Correlate

Active Metabolites

Biotransformation of the benzodiazepines diazepam results in formation of nordiazepam, a metabolite with sedative-hypnotic activity and a long duration of action.

Drug ---. **Inactive metabolite(s)**

Drug ------+ **Active metabolite(s)**

Prodrug ---+ **Drug**

Figure 1-1-9. Biotransformation of Drugs

Biotransformation Classification

There are two broad types of biotransformation, called phase I and phase II.

Phase I

- Definition: modification of the drug molecule via oxidation, reduction, or hydrolysis.
  - Microsomal metabolism

    Cytochrome P450 isozymes

    - These are major enzyme systems involved in phase I reactions. Localized in the smooth endoplastic reticulum (microsomal fraction) of cells (especially liver, but including GI tract, lungs, and kidney).
    - P450s have an absolute requirement for molecular oxygen and NADPH.
    - Oxidations include hydr6xylations and dealkylations.
    - Multiple CYP families differing by amino acid (AA) composition, by substrate specificity, and by sensitivity to inhibitors and to inducing agents.

Table 1-1-2. Cytochrome P450 Isozymes

CYP450	Substrate Example	Inducers	Inhibitors	Polymorphisms
1A1	Theophylline Acetaminophen	Aromatic hydrocarbons (smoke) Cruciferous vegetables	Quinolones Macrolides	No
2C9	Phenytoin Warfarin	General inducers*	–	Yes
2D6	Many cardiovascular and CNS drugs	None known	Haloperidol Quinidine	Yes
3A4	60% of drugs in PDR	General inducers*	General inhibitors† Grapefruit juice	No

* General inducers: anticonvulsants (barbiturates, phenytoin, carbamazepine), antibiotics (rifampin), chronic alcohol, glucocorticoids.

† General inhibitors: antiulcer medications (cimetidine, omeprazole), antibiotics (chloramphenicol, macrolides, ritonavir, ketoconazole), acute alcohol.

Clinical Correlate

Grapefruit Juice

Active components in grapefruit juice include furanocoumarins capable of inhibiting the metabolism of many drugs, including alprazolam, midazolam, atorvastatin, and cyclosporine. Such compounds may also enhance oral bioavailability by inhibiting drug transporters in the GI tract responsible for intestinal efflux of drugs.

- Nonmicrosomal metabolism

  Hydrolysis

  - Phase I reaction involving addition of a water molecule with subsequent bond breakage
  - Includes esterases and amidases
  - Genetic polymorphism exists with pseudocholinesterases
  - Example: local anesthetics

  Monoamine oxidases

  - Metabolism of endogenous amine neurotransmitters (dopamine, norepinephrine, and serotonin)
  - Metabolism of exogenous compounds (tyramine)

  Alcohol metabolism

  - Alcohols are metabolized to aldehydes and then to acids by dehydrogenases *(see* CNS section)
  - Genetic polymorphisms exist

Phase II

- Definition: Conjugation with endogenous compounds via the activity of transferases
- May follow phase I or occur directly
- Types of conjugation:

  Glucuronidation

  - Inducible
  - May undergo enterohepatic cycling
  - Reduced activity in neonates
  - Examples: morphine and chloramphenicol

Acetylation

- Genotypic variations (fast and slow metabolizers)
- Drug-induced SLE by slow acetylators with hydralazine> procainamide > isoniazid (INH)

Sulfation

- Examples: minoxidil and steroids

Glutathione (GSH) conjugation

- Depletion of GSH in the liver is associated with acetaminophen hepatotoxicity

ELIMINATION

Concerns the processes involved in the elimination of drugs from the body (and/or plasma) and their kinetic characteristics. The major modes of drug elimination are:

- Biotransformation to inactive metabolites
- Excretion via the kidney
- Excretion via other modes, including the bile duct, lungs, and sweat
- Definition: Time to eliminate 50% of a given amount (or to decrease plasma level to 50% of a former level) is called the elimination half-life (t1/2)'

Zero-Order Elimination Rate

- A constant amount of drug is eliminated per unit time; for example, if 80 mg is administered and 10 mg is eliminated every 4 h, the time course of drug elimination is:

80 mg —4h→ 70 mg —4h→ 60 mg —4h→ 50 mg —4h→ 40 mg

- Rate of elimination is independent of plasma concentration (or amount in the body).
- Drugs with zero-order elimination have no fixed half-life ($t_{1/2}$ is a variable).
- Drugs with zero-order elimination include ethanol (except low blood levels), phenytoin (high therapeutic doses), and salicylates (toxic doses).

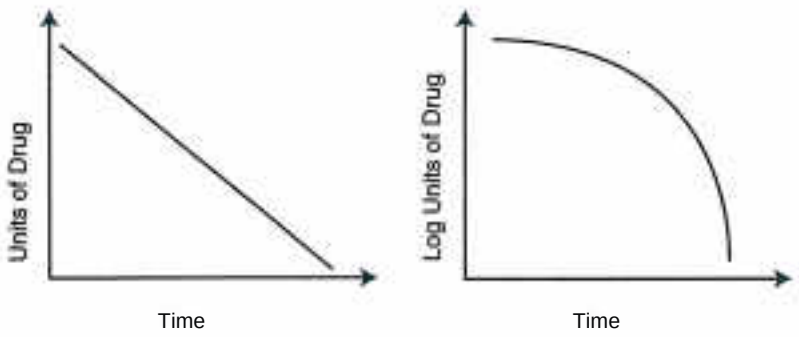
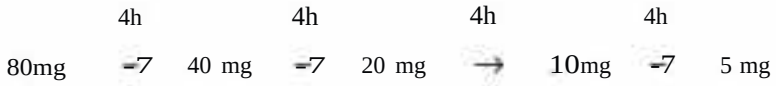


Figure 1-1-10a. Plots of Zero-Order Kinetics

First-Order Elimination Rate

- A constant fraction of the drug is eliminated per unit time (t1/2is a constant). Graphically, first-order elimination follows an exponential decay versus time.
- For example, if 80 mg of a drug is administered and its elimination half-life = 4 h, the time course of its elimination is:



- Rate of elimination is directly proportional to plasma level (or the amount presentj-« the higher the amount, the more rapid the elimination.
- Most drugs follow first-order elimination rates.
- $tl/_2$ is a constant
- t1/2is inversely related to the elimination constant (k): $tl/_2 = 0.7/k$

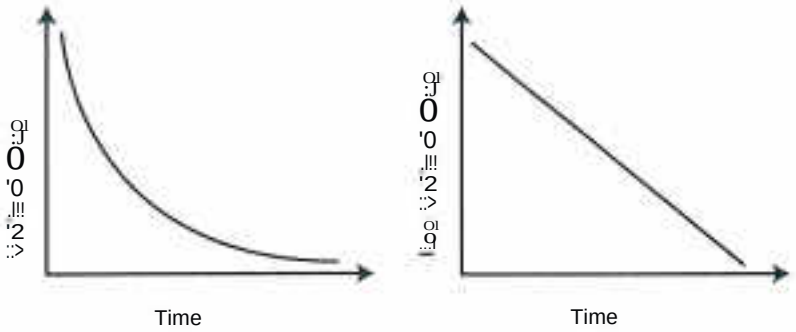


Figure 1-1-10b. Plots of First-Order Kinetics

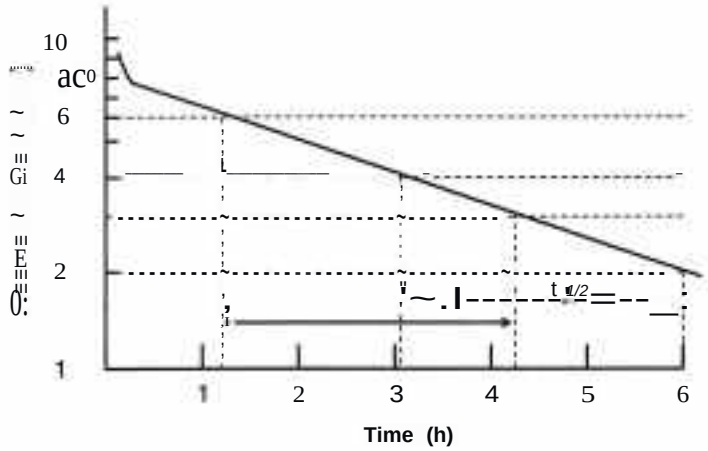
In A Nutshell

Elimination Kinetics

- Most drugs follow first order-rate falls as plasma level falls.
- Zero order is due to saturation of elimination mechanisms; e.g., drug-metabolizing reactions have reached V_{max}
- Zero order-i-elimination rate is constant; t1/2 is a variable.
- First order- elimination rate is variable; t1/2 is a constant.

Graphic Analysis

Example of a graphic analysis of $t_{1/2}$:



CO= plasma concentration at zero time

Figure 1-1-11. Plasma Decay Curve-First-Order Elimination

Figure 1-1-11 shows a plasma decay curve of-a drug with first-order elimination plotted on semilog graph paper. The elimination half-life ($t_{1/2}$) and the theoretical plasma concentration at zero time (Co) can be estimated from the graphic relationship between plasma concentrations and time. COis estimated by extrapolation of the linear plasma decay curve to intercept with the vertical axis.

Bridge to Renal

Inulin clearance is used to estimate GFR because it is not reabsorbed or secreted. A normal GFR is close to 120 mljmin.

Renal Elimination

- Rate of elimination = glomerular filtration rate (GFR) + active secretion - reabsorption (active or passive).
- Filtration is a nonsaturable linear function. Ionized and nonionized forms of drugs are filtered, but protein-bound drug molecules are not.
- Clearance (Cl):
  - Definition: volume of blood cleared of drug per unit of time
  - Cl is constant in first-order kinetic
  - Cl = GFR when there is no reabsorption or secretion and no plasma protein binding
  - Protein-bound drug is not cleared; Cl = free fraction x GFR
  - $Cl = kxV_d$

STEADY STATE

- Steady state is reached either when rate in = rate out or when values associated with a dosing interval are the same as those in the succeeding interval.

Plateau Principle

The time to reach steady state is dependent only on the elimination half-life of a drug and is independent of dose size and frequency of administration.

Figure 1-1-12 shows plasma levels (solid lines) achieved following the IV bolus administration of 100 units of a drug at intervals equivalent to every half-life $t_{1/2}$.= 4 h (r). With such intermittent dosing, plasma levels oscillate through peaks and troughs, with averages shown in the diagram by the dashed line.

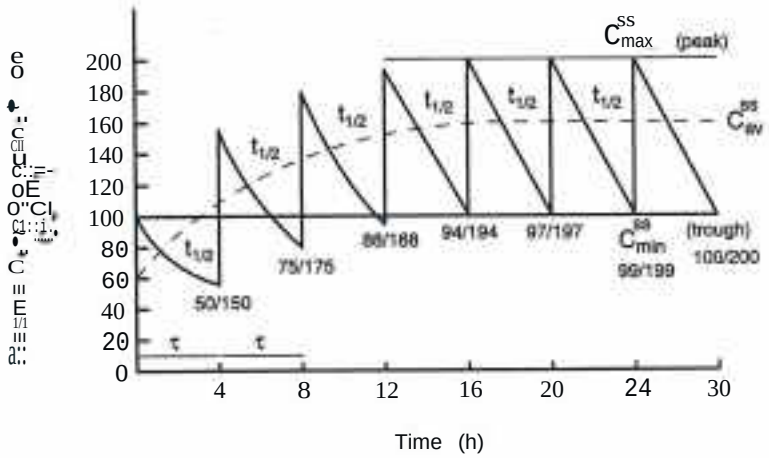


Figure 1-1-12. Oscillations in Plasma Levels Following IV Bolus Administration at Intervals Equal to Drug Half-Life

Note the following:

Although it takes> 7 $t_{1/2}$ to reach mathematical steady state, by convention clinical steady state is accepted to be reached at 4-5 $t1/_2$.

Note

$MD = C^{ss} \times Cl \times \tau$

Note

See legend on page 17.

Classic Clues

Time and Steady State

50% = 1 x half-life

90% = 3.3 x half-life

95% = 4-5 x half-life

"100"0/0 = >7 x half-life

Rate of Infusion

The graph in Figure 1-1-13 shows the increases in plasma levels of the same drug infused at five different rates. Regardless of the rate of infusion, it takes the same amount of time to reach steady state.

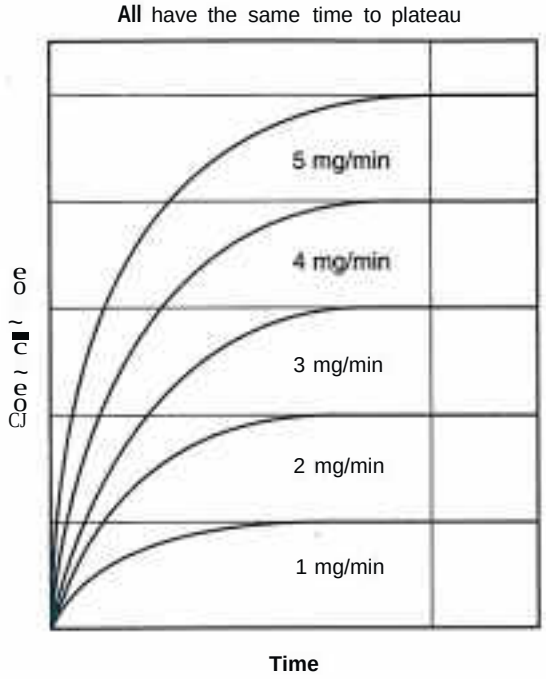


Figure 1-1-13. Effect of Rate of Infusion on Plasma Level

Note

- Remember that dose and plasma concentration (e^{SS}) are directly proportional.
- ka=C1x(SS

Rate of infusion (1<0) does determine plasma level at steady state. If the rate of infusion is doubled, then the plasma level of the drug at steady state is doubled. A similar relationship can exist for other forms of drug administration (e.g., per oral)--doubling oral doses can double the average plasma levels of a drug. Plotting dose against plasma concentration yields a straight line (linear kinetics).

Effect of Loading Dose

- It takes 4-5 half-lives to achieve steady state.
- In some situations, it may be necessary to give a higher dose (loading dose) to more rapidly achieve effective blood levels.

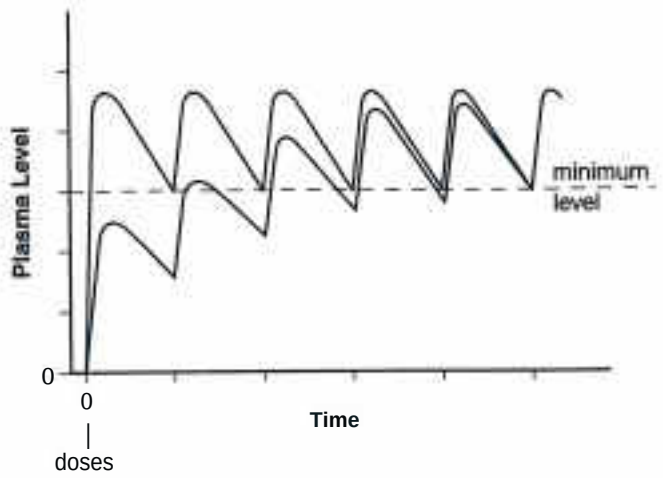


Figure 1-1-14. Effect of a Loading Dose on the Time Required to Achieve the Minimal Effective Plasma Concentration

Note

$LD = C^{ss} \times V_d$

- Such loading doses are often one time only and (as shown in Figure I-1-14) are estimated to put into the body the amount of drug that should be there at a steady state.
- For the exam, if doses are to be administered at each half-life of the drug and the minimum efficacy concentration is equivalent to C^{SS}_{min}, then the loading dose is twice the amount of the dose used for maintenance. For any other interval of dosing, Equation 6 (next page) is used.

IMPORTANT PHARMACOKINETICS CALCULATIONS

The following six relationships are important for calculations:

Single-Dose Equations

(I) Volume of distribution 01d)

$V_d = D/C^0$

(2) Half-life (t1/2)

$t_{1/2} = O.7/k$

(3) Clearance (Cl)

$CI = kxV_d$

(4) From equations 2 and 3,

$t_{1/2} = 0.7$ x ViCI

Note

C0 = cone. at time zero

Cl = clearance

C_{SS} = steady state cone.

D = dose

k = elimination constant

ka = infusion rate

LD = loading dose

MD = maintenance dose

1: = dosing interval

Vd = volume of distribution

Multiple Doses or Infusion Rate Equations

(5) Infusion rate (k_0)

$k_0 = C1 \times C''$

(6) Loading dose (LD)

$LD = V_d \times C'S$

(7) Maintenance dose (MD)

$MD = Cl \times C'S \times 1:$

Chapter Summary

The pharmacokinetic characteristics of a drug are dependent upon the processes of absorption, distribution, metabolism, and excretion. An important element concerning drug biodistribution is permeation, which is the ability to cross membranes, cellular and otherwise.

A drug's ability to permeate is dependent on its solubility, the concentration gradient, and the available surface area, which is influenced by the degree of vascularity. Ionization affects permeation because unionized molecules are minimally water soluble but do cross biomembranes, a feat beyond the capacity of ionized molecules. Figure 1-1-2 illustrates the principles associated with ionization, and Table 1-1-1 summarizes the three basic modes of transport across a membrane: passive, facilitated, and active.

Absorption concerns the processes of entry into the systemic circulation. Except for the intravascular route, some absorptive process is always involved. These have the same determinants as those of permeation. Because absorption may not be 100% efficient, less than the entire dose administered may get into the circulation.

Any orally administered hydrophilic drug will be absorbed first into the portal vein and sent directly to the liver, where it may be partially deactivated. This is the first-pass effect.

The distribution of a drug into the various compartments of the body is dependent upon its permeation properties and its tendency to bind to plasma proteins. The placental and blood-brain barriers are of particular importance in considering distribution. The Vd is a kinetic parameter that correlates the dose given to the plasma level obtained: the greater the V_d value, the less the plasma concentration.

As well as having the ability to cross the blood-brain barrier, lipophilic drugs have a tendency to be deposited in fat tissue. As blood concentrations fall, some of this stored drug is released. This is called redistribution. Because with each administration more lipophilic drug is absorbed into the fat, the duration of action of such a drug increases with the number of doses until the lipid stores are saturated.

Biotransformation is the metabolic conversion of drugs, generally to less active compounds but sometimes to iso-active or more active forms. Phase I biotransformation occurs via oxidation, reduction, or hydrolysis. Phase \I metabolism occurs via conjugation.

(Continued)

Chapter Summary *(continued)*

The cytochrome P-450 isozymes are a family of microsomal enzymes that collectively have the capacity to transform thousands of different molecules. The transformations include hydroxylations and dealkylations, as well as the promotion of oxidation/reduction reactions. These enzymes have an absolute requirement for NADPH and O_2. The various isozymes have different substrate and inhibitor specificities.

Other enzymes involved in phase I reactions are hydrolases (e.g., esterases and amidases) and the nonmicrosomal oxidases (e.g, monoamine oxidase and alcohol and aldehyde dehydrogenase).

Phase \I reactions involve conjugation, sometimes after a phase \ hydroxylation. The conjugation may be glucuronidation, acetylation, sulfation, or addition of glutathione.

Modes of drug elimination are biotransformation, renal excretion, and excretion by other routes (e.g., bile, sweat, lungs, etc.). Most drugs follow first-order elimination rates. Figures I-I-lOa and I-I-lob compare zero- and first-order elimination, and Figure \-1-11 demonstrates how the t1/2 and the theoretical zero time plasma concentration (CO) can be graphically determined. Two important relationships are dose = V_d x CO and $t_{1/2}$ = O.7/k (k = the first-order rate constant of elimination).

Renal clearance (Cl_R) represents the volume of blood cleared by the kidney per unit time and is a constant for drugs with first-order elimination kinetics. Total body clearance equals renal plus nonrenal clearance. An important relationship is Cl = k x V_d.

A steady state is achieved when the rate coming in equals the rate going out. The time to reach a steady state is dependent only on the elimination half-life. It is independent of dose and frequency of administration or rate of infusion (see Figures 1-1-12, -13, and -14).

lather equations describing relationships important for calculation are those used to determine the loading dose, infusion rate, and maintenance dose.



Pharmacodynamics

2

DEFINITIONS

- Pharmacodynamics relates to drugs binding to receptors and their effects.
- Agonist: A drug is called an agonist when binding to the receptor results in a response.
- Antagonist: A drug is called an antagonist when binding to the receptor is *not* associated with a response. The drug has an effect only by preventing an agonist from binding to the receptor.
- Affinity: ability of drug to bind to receptor, shown by the proximity of the curve to the *y* axis (if the curves are parallel); the nearer the *y* axis, the greater the affinity
- Potency: shows relative doses of two or more agonists to produce the same magnitude of effect, again shown by the proximity of the respective curves to the *y* axis (if the curves do not cross)
- Efficacy: a measure of how well a drug produces a response (effectiveness), shown by the maximal height reached by the curve

GRADED (QUANTITATIVE) DOSE-RESPONSE (D-R) CURVES

Plots of dose (or log dose) versus response for drugs (agonists) that activate receptors can reveal information about affinity, potency, and efficacy of these agonists.

Parallel and Nonparallel D-R Curves

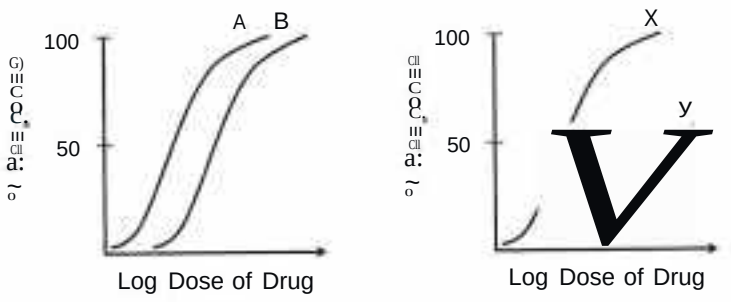


Figure 1-2-1.Comparison of D-R Curves for Two Drugs Acting on the Same *(left panel)* and on Different *(right panel)* Receptors

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Definitions

Affinity: how well a drug and a receptor recognize each other. Affinity is inversely related to the K_d of the drug. Notice the analogy to the ~ value used in enzyme kinetic studies.

Potency: the quantity of drug required to achieve a desired effect. In D-R measurements, the chosen effect is usually 50% of the maximal effect, but clinically, *any* size response can be sought.

Efficacy: the maximal effect an agonist can achieve at the highest practical concentration. Notice the analogy with the V_{max} used in enzyme kinetic studies.

It may be seen from the log dose-response curves in Figure 1-2-1 that:

1. When two drugs interact with the same receptor (same pharmacologic mechanism), the D-R curves will have parallel slopes. Drugs A and B have the same mechanism; drugs X and Y do not.

2. Affinity can be compared only when two drugs bind to the same receptor. Drug A has a greater affinity than drug B.

3. In terms of potency, drug A has greater potency than drug B, and X is more potent than Y.

4. In terms of efficacy, drugs A and B are equivalent. Drug X has greater efficacy than drug Y.

Full and Partial Agonists

- Full agonists produce a maximal response-they have maximal efficacy.
- Partial agonists are incapable of eliciting a maximal response and are less effective than full agonists.
- In Figure 1-2-2, drug B is a full agonist, and drugs A and C are partial agonists.

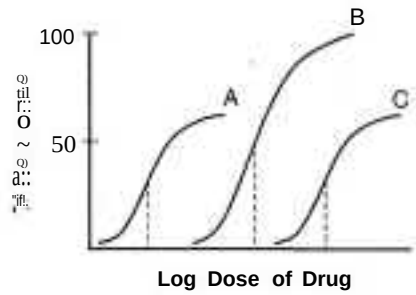

Figure 1-2-2. Efficacy and Potency of Full and Partial Agonists

- Drug A is more potent than drug C, and drug B is more potent than drug C. However, no general comparisons can be made between drugs A and B in terms of potency because the former is a partial agonist and the latter is a full agonist. At low responses, A is more potent than B, but at high responses, the reverse is true.

Duality of Partial Agonists

- In Figure 1-2-3, the lower curve represents effects of a partial agonist when used alone-its *ceiling effect* = 50% of maximal in this example.

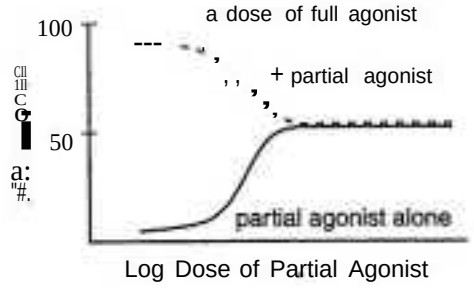

Figure 1-2-3.Duality of Partial Agonists

- The upper curve shows the effect of increasing doses of the partial agonist on the maximal response (100%) achieved in the presence of or by pretreatment with a full agonist.
- As the partial agonist displaces the full agonist from the receptor, the response is reduced-the partial agonist is acting as an antagonist.

Antagonism and Potentiation

- Graded dose-response curves also provide information about antagonists-drugs that interact with receptors to interfere with their activation byagonists.

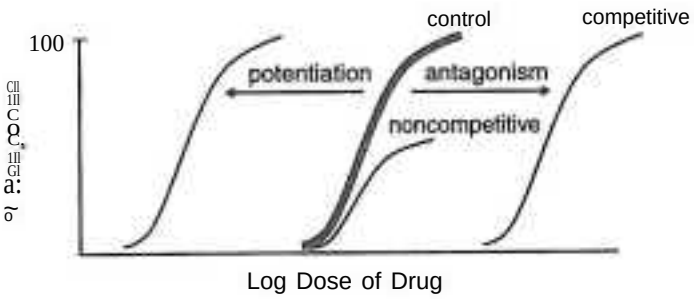

Figure 1-2-4. D-R Curves of Antagonists and Potentiators

- Pharmacologic antagonism (same receptor)
  - Competitive antagonists:
    - Cause a parallel shift to the right in the D-R curve for agonists
    - Can be reversed by ↑ the dose of the agonist drug
    - Appears to ↓ the potency of the agonist

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Parallels between Receptor Antagonists and Enzyme Inhibitors

Competitive antagonists are analogous to competitive inhibitors; they decrease affinity (↑ K_m) but not maximal response (V_{max} remains the same).

Noncompetitive antagonists decrease V_{max} but do not change the K_m.

- Noncompetitive antagonists:
  - Cause a nonparallel shift to the right
  - Can be only partially reversed by ↑ the dose of the agonist
  - Appear to ↓ the efficacy of the agonist
- Physiologic antagonism (different receptor)
  - Two agonists with opposing action antagonize each other
  - Example: a vasoconstrictor with a vasodilator
- Chemical antagonism:
  - Formation of a complex between effector drug and another compound
  - Example: protamine binds to heparin to reverse its actions
- Potentiation
  - Causes a parallel shift to the left to the D-R curve
  - Appears to ↑ the potency of the agonist

QUANTAL (CUMULATIVE) D-R CURVES

- These curves plot the percentage of a population responding to a specified drug effect versus dose or log dose. They permit estimations of the median effective dose, or effective dose in 50% of a population-ED 50.
- Quantal curves can reveal the range of intersubject variability in drug response. Steep D-R curves reflect little variability; flat D-R curves indicate great variability in patient sensitivity to the effects of a drug.

Toxicity and the Therapeutic Index (TI)

- Comparisons between ED50 and TD50 values permit evaluation of the relative safety of a drug (the therapeutic index), as would comparison between ED50 and the lethal median dose (LD50) if the latter is known.

$$TI = \frac{TD50}{ED\ 50} \quad or \quad \frac{LD50}{ED50}$$

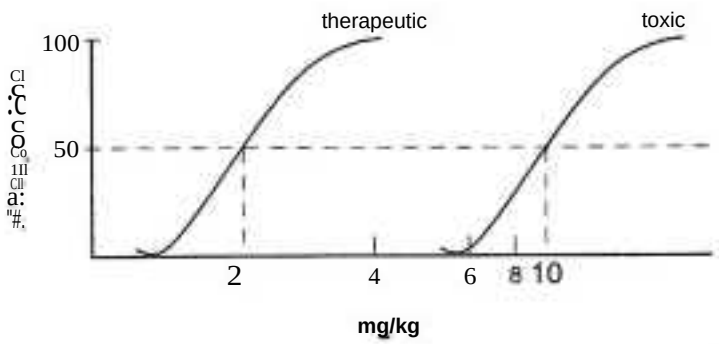

Figure 1-2-5. Quantal D-R Curves of Therapeutic and Toxic Effects of a Drug

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- As shown in Figure 1-2-5, these D-R curves can also be used to show the relationship between dose and toxic effects of a drug. The median toxic dose of a drug (TD50) is the dose that causes toxicity in 50% of a population.
- From the data shown, T1 = *10/2* = 5
- Such indices are of most value when toxicity represents an extension of the pharmacologic actions of a drug. They do not predict idiosyncratic reactions or drug hypersensitivity.

SIGNALING MECHANISMS: TYPES OF DRUG-RESPONSIVE SIGNALING MECHANISMS

- Binding of an agonist drug to its receptor activates an effector or signaling mechanism.
- Several different types of drug-responsive signaling mechanisms are known.

Intracellular Receptors

- These include receptors for steroids. Binding of hormones or drugs to such receptors releases regulatory proteins that permit activation and in some cases dimerization of the hormone-receptor complex. Such complexes translocate to the nucleus, where they interact with response elements in spacer DNA. This interaction leads to changes in gene expression. For example, drugs interacting with glucocorticoid receptors lead to gene expression of proteins that inhibit the production of inflammatory mediators.
- Other examples include intracellular receptors for thyroid hormones, gonadal steroids, and vitamin D.
- Pharmacologic responses elicited via modification of gene expression are usually slower in onset but longer in duration than many other drugs.

Membrane Receptors Directly Coupled to Ion Channels

- Many drugs act by mimicking or antagonizing the actions of endogenous ligands that regulate flow of ions through excitable membranes via their activation of receptors that are directly coupled (no second messengers) to ion channels.
- For example, the nicotinic receptor for ACh (present in autonomic nervous system [ANS] ganglia, the skeletal myoneural junction, and the central nervous system [CNS]) is coupled to a *Na+/K+* ion channel. The receptor is a target for many drugs, including nicotine, choline esters, ganglion blockers, and skeletal muscle relaxants.
- Similarly, the $GABA_A$ receptor in the CNS, which is coupled to a chloride ion channel, can be modulated by anticonvulsants, benzodiazepines, and barbiturates.

Receptors Linked Via Coupling Proteins to Intracellular Effectors

- Many receptor systems are coupled via GTP-binding proteins (G-proteins) to adenylyl cyclase, the enzyme that converts ATP to cAMP, a second messenger that promotes protein phosphorylation by activating protein kinase A. These receptors are typically "serpentine," with seven transmembrane spanning domains, the third of which is coupled to the G-protein effector mechanism.
- Protein kinase A serves to phosphorylate a set of tissue-specific substrate enzymes or transcription factors (CREB), thereby affecting their activity.

In A Nutshell

Key ANS Receptors

Ml' My <Xl: G_q activation of phospholipase C

M_2, Uz' D_2: G_j inhibition of adenylyl cyclase

~1' ~2' D_1: C, activation of adenylyl cyclase

G_s Proteins

- Binding of agonists to receptors linked to G_s proteins increases cAMP production.
- Such receptors include those for catecholamines (beta), dopamine (D!), glucagon, histamine (Hz), prostacyclin, and some serotonin subtypes.

G_j Proteins

- Binding of agonists to receptors linked to G_j proteins decreases cAMP production.
- Such receptors include adrenoreceptors (alpha.), ACh (M_Z), dopamine (D_Z subtypes), and several opioid and serotonin subtypes.

G_q Proteins

- Other receptor systems are coupled via GTP-binding proteins (G_q), which activate phospholipase C. Activation of this enzyme releases the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG) from the membrane phospholipid phosphatidylinositol bisphosphate (PIP z). The IP3 induces release of Ca^{Z+} from the sarcoplasmic reticulum (SR), which, together with DAG, activates protein kinase C. The protein kinase C serves then to phosphorylate a set of tissue-specific substrate enzymes, usually not phosphorylated by protein kinase A, and thereby affects their activity.
- These signaling mechanisms are invoked following activation of receptors for ACh (M! and M_3), norepinephrine (alpha!), angiotensin II, and several serotonin subtypes.

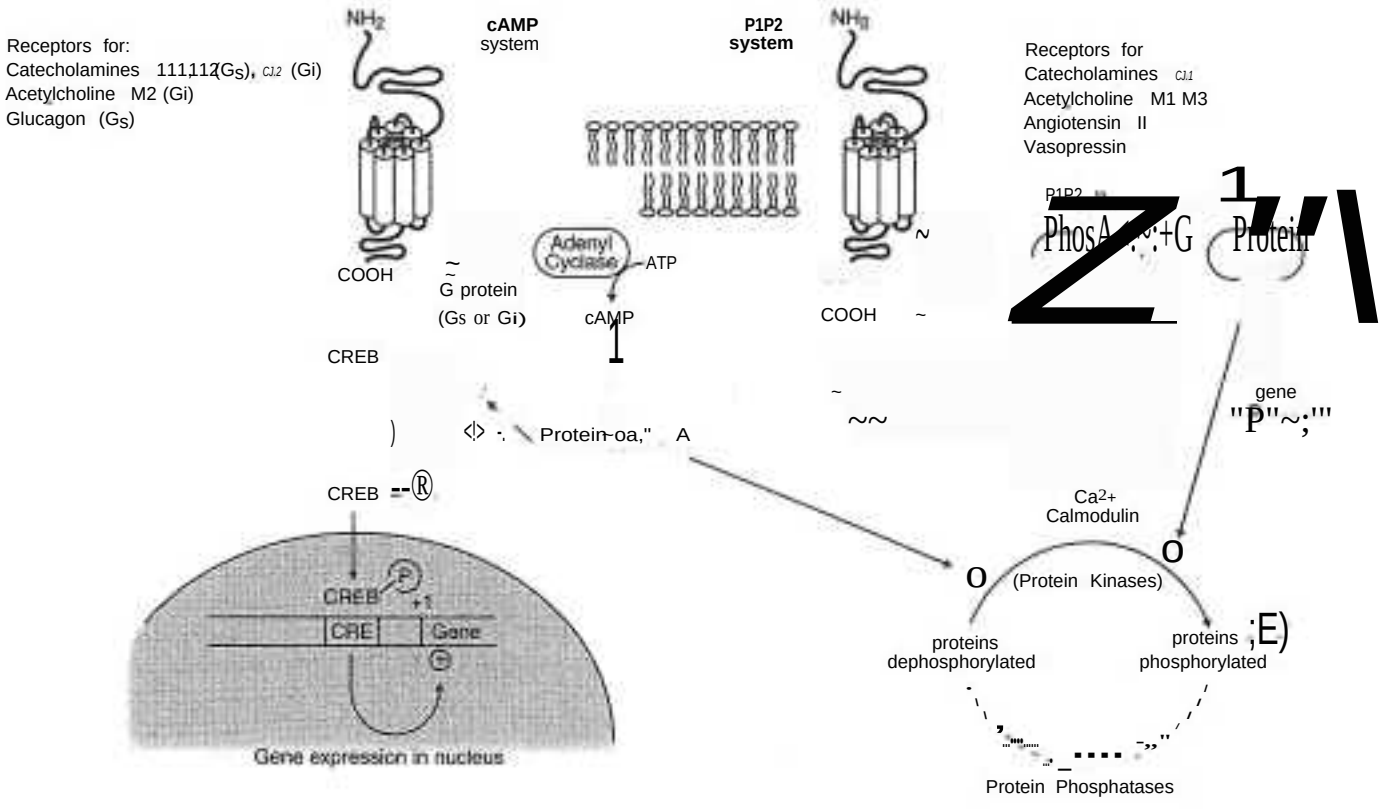


Figure 1-2-6. Receptors Using Cyclic-AMP and IP_a, DAG, Ca^{2+} as Second Messengers

Cyclic GMP and Nitric Oxide Signaling

- cGMP is a second messenger in vascular smooth muscle that facilitates dephosphorylation of myosin light chains, preventing their interaction with actin and thus causing vasodilation.
- Nitric oxide (NO) is synthesized in endothelial cells and diffuses into smooth muscle.
- NO activates guanylyl cyclase, thus increasing cGMP in smooth muscle.
- Vasodilators ↑ synthesis of NO by endothelial cells.

Receptors That Function as Enzymes or Transporters

- There are multiple examples of drug action that depend on enzyme inhibition, including inhibitors of acetylcholinesterase, angiotensin-converting enzyme, aspartate protease, carbonic anhydrase, cyclooxygenases, dihydrofolate reductase, DNA/RNA polymerases, monoamine oxidases, Na/K-ATPase, neuraminidase, and reverse transcriptase.
- Examples of drug action on transporter systems include the inhibitors of reuptake of several neurotransmitters, including dopamine, GABA, norepinephrine, and serotonin.

Receptors That Function as Transmembrane Enzymes

- These receptors mediate the first steps in signaling by insulin and growth factors, including epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). They are membrane-spanning macromolecules with recognition sites for the binding of insulin and growth factors located externally and a cytoplasmic domain that usually functions as a tyrosine kinase. Binding of the ligand causes conformational changes (e.g., dimerization) so that the tyrosine kinase domains become activated, ultimately leading to phosphorylation of tissue-specific substrate proteins.
- Guanyl cyclase–associated receptors: stimulation of receptors to atrial natriuretic peptide activates the guanyl cyclase and ↑ cyclic GMP (cGMP)

Receptors for Cytokines

- These include the receptors for erythropoietin, somatotropin, and interferons.
- Their receptors are membrane spanning and on activation can activate a distinctive set of cytoplasmic tyrosine kinases (Janus kinases [JAKs]).
- JAKs phosphorylate signal transducers and activators of transcription (STAT) molecules.
- STATs dimerize and then dissociate, cross the nuclear membrane, and modulate gene transcription.

Bridge to Biochemistry

See Chapter 9 of the Biochemistry Lecture Notes for additional discussion of signal transduction.

Clinical Correlate

Drugs acting via NO include nitrates (e.g., nitroglycerin) and M-receptor agonists (e.g., bethanechol). Endogenous compounds acting via NO include bradykinin and histamine.

DRUG DEVELOPMENT AND TESTING

The Food and Drug Administration (FDA)

The FDA regulates both the efficacy and safety of drugs but not of foods, nutritional supplements, and herbal remedies.

Preclinical Animal Studies

To initiate studies of a new drug in human subjects, the results of extensive preclinical animal studies (usually on two different animal species) must first be submitted to the FDA. These include data on:

- Organ system toxicity of the compound following acute, subacute, and chronic exposure
- Mutagenic (e.g., Ames test) and carcinogenic potential
- Effects on reproductive performance
- Data on the potential effectiveness of the drug if animal models of human disease or dysfunction exist

Clinical Testing

Initiation of human studies requires an investigational new drug (IND) exemption.

Phase 1

"Is it safe?" Dose-response studies in a small group of volunteers who do not have the target disease or dysfunction. Often includes pharmacokinetic characterization.

Phase 2

"Does it work?" Evaluation of drug effectiveness in 100 or more patients with the target disease or dysfunction in comparison with placebo and a positive control-single or double blind.

Phase 3

"How well does it work, and what are the common side effects?" Evaluation in 1,000 or more patients with the target disease or dysfunction in comparison with a placebo and a positive control-usually double blind.

Phase 4

Follows a new drug application (NDA), a request for marketing approval, and involves post-marketing surveillance of drug adverse effects. In addition to further quantitating the incidence of common side effects, this phase may reveal less common and possibly more severe toxicities that could warrant drug withdrawal.

Teratogenicity

- The FDA has classified drugs into five categories (A, B, C, D, and X).
- Class A has no risks, and Class X designates absolute contraindication.
- It is based on animal studies and, when available, human studies.
- In Class D, benefits outweigh the risk.

Table 1-2-1. FDA Classification of Drugs and Pregnancy

Class	Pregnant Human Studies	Pregnant Animal Studies	Examples
A	–	–	Folic acid Thyroid hormones
B	0 *or* –	– +	Zidovudine (AZT)
C	0 or 0	+ 0	Aspirin
D	+	+	ACE inhibitors Anticonvulsants
X	+	+	Statins, oral contraceptive pills (OCP), clomiphene, misoprostol, high-dose vitamin A

– = Studies have proven absence of teratogenicity; 0 = no studies available; + = studies have proven teratogenicity

Chapter Summary

Plots of dose or log dose against response to a drug (agonist) can be used to assess the drug's affinity to a receptor, its potency (the amount of drug required to achieve half its maximal effect), and its efficacy (the maximal effect). Full agonists achieve full efficacy; partial agonists do not. Therefore, when a partial agonist is added to a system in which a full agonist is acting at its maximal efficacy, the partial agonist acts as a competitive inhibitor, as if it were an antagonist. These effects can be studied graphically.

Antagonists are compounds that inhibit the activity of an agonist but have no effect of their own. Generally, antagonists act competitively by sharing a binding site on the receptor, but some act noncompetitively. Whether an antagonist acts competitively or noncompetitively can also be determined graphically.

Antagonism may be pharmacologic (shared receptor), physiologic (acting on different systems having opposing physiologic responses), or chemical.

Some effector molecules potentiate (i.e., enhance) the effect of an agonist.

Quantal curves are plots of the percentage of a population responding to a specific drug versus the concentration (or log concentration) of that drug. They are used to gauge the median effective pharmacological dose (ED50) or the median toxic dose (TD50). These values can be used to evaluate the relative safety of a drug (the therapeutic index).

Drugs may act on intracellular receptors, membrane receptors directly coupled to ion channels, receptors linked via coupling proteins to intracellular effectors, receptors influencing cGMP and nitric oxide signaling, receptors that function as enzymes or transporters, receptors that function as transmembrane enzymes, or receptors for cytokines.

The FDA regulates the efficacy and safety of drugs but not of foods, herbs, or nutritional supplements. Before being approved by the FDA, a drug must first undergo preclinical animal studies and then phase 1, 2, 3, and 4 clinical studies. FDA also classifies drugs and their relative risks of teratogenicity during pregnancy.

Practice Questieas

3

GENERAL PRINCIPLES

1. Which of the following routes of drug administration produces the most rapid absorption?

   A. Inhalation
   B. Intravenous
   C. Oral
   D. Rectal
   E. Sublingual

2. If a drug is highly bound to plasma proteins, it

   A. has a large volume of distribution
   B. has a high renal clearance
   C. is a likely candidate for drug interactions
   D. is most likely carried by alpha-glycoprotein
   E. is a quaternary ammonium salt

3. Most drugs gain entry to cells by

   A. passive diffusion with zero-order kinetics
   B. passive diffusion with first-order kinetics
   C. active transport with zero-order kinetics
   D. active transport with first-order kinetics
   E. passive diffusion through membrane pores

4. A patient was given a 160-mg dose of a drug IV, and 80 mg was eliminated during the first 120 minutes. If the drug follows first-order elimination kinetics, how much of the drug will remain 6 hours after its administration?

   A. None
   B. 10 mg
   C. 20 mg
   D. 40 mg
   E. 60 mg

5. A subject in whom the renal clearance of inulin is 120 mLimin is given a drug, the clearance of which is found to be 18 mLimin. If the drug is 40% plasma protein bound, what percentage of filtered drug must be reabsorbed in the renal tubules?

   A. None
   B. 12.5
   C. 25
   D. 50
   E. 75

6. If a drug is known to be distributed into total body water, what dose (mg) is needed to obtain an initial plasma level of 10 mg/L in a patient weighing 70 kg?

   A. 420
   B. 300
   C. 210
   D. 100
   E. 70

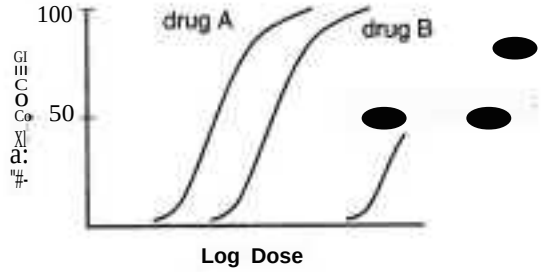
7. Which of the following is a phase I drug metabolism reaction?

   A. Acetylation
   B. Glucuronidation
   C. Methylation
   D. Reduction
   E. Sulfation

8. With chronic administration, which one of the following drugs is LEAST likely to induce the formation of hepatic microsomal drug-metabolizing enzymes?

   A. Carbamazepine
   B. Ethanol
   C. Ketoconazole
   D. Phenobarbital
   E. Rifampin

9. The data presented in the figure below show that



A. drugs A and C have equal efficacy
B. drug A is more potent than drug B
C. drug B is a partial agonist
D. drugs A and B have the same affinity and efficacy
E. drugs A and B are partial agonists

10. A sOO-mg dose of a drug has therapeutic efficacy for 6 h. If the half-life of the drug is 8 h, for how long would a l-g dose be effective?

A. 8h
B. 12 h
C. 14 h
D. 16h
E. 24h

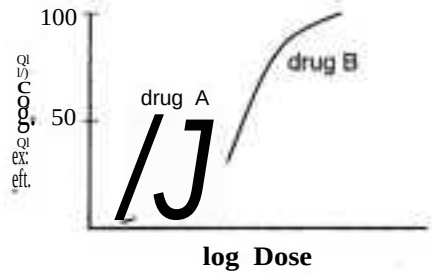
11. A drug achieves a plasma level of 16 mg/L shortly after the administration of the first oral dose. If the half-life and the dosing interval are both 6 hours, what is the approximate plasma level shortly before the administration of the 5th dose?

A. 15 mg/L
B. 24 mg/L
C. 28 mg/L
D. 30 mg/L
E. 31 mg/L

12. In the case of a drug that follows first-order elimination,

A. the rate of elimination is constant
B. the elimination half-life varies with the dose
C. the volume of distribution varies with the dose
D. the clearance varies with the dose
E. the rate of elimination varies directly with the dose

13. The curves in this figure represent isolated tissue responses to two drugs. Which of the following statements is accurate?



A. Drug A has greater efficacy than drug B
B. Drug A is more potent than drug B
C. Drug B is more potent than drug A
D. Drug B has greater efficacy than drug A
E. Both drugs have the same affinity

14. In a patient weighing 70 kg, acetaminophen has a V_d = 70 Land CI- = 350 mLimin. The elimination half-life of the drug is approximately

A. 35 min
B. 70 min
C. 140 min
D. 210 min
E. 280 min

15. Pharmacokinetic characteristics of propranolol include V_d = 300 Ll70 kg, CI = 700 mLimin, oral bioavailability f = 0.25. What is the dose needed to achieve a plasma level equivalent to a steady-state level of 20 ~g/L?

A. 4 mg
B. 8mg
C. 12mg
D. 24mg
E. 48 mg

16. With IV infusion, a drug reaches 90% of its final steady state in 10 hours. The elimination half-life of the drug must be approximately

A. 1h
B. 2h
C. 3h
D. 6h
E. 9h

17. At 12 h after N administration of a bolus dose, the plasma level of a drug is 3 mglL. If the V_d = 10 L and the elimination half-life = 6 h, what was the dose administered?

A. 120 mg
B. 180 mg
C. 240 mg
D. 480mg
E. 600 mg

18. An IV infusion of a drug is started at 400 mglh. If Cl = 50 Llh, what is the anticipated plasma level at steady state?

A. 2 mglL
B. 4mglL
C. 8 mglL
D. 16 mglL
E. 32 mglL

Answers

1. **Answer: A.** The key word is *absorption.* By definition, IV injection does not involve absorption processes because the drug is injected directly into the systemic circulation (choice B is wrong). All of the other modes of administration are associated with absorption. The inhalational mode is the most rapid because of the great area of the absorptive surface and the close proximity to the blood.

2. **Answer: C.** Drugs with extensive plasma protein binding usually have low Vd values (recall V_d = dose/CO) and slow renal elimination because only the free fraction is filtered. Albumin is the major plasma protein to which drugs bind, and the constant positive charge on quaternary amines prevents their binding to plasma proteins. Competition between drugs for plasma protein binding sites can lead to drug interactions (e.g., the displacement of warfarin by sulfonamides may increase its anticoagulant effects).

3. **Answer: B.** The permeation of most drugs through cellular membranes is by the process of passive diffusion, a nonsaturable process that follows first-order kinetics. Concentration gradient and lipid solubility of the drug are important determinants of the rate of diffusion. Only a few drug molecules are substrates for active transport processes (e.g., tubular secretion of beta-lactam antibiotics); these are saturable at high concentrations. Only very small ions (e.g., Li") or drugs (e.g., ethanol) may penetrate biomembranes via aqueous pores.

4. **Answer:** C. One half of the drug dose is eliminated in 120 min, so its elimination half-life = 2 hours. With the passage of each half-life, the amount in the body (or in the blood) will decrease to 50% of a former level. Thus, at 6 hours after drug administration, the amount of drug remaining is 160 divided by (2 x 2 x 2) or 160/8 = 20 mg.

5. **Answer: E.** The formula to use is CI = ff x GFR. From the question, ff = 0.6 (40% bound) and GFR = 120 mUmin, so the product (apparent CI) = 72 mUmin. However, the question states that the actual CI- = 18 mUmin; thus, the difference from apparent CI is 54 mUmin (72 - 18), and this represents the amount of drug reabsorbed following its glomerular filtration. Percentage reabsorption = 54/72 x 100 = 75%.

6. **Answer: A.** This is a "loading dose" question. Remember LD = Vd x *Co.* In this case, Vd = 42 L, which approximates total body water in a patient weighing 70 kg.

$$LD = 42\ L \times 10\ mg/L = 420\ mg$$

7. **Answer: D.** The reductive biotransformation of certain drug molecules containing aldehyde, ketone, or nitro groups can be catalyzed by cytochrome P450, and such reactions represent phase I drug metabolism. Phase II drug metabolism involves the transfer of chemical groupings (e.g., acetyl, glucuronide, glutathione) to drugs or their metabolites via conjugation reactions.

8. **Answer:** C. Azole antifungals (e.g., ketoconazole) are inhibitors of cytochrome P450, especially CYP3A4, the most abundant isozyme form in human liver, which metabolizes a wide range of drugs. All of the other drugs listed are known to be inducers of cytochrome P450 with chronic use.

9. **Answer: B.** The typical log dose-response figure with the parallel nature of the curves suggests that the three drugs are interacting with the same receptor system. Drugs A and B are full agonists because they achieve the maximal response. They have similar efficacy, but drug A is more potent than drug B. Drug C is a partial agonist with less efficacy than either of the other two drugs.

10. **Answer:** C. The fact that the drug has therapeutic efficacy for 6 h has no direct relationship to its half-life-it simply means that the drug is above its minimal effective concentration for 6 h. Doubling the dose (to 1 g) means that the drug level will be above the minimum for a longer period. Because the elimination half-life is 8 h, 500 mg of the drug will remain in the body 8 h after a dose of 1 g. Thus, the total duration of effectiveness must be 8 + 6 = 14 h.

11. **Answer: A.** The key word in this question is *before* the 5th dose. Immediately "after" the 5th dose, the plasma level should be approximately 30 rng/L, but just before it would be close to half of that level.

12. **Answer: E.** In first-order kinetics, the elimination rate of a drug is directly proportional to its plasma concentration, which in turn is proportional to the dose. Drugs that follow first-order elimination have a constant elimination half-life. Likewise, clearance and volume of distribution are pharmacokinetic characteristics of a drug that do not routinely change with dose, although they may vary in terms of disease or dysfunction.

13. **Answer: D.** The curves in the figure suggest that drugs A and B have similar receptor binding: Drug A is a partial agonist, and drug B is a full agonist, having greater efficacy. Drug A appears more potent than drug B below the 50% response but has no effectiveness at all above the 50% response.

14. **Answer: C.** Use the relationship:

$$t_{1/2} = \frac{0.7 \times V_d}{Cl}$$ (Make sure that all units are the same.)

$$= \frac{0.7 \times 70\,L}{350\,mL} = \frac{49}{0.35} = 140 \text{ min}$$

15. **Answer: D.** Use the relationship:

$$\text{Loading dose} = \frac{V_d \times C}{f}$$

$$= \frac{300\ L \times 20\ \mu g/L}{0.25}$$

$$= 6{,}000\ \mu g \times 4 = 6\ mg \times 4 = 24\ mg$$

16. **Answer:** C. Time to reach 90% of final steady-state plasma levels is given by: 3.3 x half-life.

Because it takes 10 h to reach 90% steady state, then

$$\text{Half-life} = \frac{10}{3.3} = 3 \text{ h}$$

To achieve "clinical" steady state usually takes approximately 5 x half-life.

17. **Answer:** A. At 12 h after IV injection (which corresponds to two half-lives of the drug), the plasma level is 3 mg/L. Extrapolating back to zero time, by "doubling" plasma level for each half-life, results in an initial plasma level at zero time (C0) = 3 x 2 x 2 mg/L = 12 mg/L.

$$\text{Dose injected} = V_d \times C_0$$

$$= 10\ \text{L} \times 12\ \text{mg/L}$$

$$= 120\ \text{mg}$$

18. **Answer: C.** An infusion rate (k_0) is given by:

$$k_0 = Cl \times C_{SS}$$

rearrange: $C_{SS} = \frac{k_0}{Cl}$

$$= \frac{400\ \text{mg/h}}{50\ \text{L/h}} = 8\ \text{mg/L}$$

SECTION II

Autonomic Pharmacology



The Autonomic Nervous System (ANS)

1

ANATOMY Of THE ANS

The ANS is the major involuntary portion of the nervous system and is responsible for automatic, unconscious bodily functions, such as control of heart rate and blood pressure and both gastrointestinal and genitourinary functions. The ANS is divided into two major subcategories: the parasympathetic autonomic nervous system (PANS) and the sympathetic autonomic nervous system (SANS).

Location of ANS Ganglia

Both the PANS and SANS have relay stations, or ganglia, between the eNS and the end organ, but the somatic system does not. An important anatomic difference between the SANS and PANS is that the ganglia of the former lie in two paraventral chains adjacent to the vertebral column, whereas most of the ganglia of the PANS system are located in the organs innervated. Figure II-1-1 highlights the major features of the ANS and the somatic systems and also shows the location of the major receptor types. These are:

- NN-Nicotinic receptors are located on cell bodies in ganglia of both PANS and SANS and in the adrenal medulla.
- NM-Nicotinic receptors are located on the skeletal muscle motor end plate innervated by somatic motor nerves.
- M_{1-3}-Muscarinic receptors are located on all organs and tissues innervated by postganglionic nerves of the PANS and on thermoregulatory sweat glands innervated by the SANS.

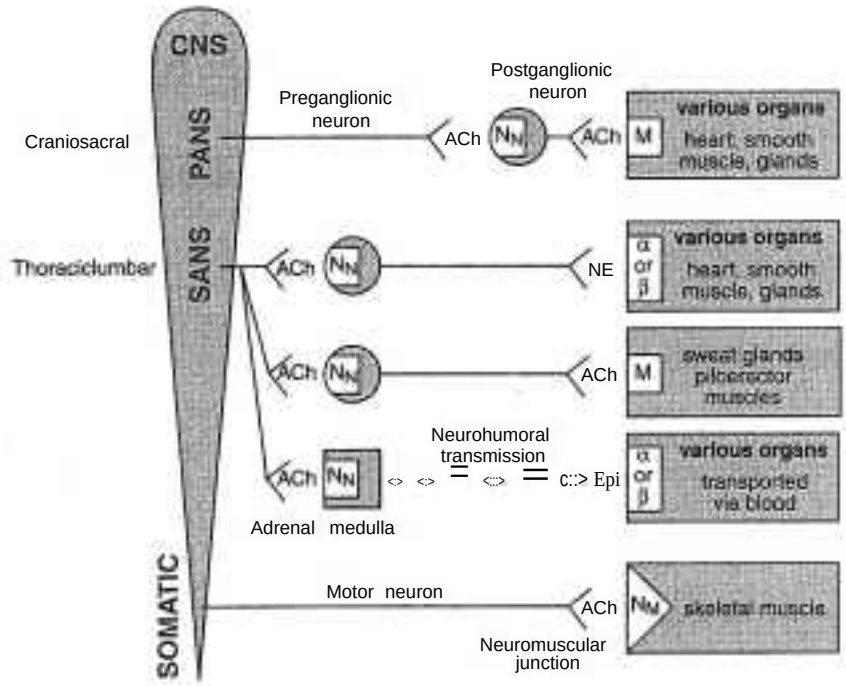


Figure 11-1-1. Anatomy of the Autonomic Nervous System

Neurotransmitters

- Acetylcholine (ACh) is the neurotransmitter at both nicotinic and muscarinic receptors in tissues that are innervated. Note that all direct transmission from the CNS (preganglionic and motor) uses ACh, but postganglionic transmission in the SANS system may use one of the organ-specific transmitters described below.
- Norepinephrine (NE) is the neurotransmitter at most adrenoceptors in organs, as well as in cardiac and smooth muscle.
- Dopamine (DA) activates D_1 receptors, causing vasodilation in renal and mesenteric vascular beds.
- Epinephrine (E, from adrenal medulla) activates most adrenoceptors and is transported in the blood.

BLOOD PRESSURE CONTROL MECHANISMS

Autonomic Feedback Loop

For a more detailed discussion, see Section II, Chapter 2, in Physiology.

- Blood pressure is the product of total peripheral resistance (TPR) and cardiac output (CO).
- Both branches of the ANS are involved in the autonomic (or neural) control of blood pressure via feedback mechanisms.
- Changes in mean blood pressure are detected by baroreceptors, which relay information to the cardiovascular centers in the brainstem controlling PANS and SANS outflow. For

example, an increase in mean blood pressure elicits baroreceptor discharge, resulting in increased PANS activity, leading to bradycardia and decreased SANS activity, which leads, in turn, to decreased heart rate, force of contraction, and vasoconstriction. The resulting decreases in cardiac output and total peripheral resistance contribute to restoration of mean blood pressure toward its normal level.

- Conversely, decreases in blood pressure elicit ANS neural feedback involving decreased PANS outflow and increased SANS activity-actions leading to increases in cardiac output and total peripheral resistance.

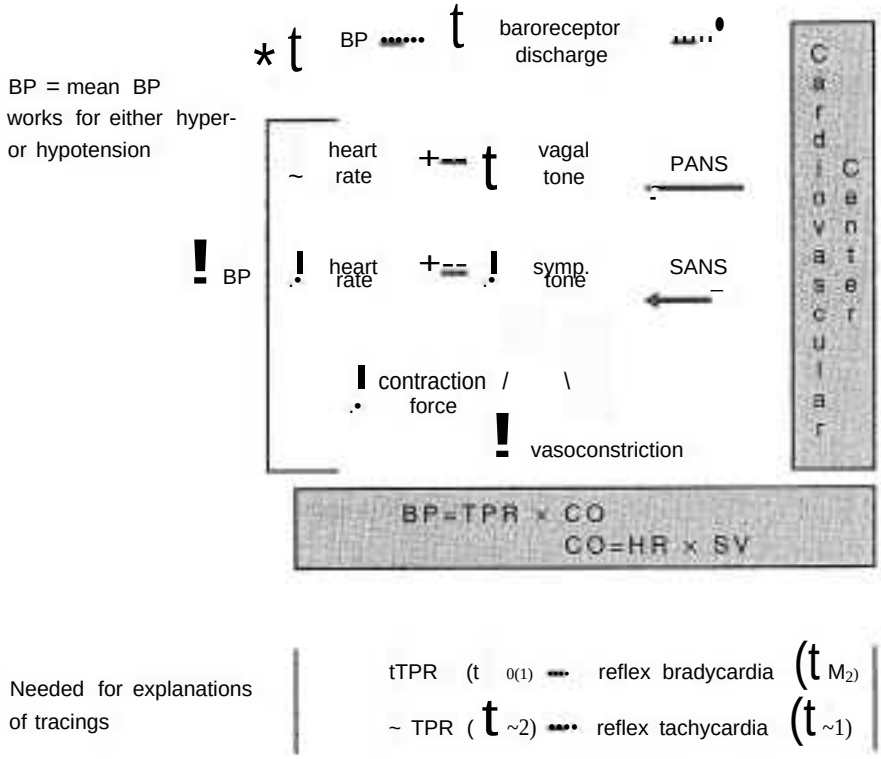


Figure 11-1-2.Automatic Feedback Loop

Note

Baroreceptor reflexes can be blocked at the ganglionic synapse with NN receptor antagonists. Alternatively, a reflex bradycardia can be blocked with muscarinic antagonists; a reflex tachycardia can be blocked with ~ı antagonists.

Hormonal Feedback loop

- Blood pressure is also regulated via the hormonal feedback loop shown in Figure-II-1-3.
- The system is affected only by *decreases* in mean blood pressure (hypotension), which result in decreased renal blood flow.
- Decreased renal pressure causes the release of renin, which promotes formation of the angiotensins.
- Angiotensin II increases aldosterone release from the adrenal cortex, which, via its mineralocorticoid actions to retain sodium and water, increases blood volume.
- Increased venous return results in an increase in cardiac output.
- Angiotensin II also causes vasoconstriction, resulting in an increase in TPR.

Note

Antihypertensive Drugs

Both the ANS (neural) and endocrine feedback loops are invoked when patients are treated with antihypertensive drugs. Such compensatory mechanisms may result in tachycardia and both salt and water retention.

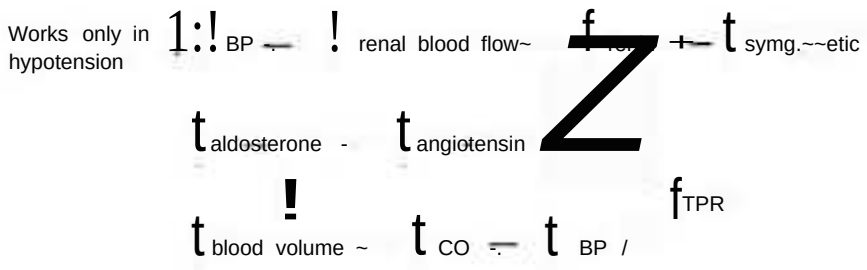


Figure 11-1-3. Hormonal Feedback Loop

Introduction to Blood Pressure/Heart Rate Tracings

A Blood pressure:

~ Systolic pressure

BASELINE Mean blood pressure

Diastolic pressure

- Increases are seen as deflections of the tracing upward (~)
- Decreases are seen as deflections of the tracing downward (~)
- Following mean blood pressure changes is enough (------)

B Heart rate:

- Increases are seen as tighter tracing
- Decreases are seen as a wider tracing (/\/\/\ )

BASELINE

One beat

C Example of a drug X changing baseline parameters by decreasing mean blood pressure and increasing heart rate:

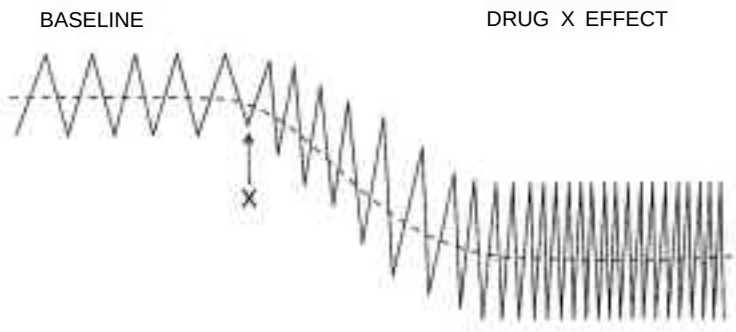


Figure 11-1-4.Blood Pressure/Heart Rate Tracings

PUPILLARY SIZE AND ACCOMMODATION MECHANISMS

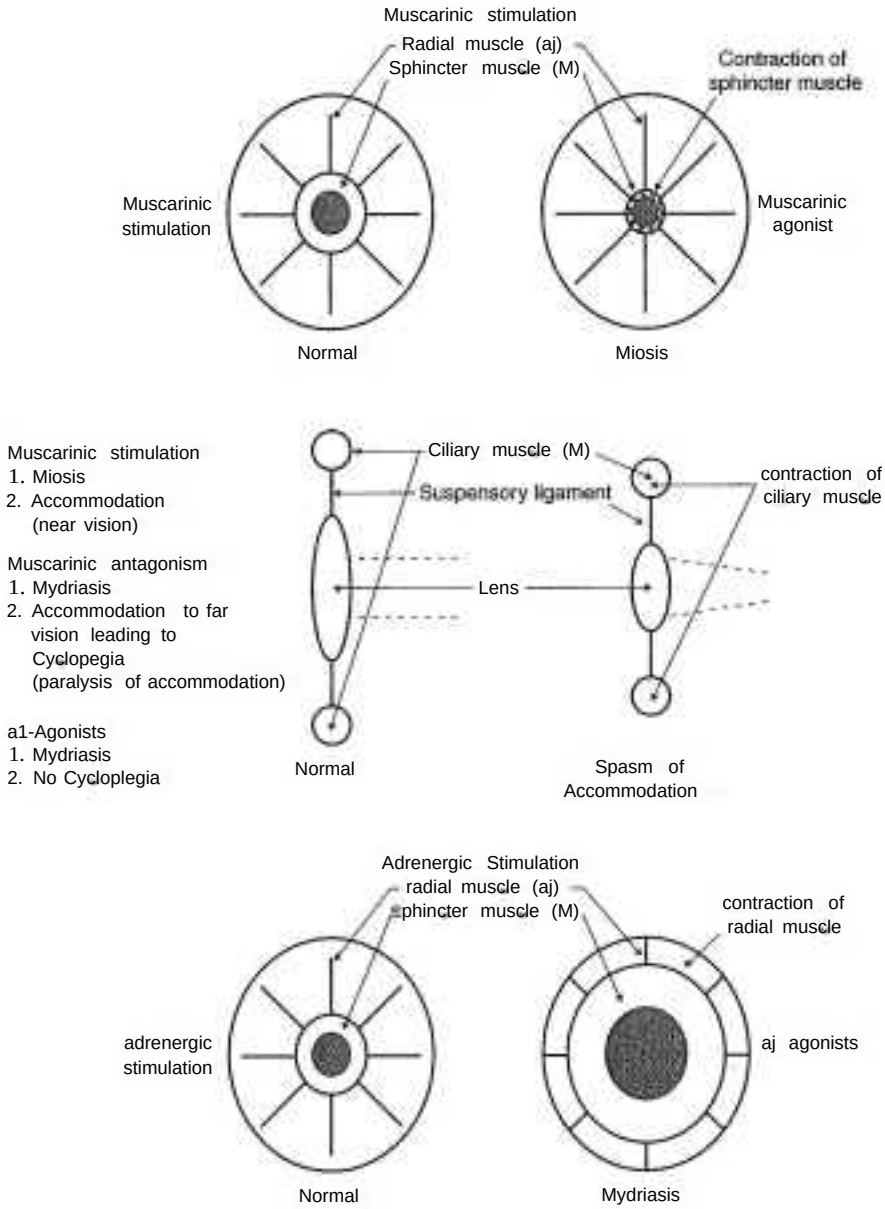


Figure 11-1-5.Effects of ANS Drugs on the Eye

Chapter Summary

The autonomic nervous system (ANS) is the major involuntary portion of the nervous system and is responsible for automatic, unconscious bodily functions. It has two major parts: the parasympathetic (PANS) and the sympathetic (SANS) systems.

Ganglia are relay systems set between the CNS and end organs. Ganglia in the SANS system are arranged in a series of parallel nodes adjacent to the vertebral column. In contrast, PANS ganglia are usually located in the innervated organ.

The major receptor types are ganglionic nicotinic (NN)' endplate nicotinic (N_M), muscarinic (M_{1-3}), and adrenergic receptor of four major subtypes (a.l'~' P_1, P_2). ACh is the neurotransmitter at all N receptors, at the M receptors innervated by postganglionic fibers of the PANS, and the thermoregulatory sweat glands innervated by the SANS. Norepinephrine (NE) is the neurotransmitter at adrenoreceptors innervated by the SANS. NE and epinephrine (E) are released from the adrenal medulla. Dopamine (DA) receptor activation leads to vasodilation in some vascular beds.

Blood pressure (BP) is a product of the total peripheral resistance (TPR) times the cardiac output (CO). The CO is equal to the heart rate (HR) times the stroke volume (51/). The autonomic (neural) system helps regulate the BP through feedback control involving the baroreceptors, the cardiovascular centers in the brainstem, and the PANS and SANS, which act in an opposing but coordinated manner to regulate the pressure.

BP is also regulated by hormonal feedback (humoral). Hypotension decreases renal blood flow and activates the release of renin, which leads to the formation of angiotensin **II,** which in turn stimulates the release of aldosterone from the adrenal cortex. Aldosterone promotes water and salt retention, increasing blood volume and as a consequence increases SV and CO.

Cholinergic Pharmacology

2

CHOLINERGIC NEUROEFFECTOR JUNCTIONS

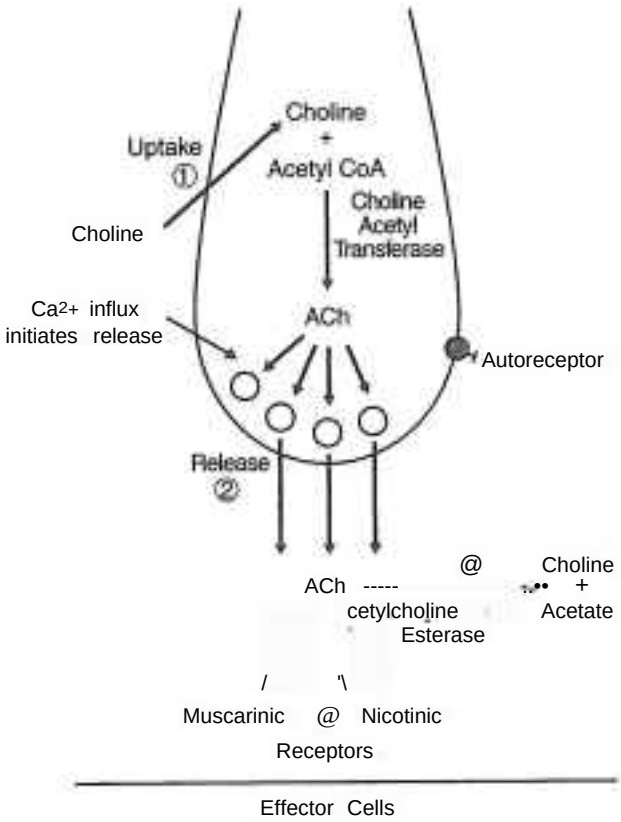


Figure 11-2-1. Cholinergic Neuroeffector Junction

~!!~~@!~]~~~

CD Hemicholinium

O Botulinum toxin

C) Acetylcholinesterase (AChE) inhibitors

® Receptor agonists and antagonists

- Choline is accumulated in cholinergic presynaptic nerve endings via an active transport mechanism linked to a Na+ pump.
- Choline uptake is inhibited by hemicholinium (CD in Figure II-2-l). ACh is synthesized from choline and acetyl-CoA via choline acetyltransferase (ChAT) and accumulated in synaptic vesicles.
- Presynaptic membrane depolarization opens voltage-dependent Ca^{2+} channels, and the influx of this ion causes fusion of the synaptic vesicle membranes with the presynaptic membrane, leading to exocytosis of ACh. Botulinum toxin (® in Figure II-2-1) interacts with synaptobrevin and other proteins to prevent ACh release and is used in blepharospasm, strabismus/hyperhydrosis, dystonia, and cosmetics.

- Some cholinergic nerve endings have presynaptic autoreceptors for ACh that on activation may elicit a negative feedback of transmitter release.
- Inactivation via acetylcholinesterase (AChE) is the major mechanism of termination of postjunctional actions of ACh.
- AChE is a target for inhibitory drugs (indirect-acting cholinomimetics). Note that such drugs can influence cholinergic function only at innervated sites where ACh is released.
- Reversible AChE inhibitors (® in Figure II-2-1) include edrophonium, physostigmine, and neostigmine. Irreversible AChE inhibitors include echothiophate, malathion, and parathion.
- Postjunctional receptors (N and M) (® in Figure II-2-l) activated by ACh are major targets for both activating drugs (direct-acting cholinomimetics) and blocking agents.

In A Nutshell

- M receptor activation -+,l, CJfunction
- i secretions and i smooth muscle contraction
- All M receptor activators and blockers are nonspecific.

Table 11-2-1. Muscarinic - Receptor Activation

Target		Receptor	Response
Eye	Sphincter	M_3	Contraction-miosis
	Ciliary muscle	M_3	Contraction-accommodation for near vision
Heart	SA node	M_2	J, Heart rate (HR)-negative chronotropy
	AVnode	M_2	J, Conduction velocity-negative dromotropy
			No effects on ventricles, Purkinje system
Lungs	Bronchioles	M_3	Contraction-bronchospasm
	Glands	M_3	Secretion
GI tract	Stomach	M_3	i Motility-eramps
	Glands	M_1	Secretion
	Intestine	M_3	Contraction-diarrhea, involuntary defecation
Bladder		M_3	Contraction (detrusor), relaxation (trigone/sphincter), voiding, urinary incontinence
Sphincters		M_3	Relaxation, except lower esophageal, which contracts
Glands		M_3	Secretion-sweat (thermoregulatory), salivation, and lacrimation
Blood vessels (endothelium)		M_3	Dilation (via NO/endothelium-derived relaxing factor)-no innervation, no effects of indirect agonists

Table II-2-2. Nicotinic Receptor Activation

Target	Receptor	Response
Adrenal medulla	NN	Secretion of epinephrine and NE
Autonomic ganglia	NN	Stimulation-net effects depend on PANS/SANS innervation and dominance
Neuromuscular junction	N_M	Stimulation-twitch/hyperactivity of skeletal muscle

Note: N receptors desensitize very quickly upon exessive stimulation.

Table II-2-3. Cholinergic Receptor Mechanisms

M_1 and M;	G_q coupled	t phospholipase C ~ t IP3' DAG, Ca^{2+}
M_2	G_j coupled	J, adenylyl cyclase ~J, cAMP
NNandNM	No 2nd messengers	activation (opening) of Na/K channels

MUSCARINIC RECEPTOR AcnvATORS

Muscarinic Agonists

Table II-2-4. Properties of Direct-Acting Cholinomimetics

Drug	Activity	AChE Hydrolysis	Clinical Uses
ACh	MandN	+++	Short half-life-no clinical use
Bethanechol	M	–	Rx-ileus (postop/neurogenic), urinary retention
Methacholine	M>N	+	Dx-bronchial hyperreactivity
Pilocarpine	M	–	Rx-glaucoma (topical), xerostomia

Bridge to Physiology and Anatomy

Blood vessels are solely innervated by the SANS, so the stimulation of autonomic ganglia results in vasoconstriction.

Conversely, the gastrointestinal tract is dominated by the PANS,so ganglionic stimulation causes increased gastrointestinal motility and secretions.

Clinical Correlate

Alzheimer Disease

Late-onset dementia with progressive memory loss and cognitive decline. Neuropathology includes neurofibrillary tangles, amyloid plaques, and loss of ACh neurons in Meynert's nucleus-rationale for clinical use of AChE inhibitors.

Acetylcholinesterase Inhibitors

Table 11-2-5. Properties ofIndirect-Acting Cholinomimetics

Drug	Characteristics	Clinical Uses
Edrophonium	Short-acting	Dx-myasthenia; used to differentiate myasthenia from cholinergic crisis
Physostigmine	Tertiary amine (enters CNS)	Rx-glaucoma; antidote in atropine overdose
Neostigmine, pyridostigmine	Quaternaryamines (no CNS entry)	Rx-ileus, urinary retention, myasthenia, reversal of nondepolarizing NM blockers
Donepezil, tacrine	Lipid-soluble (CNS entry)	Rx-Alzheimer disease
Organophosphates	Lipid-soluble, irreversible inhibitors	Rx-glaucoma (echothiophate) Note: use as insecticides (malathion, parathion) and as nerve gas (sarin)

Toxicity of AChE Inhibitors

As insecticides

- Long-acting irreversible inhibitors (both carbamates and organophosphates)
- Wide use in agriculture as insecticides
- Examples: malathion and parathion

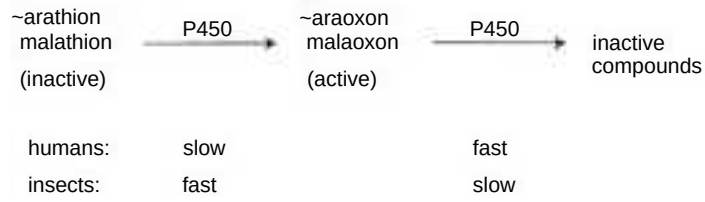


Figure 11-2-2.Activation of Organophosphate Insecticides

Classic Clue

AChE inhibitor poisoning: "Durnbbelss"

Diarrhea

Urination

Miosis

Bradycardia

Bronchoconstriction

Excitation (Muscle and CNS)

Lacrimation

Salivation

Sweating

Acute toxicity

- Excessive muscarinic and nicotinic stimulations
- Muscarinic effects:
  - Diarrhea
  - Urination
  - Miosis
  - Bradycardia

- Bronchoconstriction
- Lacrimation
- Salivation
- Sweating
- CNS stimulation

- Nicotinic effects:
  - Skeletal muscle excitation followed by paralysis
  - CNS stimulation

Management

- Muscarinic effects: atropine
- Regeneration of AChE: pralidoxime (2-PAM)
- Time-dependent aging requires use of 2-PAM as soon as possible *(see* Figure II-2-3).

Irreversibly acting cholinomimetics:

These compounds phosphorylate the esteratic site on AChE, at serine hydroxyl groups

1) phosphorylation; reversible by pralidoxime (2-PAM)
2) removal of a part of the organophosphate molecule (aging). Complex no longer reversible by 2-PAM.

R = leaving group
P = organophosphate

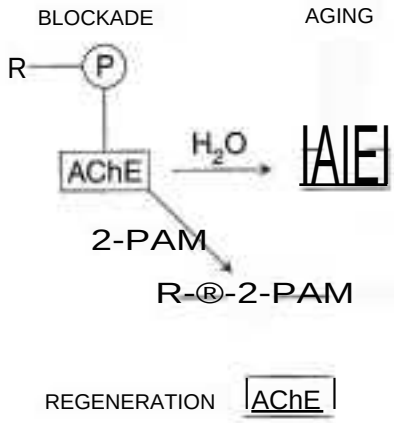


Figure 11-2-3.Effects of Organophosphate on AChE

Chronic toxicity

- Peripheral neuropathy causing muscle weakness and sensory loss
- Demyelination not due to AChE inhibition

MUSCARINIC RECEPTOR ANTAGONISTS

Atropine

- Prototype of the class
- As a tertiary amine, it enters CNS
- Other M blockers differ mainly in their pharmacokinetic properties

Pharmacologic Effects

- Atropine effects in order of increasing dose are:
  - Decreased secretions (salivary, bronchiolar, sweat)
  - Mydriasis and cycloplegia
  - Hyperthermia (with resulting vasodilation)
  - Tachycardia
  - Sedation
  - Urinary retention and constipation
  - Behavioral excitation and hallucinations
- Other classes of drugs with antimuscarinic pharmacology:
  - Antihistamines
  - Tricyclic antidepressants
  - Antipsychotics
  - Quinidine
  - Amantadine
  - Meperidine
- Treatment of acute intoxication:
  - Symptomatic ± physostigmine

Table II-2-6. Clinical Uses and/or Characteristics of M Blockers

Drug	Clinical Uses and/or Characteristics
Atropine	Antispasmodic, antisecretory, management of AChE inhibitor Ol), antidiarrheal, ophthalmology (but long action)
Tropicamide	Ophthalmology (topical)
Ipratropium	Asthma and COPD (inhalational)-no CNS entry, no change in mucus viscosity
Scopolamine	Used in motion sickness, causes sedation and short-term memory block
Benztropine, trihexyphenidyl	Lipid-soluble (CNS entry) used in parkinsonism and in acute extrapyramidal symptoms induced by antipsychotics

!!!~|~>>>!!,!,~!~~"~NICOTINIC RECEPTOR ANTAGONISTS

ANS Dominance

For effector tissues with dual innervation, PANS is dominant. These include the SA and AV nodes of the heart, the pupil, GI and GU muscles, and sphincters. SANS is dominant only in terms of vascular tone and thermoregulatory sweat glands.

Ganglion Blocking Agents

- Drugs: hexamethonium and mecamylamine
- Reduce the predominant autonomic tone *(see* Table II-2-7)
- Prevent baroreceptor reflex changes in heart rate *(see* Figure II-2-4)
- Most are no longer available clinically because of toxicities (rarely, mecamylamine in hypertension)

Table 11-2-7. Characteristics of Ganglion Blocking Agents

Effector	System	Effect of Ganglion Blockade
Arterioles	SANS	Vasodilation, hypotension
Veins	SANS	Dilation, ↓ venous return, ↓ CO
Heart	PANS	Tachycardia
Iris	PANS	Mydriasis
Ciliary muscle	PANS	Cycloplegia
GI tract	PANS	↓ Tone and motility-constipation
Bladder	PANS	Urinary retention
Salivary glands	PANS	Xerostomia
Sweat glands	SANS	Anhydrosis

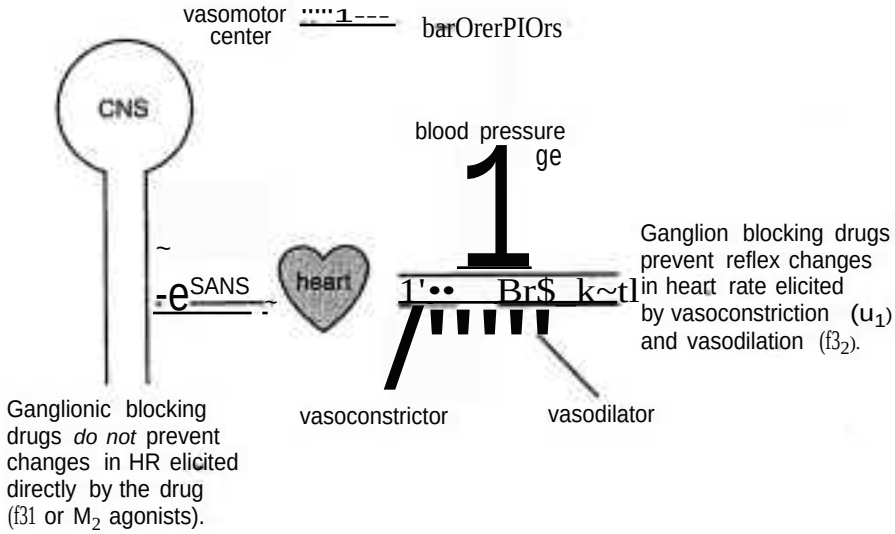


Figure 11-2-4Algorithm: Reflex Control of Heart Rate

Neuromuscular Blocking Drugs

See CNS section about Anesthetics.

Chapter Summary

Acetylcholine (ACh) is synthesized from acetate and choline in the synaptic nerve via choline acetyltransferase and is stored in the synaptic vesicles and released by Ca^{2+} influx upon depolarization. The ACh then binds to a receptor on the other side of the synaptic junction, thereby transmitting the signal. Acetylcholinesterase (AChE) hydrolyzes the ACh and ends the signal. Cholinergic drugs are those that affect this process either by influencing ACh levels or by acting directly on the nicotinic or muscarinic receptors.

Choline uptake is inhibited by hemicholinium. Botulinum toxin binds to synaptobrevin and prevents ACh release, and AChE inhibitors slow its rate of breakdown. Several reversible AChE inhibitors are useful pharmacologic agents; the irreversible AChE inhibitors are generally poisons.

A cholinomimetic is a drug that imitates ACh. Nicotine acts as a cholinomimetic on nicotinic receptors, whereas bethanechol and pilocarpine are cholinomimetic drugs that act on muscarinic receptors.

Other drugs are ACh receptor blockers. Specific blocking agents acting on ganglionic nicotinic (NN) receptors are hexamethonium and mecamylamine. Those acting on the end-plate nicotinic receptors (N_M) are tubocurarine, atracurium, and succinylcholine. Those acting on muscarinic (M) receptors include atropine, benztropine, and scopolamine.

All M-receptor activators are nonspecific (they act on M_{1-3}), and, in general, M-receptor activation decreases cardiovascular function and increase secretions and smooth muscle contraction. Table 11-2-1 summarizes the type of M receptor involved and the specific end-organ responses to M-receptor activators.

Table 11-2-2summarizes the effects of nicotinic receptor activation on the adrenal medulla, the autonomic ganglia, and the neuromuscular junction. The effect of autonomic ganglia stimulation depends upon the transmission system used to connect the ganglia to the end organ. Blood vessels are innervated by SANS, resulting in vasoconstriction. PANS innervates the gut, the end result being increased motility and secretion.

Table 11-2-3summarizes the receptor mechanisms used by the various receptor types.

Table 11-2-4summarizes the activity, properties, and clinical uses for the direct-acting cholinomimetics, and Table 11-2-5 does the same for the indirect-acting ones.

Long-acting AChE inhibitors are commonly used as insecticides. Although these are less toxic for humans, they still provide a hazard, causing poisoning with both acute and chronic symptoms caused by both muscarinic and nicotinic hyperactivity ("dumbbelss").

Therapy for acute poisoning by AChE inhibitors includes administration of M blockers (atropine) and pralidoxime (HAM), which helps reactivate AChE.

Atropine is the prototype of muscarinic receptor antagonist drugs. In simple terms, increasing doses of atropine progressively decreases secretions and causes mydriasis, blurred vision, tachycardia, constipation, and urinary retention. Overdoses of over-the-counter medications containing M blockers are common causes of toxicity. Management is largely symptomatic, although physostigmine may be useful because it helps counteract both central and peripheral effects. The clinical uses and properties of the M-blocking drugs are summarized in Table 11-2-6.

(Continued)

Chapter Summary *(continued)*

The NN antagonists act as ganglionic blockers. They will therefore affect both the SANS and PANStracts.

Ganglionic blockade prevents ANS reflexes. Table 11-2-7summarizes specific effects of ganglionic blocking agents and the transmission system employed for various specific organs.

Figure 11-2-4summarizes the effects of ganglionic blockers on drugs that modify blood pressure, causing a reflex change in heart rate, and on drugs that act directly at the SA node to change the heart rate.



Adrenergic Pharmacology

3

CATECHOLAMINE SYNTHESIS, ACTION, AND DEGRADATION

The important aspects of the adrenergic neuroeffector junction are summarized in Figure II-3-1.

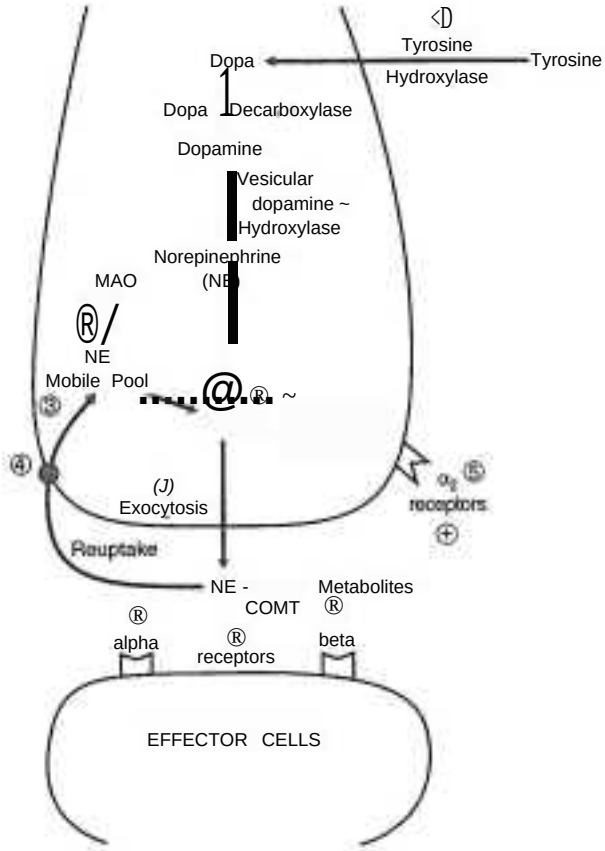


Figure 11-3-1.Adrenergic Neuroeffector Junction

~>i~,~,~,~~~I!!~

CD Methyl-p-tyrosine

Q) MAO inhibitors

(3) Releasers

® Reuptake blockers

(5) α_2 agonists and antagonists

® Reserpine

(j) Guanethidine

® Agonists and blockers of a]' ~1 receptors

Table 11-3-1. Adrenergic Receptor Activation

Receptor	Response
α_1	
Eye-radial (dilator) muscle	Contraction-mydriasis
Arterioles (skin, viscera)	Contraction- ↑ TPR- ↓ diastolic pressure, ↑ afterload
Veins	Contraction- ↑ venous return- ↑ preload
Bladder trigone and sphincter	Contraction-urinary retention
Male sex organs	Vas deferens-ejaculation
Liver	↑ Glycogenolysis
Kidney	↓ Renin release
α_2	
Prejunctional nerve terminals	↓ Transmitter release and NE synthesis
Platelets	Aggregation
Pancreas	↓ Insulin secretion
β_1	
Heart SA node	↑ HR (positive chronotropy)
AV node	↑ Conduction velocity (positive dromotropy)
Atrial and ventricular muscle	↑ Force of contraction (positive inotropy), conduction velocity? CO and oxygen consumption
His-Purkinje	↑ Automaticity and conduction velocity
Kidney	↓ Renin release
β_2 (mostly not innervated)	
Blood vessels (all)	Vasodilation-↓ TPR-↓ diastolic pressure-↓ afterload
Uterus	Relaxation
Bronchioles	Dilation
Skeletal muscle	↑ Glycogenolysis-contractility (tremor)
Liver	↑ Glycogenolysis
Pancreas	↑ Insulin secretion
D_1 (peripheral)	
Renal, mesenteric, coronary vasculature	Vasodilation-in kidney ↑ RBF, ↑ GFR, ↑ Na^+ secretion

In A Nutshell

Adrenoceptor Sensitivity

Beta receptors are usually more sensitive to activators than alpha receptors. With drugs that exert both effects, the beta responses are dominant at low doses; at higher doses, the alpha responses will predominate.

Note

Dopamine Use in Shock

D_1 β_1 α_1

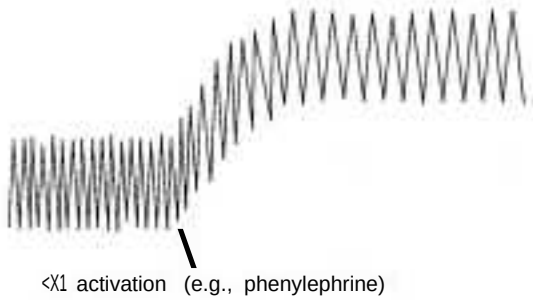
increasing doses of dopamine

Table 11-3-2. Mechanisms Used by Adrenergic Receptors

(l;j	G_q coupled	t phospholipase C -7 t IP3' DAG, Ca^{2+}
(1;2	G_i coupled	J„ Adenylyl cyclase -7 J„ cAMP
~j ~2 Dj	G_s coupled	t Adenylyl cyclase -7 t cAMP

DIRECT-ACTING ADRENOCEPTOR AGONISTS

U_1 Agonists



- <X1:tTPR, tBP
- Potential reflex bradycardia
- No change in pulse pressure

Figure 11-3-2.Effect of Alpha Activators on Heart Rate and Blood Pressure

- Systemically, t mean blood pressure via vasoconstriction
- t BP may elicit a reflex bradycardia
- Cardiac output may be J„ but also offset by t venous return
- Drugs and uses:
  - Phenylephrine: nasal decongestant and ophthalmologic use (mydriasis without cycloplegia)
  - Methoxamine: paroxysmal atrial tachycardia through vagal reflex

U_2 Agonists

Stimulate prejunctional receptors in the CNS to decrease sympathetic outflow. Primary use is in mild to moderate HTN.

- Drugs and uses: donidine and methyldopa (mild to moderate hypertension)
- *See* Cardiovascular section.

~ Agonists



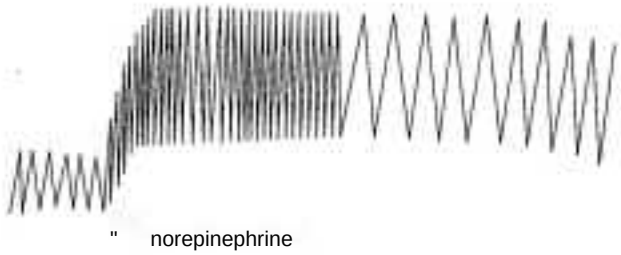
- ~1: ↑ HR, ↑ SV, ↑ CO, and ↑ pulse pressure
- ~2: ↓ TPR, ↓ BP

Figure 11-3-3.Effect of Beta Receptor Activation on Heart Rate and Blood Pressure

- Systemically, ↓ mean BP via vasodilation (~2) and ↑ HR (~l)
- Drugs and uses:
  - Isoproterenol (~l = ~2): bronchospasm, heart block, and bradyarrhythmias. Side effects include flushing, angina, arrhythmias.
  - Dobutamine (~l > ~2): congestive heart failure
  - Selective ~2 agonists:
    - Salmeterol, albuterol, and terbutaline used in asthma
    - Ritodrine, used in premature labor

Mixed-Acting Agonists: Norepinephrine vs. Epinephrine

Norepinephrine (al' a_2, ~l)



- a_1: ↑ TPR, ↑ BP
- ~1: ↑ HR, ↑ SV, ↑ CO, ↑ pulse pressure
- Potential reflex bradycardia
- No effect on ~2

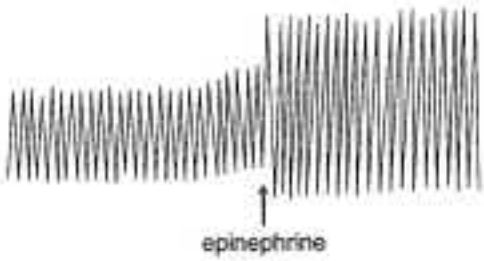
Figure 11-3-4.Effect of Norepinephrine on Heart Rate and Blood Pressure

Epinephrine (a_1, a_2, ~l' ~2)



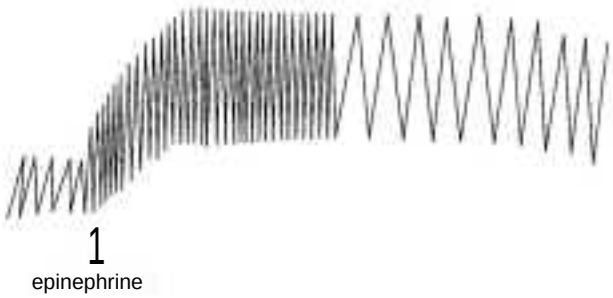
- ~1: i HR, r SV, i CO, t pulse pressure
- ~2: J, TPR, J, BP

Figure 11-3-5aEffect of Low-dose Epinephrine on Heart Rate and Blood Pressure



- ~1: i HR, i SV, t CO, t pulse pressure
- ~2: J, TPR, J, BP
- <Xl: r TPR, r BP

Figure 11-3-5bEffect of Medium-Dose Epinephrine on Heart Rate and Blood Pressure



- <Xl: t TPR, r BP
- Potential reflex bradycardia
- ~1: i HR, i SV, t CO, i pulse pressure
- ~2: J, TPR, J, BP

Figure 11-3-5cEffect of High-dose Epinephrine Is Similar to Norepinephrine

- Dose-dependent effects:
  - Low-dose.jl., ~2 stimulation *(see* Figure II-3-5a)
  - High-dose: (X]' ~l (~2) *(see* Figure II-3-5c)
- ~2 -specific effects:
  - Smooth muscle relaxation: bronchioles, uterus, blood vessels
  - Metabolic effects:
    - t glycogenolysis (muscle and liver)
    - t gluconeogenesis
    - t mobilization and use of fat

- Differentiation of high-dose epinephrine versus norepinephrine:
  - Epinephrine reversal: Use of α_1 blocker to reverse hypertension to hypotension in a patient receiving too much epinephrine
  - Hypertension was due to predominant α_1 tone on the vasculature
  - Hypotension results from unmasking β_2 receptors

Uses of Norepinephrine and Epinephrine

- Cardiac arrest
- Adjunct to local anesthetic
- Hypotension
- Anaphylaxis (epinephrine only)
- Asthma (epinephrine only)

Classic Clue

Indirect-acting adrenoceptor agonists act only on effector tissues innervated by SANS.

Denervated effector tissues are nonresponsive because these drugs act either to release transmitter from nerve terminals or to inhibit neurotransmitter reuptake.

INDIRECT-ACTING ADRENERGIC RECEPTOR AGONISTS

- Releasers:
  - Displace norepinephrine from mobile pool
  - Drug interaction: MAO_A inhibitors (hypertensive crisis)
  - Tyramine (red wine, cheese)
    - Oral bioavailability is limited by MAO-A metabolism in gut and liver
    - MAO-A inhibition $\uparrow$ bioavailability, resulting in hypertensive crisis
  - Amphetamines
    - Clinical use of methyl phenidate in narcolepsy and ADHD
    - Psychostimulant due to central release of DA, NE, SHT
  - Ephedrine (cold medication)
- Reuptake inhibitors:
  - Cocaine
  - Tricyclic antidepressant (in part)

In A Nutshell

Forms of MAO

MAO type A: mainly in liver, but 8nywhere (metabolizes NE, 5HT, and tyramine).

MAO type B: mainly in arain (metabolizes DA).

α RECEPTOR ANTAGONISTS

- $\downarrow$ TPR, $\downarrow$ mean BP
- May cause reflex tachycardia and salt and water retention
- Major uses:
  - Hypertension
  - Pheochromocytoma (nonselective α blocker)
  - Benign prostatic hyperplasia (BPH; selective α_1 blocker)
- Drugs:
  - Nonselective blocker:
    - Phentolamine, competitive inhibitor
    - Phenoxybenzamine, noncompetitive inhibitor

- Selective a_1 blocker:
  - Prazosin, doxazosin, terazosin, tamsulosin
- Selective a_2 blocker:
  - Yohimbine: used in postural hypotension and impotence
  - Mirtazapine: used as antidepressant

P RECEPTOR ANTAGONISTS

- PI blockade:
  - ↓ HR, ↓ SV, ↓ CO
  - ↓ renin release
  - ↓ aqueous humor production
- P_2 blockade:
  - May precipitate bronchospasm (in athsmatics) and vasospasm (in patients with vasospastic disorders)
  - Metabolic effects
    - Blocks glycogenolysis, gluconeogenesis
    - ↑ LDLs, TGs

Table II-3-3. Characteristics of Some Beta Blockers

Drugs	PI-Selective	ISA	Sedation	Blood Lipids
Acebutolol	+	++	+	–
Atenolol	+	–	–	↑↑
Metoprolol	+	–	+	↑↑
Pindolol	–	++	+	–
Propranolol	–	–	+++	↑↑
Timolol	–	–	++	↑↑

- Cardioselectivity (PI):
  - Less effect on vasculature, bronchioles, uterus, and metabolism
  - Safer in asthma, diabetes, peripheral vascular diseases
- Intrinsic sympathomimetic activity (ISA):
  - Act as partial agonists
  - Less bradycardia (PI)
  - Slight vasodilation or bronchodilation (P_2)
  - Minimal change in plasma lipids (P_2)
- Pharmacokinetic properties:
  - No CNS entry of atenolol
- General uses of beta-blockers:
  - Angina, hypertension, post-MI (all drugs)
  - Antiarrhythmics (class II: propranolol, acebutolol, esmolol)

Clinical Correlate

Chronic use of beta blockers (e.g., in angina, HTN) leads to receptor upregulation.

During withdrawal from use, it is important to taper dose to avoid excessive cardiovascular effects (rebound effects) of endogenous amines.

Clinical Correlate

Glucagon and the Heart

Positive inotropic and chronotropic, not via activation of a_1 receptors, but through glucagon receptors that are G-protein linked to adenylyl cyclase –7 basis for its use in beta-blocker overdose.

- Glaucoma (timolol)
- Migraine, thyrotoxicosis, performance anxiety, essential tremor (propranolol)

- Combined alpha-I and beta blocking activity:
  - Labetalol and carvedilol
  - Uses in CHF
- K+-channel blockade and ~-blocking activity
  - Sotalol
  - Use as antiarrhythmic (class III)

Chapter Summary

Neurotransmission across adrenergic junctions is mediated by norepinephrine (NE). Adrenergic effectors may act indirectly by influencing NE synthesis, monoamine oxidase (MAO) enzymes, the mobile NE pool, the NE transporter, prejunctional a-adrenoceptors, granule uptake, or release of NE, or they may act directly on the postjunctional receptor as agonists or antagonists.

Excess NE normally subjects tyrosine hydroxylase to feedback inhibition, making this enzyme the rate-limiting step in the synthetic pathway of NE and epinephrine. Tyrosine conversion to DOPA can be inhibited by methyl-p-tyrosine, a tyrosine hydroxylase inhibitor.

MAO inhibitors regulate presynaptic NE levels.

Amphetamine, ephedrine, and tyramine act, in part; by releasing NE from the mobile pool (NE stored outside granules but within the neuron).

Cocaine and the tricyclic antidepressants act by inhibiting NE reuptake, which normally removes NE from the environment and makes it unavailable as a transmitter and also conserves it for future use.

Prejunction availability of NE can also be decreased by inhibiting NE release from the granules. This can be achieved by drugs such as donidine or methyldopa, which are activators of the prejunctional ~-adrenoceptor; by drugs such as guanethidine, which act directly on the granules; or by drugs such as reserpine, which reduce NE levels by inhibiting granule uptake.

Table 11-3-1summarizes the distribution and physiologic effects associated with the activation of alpha 1 and 2, beta 1 and 2, and D] receptors. Table 11-3-2summarizes the mechanism through which these receptors work.

The major direct-acting adrenoceptor agonist drugs are described. The alpha agonist phenylephrine increases mean BP, has no effect on pulse pressure, and elicits a reflex bradycardia. Isoproterenol, a beta agonist, decreases mean BP, increases pulse pressure, and causes marked tachycardia. Cardiovascular effects of norepinephrine (NE) are similar to phenylephrine, but it is also a cardiac ~1 adrenoceptor activator. The cardiovascular effects of epinephrine (E) are betalike at low doses and alphalike at high doses.

The nonselective alpha blockers (phentolamine, phenoxybenzamine) are described. The a(selective blockers (e.g., prazosin) are used in hypertension and BPH.

The properties, clinical uses, and adverse effects of the nonselective beta receptor antagonist propranolol are described. A comparison of beta adrenoceptor antagonists that are cardioselective and those that have intrinsic sympathomimetic activity is made (Table 11-3-3). Drugs that block both alpha and beta adrenoceptors are identified.

Autonomic Drugs: Gleucoma Treatment and ANS Practice Problems

4

GLAUCOMA TREATMENT

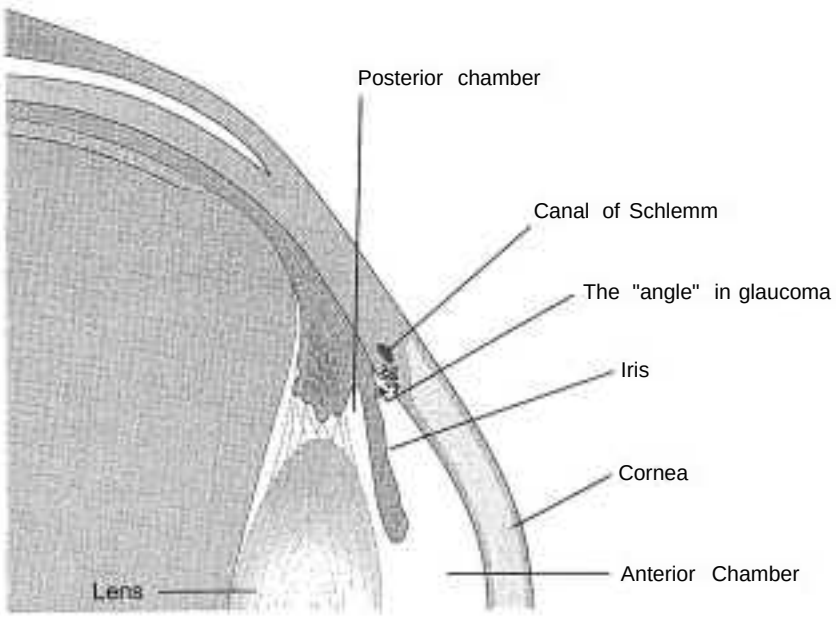


Figure 11-4-1.Anatomy of the Eye Showing Irido-Corneal Angle Where Aqueous Humor Is Recirculated

Glaucoma

Open-Angle Glaucoma

A chronic condition with increased intraocular pressure (lOP) due to decreased reabsorption of aqueous humor, leading to progressive (painless) visual loss and, if left untreated, blindness. lOP is a balance between fluid formation and its drainage from the globe. Strategies in drug treatment of glaucoma include the use of beta blockers to decrease formation of fluid by ciliary epithelial cells and the use of muscarinic activators to improve drainage through the canal of Schlemm (see Table II-4-l).

Closed-Angle Glaucoma

An acute (painful) or chronic (genetic) condition with increased lOP due to blockade of the canal of Schlemm. Emergency drug management prior to surgery usually involves cholinomimetics, carbonic anhydrase inhibitors, and/or mannitol.

Treatment

Table 11-4-1. Mechanism of Action of Drugs Used to Treat Glaucoma

Drug	Drug Class	Mechanism of Action
Pilocarpine, echothiophate	Cholinomimetic	Activation of M receptors causes contraction of ciliary muscle, which increases flow through the canal of Schlemm; echothiophate is an organophosphate AChE inhibitor ~ i outflow
Timolol	Beta blockers	Block actions of NE at ciliary epithelium ,j, aqueous humor formation

Note

Antimuscarinic drugs and ;:(1 agonists are contraindicated in closed-angle glaucoma.

ANS PRACTICE PROBLEMS

Answers and explanations to the following practice questions (pages 66-71) are found on pages 83-84.

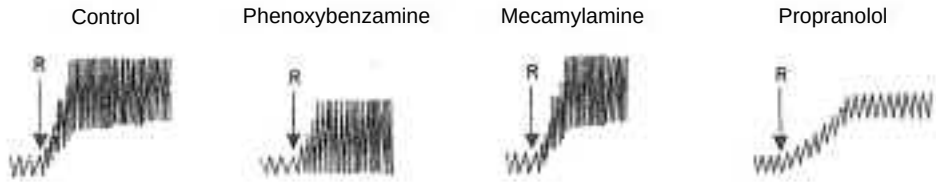


Figure 11-4-2

R is
A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. terbutaline

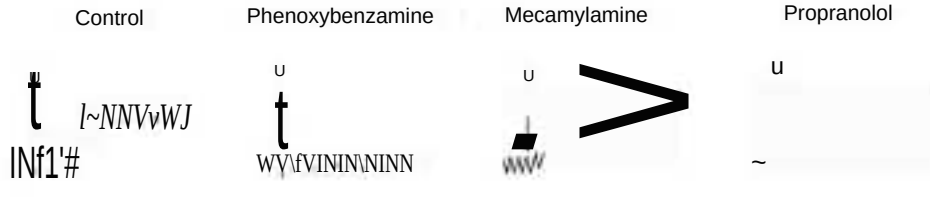


Figure 11-4-3

U is
A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. tyramine

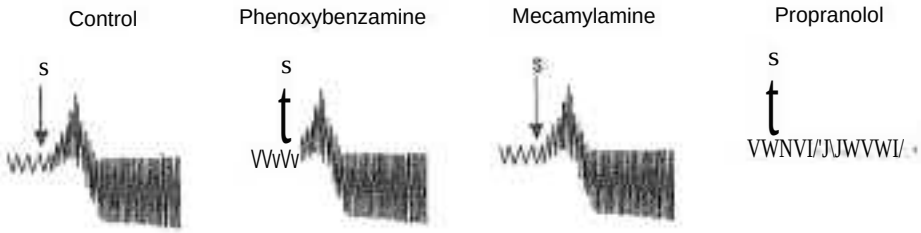
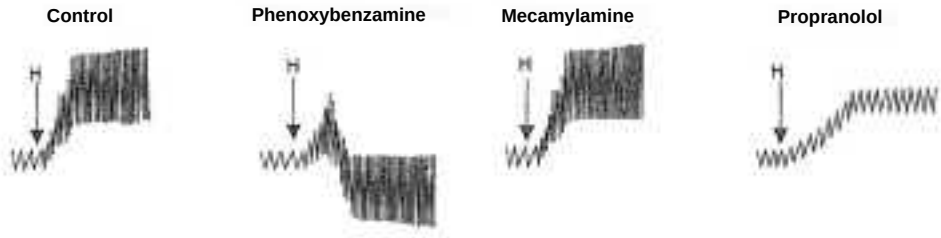


Figure 11-4-4

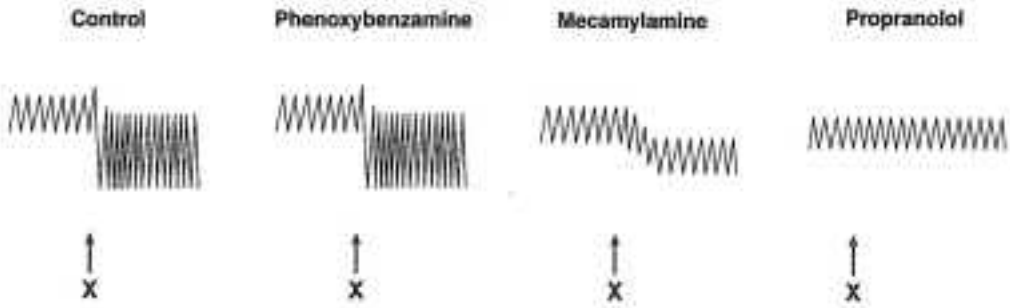
S is
A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. terbutaline

Figure 11-4-5



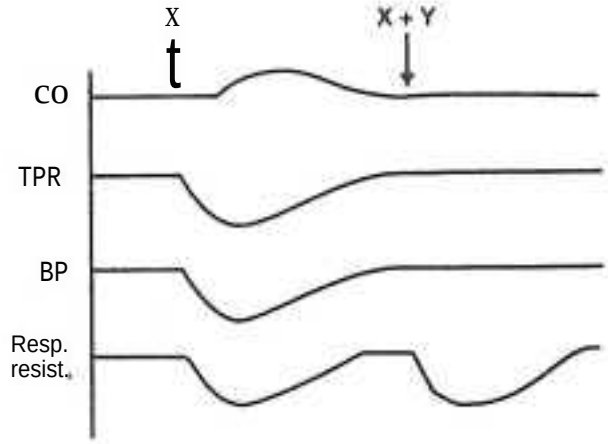
H is
A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. albuterol

Figure II-4-6



Drug X is most like

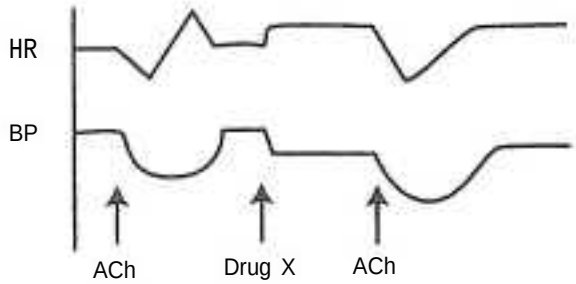
A. epinephrine
B. isoproterenol
C. norepinephrine
D. phenylephrine
E. terbutaline



X and Yare, respectively:

A. isoproterenol and propranolol
B. epinephrine and phenoxybenzamine
C. norepinephrine and phentolamine
D. terbutaline and phenylephrine
E. acetylcholine and hexamethonium

Figure 11-4-1

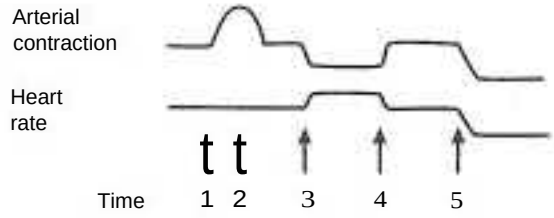


What is drug X?

A. Hexamethonium
B. Neostigmine
C. Atropine
D. Scopolamine
E. Ipratropium

What would you expect to see if the infused drug was neostigmine?

Figure 11-4-8



Given the following information:
- Contractile force is measured in an isolated arterial preparation, and heart rate is measured in an isolated heart preparation.
- One drug is added at each specified time.
- No washout between drugs

A. Bethanechol
B. Epinephrine
C. Phenoxybenzamine
D. Pindolol
E. Methoxamine

Time 1:
Time 2:
Time 3:
Time 4:
Time 5:

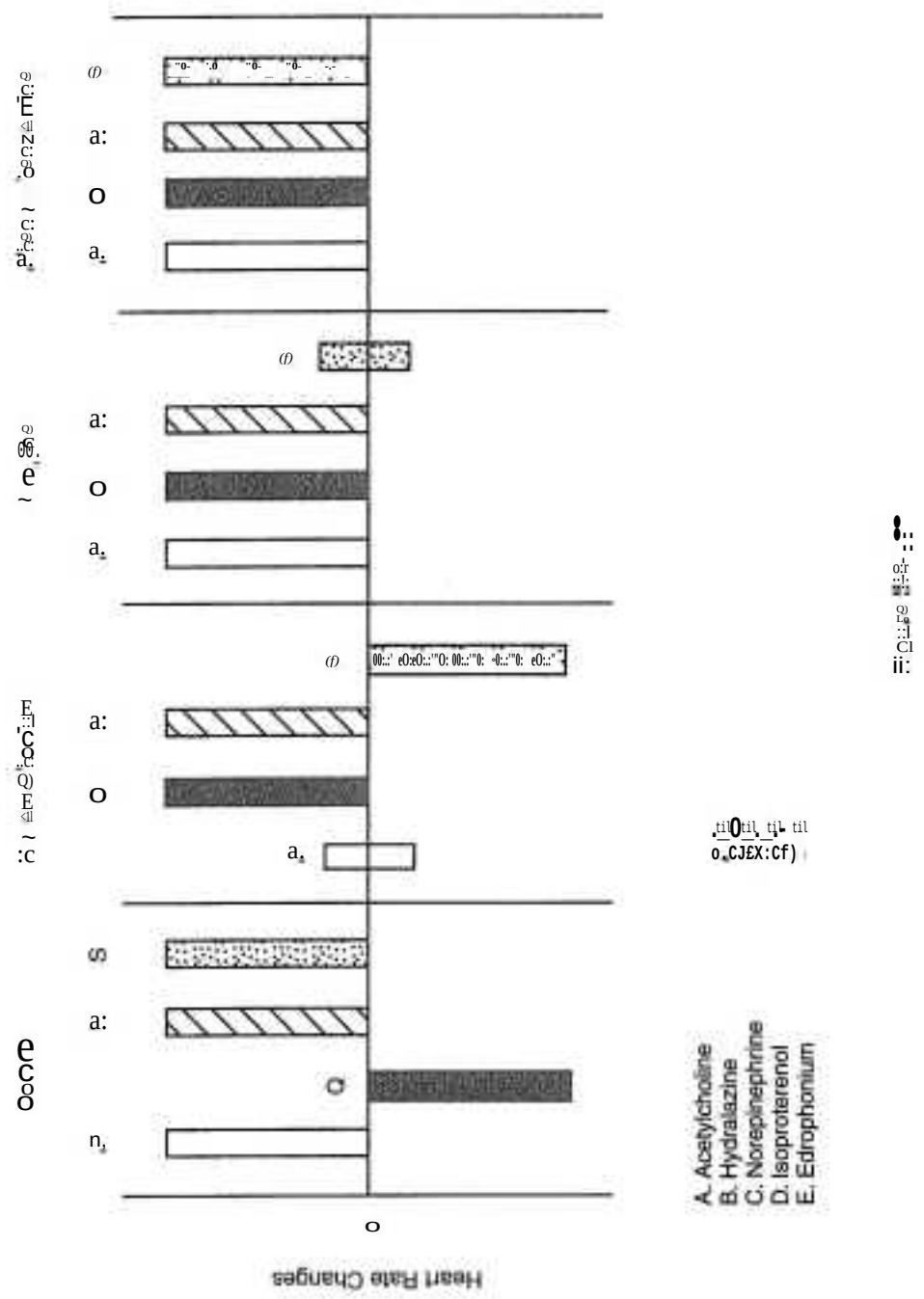
Figure 11-4-9

	RIGHT EYE	LEFT EYE
Without treatment	O	O
With tyramine	O	O
With epinephrine	O	O

The circles above represent the size of the pupils of a patient's eyes, without treatment and with two different treatments. The responses are compatible with the conclusion that the left eye had:

A. beta adrenergics blocked
B. alpha adrenergics blocked
C. cholinesterase inhibited
D. muscarinic receptors blocked
E. sympathetic denervation

Figure 11-4-10



Chapter Summary

The drugs used to treat open-angle glaucoma and their modes of action are summarized in Table 11-4-1.

The effects of autonomic drugs affecting the cardiovascular system are summarized visually in Figures 11-4-2through 11-4-11.

Autonomic Drug List and Practice Questions

5

Cholinergic Receptor Activators

Direct activators: bethanechol (M), methacholine (M and N), nicotine (N), pilocarpine (M)

AChE inhibitors: reversible-edrophonium, physostigmine, neostigmine

AChE inhibitors: irreversible-echothiophate, malathion, parathion

Cholinergic Receptor Antagonists

Muscarinic blockers: atropine, benztropine, ipratropium, scopolamine

Ganglionic blockers: hexamethonium, mecamylamine

Adrenergic Receptor Activators

a_1 agonists: phenylephrine, methoxamine

a_2 agonists: clonidine, methyldopa

~ agonists: isoproterenol, (~j = ~z)' dobutamine (~j > ~z)

~z agonists: albuterol, ritodrine, terbutaline, salmeterol

Mixed: dopamine (D_1, β_1, α_1), epinephrine (α_1, α_2, β_1, β_2), norepinephrine (α_1, α_2, β_1)

Indirect-acting: amphetamine, cocaine, ephedrine, tyramine

Adrenergic Receptor Antagonists

a_1 antagonists: doxazosin, prazosin, terazosin

a_2 antagonists: yohimbine, mirtazapine

Mixed a antagonists: phenoxybenzamine, phentolamine

~j (cardioselective) antagonists: acebutolol, atenolol, metoprolol

~l' ~z (nonselective): pindolol, propranolol, timolol

a_1 and ~ antagonists: carvedilol, labetalol

Chapter Summary

Drugs acting as cholinergic receptor activators or antagonists and those acting as adrenergic receptor activators or antagonists are listed.

ANS DRUGS

Review Questions

1. Vagal stimulation causes bradycardia, which can be blocked by
   A. atenolol
   B. atropine
   C. prazosin
   D. phenylephrine
   E. propranolol

2. Which one of the following effects is not caused by the ingestion of mushrooms that contain pilocarpine?
   A. Bradycardia
   B. Bronchospasm
   C. Diarrhea
   D. Hypertension
   E. Lacrimation

3. An increase in the cytosolic concentration of norepinephrine in sympathetic nerve endings leads to
   A. activation of dopa decarboxylase
   B. increased release of norepinephrine
   C. inhibition of tyrosine hydroxylase
   D. stimulation of MAO
   E. none of the above

4. Urination in the human subject is decreased by
   A. acetylcholine
   B. benztropine
   C. edrophonium
   D. nicotine
   E. physostigmine

5. A 5-year-old child becomes ill while visiting relatives who have a farm in Arkansas. His symptoms include severe abdominal cramps with vomiting and diarrhea and profuse lacrimation and salivation. Pupillary constriction is marked. If these symptoms are due to chemical toxicity, the most likely cause is exposure to

   A. chlorophenoxy acetic acid (herbicide)
   B. ethylene glycol (antifreeze)
   C. lead-based paint (pica)
   D. parathion (insecticide)
   E. coumadin (rat poison)

6. The activation of muscarinic receptors in bronchiolar smooth muscle is associated with

   A. activation of adenylyl cyclase
   B. decrease in cAMP formation mediated by G-proteins
   C. increase in IP_3 and DAG
   D. inhibition of protein kinase C
   E. opening of Na^+/K^+ cation channels

7. Overuse of certain decongestants that are indirect-acting sympathomimetics can lead to a diminished response. Tachyphylaxis in such cases is most probably due to

   A. blockade of prejunctional adrenoceptors
   B. compensatory cholinergic responses
   C. induction of the metabolism of the applied drug
   D. inhibition of impulse conduction in sympathetic nerves
   E. reduced stores of available neurotransmitter

8. The effects of a ganglion blocking agent may be predicted by knowledge of ANS innervation of effector systems and which branch of the ANS exercises dominance in terms of organ and tissue responsivity. With this principle in mind, one can anticipate that hexamethonium will cause

   A. abolition of the circulatory reflex
   B. cycloplegia
   C. reduction of bladder tone
   D. xerostomia
   E. all of the above

9. An 11-year-old boy was brought to the ER by some of his friends because he "started going crazy" after eating seeds from a plant while "trying to get high." The boy was incoherent; his skin was hot and dry. His pupils were dilated and unresponsive to light. Blood pressure was 180/105, pulse 150, and rectal temp 40°C. The presumptive diagnosis was drug toxicity due to the ingestion of a compound similar to

   A. cannabis
   B. digoxin
   C. mescaline
   D. phencyclidine
   E. scopolamine

10. Reflex tachycardia is most likely to occur after the systemic administration of

A. albuterol
B. methoxamine
C. phenylephrine
D. propranolol
E. mecamylamine

11. Cardiovascular effects of a new drug (X) that activates autonomic receptors are shown in the table below:

Parameter	Control	Drug X
Systolic BP	120 mm Hg	1l0mm Hg
Diastolic BP	85 mm Hg	55mmHg
Heart rate	60/min	120/min

The most probable receptor affinities of drug X are

A. α_1, α_2
B. α_1, α_2, β_1
C. β_1, β_2
D. M_2
E. N_M

12. Which one of the following sites is characterized by adrenergic neurohumoral transmission?

A. Parasympathetic preganglionic fibers
B. Sympathetic postganglionic fibers
C. Sympathetic fibers in the adrenal medulla
D. Synaptic fibers in the ecrine gland
E. Parasympathetic postganglionic nerve endings

13. Activation of prejunctional α_2 receptors on sympathetic nerve endings is associated with

A. activation of adenylyl cyclase
B. decrease in cAMP formation
C. increase in IP_3 and DAG
D. inhibition of protein kinase C
E. opening of Na+/K+ cation channels

14. The data in the table below show the effects of four drugs (#1-4) on mean blood pressure administered as individual agents before and after treatment with prazosin. The arrows denote the direction and intensity of drug actions on blood pressure.

Condition	Drug #1	Drug #2	Drug #3	Drug #4
Before prazosin	↑↑	↑↑	↓↓	↑
After prazosin	↑	↑	↓↓	↓

The order of drug #1 through drug #4 is best represented by

A. epinephrine-tyramine-isoproterenol-norepinephrine
B. tyramine-isoproterenol-norepinephrine-epinephrine
C. norepinephrine-isoproterenol-epinephrine-tyramine
D. isoproterenol-epinephrine-tyramine-norepinephrine
E. norepinephrine-tyramine-isoproterenol-epinephrine

15. Ocular effects that include mydriasis and fixed far vision are characteristic of

A. mecamylamine
B. neostigmine
C. phentolamine
D. phenylephrine
E. timolol

16. Following a myocardial infarct, a 40-year-old male patient is being treated prophylactically with propranolol. In terms of adverse effects of the drug, which of the following is most likely to occur with use of this specific beta blocker?

A. Bradycardia, mydriasis, sweating
B. Bronchoconstriction, hyperglycemia, and hypotension
C. Hypoglycemia, hyperlipidemia, and sedation
D. Micturition and mydriasis
E. Migraine headaches and AV block

17. Following pretreatment with a muscarinic receptor blocking agent, the IV administration of norepinephrine is likely to result in

A. ↑ HR and ↑ BP
B. ↓ HR and ↓ BP
C. ↓ HR and ↓ BP
D. ↓ HR and ↓ BP
E. no effect on HR, but ↑ BP

18. A 45-year-old Nobel Prize-winner in chemistry has recently been the recipient of a heart transplant. Patient education has included both verbal and written descriptions of the potential cardiovascular effects of pharmacologic agents. Which one of the following drugs is least likely to cause tachycardia in this patient?

A. Amphetamine
B. Dobutamine
C. Epinephrine
D. Isoproterenol
E. Norepinephrine

19. A colleague with myasthenia gravis wants you to assist him to the ER because he is weak and has found it difficult to titrate his drug dosage because he has had the "flu." You note that he has a slight temperature, shallow respirations, and a gray-blue skin pallor. Because you know about the problem of distinguishing between cholinergic excess and under-treatment in the myasthenic patient, you would probably recommend that your colleague be given

A. albuterol
B. edrophonium
C. propranolol
D. physostigmine
E. scopolamine

20. Tonometric measurements in a 55-year-old patient revealing a consistent increase in lOP, together with abnormalities in central visual field testing, are diagnostic of open-angle glaucoma. A number of pharmacologic treatments can slow the progression of the disease, which can ultimately lead to complete blindness if left untreated. Which one of the following statements about such drug therapy is accurate?

A. Beta blockers cause ciliary muscle contraction, increasing aqueous humor outflow
B. Cholinomimetics decrease the secretion of aqueous humor
C. Topical use of nonselective beta blockers can worsen asthma
D. Activation of alpha receptors leads to miosis
E. Topical use of AChE inhibitors leads to mydriasis

21. Labetalol is an effective antihypertensive agent that, like propranolol, is capable of blocking beta receptors. An important difference between the two drugs is that labetalol

A. is a selective blocker of cardiac β_1 receptors
B. has intrinsic sympathomimetic activity
C. is available only for intravenous use
D. has α_1 receptor blocking actions
E. stimulates β_2 receptors in bronchioles

22. Physostigmine differs from bethanechol in having effects on

A. bladder tone
B. bowel motility
C. heart rate
D. salivary glands
E. skeletal muscle

Questions 23-25

The table below shows the effects of three receptor activators on heart rate in anesthetized animals, administered as individual drugs and following pretreatment with one of four different receptor antagonists. The arrows denote the direction of effects on heart rate; the symbol (-) denotes no change from normal HR.

Antagonist Pretreatment	**Agonist 1**	Agonist 2	Agonist 3
None	r	J,	J,
Atropine	r	-	r
Prazosin	i	-	r
Propranolol	-	J,	J,
Mecamylamine	t	-	r

Identify the agonist drugs from the following list:

A. Acetylcholine
B. Epinephrine
C. Norepinephrine
D. Methoxamine
E. Physostigmine

23. Agonist 1

24. Agonist 2

25. Agonist 3

Answers

1. **Answer: B.** Bradycardia due to vagal stimulation is elicited by activation of muscarinic receptor in the heart. Atropine, which is an antagonist at M receptors, blocks bradycardia elicited by stimulation of the vagus, including reflex bradycardia due to increases in mean BP caused by vasoconstrictors.

2. **Answer: D.** Pilocarpine is present in several mushroom species including *Amanita mU5-caria,* the ingestion of which is associated with the stimulation of M receptors (parasympathomimetic effects). The activation by pilocarpine of M receptors present on vascular endothelial cells would lead to hypotension (not hypertension) via the release of NO (EDRF). All of the other effects listed are typical of excessive stimulation of M receptors.

3. **Answer: C.** Tyrosine hydroxylase, the rate-limiting step in the synthesis of NE in sympathetic nerve endings, is subject to feedback inhibition by NE. In some sympathetic nerve endings (e.g., in the heart), tyrosine hydroxylase is also inhibited via NE activation of prejunctional (X2 receptors .

4. **Answer: B.** Urinary retention is a well known adverse effect of drugs that have antagonist effects on muscarinic receptors. In addition to the prototypic drug atropine, M blockers include drugs used in Parkinson disease, such as benztropine. Acetylcholine directly and AChE inhibitors (edrophonium, physostigmine) indirectly activate M receptors in the GU system, causing bladder contraction with voiding and incontinence. Activation of nicotinic receptors in ANS ganglia would lead to the stimulation of PANS functions.

5. **Answer: D.** The symptoms of cholinergic excess seen in this child are indicative of exposure to insecticides such as the organophosphate parathion, which cause irreversible inhibition of acetylcholinesterase. Other symptoms may include CNS excitation and stimulation of the skeletal NMJ, ultimately leading to paralysis of respiratory muscles-"DUMBBELSS." In addition to symptomatic support, management of AChE inhibitor poisoning involves the use of atropine and 2-PAM.

6. **Answer:** C. Muscarinic receptors present in bronchiolar smooth muscle are of the M_3 subtype coupled via G_q proteins to phospholipase C. Activation of this enzyme causes hydrolysis of phosphatidylinositol bisphosphate, with release of IP_3 and DAG (the latter activates protein kinase *C).* Decreased formation of cAMP mediated via a G_i protein occurs with activation of M_2 receptors such as those in the heart. Cation channel opening occurs in response to activation of nicotinic receptors.

7. **Answer:** E. Tachyphylaxis, a rapid loss of pharmacologic activity, frequently occurs with indirect-acting sympathomimetics such as amphetamine, ephedrine, and pseudoephedrine. These drugs act to release NE from the mobile pool in sympathetic nerve endings. With excessive use of these agents, the NE stores may become depleted, resulting in a decreased response of vascular smooth muscle in terms of vasoconstriction.

8. **Answer: E.** Except for blood vessels and the thermoregulatory sweat glands, the dominant tone in terms of ANS function is parasympathomimetic. Ganglion blockers (hexamethonium, mecamylamine, trimethaphan) reduce dominant tone and cause a relaxation of GI and GU smooth muscle, plus decreased salivation. Because the ciliary muscle of the eye is only PANS innervated, ganglion blockers cause cycloplegia. Finally, ganglion blockers will abolish all autonomic reflexes.

9. Answer: E. The signs and symptoms experienced by this boy are highly suggestive of the ingestion of a compound with strong muscarinic receptor blocking actions. The leaves and seeds of jimsonweed *(Datura stramonium)* contain anticholinergic compounds, including atropine, hyoscyamine, and scopolamine-approximately 50 seeds may cause severe toxicity. In addition to symptomatic support, management of poisoning (or drug overdose) due to M blockers may involve use of the AChE inhibitor physostigmine.

10. Answer: A. Although used primarily via inhalation for asthma, systemic effects of albuterol include vasodilation due to its ~2 receptor activation. This can result in a decrease in PVR and mean BP, which elicits a reflex tachycardia. Methoxamine and phenylephrine are (X- receptor activators causing vasoconstriction, which would result in reflex bradycardia. Ganglion blockers (mecamylamine) prevent autonomic reflexes, and a reflex increase in heart rate could not occur in the presence of a beta blocker (propranolol).

11. Answer: C. A decrease in mean blood pressure, an increase in pulse pressure, plus a marked increase in heart rate are characteristic of a drug such as isoproterenol. PVR and mean BP are decreased because of activation of ~2 receptors in the vasculature. Systolic BP decreases less than diastolic BP because of activation of ~1 receptors in the heart, leading to an increase in stroke volume, as well as the increase in heart rate.

12. Answer: C. The term *neurohumoral* means "nerve-blood." The only site in the ANS where neurohumoral transmission occurs is the adrenal medulla, where sympathetic nerve activity elicits the release of catecholamines into the blood.

13. Answer: B. Decreased formation of cAMP mediated via a G_i protein is associated with activation of prejunctional receptors that can function as auto receptors to inhibit release of NE from sympathetic nerve endings. A similar mechanism involving G_i protein inhibition of adenylyl cyclase occurs with activation of M_2 receptors (see answer 6).

14. Answer: E. Of the drugs listed, only isoproterenol causes a decrease in mean blood pressure, because it activates beta receptors and has no effect on alpha receptors. This permits identification of drug #3 as isoproterenol. Prazosin is an alpha blocker, so one can anticipate that this drug would antagonize any increases in blood pressure that result from activation of (X1 receptors in the vasculature. Epinephrine (high dose), norepinephrine, and tyramine all exert pressor effects via activation of (X1 receptors. However, only epinephrine is active on ~2 receptors, and this action would be revealed by vasodilation and a reversal of its pressor effects following treatment with an alpha blocker-"epinephrine reversaL" Thus, drug #4 can be identified as epinephrine.

15. Answer: A. Mydriasis and fixed far vision can be due to either muscarinic receptor antagonists or ganglionic blockade. Because no M blockers are listed, the correct answer is mecamylamine. Alpha agonists (phenylephrine) have no effects on the focus of the eye. The cholinesterase inhibitor (neostigmine) and alpha blocker (phentolaminelcause miosis. Ocular effects of the beta blocker (timolol) are restricted to decreased formation of aqueous humor by the ciliary epithelium.

16. Answer: C. Propranolol is a nonselective beta blocker and can cause bradycardia, bronchoconstriction, hypotension, and AV block. The drug also causes hypoglycemia and CNS effects, including sedation. The chronic use of propranolol is associated with changes in plasma lipids, including elevations in both LDL cholesterol and triglycerides. Mydriasis is associated with blockade of M receptors, and both micturition and sweating result from activation of such receptors. One of the clinical uses of propranolol is the treatment of migraine headaches.

17. Answer: A. Norepinephrine activates (X1 and ~1 receptors, causing increases in PVR and CO. The increase in mean BP can elicit reflex bradycardia (vagal outflow leads to stimulation of cardiac M receptors), which may overcome the direct stimulatory effects of NE on the heart. However, reflex bradycardia is not possible following pretreatment with an M blocker. Thus, HR increases because of the direct activation of cardiac ~1 receptors by NE.

18. Answer: A. This question is to remind you that indirect-acting sympathomimetics require innervation of the effector organ to exert effects. In this case, amphetamine would not be effective because the transplanted heart lacks sympathetic innervation; thus, there is no "mobile pool" of NE capable of being released by a drug. However, transplanted hearts retain receptors, including those (~1) responsive to direct-acting sympathomimetics. Heart transplants are not responsive to AChE inhibitors because they, too, are indirect acting and require vagal innervation to exert effects on the heart.

19. Answer: B. Edrophonium is a very short-acting (reversible) AChE inhibitor that has been used in the diagnosis of myasthenia gravis. The drug is useful for distinguishing between muscle weakness attributable to excessive cholinergic receptor stimulation (usually due to overdose of a AChE inhibitor) and the symptoms of myasthenia (reflecting inadequate treatment). If symptoms improve with a single dose of edrophonium, then an increase in the dose of neostigmine or pyridostigmine is indicated. If symptoms worsen, then the dose of neostigmine should be reduced.

20. Answer: C. This question helps review ANS drug actions on the eye. The pupil is controlled reciprocally by the SANS (iris dilator, alpha) and the PANS (iris sphincter, muscarinic); thus, alpha agonists cause mydriasis, and AChE inhibitors cause miosis (answers D and E are "opposites"). Ciliary muscle contraction is controlled by the PANS, so cholinomimetics lower lOP by putting tension on the trabecular network to facilitate outflow of aqueous humor through the canal of Schlemm-beta blockers decrease the secretory activity of ciliary epithelial cells (answers A and B are "opposites"). Topical use of nonselective beta blockers can indeed worsen asthma!

21. Answer: D. The effectiveness of labetalol in the management of hypertension and in severe hypertensive states appears to be due to a combination of antagonistic actions at both alpha and beta adrenoceptors. Labetalol is not a ~1 selective blocking agent (unlike atenolol and metoprolol), and (unlike pindolol and acebutolol) it lacks intrinsic sympathomimetic activity. Labetalol is available for both peroral and parenteral use; unfortunately, it blocks ~2 receptors in bronchiolar smooth muscle.

22. Answer: E. As an inhibitor of AChE, physostigmine exerts effects to enhance the actions of ACh at all innervated effector sites where ACh is a neurotransmitter. These include all ANS ganglia, PANS postganglionic neuroeffector junctions, and SANS innervation of thermoregulatory sweat glands. Bethanechol, an analog of ACh, activates M receptors and has no effects at conventional dose levels on nicotinic receptors such as those in ANS ganglia and the skeletal NMJ.

23. Answer: B; 24. Answer: D; 25. Answer: C

Agonist 1 increases HR, presumably through direct activation of cardiac ~1 receptors because the effect is blocked by propranolol but is not influenced by the alpha blocker (prazosin), the ganglion blocker (trimethaphan), or blockade of M receptors (atropine). Only two of the listed drugs directly activate cardiac receptors: epinephrine and norepinephrine. For NE, any direct cardiac stimulation is counteracted by reflex bradycardia resulting from the increase in mean BP via its activation of (X1 receptors in blood vessels (it has no effects on ~2 vascular receptors). Therefore, agonist 1 is identified as epinephrine (presumably at low dose).

Although both ACh and the AChE inhibitor (physostigmine) can decrease HR by causing activation of M receptors in the heart, this action would not be antagonized or reversed by the ganglion blocker trimethaphan.

To identify agonists 2 and 3, recognize that although the alpha blocker prazosin simply neutralizes the effect of agonist 2 on HR, it reverses the effect of agonist 3. This could occur only if agonist 3 was capable of ~1 receptor activation in the heart. Direct cardiac stimulation could occur with norepinephrine (agonist 3) but not with methoxamine (agonist 2), which is a selective alpha adrenoceptor agonist.

Explanations to Figures 11-4-2 through 11-4-11: Drug Identification from Effects on Heart Rate and Blood Pressure.

Figure 11-4-2: The effects of Drug R are changed by treatment with either an alpha or beta-blocker, so Drug R must have activity at both receptors (choices C, D, and E are ruled out). A pressor dose of epinephrine would be "reversed" by an alpha-blocker, not just decreased! Drug R is norepinephrine.

Figure 11-4-3: The effects of Drug U are changed by treatment with the alpha-blocker, but not by the beta-blocker. Drug U must be an alpha-activator with no beta actions, the only choice is phenylephrine.

Figure 11-4-4: The effects of Drug S are changed by treatment with the beta-blocker, but not by the alpha blocker (choices A, B, and C are ruled out). Terbutaline is ~2 selective and would not increase heart rate directly. Drug S is isoproterenol. Note that option A would have been a possibility but one would have to assume a low-dose of epinephrine.

Figure 11-4-5: The effects of Drug H are changed by treatment with either an alpha- or beta-blocker, so Drug H must have activity at both receptors (choices C, D, and E are ruled out). "Reversal" of a pressor effect can only occur if the drug has ~2 activity (choice B is ruled out). Drug H is epinephrine.

Figure 11-4-6: Mecamylamine blocked reflexed tachycardia induced by Drug X, which dropped blood pressure by vasodilation. Propranolol prevented all responses. Drug X is a ~2 agonist (terbutaline).

Figure 11-4-7: Drug X decreases TPR and BP, eliciting a reflex sympathetic discharge (note delay in response), resulting in increased CO. There is no direct effect on CO (choices A, B, C, and E are ruled out). Drugs X and Y are terbutaline and phenylephrine. Note that the alpha agonist does not antagonize the decrease in respiratory resistance (a ~2 response).

Figure 11-4-8: ACh (used as a drug) decreases blood pressure and heart rate, but the latter effect is overcome and reversed by a sympathetic reflex. Because Drug X abolishes only the reflex tachycardia, it must be the ganglion blocker hexamethonium (choice A). Remember, AChE inhibitors do not vasodilate because there is no parasympathetic innervation of the vasculature!

Figure 11-4-9: No autonomic reflexes are possible in isolated preparations! Arterial contraction due to the alpha agonist (choice E) is reversed by the alpha-blocker (choice C). Arteriolar relaxation and tachycardia due to epinephrine (choice B) is reversed by the beta-blocker (choice D). Bethanechol (choice A) causes both arteriolar relaxation and bradycardia.

Figure 11-4-10: Classic example showing that denervated tissues do not respond to indirect-acting agonists. In this case, tyramine fails to cause mydriasis in the left eye, but this eye is more responsive than the right eye to epinephrine (denervation supersensitivity).

Figure 11-4-11: Block of tachycardia due to Drug P by hexamethonium is indicative of a sympathetic reflex that follows a decrease in BP due to a vasodilator (choice B). "Reversal" of bradycardia due to Drug Q by hexamethonium indicates a vagal reflex elicited by vasoconstriction (e.g., alpha activation) masking cardiac stimulation (e.g., beta activation) typical of norepinephrine (choice C). Tachycardia due to Drug R is unaffected by any antagonist, indicative of a beta activator **(choice** D). "Reversal" of tachycardia due to Drug S by hexamethonium indicates a sympathetic reflex masking a vagotomimetic action typical of a muscarinic activator **(choice** A); this is confirmed by the effect of atropine.

SECTION In

Cardiac and Rena l Pharmaco bgy

Fundamental (oocep ts

1

CARDIAC ACTION POTENTIAL

Fast-Response Fibers: Cardiac Muscle, His-Purkinje System

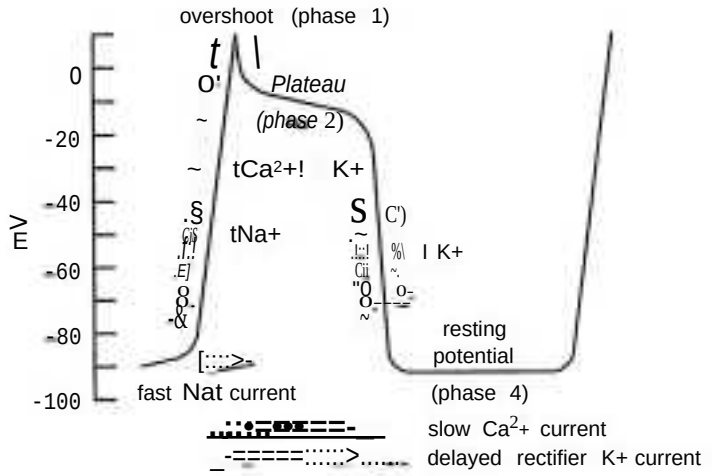


Figure 11I-1-1.Cardiac Action Potentials in Fast-Response Fibers

Phase 0

- Na+ channels open-sodium enters the cell down its concentration gradient (fast IN)' causing membrane depolarization.
- Rate of depolarization depends on number of Na" channels open, which in turn depends on resting membrane potential of the cell.
- Class I antiarrhythmic drugs can slow or block phase 0 in fast-response fibers.

Phase 1

- Na+ channels are inactivated.
- In some His-Purkinje cells, transient outward K+ currents and inward cr currents contribute to the "notch" and overshoot.
- Antiarrhythmic drugs have no significant effects on these transient currents.

Phase 2

- Plateau phase in which a slow influx of Ca2+ ($I_{Ca\text{-}L}$) is "balanced" by a late-appearing outward K+ current (the delayed rectifier current I_K).
- Antiarrhythmic drugs have no significant effects on these currents during this phase of the action potential (AP).

Phase 3

- Repolarization phase in which the delayed rectifier K+ current rapidly increases as the Ca^{2+} current dies out because of time-dependent channel inactivation.
- Class III antiarrhythmic drugs slow this repolarization phase.
- Note that during phases 0 through 3 a slow Na" current ("window current") occurs, which can help prolong the duration of the action potential.

Phase 4

- Return of membrane to resting potential-maintained by activity of the Na+/K+-Al'Pase,

Responsiveness

- Capacity of a cell to depolarize, associated with the number of Na+ channels in a ready state (see Figure III-1-4, page 90).
- This in turn depends on resting membrane potential: the more negative the resting potential (RP), the faster the response.

Conductance

Rate of spread of an impulse, or conduction velocity-three major determinants:

- Rate of phase 0 depolarization-as V_{max} decreases, conduction velocity decreases and vice versa.
- Threshold potential-the less negative, the slower the conduction velocity.
- Resting potential-the more negative the RP, the faster the conduction.

Slow-Response Fibers (SA and AV Nodes, Specialized Cells)

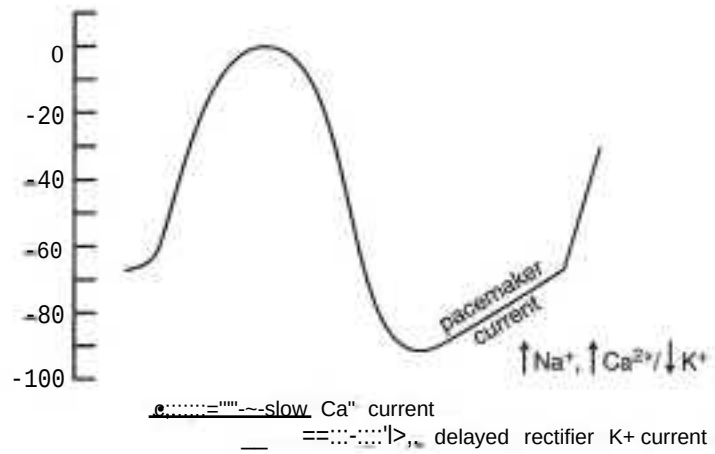


Figure 11I-1-2. Cardiac Action Potentials in Slow-Response Fibers

- No appreciable Na+ current during phase 0 in these cells because the Na channels are either absent or in an inactive form because of the existing voltage.
- Depolarization depends on activation of Ca2+ channels (ICa-L and lCa-T)'
- Class IV antiarrhythmic drugs can slow or block phase 0 in slow-response fibers.
- During repolarization, the Ca^{2+} currents are opposed and overcome by the delayed rectifier K+ current. The relative magnitudes of these opposing currents determine the "shape" of the action potential.
- The major distinctive feature of slow fibers is their spontaneous depolarization, shown by the rising slope of phase 4 of the AP, referred to as the pacemaker potential or "pacemaker current." Although not completely understood, pacemaker potential is a composite of inward Na+ (If) and Ca^{2+} (ICa-T) currents and outward K+ currents (IK)'
- Class II and IV antiarrhythmic drugs can slow phase 4 in pacemaker fibers.

Automaticity

- The ability to depolarize spontaneously confers automaticity on a tissue.
- The fastest phase 4 slope will determine the pacemaker of the heart, which is normally the SA node.

Refractoriness

- The inability to respond to a stimulus-property of all cardiac cells.

Effective Refractory Period (ERP)

- No stimulus, of any magnitude, can elicit a response.
- Lasts into late stage 3 of the AP because Na+ channels are effectively inactivated and not in the "ready" state.
- Blockers of K+ channels prolong the ERP.

Relative Refractory Period (RRP)

- A strong stimulus can elicit a response, but the timing will be out of sync with the rest of the heart and arrhythmias may occur.
- Ratio of ERP to the action potential duration (APD) is a measure of refractoriness, as illustrated in Figure III -1-3. Decreases in ERP favor the formation and propagation of premature impulses.

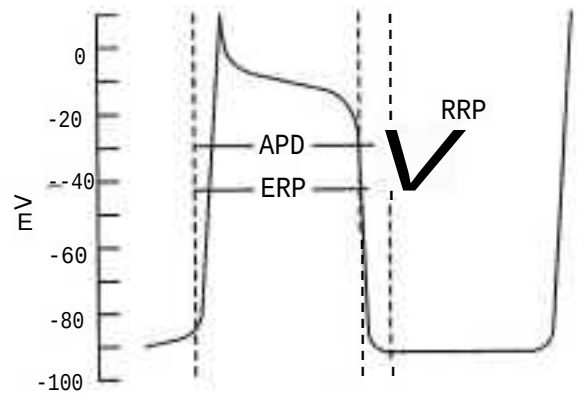


Figure 11I-1-3.Relationship of ERP to APD

Na+ CHANNEL

Activation

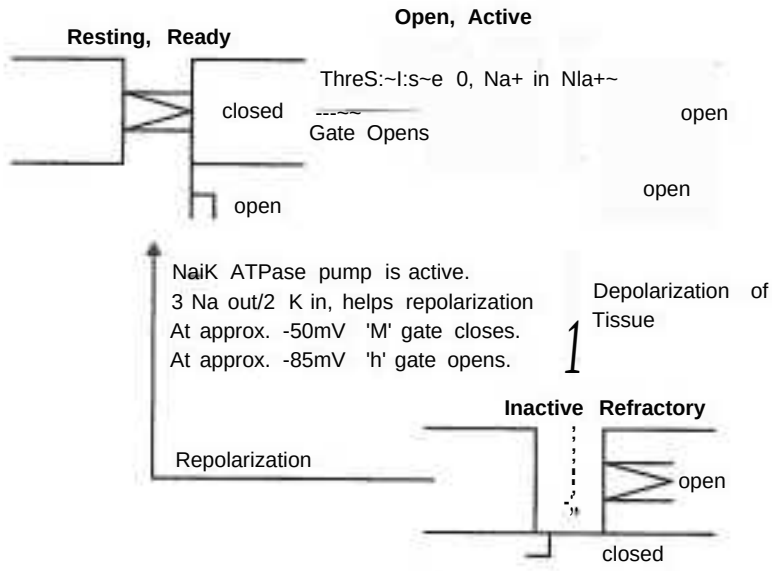


Figure 11I-1-4.Mechanism of Action of Voltage-Gated Na+ **Channels**

- This voltage-gated channel, which is responsible for the fast Na current (IN)' exists in three conformations:
  - Resting or ready state
  - Open or active state
  - Inactivated or refractory state
- The channel has two gates: M (activating) and h (inactivating), both of which are sensitive to voltage changes.
- Inactivation of the h gate is slower; therefore, it stays open longer and the Na channel is active.

Recovery

- Rate of recovery of the Na channel is dependent on resting potential (RP).
- Fastest rate of recovery occurs at normal RP, and recovery slows as membrane voltage increases.
- Rate of recovery is slower in ischemic tissue because cells may be partly depolarized at rest. This reduces the number of channels able to participate in the next depolarization, which leads to a decrease in conduction rate in ischemic tissue.
- Na channel blockers also slow the rate of recovery in such tissues.

ANS REGULATION OF HEART RATE

- Nodal tissue, especially that of the SA node, is heavily innervated by both PANS and SANS fibers activating M_2 and PI receptors, respectively.
- Phase 4 slope is increased by an increase in cAMP resulting from PI receptor activation and slowed by a decrease in cAMP resulting from M_2 receptor activation.
- Increase in cAMP will:
  - Increase upstroke velocity in pacemakers by increase of I_{Ca-L}
  - Shorten AP duration by increase of I_K
  - Increase HR by increase of If' thus increasing slope of phase 4
- Decrease in cAMP:
  - Does the opposite plus produces a K+ current (IKJACh)' which slows the rate of diastolic depolarization and thus decreases HR
  - Beta blockers prevent cAMP formation, with primary effects on SA and AV nodal tissues.

Chapter Summary

The sequences of ionic events in the action potential of cardiac cells are described.

Depolarization (phase 0) is due to Na+ influx in fast fibers and due to Ca^{2+} influx in SA and AV nodal cells. Class I antiarrhythmic drugs block Na+ influx and class IV antiarrhythmics block Ca^{2+} influx.

Repolarization (phase 3) in all cardiac cells is due to K+ efflux (delayed rectifier current) and this is blocked by class IA and class III antiarrhythmic drugs. Pacemaker currents (phase 4) are blocked by class II and class IV drugs.

Responsivity, capacity of a cell for depolarization, depends on resting membrane potential; conductance is the rate of potential spread; refractoriness is the inability to respond to excitation.

Figure 111-1-4depicts the M and h gates of cardiac Na+ channels. Three conformations exist-resting (ready), active (open), and inactive (refractory). Class I drugs are least active when Na" channels are in the resting state (state-dependent actions).

Actions of class II antiarrhythmics (beta blockers) involve antagonism of SANS-mediated increases in cAMP, especially at SA and AV nodal cells to slow phase 0 and 4 of the action potential.

Antiarrhythmic Drugs

2

CLASS I: Na+ CHANNEL BLOCKERS

Class IA

- Antiarrhythmic: block fast Na+ channels (J_{Na}, I_N)
- Preferentially in the open or activated state-"state-dependent" blockade
- ↑ action potential duration (APD) and effective refractory period (ERP)
- Also blocks K+ channel (prolongs repolarization)
- Drugs:
  - **Quinidine**
    - In addition to the above, causes muscarinic receptor blockade, which can ↓ HR and AV conduction.
    - May also cause vasodilation via alpha block with possible reflex tachycardia.
    - Orally effective, wide clinical use in many arrhythmias; in atrial fibrillation, need initial digitalization to slow AV conduction.
    - Adverse effects: cinchonism (GI, tinnitus, ocular dysfunction, CNS excitation), hypotension, prolongation of QRS and ↓ QT interval associated with syncope (torsades) .
    - Drug interactions: hyperkalemia enhances effects and vice versa; displaces digoxin from tissue binding sites, enhancing toxicity.
  - **Procainamide**
    - Less muscarinic receptor block
    - Metabolized via N-acetyltransferase (genotypic variation) to N-acetyl procainamide (NAPA), an active metabolite
    - Adverse effects: systemic lupus erythematosus (SLE)-like syndrome (30% incidence) more likely with slow acetylators; hematotoxicity (thrombocytopenia, agranulocytosis); CV effects (torsades)

Class 1B

- Antiarrhythmic: block fast Na+ channels (J_{Na}, INa)
- Block inactivated channels-preference for tissues partly depolarized (slow conduction in hypoxic and ischemic tissues). This results in an increased threshold for excitation and less excitability of hypoxic heart muscle.
- J_{Na}, APD-due to block of the slow Na+ "window" currents, but this increases diastole and extends the time for recovery.

Note

For the exam, you should understand which effect is antiarrhythmic (slows heart) and which is proarrhythmic (speeds up heart).

Note

Quinidine is a weak base, and antacids increase its absorption, thus greatly increasing its toxicity.

- Drugs and uses:
  - Lidocaine
    - Post-MI
    - Open-heart surgery
    - Digoxin toxicity
    - Side effects: eNS toxicity (seizures); least cardiotoxic of conventional anti-arrhythmics
    - IV use because of first-pass metabolism
  - Mexiletine and tocainide
    - Same uses as lidocaine
    - Oral formulations

Class IC

- Block fast Na+ channels (↓ IN)' especially His-Purkinje tissue
- No effect on APD
- No ANS effects
- Drug:
  - Flecainide
    - Limited use because of proarrhythmogenic effects, leading to ↑ in sudden death post-MI and when used prophylactically in VT

CLASS II: BETA BLOCKERS

- Prevent ~-receptor activation, which would normally ↑ cAMP
- ↓ SA and AV nodal activity
- ↓ Slope of phase 4 (diastolic currents) of AP in pacemakers
- Drugs:
  - Propranolol (nonselective) and the cardioselective drugs: acebutolol and esmolol
  - Uses:
    - Prophylaxis post-MI and in supraventricular tachyarrhythmias (SVTs)
    - Esmolol (IV) is used in acute SVTs

CLASS III: Ie CHANNEL BLOCKERS

- ↓ I_K (delayed rectifier current) slowing phase 3 (repolarization) of AP
- ↑ APD and ERP, especially in Purkinje and ventricular diseases
- Drugs:
  - Amiodarone
    - Mimics classes I, II, III, and IV
    - Increase APD and ERP in all cardiac tissues
    - Uses: any arrhythmias
    - $t1/_2$ >80 days

- Binds extensively to tissues (large Vd and multiple effects)
- Side effects:
  - Pulmonary fibrosis
  - Blue pigmentation of the skin ("smurf skin")
  - Phototoxicity
  - Corneal deposits
  - Hepatic necrosis
  - Thyroid dysfunction

- Sotalol:
  - ↓ I_{K}, slowing phase III
  - ~1 blockade, leading to ↓ HR, ↓ AV conduction
  - Use: life-threatening ventricular arrhythmia

CLASS IV: Ca^{2+} CHANNEL BLOCKERS

- Block slow cardiac Ca^{2+} channels
- ↓ phase 0, ↓ phase 4
- ↓ SA, ↓ AV nodal activity
- Drugs:
  - Verapamil and diltiazem
    - Prototype Ca2+-channels blockers *(see* Antihypertensive Drugs and Antianginal Drugs chapters in this section)
    - Uses: supraventricular tachycardias
    - Side effects: constipation (verapamil), dizziness, flushing, hypotension, AV block
    - Drug interaction:
      - Additive AV block with ~-blockers, digoxin
      - Verapamil displaces digoxin from tissue-binding sites

UNCLASSIFIED

- Adenosine
  - Activates adenosine receptors: causes Gi-coupled decrease in cAMP
  - ↓ SA and AV nodal activity
  - Uses: DOC for paroxysmal supraventricular tachycardias and AV nodal arrhythmias
  - Administered IV: $t_{1/2}$ <10 seconds
  - Side effects: flushing, sedation, dyspnea
  - Adenosine is antagonized by theophylline
- Magnesium
  - Use: torsades
  - Drugs causing torsades include:
    - Potassium-channel blockers (class 1A and class III)
    - Antipsychotics (thioridazine)
    - Tricyclic antidepressants

Clinical Correlate

Long QT Syndrome

A familial condition associated with increased risk of ventricular arrhythmias may result from mutation in the gene encoding cardiac potassium channels. Class IA and class III antiarrhythmic drugs may increase the risk of torsades in such patients.

Treatment of Torsades

- Correct hypokalemia.
- Correct hypomagnesemia.
- Discontinue drugs that prolong the QT interval.
- Attempt to shorten APD with drugs (e.g., isoproterenol) or electrical pacing.

Clinical Correlate

Potassium

Both hyperkalemia and hypokalemia are arrhythmogenic.

Chapter Summary

The class I antiarrhythmic drugs block Na' channels. Class IA drugs are state-dependent blockers of fastNa+ channels, and they increase the action potential duration (APD). Quinidine, in addition, is an M blocker and can increase the heart rate and AV conduction. Procainamide has less M block than quinidine and no alpha block. The uses and contra indications of quinidine and procainamide are provided.

Class IB drugs are less state-dependent blockers of fast Na" channels, and they decrease the APD. The uses for lidocaine, mexiletine, and tocainide are discussed, as are the metabolism and adverse effects of lidocaine.

The class IC drug flecainide blocks fast Na" channels, especially of His-Purkinje cells, and has no effect on the APD and no ANS effects.

Class II antiarrhythmic drugs are beta-blockers that decrease SA and AV nodal activity, decrease the phase 4 slope, and prevent ~1 adrenoceptor activation, thereby circumventing the normal increase in cAMP. Propranolol is nonselective; acebutolol and esmolol are selective. Their antiarrhythmic use is discussed.

Class III antiarrhythmic drugs are K+-channel blockers that increase the APD and effective refractory period (ERP), especially in Purkinje and ventricular tissues. Amiodarone and sotalol are the examples discussed.

Class IV antiarrhythmic drugs are Ca^{2}+-channel blockers that decrease the SA and AV nodal activity and the slope of phase 4 of the action potential in pacemakers. The uses and adverse effects of verapamil are indicated.

Adenosine and magnesium are two unclassified antiarrhythmic drugs. Adenosine decreases SA and AV node activity and increases the AV node refractory period. Magnesium has possible use in torsades. Drugs (other than classes la and III antiarrhythmics) associated with torsades include thioridazine and tricyclic antidepressants.

Antihypertensive Drugs

3

DRUG STRATEGY

- tTPR
- J. CO
- J. body fluid volume
- t BP may result in homeostatic regulation:
  - Reflex tachycardia rt sympathetic activity)
  - Edema rt renin activity)

DRUGS ALTERING SYMPATHETIC ACTIVITY

- (X,2 agonists: clonidine and methyldopa (prodrug)
  - (X,2 stimulation:
    - o t in sympathetic outflow
    - o t TPR but also t HR
  - Uses:
    - o Mild-to-moderate hypertension (both)
    - o Opiate withdrawal (clonidine)
    - o Hypertensive management in pregnancy (methyldopa)
  - Side effects:
    - o Positive Coombs test (methyldopa)
    - o CNS depression (both)
    - o Edema (both)
  - Drug interactions:
    - o Tricyclic antidepressants t antihypertensive effects of (X,2 agonists
- Drugs interfering with storage vesicles
  - Reserpine
    - o Destroys vesicles:
      - t CO and t TPR (t norepinephrine in periphery)
      - t norepinephrine, t dopamine, t serotonin in CNS
    - o Side effects:
      - Depression (often severe)
      - Edema
      - t gastrointestinal secretions

- **Guanethidine**
  - o Accumulated into nerve endings by reuptake
  - o Binds vesicles
  - o Inhibits norepinephrine release
  - o Side effects:
    - Diarrhea
    - Edema
  - o Drug interactions: tricyclic antidepressants block reuptake and the action of guanethidine

- (XI blockers
  - t arteriolar and venous resistance
  - Reflex tachycardia
  - Drugs: **prazosin, doxazosin, terazosin**
  - Uses:
    - o Hypertension
    - o BPH: t urinary frequency and nocturia by t the tone of urinary sphincters
  - Side effects:
    - o "First-dose" syncope
    - o Orthostatic hypotension
    - o Urinary incontinence
  - Advantage: good effect on lipid profile, (I HDL, t LDL)

- ~ blockers
  - Mechanism *(See* ANS section)
  - Side effects:
    - o Cardiovascular depression
    - o Fatigue
    - o Sexual dysfunction
    - o t LDLs and TGs
  - Cautions in use:
    - o Asthma
    - o Vasospastic disorders
    - o Diabetics (alteration of glycemia and masking of tachycardia due to hypoglycemic events)

DIRECT-ACTING VASODILATORS

Drugs Acting Through Nitric Oxide

- **Hydralazine**
  - t TPR via arteriolar dilation
  - Use: moderate-to-severe hypertension
  - Side effects:
    - o SLE-like syndrome and slow acetylators
    - oEdema
    - o Reflex tachycardia

- Nitroprusside
  - – t TPR via dilation of both arterioles and venules
  - Use: hypertensive emergencies (DOC used IV)
  - Side effect: cyanide toxicity (coadministered thiosulfate; *see* Clinical Correlate)

Drugs Acting to Open Potassium Channels

- Drugs: minoxidil and diazoxide
  - Open K+ channel, causing hyperpolarization of smooth muscle
  - Results in arteriolar vasodilation
  - Uses:
    - o Hypertensive emergencies (diazoxide)
    - o Severe hypertension (minoxidil)
    - o Baldness (topical minoxidil)
  - Side effects:
    - o Hypertrichosis (minoxidil)
    - o Hyperglycemia (t insulin release [diazoxide])
    - oEdema
    - o Reflex tachycardia

CALCIUM-CHANNEL BLOCKERS (CCBs)

- Block L-type Ca^{2+} channels in heart and blood vessels
- Results in t intracellular Ca^{2+}
- Causes t CO (verapamil and diltiazem), t TPR (all CCBs)
- Drugs: verapamil, diltiazem, diliydropyridines (-"dipines", prototype: nifedipine)

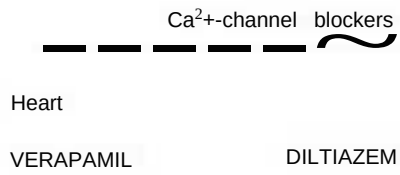


Figure 11I-3-1.Cardiac or Vascular Selectivity of Major Ca^{2+}-Channel Blockers

- Uses:
  - Hypertension (all drugs)
  - Angina (all drugs)
  - Antiarrhythmics (verapamil, diltiazem)
- Side effects:
  - Reflect tachycardia ("-dipine"s)
  - Gingival hyperplasia ("-dipine"s)
  - Constipation (verapamil)

Clinical Correlate

Cyanide Poisoning

Sodium nitrite or amyl nitrite can be used in cyanide poisoning. They promote formation of methemoglobin, which binds CW ions, forming cyanomethemoglobin. This prevents the inhibitory action of CN- on complex IV of the electron transport chain. Cyanomethemoglobin is then reconverted to methemoglobin by treatment with sodium thiosulfate, forming the less toxic thiocyanate ion (SCN-).

~~~~!~~!~",.~~!~!.

Vasodilators may have specificity.

Arteriolar: Ca^{2+}-channel blockers, hydralazine, K+-channel openers

Venular: nitrates

Both arteriolar and venular: "the rest"

Orthostatic (postural) hypotension results from venular dilation (not arteriolar) and mainly results from (Xl blockade or decreased sympathetic tone.
~~~~

DIURETICS *(See* Chapter 6)

Thiazide and loop diuretics are commonly used in the management of hypertension.

ANGIOTENSIN-CONVERTING INHIBITORS (ACEls) AND ANGIOTENSIN-RECEPTOR BLOCKERS (ARBs)

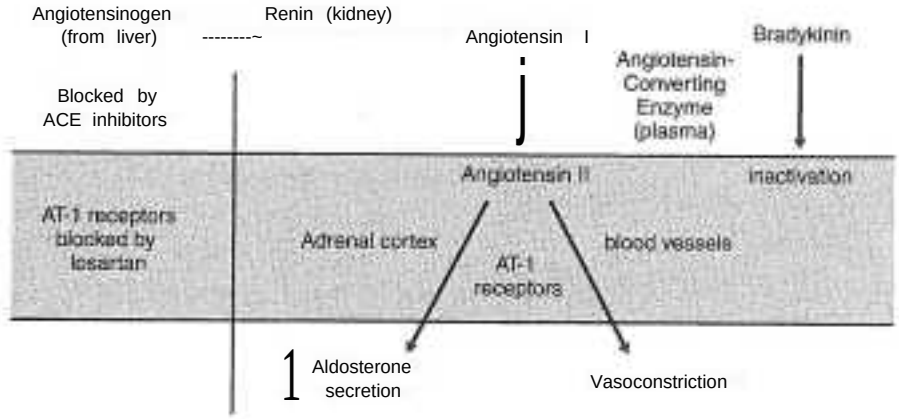


Figure 11I-3-2.The Angiotensin System

- Drugs:
  - ACEls: captopril (and other "-prils")
    - Block formation of angiotensin II
    - Resulting in prevention of ATj-receptor stimulation
    - -t aldosterone, vasodilation
    - ACEls prevent bradykinin degradation
  - ARBs: losartan (and other "-sartans")
    - Block ATj receptors
    - Same results as ACEls on BP mechanisms
    - ARBs do not interfere with bradykinin degradation
- Uses:
  - Mild-to-moderate hypertension
  - Protective of diabetic nephropathy
  - CHF
- Side effects:
  - Dry cough (ACEls)
  - Hyperkalemia
  - Acute renal failure in renal artery stenosis
  - Angioedema
- Contraindication: pregnancy

KIPLAUa meulcail III

INDICATIONS FOR USE OF ANTIHYPERTENSIVE DRUGS IN (OMORBID CONDITIONS

Table III-3-1. Use of Antihypertensive Drugs in Comorbid Conditions

Indication	Suitable Drug(s)
Angina	Beta blockers, CCBs
Diabetes	ACEIs,ARBs
Heart failure	ACEIs, ARBs
Post-MI	Beta blockers
BPH	Alpha blockers
Dyslipidemias	Alpha blockers, CCBs, ACEIs/ARBs

TREATMENT OF PULMONARY HYPERTENSION

- Bosentan
  - Endothelin (ET)-1 is a powerful vasoconstrictor through ET-A and -B receptors
  - Bosentan is an ETA receptor antagonist
  - Administered orally
  - Side effects are associated with vasodilation (headache, flushing, hypotension, etc.)
  - Contraindication: pregnancy
- Prostacyclin (PGI_2): epoprostenol
  - Administered via infusion pumps
- Sildenafil
  - Inhibits type V PDE
  - t cGMP
  - Pulmonary artery relaxation
  - J. pulmonary hypertension

Chapter Summary

Hypertension (HTN) is a major risk factor for stroke, heart failure, renal disease, peripheral vascular disease, and coronary artery disease. Factors inducing HTN include decreased vagal tone, increased sympathetic tone, increased renin-angiotensin activity, and excess water retention.

Treatments for HTN aim to reduce sympathetic tone and blood volume and/or relax vascular smooth muscle. However, homeostatic mechanisms may lead to compensatory increases in heart rate and/or salt and water retention.

The metabolic characteristics, clinical uses, and potential adverse effects of sympathoplegic drugs, which decrease peripheral resistance by decreasing sympathetic tone, are discussed. Those sympathoplegic drugs that act indirectly via the CNS include methyldopa and clonidine. Sympathoplegic drugs also may act directly as adrenergic neuron blockers, alpha blockers, or beta blockers. Examples of each class are provided.

Direct-acting vasodilators lower the peripheral vascular resistance mainly by causing arteriolar dilation. Drugs discussed are nitroprusside, hydralazine, minoxidil, and diazoxide.

Calcium channel blockers (CCBs) enhance vasodilation by blocking L-type Ca^{2+} channels in cardiac and vascular tissues. Drugs considered are verapamil, diltiazem, and dihydropyriodines.

Drugs that act via the renin-angiotensin system are the angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril) and the angiotensin-II (AT-1) blockers (ARBs; e.g., losartan). Figure 111-3-2 illustrates the angiotensin system and the pharmacologic effects of these drugs. Their clinical uses and adverse affects are discussed.

Both thiazide and loop diuretics are used to treat HTN. The diuretics are discussed in more detail elsewhere.

Table 111-3-1 summarizes the use of antihypertensives in comorbid conditions.

Bosentan, epoprostenol, and sildenafil are used in pulmonary hypertension.

Drugs for Heart Failure

4

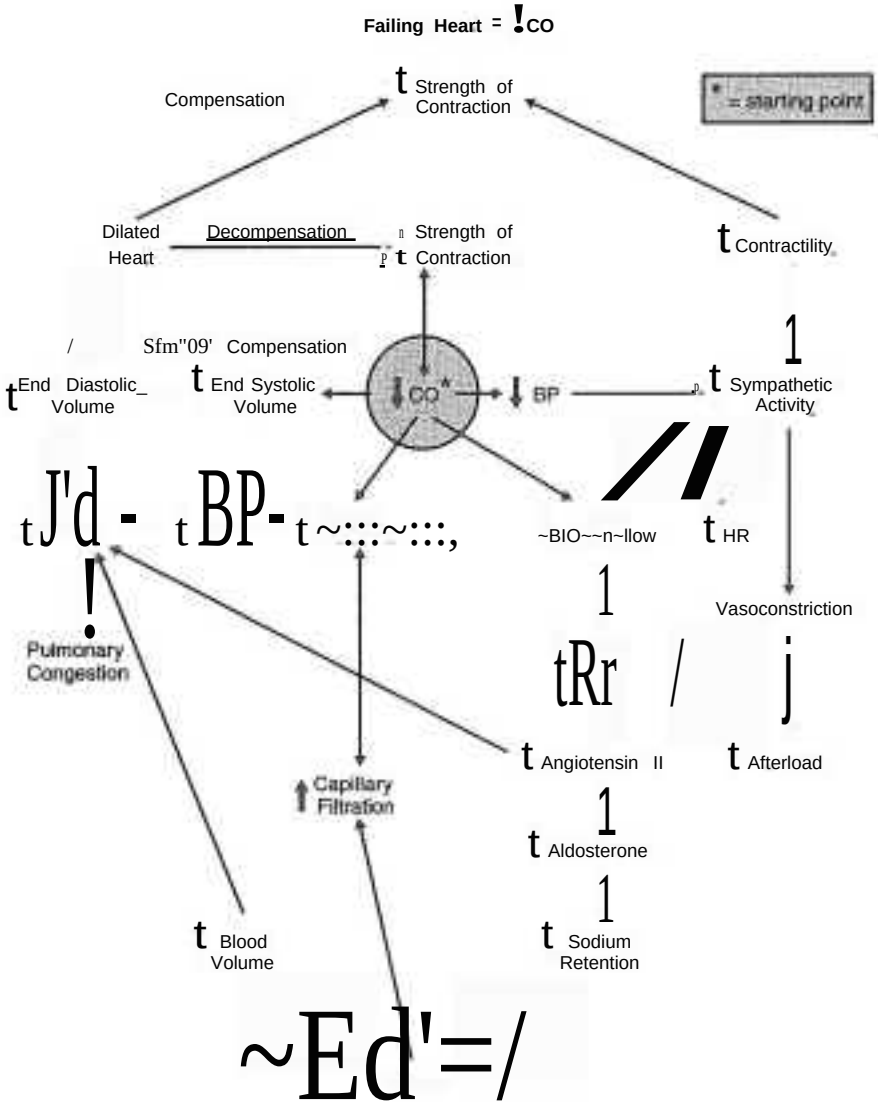


Figure 11I-4-1.The Failing Heart

Pharmacotherapy aimed at:

- ↓ preload: diuretics, ACEIs, ARBs, and venodilators
- ↓ afterload: ACEIs, ARBs, and arteriodilators
- ↑ contractility: digoxin, beta agonists
- ↓ remodeling of cardiac muscle: ACEIs, ARBs, spironolactone

Whereas digoxin does not improve survival, ACEIs, ARBs, carvedilol, and spironolactone have been proven beneficial in CHF. ACEIs and ARBs are currently drugs of choice for the chronic management of CHF. Inotropes are more beneficial in management of acute CHF.

INOTROPES

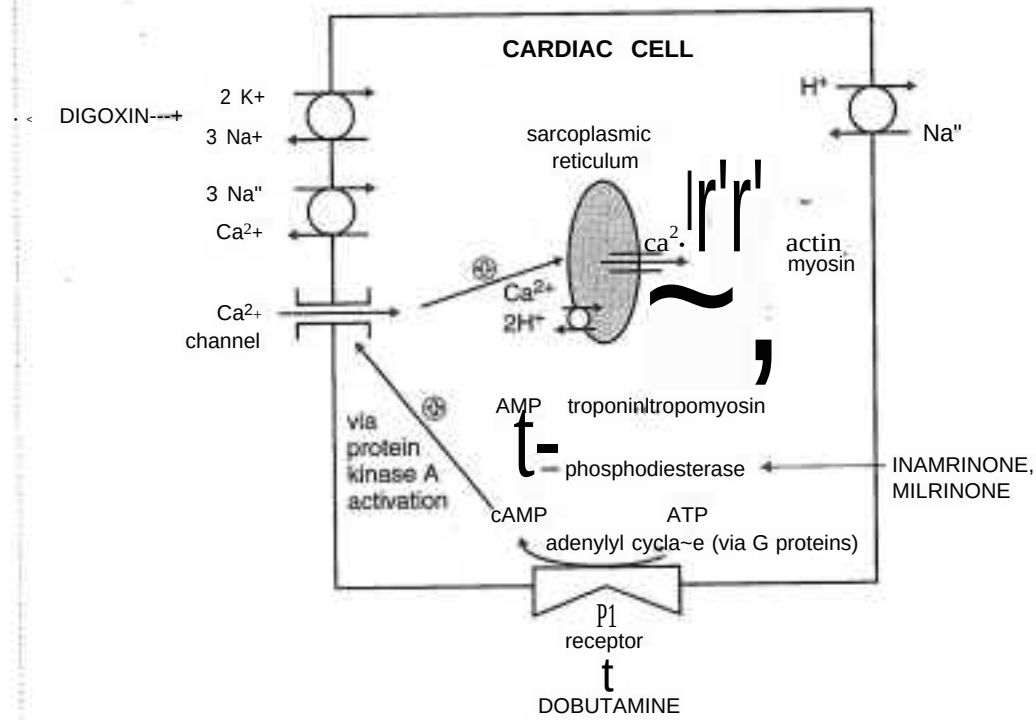


Figure 11I-4-2.Mechanism of Action of Inotropes

- Digoxin
  - Direct effect: inhibition of cardiac Na+-K+ ATPase
    - Results in ↑ intracellular Na+
    - ↓ Na+/Ca2+ exchange
    - ↑ intracellular Ca2+
    - ↑ Ca2+ release from sarcoplasmic reticulum
    - ↑ actin-myosin interaction
    - ↑ contractile force
  - Indirect effect: inhibition of neuronal Na+-K+ ATPase
    - Results in ↑ vagal and sympathetic stimulation

- Pharmacokinetics:
  - Long $t_{1/2}$: need loading dose (LD)
  - Renal clearance: caution in renal impairment
  - Tissue protein binding (large Vd): displacement by other drugs (verapamil, quinodine)
- Uses:
  - CHF
  - Supraventricular tachycardias, except Wolff-Parkinson- White syndrome *(see* margin note)
- Side effects:
  - Early signs include anorexia, nausea, ECG changes
  - Later signs include disorientation, visual effects (halos)
  - In toxic doses, any cardiac arrhythmias
- Management of toxicity
  - Use of Fab antibodies toward digoxin
  - Supportive therapy (electrolytes and antiarrhythmics class IE)
- Drug interactions:
  - Diuretics: J, K^+, J, Mg^{2+}, i Ca^{2+}
  - Quinidine and verapamil
  - Sympathomimetics

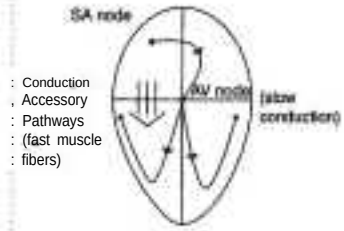
• Phosphodiesterase inhibitors: inamrinone and milrinone
- i cAMP in heart muscle; results i inotropy
- i cAMP in smooth muscle; results in J, TPR

• Sympathomimetics: dobutamine and dopamine

• Other drugs:
- Diuretics
  - Loops for associated backward failure
  - Spironolactone to J, remodeling (with ACEIs)
- Metoprolol and carvedilol
- Nesiritide
  - Recombinant form of human B-type natriuretic peptide (rh BNP)
  - Binds to natriuretic peptide receptors, thus i cGMP, resulting in vasodilation
  - Used in acutely decompensated CHF

. Note

: Wolff-Parkinson-White
: Syndrome



.• Do:
- block accessory pathway with I_A or III

'. Don't:
- slow AVconduction
- avoid digoxin, p-blocker, Ca^{2+}-channel blocker, adenosine

Chapter Summary

Heart failure is an inability of the heart to pump with sufficient vigor to maintain an adequate cardiac output. The mechanisms involved are discussed and are illustrated in Figure 111-4-1.

Drugs used to treat heart failure include those that decrease preload (e.g., diuretics, ACEIs, ARBs, and venodilators), those that decrease afterload (e.g., ACEIs, ARBs, and arteriodilators), and those that increase cardiac contractibility (e.g., digoxin and beta agonists).

Digoxin enhances cardiac contraction by inducing a series of responses initiated by inhibiting the Na+/K+ATPase. Figure 111-4-2 shows how inhibition of cardiac membrane Na+/K+ATPase leads to increased contractility.

Although digoxin ameliorates symptoms, it does not increase survival. That is why the ACEIs are the primary choice for treating heart failure.

Digoxin has potential toxic effects that are in part dependent upon the electrolyte balance.

Bipyridines, sympathomimetics, diuretics, beta blockers, and nesiritide also have uses in treating heart failure. Rationales for their use are indicated. A newer drug, nesiritide, is a recombinant form of natriuretic peptide.

Antianginal Drugs

5

RATIONALE FOR USE

Angina pectoris is the principal syndrome of ischemic heart disease, anginal pain occurring when oxygen delivery to the heart is inadequate for myocardial requirement

- Classic angina (angina of effort or exercise) is due to coronary atherosclerotic occlusion
- Vasospastic or variant angina (Prinzmetal) is due to a reversible decrease in coronary blood flow

Drug Strategies in Classic and Vasospastic Angina

Drug strategies in classic and vasospastic angina involve:

i oxygen delivery by J, vasospasm (nitrates and CCBs).

J, oxygen requirement by J, TPR, CO, or both (nitrates, CCBs, and beta blockers).

NITRATES

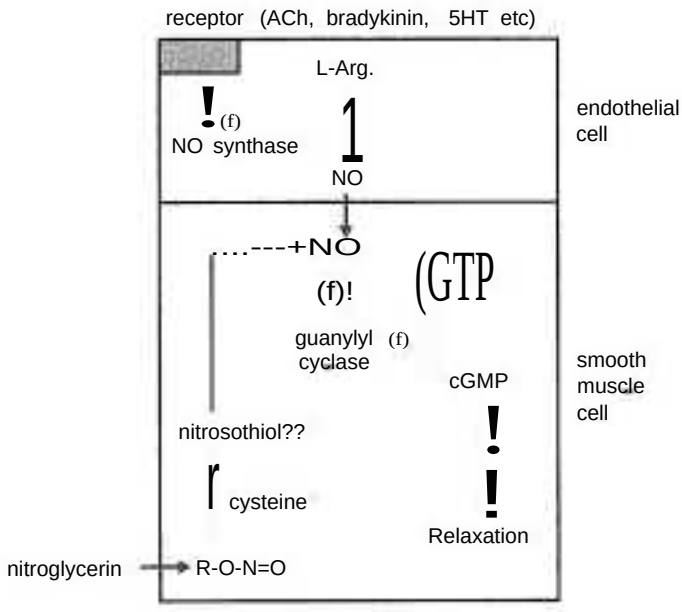


Figure 11I-5-1. Nitrates and the Nitric Oxide Pathway

- Nitrates are prodrugs of nitric oxide
- Venodilation → ↓ preload → ↓ cardiac work → ↓ oxygen requirement
- Nitrates ↓ infarct size and post-MI mortality
- Drugs:
  - Nitroglycerin: sublingual, transdermal, and IV formulations
  - Isosorbide: oral, extended release for chronic use
  - Side effects:
    - Flushing, headache, orthostatic hypotension
    - Reflex tachycardia and fluid retention
    - Methemoglobinemia
  - Cautions and contraindications:
    - Tachyphylaxis with repeated use
    - Cardiovascular toxicity with sildenafil *(see* Clinical Correlate, left)

Clinical Correlate

Sildenafil (Viagra)

Phosphodiesterase 5 (PDE5) is found in blood vessels supplying the corpora cavernosa. Sildenafil inhibits PDE5 → ↑ cGMP → vasodilation → ↑ blood flow → ↑ erectile response. If used concomitantly with nitrates or other potent vasodilators, the excessive fall in blood pressure may lead to death from cardiovascular causes, including myocardial infarct.

CALCIUM CHANNEL BLOCKERS (CCBs)

- All CCBs can be used.
- Nifedipine is important for vasospastic angina.
- *See* Antihypertensive chapter in this section.

BETA BLOCKERS AND CARVEDILOl

- Used in angina of effort
- P-blockers are contraindicated in vasospastic angina
- Carvedilol is clinically equivalent to isosorbide in angina of effort

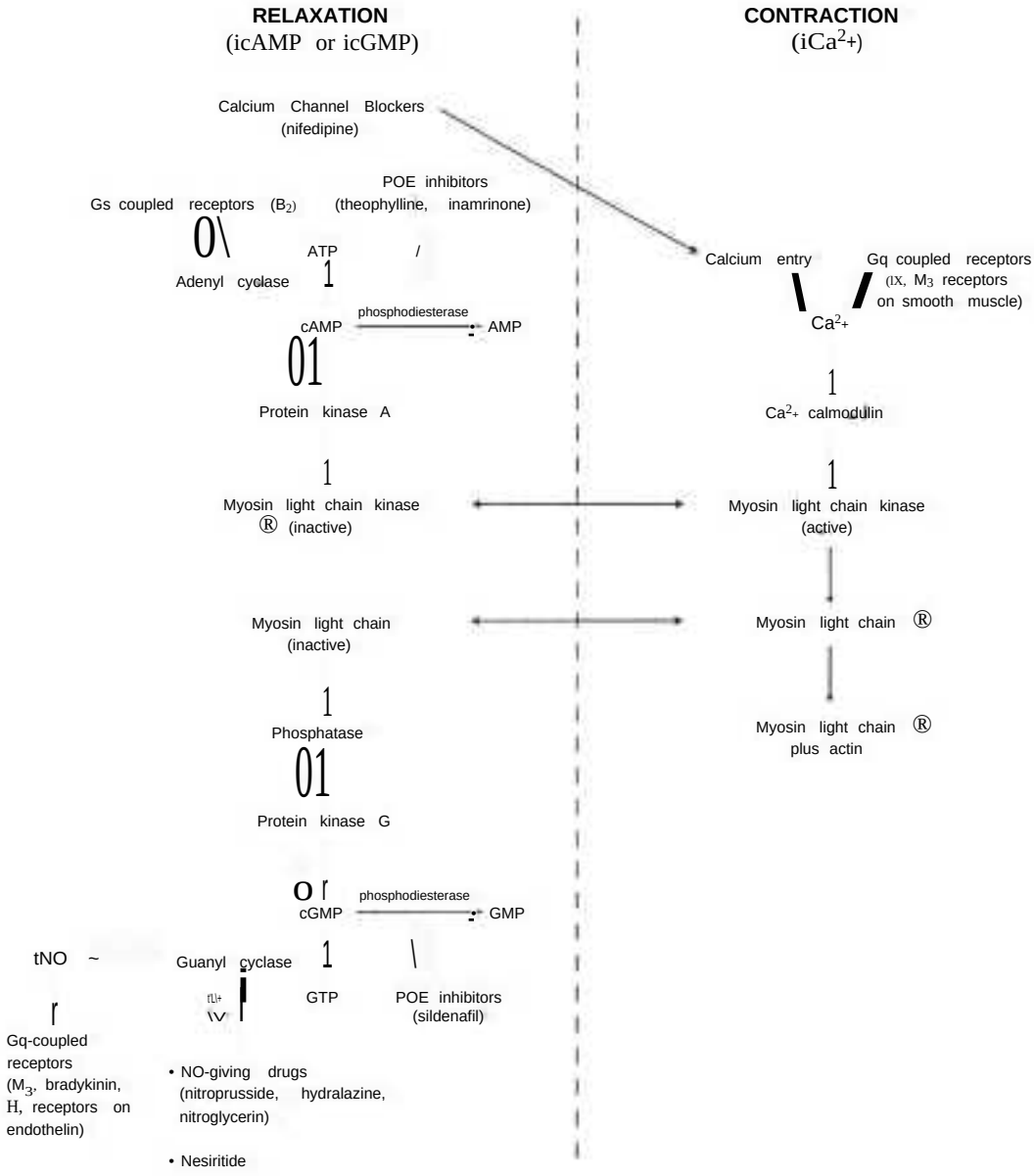


Figure 11I-5-2. Mechanisms of Smooth Muscle Contraction and Relaxation and Drugs Affecting Them

Chapter Summary

Angina is the principal syndrome caused by ischemic heart disease. The three variants are classic, Prinzmetal, and unstable.

The drug strategies are to increase oxygen supply by decreasing vasospasm (nitrates and calcium channel antagonists [CCBs]) and to decrease cardiac oxygen requirements by decreasing peripheral vascular resistance and/or cardiac output (nitrates, CCBs, and beta blockers).

Nitrates increase NO concentrations. Increased NO activates guanylyl cyclase; this increases cGMP levels, which dephosphorylates myosin light chains, decreasing their association with actin and thereby promoting smooth muscle relaxation. These mechanisms are summarized in Figure 111-5-1.

NO-enhancing drugs used to treat angina include nitroglycerin and isosorbide.

The adverse effects of the nitrates are also considered.

CCBs decrease contractility and increase vasodilation by preventing the influx of Ca^{2+} required for muscle contraction. The sequence of reactions involved is summarized in Figure 111-5-2. The CCBs considered are the dihydropyridines (e.g., nifedipine), verapamil, and diltiazem.

Beta blockers act directly on the heart by decreasing the heart rate, the force of contraction, and cardiac output, thereby decreasing the work performed.

Diuretics

6

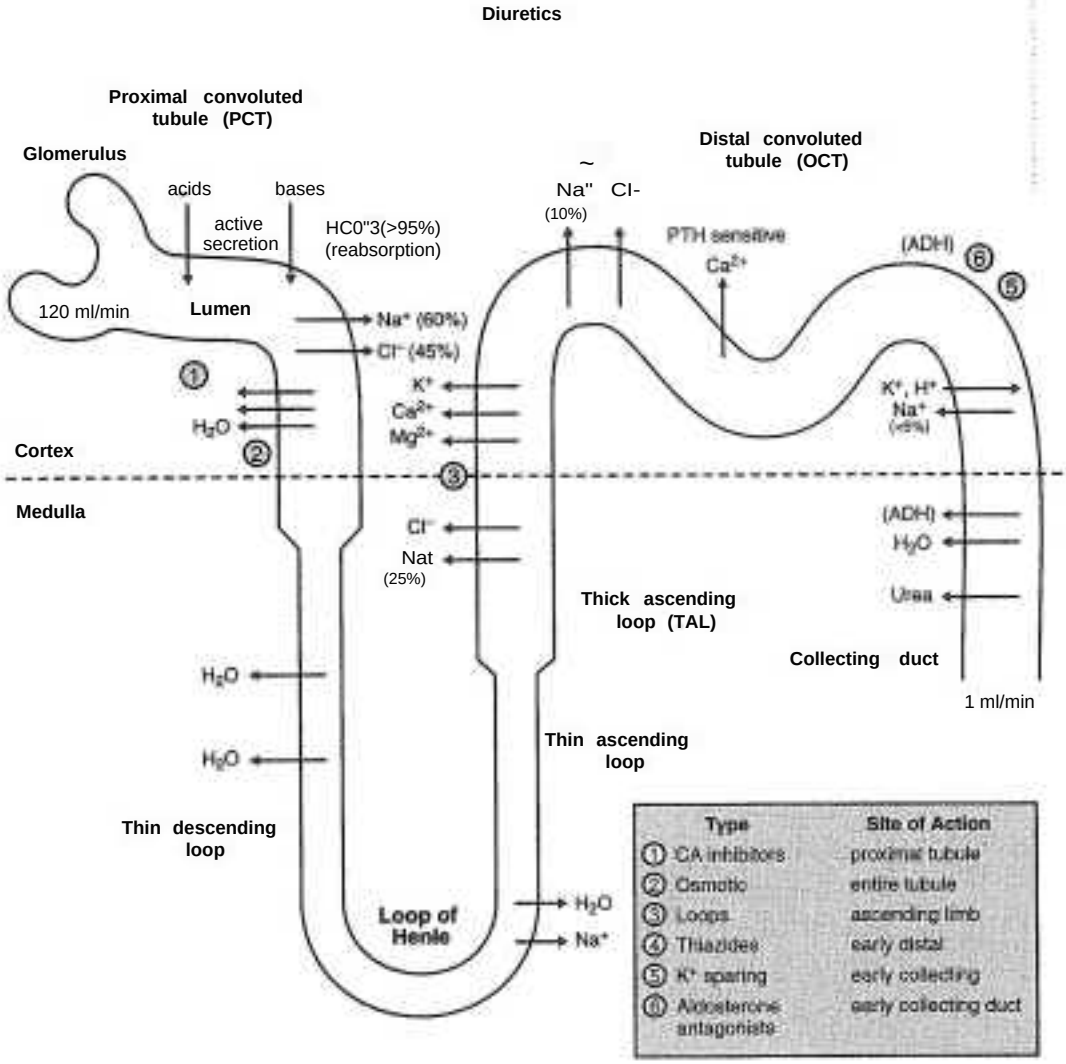


Figure 11I·6·1. Actions of Diuretics at the Various Renal Tubular Segments

Hypokalemia and Alkalosis

Diuretics that block Na+ reabsorption at segments above the collecting ducts will increase sodium load to the collecting tubules and ducts ("downstream"). This results in increased loss of K+ ~ hypokalemia, and in the case of both loop and thiazide diuretics the associated loss of H+ results in alkalosis.

OSMOTIC DIURETICS

- Mannitol (IV) inhibits water reabsorption throughout the tubule.
- It increases urine volume.
- Uses:
  - ↓ lOP in glaucoma
  - ↓ intracerebral pressure
  - Anuric states
  - Rhabdomyolysis
- Side effects: acute hypovolemia

CARBONIC ANHYDRASE INHIBITORS

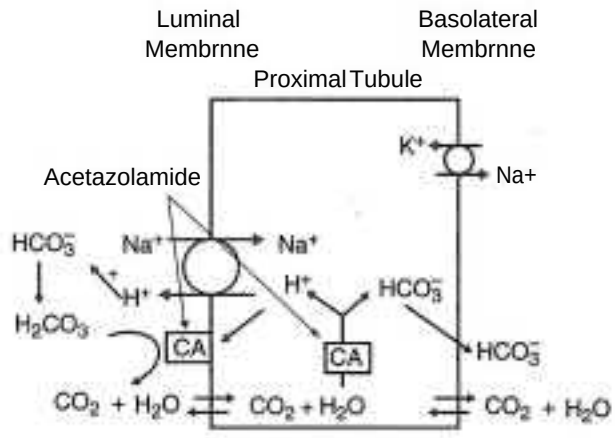


Figure 11I-6-2Actions of Carbonic Anhydrase Inhibitors

- Drugs: acetazolamide and dorzolamide
- Mechanism: carbonic anhydrase inhibition, results in:
  - ↓ H+ formation inside PCT cell
  - ↓ Na+/H+ antiport
  - ↑ Na+ and HCO_3^- in lumen
  - ↑ diuresis
- Uses:
  - Glaucoma
  - Acute mountain sickness
  - Metabolic alkalosis
- Side effects:
  - Bicarbonaturia and acidosis
  - Hypokalemia
  - Hyperchloremia

- Paresthesias
- Renal stones
- Sulfonamide hypersensitivity

LOOP DIURETICS

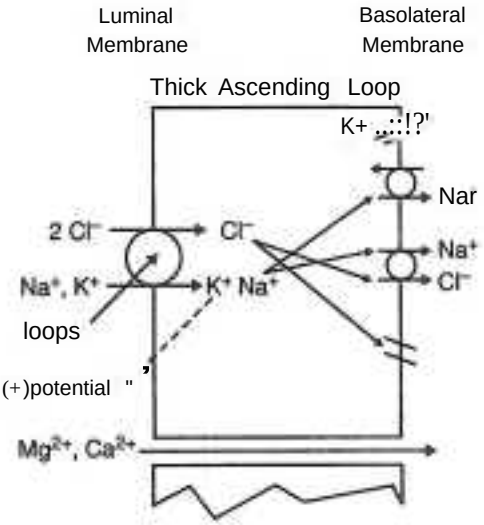


Figure 11I-6-3Actions of Loop Diuretics on the Thick Ascending Loop (TAL)

- Drugs: ethacrynic acid and furosemide
- Mechanism: Na+/K+I2Cl- transporter inhibition, results in:
  - J, intracellular K+ in TAL
  - J, back diffusion of K+
  - J, positive potential
  - J, reabsorption of Ca^{2+} and Mg^{2+}
  - i diuresis
- Uses:
  - Acute pulmonary edema
  - Heart failure
  - Hypertension
  - Refractory edemas
  - Acute renal failure
  - Anion overdose
  - Hypercalcemic states
- Side effects:
  - Sulfonamide hypersensitivity (furosemide)
  - Hypokalemia and alkalosis

Note

Allergies to Sulfonamide-Containing Drugs

Cross allergenicity with:

- Carbonic anhydrase inhibitors
- All loop diuretics, except ethacrynic acid
- Thiazides
- Sulfa antibiotics
- Celecoxib

- Hypocalcemia
- Hypomagnesemia
- Hyperuricemia
- Ototoxicity (ethacrynic acid > furosemide)

• Drug interactions
- Aminoglycosides (enhanced ototoxicity)
- Lithium (chronic loop administration, J, clearance)
- Digoxin rt toxicity due to electrolyte disturbances)

THIAZIDES

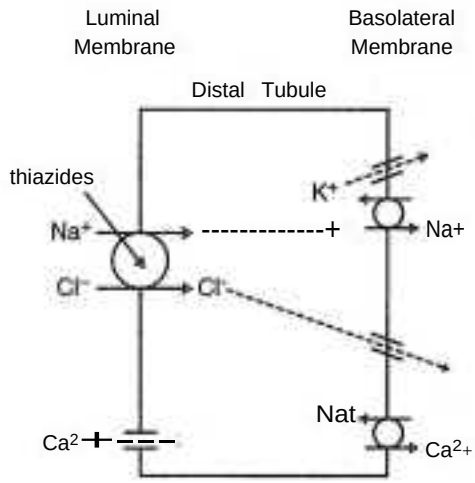


Figure 11I-6-4.Actions of Thiazides on the Distal Convoluted Tubule (OCT)

• Drugs: hydrochlorothiazide and indaparnide
• Mechanism: Na+/Cl- transporter inhibition, results in:
- i luminal Na+ and Cl- in DCT
- i diuresis
• Uses:
- Hypertension, CHF
- Nephrolithiasis (calcium stones)
- Nephrogenic diabetes insipidus
• Side effects:
- Sulfonamide hypersensitivity
- Hypokalemia and alkalosis
- Hypercalcemia
- Hyperuricemia
- Hyperglycemia
- Hyperlipidemia (except indapamide)

- Drug interactions and cautions:
  - Digoxin (i toxicity due to electrolyte disturbances)
  - Avoid in patients with diabetes mellitus

K+-SPARING AGENTS

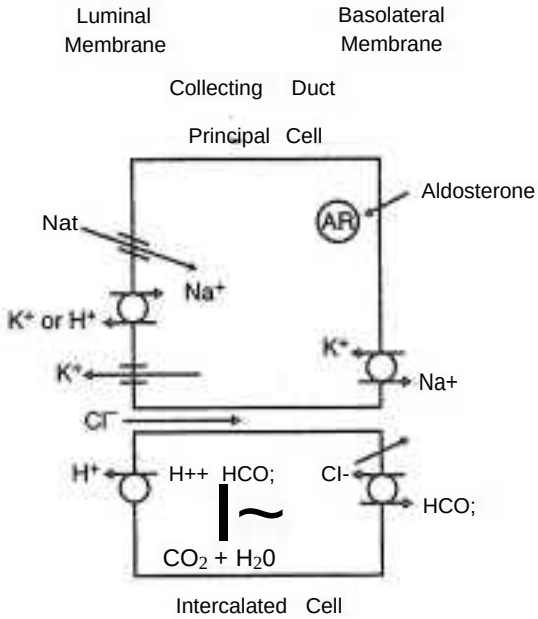


figure 11I-6-5. Actions of Potassium-Sparing Agents on Collecting Tubules

- Drugs:
  - Spironolactone: aldosterone-receptor antagonist
    - Uses:
      - Hyperaldosteronic state
      - Adjunct to K+-wasting diuretics
      - Antiandrogenic uses (female hirsutism)
      - Congestive heart failure
    - Side effects:
      - Hyperkalemia and acidosis
      - Antiandrogen
  - Amiloride and triamterene: Na+-channel blockers
    - Use: adjunct to K+-wasting diuretics, lithium-induced nephrogenic diabetes insipidus (amiloride)
    - Side effects: hyperkalemia and acidosis

Note

Eplerenone is a selective aldosterone receptor blocker devoid of antiandrogenic effect.

Table III-6-1. Summary of the Modes of Action and Effects of the Various Classes of Diuretics

Drug	**Mechanisms** of Action	**Urinary Electrolytes**	Blood pH
Acetazolamide	Inhibition of carbonic anhydrase in PCT	tNa+ r K+ ttHC0$_3$-	Acidosis
Ethacrynic acid, furosemide, torsemide	Inhibition of Na+/K+/2CI- cotransporter in TAL	ttNa+ tK+ t Ca^{2+} t Mg^{2+} r Cl-	Alkalosis
Hydrochlorothiazide, indapamide, metolazone	Inhibition of Na+/Cl- cotransporter in DCT	tNa+ tK+ t Cr J- Ca^{2+}	Alkalosis
Amiloride, triamterene, spironolactone, eplerenone	Block Na+ channels, block aldosterone receptors in collecting tubule	t Na+ (small) J- K+	Acidosis

Chapter Summary

Diuretics are used to treat HTN, heart failure, edema, renal dysfunction, hypercalcemia, renal stones, glaucoma, and mountain sickness. In addition to their diuretic action, the loop and thiazide diuretics also cause vasodilation.

Figure 111-6-1illustrates the water and ion exchange occurring in the various segments of a renal tubule and the site of action of the different classes of diuretics.

The positive and negative effects of IV mannitol, an osmotic diuretic, are discussed.

Carbonic anhydrase inhibitors (e.g., acetazolamide) act in the proximal tubule to decrease absorption of Na+ and bicarbonate. The mechanisms involved are summarized in Figure 111-6-2.The clinical uses and adverse affects are listed.

Loop diuretics (e.g., ethacrynic acid and furosemide) inhibit the Na+jK+j2C1- cotransporter on the luminal membrane of the thick ascending loop. The mechanisms causing their diuretic actions (Figure 111-6-3)and their clinical uses and adverse effects are discussed.

The thiazides (e.g., hydrochlorothiazide and indapamide) inhibit the Na+jCl- cotransporter on the luminal membrane of the distal convoluted tubule. The mechanisms leading to their diuretic actions (Figure 111-6-4)and their clinical uses and adverse effects are discussed.

Spironolactone, amiloride, and triamterene are K+-sparing, weak diuretics that act at the collecting tubule and duct level. The mechanisms leading to their diuretic actions (Figure 111-6-5)and their clinical uses and adverse effects are discussed.

Table 111-6-1summarizes the mechanisms of action, the urinary electrolyte patterns, and the resultant blood pH associated with administration of the various classes of diuretics.

Antihyperlipidemics

7

- ↑ risk of atherosclerosis is associated with hypercholesterolemia
- ↑ risk of cardiovascular and cerebrovascular diseases
- Treatment goal is to ↓ LDL cholesterol and atheroma plaque formation

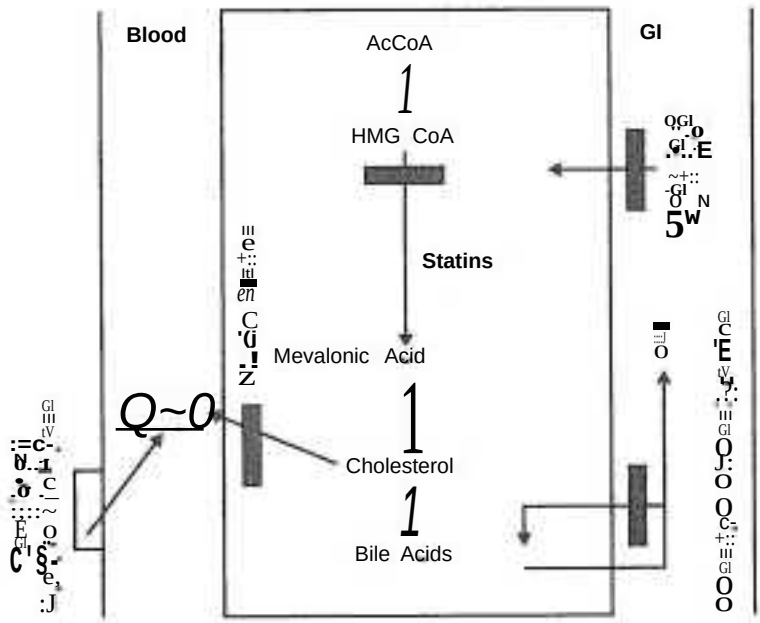


Figure 11I-7-1.Site of Action of Statins, Niacin, and Gemfibrozil on the Sythesis of Lipids

HMG-CoA REDUCTASE INHIBITORS

- Drugs: **lovastatin**, and other "-statins"
- Mechanisms:
  - HMG-CoA reductase inhibition, results in:
    - ↓ liver cholesterol
    - ↑ LDL-receptor expression
    - ↓ plasma LDL
  - ↓ VLDL synthesis results in: ↓ triglyceridemia

- Side effects:
  - Myalgia, myopathy (check creatine kinase)
  - Rhabdomyolysis
  - Hepatotoxicity (check liver function tests)
- Drug interaction:
  - Gemfibrozil et rhabdomyolysis)
  - Cytochrome P450 inhibitors enhance toxicity of statins

BILE ACID SEQUESTRANTS

- Drugs: cholestyramine, and colestipol
- Mechanism: complexation of bile salts in the gut, results in:
  - J, enterohepatic recirculation of bile salts
  - t synthesis of new bile salts by the liver
  - J, liver cholesterol
  - t LDL-receptor expression
  - J, blood LDL
- Side effects:
  - t VLDL and triglycerides
  - Gastrointestinal disturbances
  - Malabsorption of lipid-soluble vitamins
- Drug interactions with orally administered drugs (warfarin, thiazides, digoxin, etc.)
- Contraindication: hypertriglyceridemia

NICOTINIC ACID (NIACIN, VITAMIN B_3)

- Mechanism: inhibition ofVLDL synthesis, results in:
  - J, plasma VLDL
  - J, plasma LDL
  - t plasma HDL
- Side effects:
  - Flushing, pruritus, rashes (use aspirin)
  - Hepatotoxicity

GEMFIBROIll

- Mechanism: activation of lipoprotein lipases, results in:
  - J, VLDL and IDL
  - Modest J, LDL
  - t HDL in most patients
  - In some patients with combined hyperlipidemias can t LDL
  - Used in hypertriglyceridemia

- Side effects:
  - Gallstones
  - Myositis

EZIETIMIBE

- Mechanism: prevents intestinal absorption of cholesterol, results in J, LDL
- Side effect: gastrointestinal distress

Table III-7-1. Summary of Antihyperlipidemic Uses

Lab Findings	Drugs
t Cholesterol	Cholestyramine, colestipol, ezetimibe
i Triglycerides	Gemfibrozil
i Cholesterol and triglycerides	Statins and niacin, ezetimibe

Chapter Summary

An aberrant serum lipid profile is associated with increased risk of artherosclerosis and cardiac heart disease.

Lovastatin and the other statins inhibit the rate-limiting step in cholesterol synthesis, HMG-CoA reductase. This lowers liver cholesterol, plasma LDL, and the hepatic synthesis of VLDL and apo B. Statins also cause a small increase in HOL, and atorvastatin lowers triglycerides *(TGs).* The adverse effects are listed.

Cholestyramine and colestipol are bile acid sequestrants that enhance cholesterol loss into the feces, thereby stimulating new bile salt synthesis, which lowers liver cholesterol levels and consequently plasma LOL levels. Their adverse effects are also listed.

Nicotinic acid inhibits the hepatic synthesis of VLOL and apoprotein. It also increases HOL levels and decreases plasma VLOL, LOL, and TG levels. The adverse effects are listed.

Gemfibrozil activates lipoprotein lipase, thus decreasing VLOL, TG, and LOL levels. The adverse effects are listed.

Ezetimibe prevents cholesterol absorption.

Cardiac and Renal Drug List and Practice Questions

8

Table III-8-1. The Major Cardiovascular and Renal Drugs

Antiarrhythmics	Antihypertensives	Antianginals
lA quinidine, procainamide	a_2 agonists: clonidine, methyldopa	Nitrates: nitroglycerin, isosorbide
IB lidocaine	Neuron blockers: reserpine, guanethidine	CCBs: verapamil, nifedipine
1C flecainide	a blockers: prazosin, doxazosin, etc.	~ blockers: propranolol, etc.
II propranolol, acebutolol (ISA) esmolol	~ blockers: propranolol, metoprolol, acebutolol, labetalol, etc.	
III amiodarone, sotalol	ACEIs: captopril, etc., and ARBs: losartan, etc.	
IV verapamil, diltiazem	Vasodilators: hydralazine, nitroprusside, diazoxide, minoxidil	
Adenosine	CCBs: verapamil, nifedipine, etc.	
	Pulmonary hypertension: bosentan, epoprostenol, sildenafil	
Diuretics	Drugs for Heart Failure	Antihyperlipidemics
CA inhibitors: acetazolamide	Digoxin	Resins: cholestyramine, colestipol
Loops: ethacrynic acid, furosemide	Bipyridines: inamrinone, milrinone; ~ agonists: dobutarnine, dopamine	Statins
Thiazides-hydrochloro-thiazide, indapamide	a ~blocker: carvedilol	Other: nicotinic acid, ezetirnibe, gemfibrozil
K+ sparing: arniloride, triamterene, spironolactone, eplerenone	Diuretics, vasodilators, nesiritide	

CARDIAC AND RENAL PHARMACOLOGY

Review Questions

1. Following a myocardial infarct, a 40-year-old male patient is being treated with a drug that affords prophylaxis against cardiac arrhythmias. He complains of dizziness and feelings of nausea but has not vomited. Sometimes he sees "double," and bright lights bother him. ECG reveals prolongation of the QRS complex and increased QT interval. The drug most likely to be responsible for these effects is

   A. acebutolol
   B. lidocaine
   C. procainamide
   D. quinidine
   E. verapamil

2. Which one of the following drugs is associated with the development of a lupus-like syndrome, especially in patients identified as "slow acetylators"?

   A. Amiodarone
   B. Clonidine
   C. Nitroglycerin
   D. Procainamide
   E. Terazosin

3. Which one of the following actions is characteristic of amiloride?

   A. Alkalosis
   B. Block ofNa reabsorption in the proximal tubule
   C. Hyperkalemia
   D. Increased tubular reabsorption of Ca^{2+}
   E. Bicarbonaturia

4. The most common manifestation of lidocaine toxicity is

   A. CNS dysfunction
   B. drug fever
   C. hypertension
   D. hypokalemia
   E. torsades

5. Although not strictly "alternative medicine," the incubation of a West Indian centipede in alcohol for several weeks is alleged to result in the formation of a compound that has effectiveness in erectile dysfunction. If this compound is similar to sildenafil and inhibits phosphodiesterases, it would be contraindicated in a patient who is being treated with

   A. amiodarone
   B. hydrochorothiazide
   C. isosorbide dinitrate
   D. lovastatin
   E. propranolol

6. A patient with hyperthyroidism develops a cardiac arrhythmia. Optimal treatment of the patient should include management with

   A. amiodarone
   B. quinidine
   C. digoxin
   D. lidocaine
   E. propranolol

7. Metoprolol is preferred over propranolol in some patients because it

   A. causes less cardiodepression
   B. is less likely to cause bronchoconstriction
   C. has both alpha- and beta-adrenoceptor blocking effects
   D. is more effective as an antiarrhythmic
   E. has greater prophylactic value post-Ml

8. Calcium channel antagonists

   A. t intracellular cAMP
   B. J- myocardial contractility
   C. i reactivation of Na" channels
   D. J- intracellular K+
   E. i conduction velocity

9. A 75-year-old patient suffering from congestive heart failure accidentally ingests a toxic dose of digoxin. Clinical consequences due to the toxic effects of cardiac glycosides are LEAST likely to include

   A. bigeminy
   B. hypokalemia
   C. nausea and vomiting
   D. premature ventricular beats
   E. visual disturbances

10. In a patient weighing 70 kg, the volume of distribution of lidocaine is 80 L, and its clearance is 28 Llh. The elimination half-life of lidocaine in this patient approximates

   A. 0.2h
   B. 0.5 h
   C. 1.0h
   D. 2.0h
   E. 4.0h

11. In terms of the ability of drugs like digoxin to increase cardiac contractility, their primary action on cardiac cells is

    A. activation of adenylyl cyclase
    B. inactivation of Na channels
    C. activation of the slow Ca^{2+} channel
    D. inhibition of Na+/K+-ATPase
    E. activation of the Na+/C!- cotransporter

12. Which one of the following is LEAST likely to occur following treatment of a hypercholesterolemic patient with cholestyramine?

    A. Increased elimination of bile salts
    B. Decreased circulating cholesterol
    C. Enhanced receptor-mediated endocytosis of LDL
    D. Decreased plasma HDL
    E. Elevation of plasma triglycerides

13. A new diuretic is being studied in human volunteers. Compared with placebo, the new drug increases urine volume, decreases urinary Ca^{2+}, increases plasma pH, and decreases serum K+. If this new drug has a similar mechanism of action to an established diuretic, it probably

    A. blocks the NaCl cotransporter in the DCT
    B. blocks aldosterone receptors in the CT'
    C. inhibits carbonic anhydrase in the PCT
    D. inhibits the Na+/K+/2Cl- cotransporter in the TAL
    E. acts as an osmotic diuretic

14. Which one of the following drugs is most likely to block K+ channels in the heart responsible for the delayed rectifier current?

    A. Amiodarone
    B. Flecainide
    C. Lidocaine
    D. Phenytoin
    E. Verapamil

15. The treatment of hyperlipidemic patients with nicotinic acid (niacin) results in

    A. increases in VLDL
    B. decreases in both plasma cholesterol and TGs
    C. inhibition of HMG-CoA reductase
    D. decreases in HD L
    E. no change in total cholesterol in the plasma

16. Which one of the following drugs is most likely to cause symptoms of severe depressive disorder when used in the treatment of hypertensive patients?

A. Captopril
B. Hydrochlorothiazide
C. Prazosin
D. Nifedipine
E. Reserpine

17. Enhancement of the effects of bradykinin is most likely to occur with drugs like

A. clonidine
B. diazoxide
C. lisinopril
D. losartan
E. propranolol

18. Following a myocardial infarction, a patient in the emergency room of a hospital develops ventricular tachycardia. The best way to manage this situation is with the administration of

A. adenosine
B. diltiazem
C. esmolol
D. lidocaine
E. flecainide

19. Following an acute myocardial infarction, a patient develops signs of pulmonary edema requiring drug management. What effect would digoxin and a high dose of dopamine have in common if each was administered individually to the patient?

A. ↓ TPR
B. ↓ venous return
C. ↓ AV conduction
D. ↓ cAMP
E. ↑ ventricular contractility

20. Which one of the following is the most appropriate drug to use for the patient described in parentheses?

A. Captopril (60-year-old woman with diabetic nephropathy)
B. Nitroprusside (50-year-old man with BP of *140195)*
C. Losartan (29-year-old pregnant woman)
D. Propranolol (40-year-old patient with peripheral vascular disease)
E. Reserpine (37-year-old patient with pheochromocytoma)

21. In a patient suffering from angina of effort, nitroglycerin may be given sublingually because this mode of administration

A. bypasses the coronary circulation
B. causes less reflex tachycardia than oral administration
C. improves patient compliance
D. has a decreased tendency to cause methemoglobinemia
E. avoids first-pass hepatic metabolism

22. A 90-year-old male patient with HTN is being treated with furosemide, lisinopril, and spironolactone. Because of a fainting spell, he is brought to the ER, where his BP supine is 105/60, falling to 65/42 when he is asked to sit up. Which one of the following statements about the case is most reasonable?

A. The fainting may be due to spironolactone-induced hypokalemia.
B. Loop diuretics should never be used in combination with ACEIs.
C. Fainting may be due to hyperuricemia caused by the loop diuretic.
D. Spironolactone is proven to increase survival when used to treat HTN.
E. Fainting may be unrelated to his drug treatment.

23. A patient with a supraventricular tachycardia has an atrial rate of 2S0/min with a ventricular rate of l40/min via a 2:1 AV nodal transmission. After treatment with a drug, the atrial rate slowed to ISO/min, but the ventricular rate increased to lSO/minl Which of the following drugs was most likely to have been given to this patient?

A. Adenosine
B. Digoxin
C. Esmolol
D. Quinidine
E. Verapamil

Answers

1. Answer: **D.** The symptoms described are those of cinchonism, which usually include tinnitus and, when more severe, CNS effects including hallucinations. Cinchonism is characteristic of quinidine and its optical isomer, the antimalarial drug quinine. Like most antiarrhythmic drugs, quinidine can cause cardiac arrhythmias heralded by the ECG changes described.

2. Answer: D Procainamide is metabolized by N-acetyltransferase (a phase II drug metabolism reaction) to form N-acetyl-procainamide (NAPA), which itself has antiarrhythmic activity. Patients who are classified as slow acetylators may develop SLE-like symptoms when treated with procainamide. Other drugs metabolized via N-acetyltransferase, including isoniazid and hydralazine, have also been associated with lupus-like symptoms in slow acetylators.

3. Answer: C. Amiloride and triamterene block Na^+ channels in the collecting tubules (not proximal) and are used as K^+-sparing agents because the reabsorption of Na^+ in the CT is coupled (indirectly) to the secretion of K^+ ions. Hyperkalemia is characteristic of these drugs and may lead to clinical consequences at high doses, or if patients fail to discontinue K^+ supplements or ingest foodstuffs high in K^+. Because Na^+ reabsorption is associated with secretion of protons, these drugs cause retention of H^+ ions, leading to acidosis. They have no significant effects on the renal elimination of Ca^{2+} or bicarbonate ions.

4. Answer: A. Lidocaine, a class IB drug, is the least likely antiarrhythmic agent to cause cardiac depression but does cause CNS effects, which can range from drowsiness to excitation, culminating in seizures. Used only IV, lidocaine is one of the safest drugs in terms of likelihood of causing a cardiac arrhythmia, and its use has not been associated with torsades de pointes ventricular arrhythmias. The drug has vasodilating actions, leading to decreases in blood pressure. It does not cause drug fever or change plasma K^+ levels.

5. Answer: C. Sildenafil (a PDE5 inhibitor) is contraindicated in patients who are taking nitrates such as isosorbide or nitroglycerin because of untoward cardiovascular toxicity and the occurrence of sudden death. The marked hypotension caused by such drug combinations elicits reflex tachycardia, with potential to cause cardiac arrhythmias. Interactions of this type have not been reported between sildenafil and the other drugs listed, but caution is advised in patients who are being treated with any drug that has strong vasodilating actions.

6. Answer: E. Increased sympathetic activity is a major problem in hyperthyroidism and is best managed by use of beta blockers, which can offset cardiac stimulatory effects. Propranolol has an ancillary action in thyrotoxicosis in that it prevents conversion of T_4 to T_3 via its inhibition of 5' deiodinase. Amiodarone causes difficult-to-predict adverse effects on thyroid function and would not be appropriate in a patient with hyperthyroidism. Quinidine is a class IA antiarrhythmic, which is associated with tachycardia as a side effect. Digoxin is not ideal because of its complex actions on the heart, which include both inhibition and stimulation.

7. Answer: **B.** Propranolol is a nonselective blocker of beta adrenoceptors, whereas metoprolol is PI-selective. Metoprolol is less likely to block receptors in the bronchiolar smooth muscle and is less likely to cause bronchoconstriction, especially in asthmatic patients. Propranolol and metoprolol are considered to be equally effective as antiarrhythmics and in post-Ml prophylaxis, and both are cardiodepressant, Drugs that appear to have both alpha- and beta-blocking actions include carvedilol and labetalol.

8. **Answer: B.** Calcium channel antagonists decrease myocardial contractility by blocking the influx of Ca^{2+} ions through voltage-dependent Lrype channels in the cardiac cell membrane. CCBs have no effects on Na+ channels, they do not change intracellular K+ levels, and they decrease (not increase) conduction velocity.

9. **Answer: B.** The operative word in this question is *consequence.* Characteristic overdose toxicity of digoxin (or digitoxin) includes gastrointestinal distress, changes in the ECG (including premature ventricular beats and bigeminy), and visual dysfunctions such as halos around lights. Hypokalemia is not a consequence of digitalis toxicity, although it increases the severity of such toxicity, and efforts should be made to restore serum K+ to the normal range. Hyperkalemia is a consequence of severe digitalis toxicity due to inhibition of the Na+fK+-ATPases present in major body tissues, including skeletal muscle. Elevations of serum K+ further complicate management of digitalis overdose because they may lead to reentrant arrhythmias.

10. **Answer: D.** Back to basic principles! Recall that the relationship between half-life, volume of distribution, and clearance is given by:

$$t_{1/2} = \frac{0.7 \times V_d}{Cl} = \frac{0.7 \times 80}{28} = \sim = 2h$$

In the management of cardiac arrhythmias such as those caused by digitalis, lidocaine is administered IV because it has poor oral bioavailability. Its relatively short half-life is due to its hepatic metabolism via liver cytochrome P450.

11. **Answer: D.** Cardiac glycosides increase contractility by inhibiting the Na+/K"-AfPase pump, causing an increase in intracellular Na. This, in turn, increases intracellular Ca by slowing down Na+fCa^{2+} exchange. The increase in intracellular Ca^{2+} leads to its binding to the troponin-tropomyosin complex, causing an allosteric change and facilitating the interaction between actin and myosin.

12. **Answer: D.** Cholestyramine and colestipol are resins that sequester bile acids in the gut, preventing their reabsorption. This leads to release of their feedback inhibition of 7-alpha hydroxylase and the diversion of cholesterol toward new synthesis of bile acids. Increase in high-affinity LDL receptors on hepatocyte membranes decreases plasma LDL. These drugs have a small but significant effect to increase plasma HDL rather than decrease it, but their ability to increase TGs precludes their clinical use in the management of hypertriglyceridemias.

13. **Answer: A.** The effects described are typical of thiazide diuretics, which inhibit the *Na+f* Cl- cotransporter in the distal convoluted tubule. This action facilitates reabsorption of Ca^{2+}, which is the basis for the use of thiazides in nephrolithiasis, and which can result in hypercalcemia. The increased load of Na+ in the collecting tubules leads to increased excretion of both K+ and H+, so hypokalemia and alkalosis may occur.

14. **Answer: A.** Amiodarone is a highly effective antiarrhythmic drug, in part because of its multiple actions, which include Na" channel block, beta adrenoceptor block, K+ channel block, and Ca^{2+} channel block. Drugs that block K+ channels (which include class IA and class III antiarrhythmics) prolong APD and ERP and predispose toward torsades de pointes ventricular arrhythmias. Flecainide is a class IC drug, lidocaine and phenytoin are class IE, and verapamil is class IV, none of which inhibits the delayed rectifier K+ current responsible for membrane repolarization during the cardiac action potential.

15. Answer: B. Nicotinic acid inhibits the synthesis of the VLDL apoprotein and decreases VLDL production. Its use results in decreases of both cholesterol and triglycerides, so total cholesterol in the plasma decreases. The drug is not an inhibitor of HMG-CoA reductase, and it increases plasma HDL to a greater extent than any other available antihyperlipidemic drug.

16. Answer: E. In addition to decreasing the storage of NE in sympathetic nerve endings, reserpine causes a dose-dependent depletion of brain amines, including NE and serotonin. Symptoms of depression are thought to be related to a functional deficiency in noradrenergic and/or serotonergic neurotransmission in the CNS-the "amine hypothesis of depression." Although other drugs used in the management of HTN may cause CNS effects, reserpine is the most likely drug to cause severe depression.

17. Answer: C. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II and lower blood pressure by decreasing both the formation of aldosterone formation and the vasoconstrictive action of All at AT-1 receptors. ACEIs also inhibit the metabolism of bradykinin, and this leads to additional hypotensive effects, because bradykinin is an endogenous vasodilator. Unfortunately, increases in bradykinin are associated with side effects, including cough and angioedema. Losartan, which blocks AT-1 receptors, does not increase bradykinin levels.

18. Answer: D. Arrhythmias following a myocardial infarct are best managed by IV lidocaine. Class IB drugs act primarily on ventricular muscle and, in the case of lidocaine, concentrate in ischemic tissues. Adenosine is indicated for SVTs and nodal tachycardias. The primary actions of both beta blockers (esmolol) and CCBs (diltiazem) are at the AV node-they are not particularly effective in ventricular arrhythmias. Flecainide, a class IC drug, has been implicated in sudden deaths post-MI.

19. Answer: E. In heart failure following a myocardial infarct, digoxin and dopamine (at high doses) can improve cardiac function (and relieve pulmonary congestion) by exerting a positive inotropic effect; they each increase cardiac contractility. Lower doses of dopamine, may also cause vasodilation that can decrease TPR and venous return, but this action is not characteristic of the cardiac glycosides. The vagomimetic effect of digoxin, which decreases AV conduction, is not a property of the other drugs. Drugs that exert positive inotropic effects via activation of beta adrenoceptors increase (not decrease) cAMP.

20. Answer: A. ACEIs slow the progression of diabetic nephropathy and are indicated for management of HTN in such patients. Nitroprusside is used IV in severe HTN or hypertensive crisis, not for management of mild-to-moderate HTN. Losartan, which blocks AT-1 receptors, is associated with teratogenic effects during fetal development, as are the ACEIs. Nonselective beta blockers are not ideal for patients who suffer from peripheral vascular disease, diabetes, or asthma. Reserpine causes the release of amines from tumor cells, exacerbating HTN in pheochromocytoma.

21. Answer: E. The sublingual administration of a drug avoids its absorption into the portal circulation and hence eliminates the possibility of first-pass metabolism, which can often have a major impact on oral bioavailability. Given sublingually, nitroglycerin is more effectively absorbed into the systemic circulation and has improved effectiveness in angina by this mode of administration. Effective absorption is unlikely to decrease reflex tachycardia or propensity toward methemoglobinemia. There is no bypass of the coronary circulation-nitrates actually decrease coronary vasospasm, which makes them effective in variant angina.

22. Answer: E. In approaching the answer to this question, try to sort out the incorrect statements. Spironolactone does not cause hypokalemia, but hyperkalemia. Although loop diuretics may cause hyperuricemia, there is no connection between elevations of uric acid and fainting episodes. When used with ACEIs in the treatment of heart failure, spironolactone is reported to increase survival, but there is no evidence of similar efficacy in patients with HTN. Obviously, statement B is erroneous (never choose "never"). Although postural hypotension from the combination of antihypertensive drugs is most likely responsible for the fainting episode in this patient, there could also be alternative explanations!

23. Answer: D. An increase in AV conduction is characteristic of quinidine, which exerts quite marked blocking actions on muscarinic receptors in the heart. Thus, an atrial rate, formerly transmitted to the ventricles in a 2:1 ratio, may be transmitted in a 1:1 ratio after quinidine. This effect of quinidine can be offset by the prior administration of an antiarrhythmic drug that decreases AV nodal conduction, such as digoxin or verapamil. All of the drugs listed (except quinidine) slow AV nodal conduction, but adenosine and esmolol (a beta blocker) are very short-acting agents used IV only.

SECTION IV

CNS Pharmacology

Sedative-Hypnotic-Anxiolytic Drugs

1

- Drugs: benzodiazepines (BZs), barbiturates, and alcohols

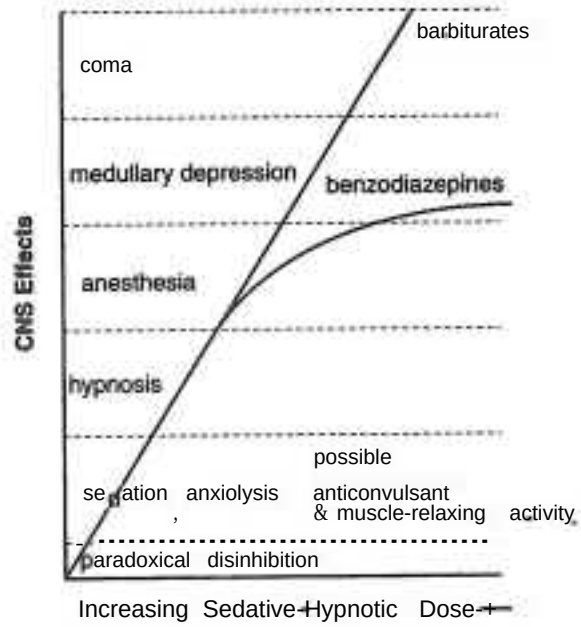


Figure IV-1-1. CNS Effects Associated with Increasing Doses of Sedative-Hypnotic (S-H) Drugs

- Cause dose-dependent CNS depression that extends from sedation to anesthesia to respiratory depression and death
- BZs reach a plateau in CNS depression; barbiturates and alcohol do not

- Mechanisms:

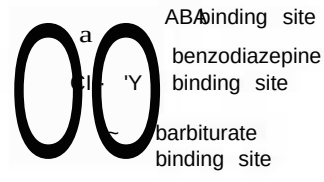


Figure IV-1-2. Site of Action of Drugs on the $GABA_A$ Complex

- $GABA_A$ activation ↑ Cl^- influx
- $GABA_B$ activation ↑ K^+ efflux
- Both mechanisms result in membrane hyperpolarization
  - Benzodiazepines:
    - Potentiate GABA
    - ↑ the frequency of Cl- channel opening
    - Have no GABA mimetic activity
    - Act through BZ receptors
    - These receptors are part of the $GABA_A$ complex
    - BZ_1 mediates sedation
    - BZ_1 mediates antianxiety and impairment of cognitive functions
  - Barbiturates:
    - Prolong GABA activity
    - ↑ duration of Cl^- channel opening
    - Have GABA mimetic activity at high doses
    - Do not act through BZ receptors
    - Have their own binding sites on the $GABA_A$ complex
    - Also inhibit complex I of electron transport chain

Clinical Correlate

Rumazenil

This nonspecific BZ receptor antagonist is used to reverse the CNS depression caused by BZs used in anesthesia or in BZ overdose. Flumazenil cannot reverse the CNS depression caused by barbiturates and alcohols.

- Uses of BZs:

Table IV-I-I. The Uses of Various Benzodiazepines

Drug	Indications
Alprazolam	Anxiety, panic, phobias
Diazepam	Anxiety, preop sedation, muscle relaxation, withdrawal states
Lorazepam	Anxiety, preop sedation, status epilepticus (IV)
Midazolam	Preop sedation, anesthesia IV
Temazepam	Sleep disorders
Oxazepam	Sleep disorders, anxiety

- Pharmacokinetics of BZs:
  - Liver metabolized to active compounds, except for oxazepam, temazepam, and lorazepam
  - Variable tl/Zs and durations of action:

Midazolam < oxazepam < temazepam < alprazolam < lorazepam < diazepam

- Uses of barbiturates:
  - Phenobarbital is used for seizures
  - Thiopental is used for induction of anesthesia
- Pharmacokinetics of barbiturates:
  - Liver metabolized, sometimes to active compounds
  - General inducers of cytochrome P450s
  - Contraindication in porphyrias
- Tolerance to and dependence on sedative-hypnotics:
  - Chronic use leads to tolerance
  - Cross-tolerance occurs between BZs, barbiturates, and ethanol
  - Psychologic and physical dependence occur
  - But abuse liability of BZs is < ethanol or barbiturates

- Withdrawal signs of BZs:
  - Rebound insomnia
  - Anxiety
  - Seizures when BZs were used as anti epileptic or in high doses
- Withdrawal signs of barbiturates and ethanol:
  - Anxiety
  - Agitation
  - Life-threatening seizures (delirium tremens with alcohol)
- Management of withdrawal: supportive and long-acting BZs

- Drug interactions
  - $GABA_A$ drugs are:
    - Additive with other eNS depressants (possible life-threatening respiratory depression), such as anesthetics, antihistamines, opiates, l3-blockers, etc.
    - Barbiturates induce metabolism of most lipid-soluble drugs, such as oral contraceptives, carbamazepine, phenytoin, warfarin, etc.
- Non-BZ drugs:
  - Zolpidem and zaleplon
    - BZ_1 receptor agonist
    - Less effect on cognitive function (BZ_2-mediated)
    - Overdose reversed by flumazenil
    - Used in sleep disorders
    - Less tolerance and abuse liability
  - Buspirone
    - No effect on GABA
    - 5-HT lA partial agonist
    - Used for generalized anxiety disorders
    - Nonsedative
    - Takes 1 to 2 weeks for effects

Chapter Summary

Sedative-hypnotic-anxiolytic drugs include the benzodiazepines, barbiturates, and alcohols.

S-H drugs ideally should reduce anxiety without affecting mental or motor function. However, most do affect mental or motor function. Figure IV-l-l illustrates the relative effects on these functions of classes of S-H drugs at increasing concentrations.

Most S-H drugs facilitate GABA action by binding to the $GABA_A$ receptor, which has one binding site for barbiturates and alcohol and another for benzodiazepines (Figure IV-1-2). The binding of these drugs at these sites leads to increased (1- influx, potentiating the inhibitory transmitter effects of GABA. The differences in action of the various S-H drugs relates to the differences in the binding site used. Further heterogeneity is introduced by the existence of two subtypes of benzodiazepine receptors, BZ_j and BZ_2.

The benzodiazepines are used to treat anxiety states and sleep disorders. Dose-dependent CNS depression does occur but can be reversed by flumazenil. Chronic use can lead to tolerance and dependency with rebound effects upon withdrawal. Table IV-l-l summarizes the various benzodiazepines and their indications.

Phenobarbital is used to treat seizures, and thiopental is used as an IV anesthetic. Barbiturates induce deep CNS depression at high doses, and there is no antidote.

The barbiturates induce drug-metabolizing enzymes, including the P450 system, leading to potential drug interactions. They also stimulate heme synthesis and are contraindicated in porphyrias.

Tolerance, dependence, and severe withdrawal symptoms are associated with chronic barbiturate use.

Zolpidem and zaleplon are nonbenzodiazepines that bind to the BZ_1 receptors and therefore are more specific hypnotics. Buspirone is an anxiolytic that does not work through the GABA system. It is nonsedating and does not cause dependence but takes a week or two to show antianxiety effects.

AIcohols

2

- All alcohols cause eNS depression, in part through GABA mimetic activity.
- All alcohols cause metabolic acidosis.

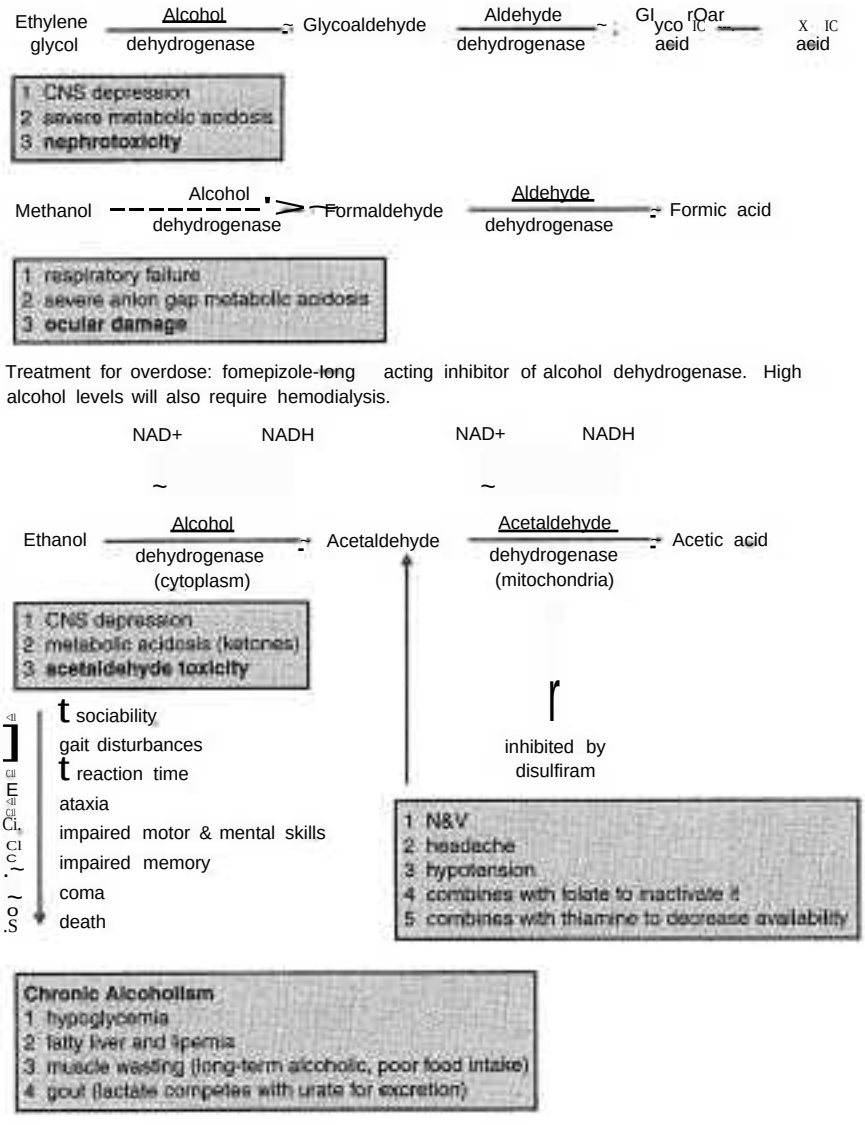


Figure IV-2-1. Metabolism and Pharmacologic Actions of the Alcohols

Clinical Correlate

Alcohol and Pregnancy

The fetal alcohol syndrome is characterized by growth restriction, midfacial hypoplasia, microcephaly, and marked CNS dysfunction, including the frequent occurrence of mental retardation.

In A Nutshell

Drugs that cause disulfiram-like effects:

- Metronidazole
- Cefamandole
- Cefoperazone
- Cefotetan
- Chlorpropamide

Anticonvulsants

3

- Seizures result from episodic electrical discharges in cerebral neurons associated with prolonged depolarization, during which sustained, high-frequency, repetitive firing (SHFRF) occurs, followed by prolonged hyperpolarization. The goal of drug management is restoration of normal patterns of electrical activity.
- Mechanisms of action:
  - ↓ axonal conduction by preventing Na^+ influx through fast Na channels-carbamazepine, phenytoin
  - ↑ inhibitory tone by facilitation of GABA-mediated hyperpolarization-barbiturates, benzodiazepines
  - ↓ excitatory effects of glutamic acid-lamotrigine, topiramate (blocks AMPA receptors); felbamate (blocks NMDA receptors)
  - ↓ presynaptic Ca^{2+} influx through type-T channels in thalamic neurons-ethosuximide and valproic acid

Table IV-3-1. Seizure States and Drugs of Choice

Seizure Type	Drugs of Choice
Partial-simple or complex	Valproic acid, phenytoin, carbamazepine
General-tonic-clonic	Valproic acid, phenytoin, carbamazepine
General-absence	Ethosuximide
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*

*IV fosphenytoin is more water soluble.

- Primary anticonvulsants
  - Phenytoin
    - Blocks axonal Na^+ channels in their inactivate state
    - Prevents seizure propagation
    - Uses: seizure states

- Pharmacokinetics:
  - Variable absorption
  - Nonlinear kinetics
  - Induction of cytochrome P450s
  - Zero-order kinetic of elimination
- Side effects:
  - CNS depression
  - Gingival hyperplasia
  - Hirsutism
  - Osteomalacia (↓ vitamin D)
  - Megaloblastic anemia (↓ folate)
  - Aplastic anemia (check hematology lab results)
- Teratogenicity: cleft lip and palate

- **Carbamazepine**
  - Mechanism identical to phenytoin
  - Uses:
    - Seizure states
    - DOC for trigeminal neuralgia
  - Pharmacokinetics: induces cytochrome P450, including its own metabolism
  - Side effects:
    - CNS depression
    - Osteomalacia
    - Megaloblastic anemia
    - Aplastic anemia
    - Exfoliative dermatitis
    - ↑ ADH secretion (dilutional hyponatremia)
  - Teratogenicity:
    - Cleft lip and palate
    - Spina bifida

- **Valproic acid**
  - Mechanism:
    - Similar to phenytoin
    - But also inhibition of GABA transaminase
    - Blockade of T-type Ca^{2+} channels
  - Uses:
    - Seizure states
    - Mania of bipolar disorders
    - Migraines
  - Pharmacokinetics: inhibits cytochrome P450s

- Side effects:
  - Hepatotoxicity (from toxic metabolite)
  - Thrombocytopenia
  - Pancreatitis
  - Alopecia
- Tetragenecity: spina bifida

- **Ethosuximide**
  - Mechanism: blockade ofT-type Ca^{2+} channels and thalamic neurons
  - Use: absence seizures

- General features of anticonvulsant drug use:
  - Anticonvulsants are additive with other CNS depressants
  - Avoid abrupt withdrawal, which may precipitate seizures
  - ↓ efficacy of oral contraceptives via induction of cytochrome P450
  - Phenobarbital is considered safest during pregnancy
- Other anticonvulsant drugs
  - **Felbamate** and **lamotrigine**
    - Block Na+ channels and glutamate receptors
    - Used in seizure states (often adjunct therapy)
    - Side effects:
      - Hepatotoxicity (both)
      - Aplastic anemia (felbamate)
      - Stevens-Johnson syndrome (lamotrigine)
  - **Gabapentin**
    - ↑ GABA effects
    - Used in seizure states, neuropathic pain (such as postherpetic neuralgia)
    - Side effect: aplastic anemia, liver failure, are rare

Chapter Summary

Seizures are caused by episodic electrical discharges in cerebral neurons. These trigger repetitive firing and prolonged hyperpolarization. The goal of drug management is to restore normal electrical patterns. Different classes of drugs do this by acting on different receptor/transmitter systems, which are listed.

Table IV-3-1summarizes the drugs of choice available to treat each of the several types of seizures.

The mechanisms of action, metabolism, and the adverse effect of the primary anticonvulsant drugs (phenytoin, carbamazepine, ethosuximide, valproic acid, and the barbiturates and benzodiazepines) are discussed.

Anticonvulsive drugs in general have additive depressive effects when used with other depressant drugs, cause a precipitation of seizures upon abrupt withdrawal, and decrease the efficiency of oral contraceptives.

Newer anticonvulsants listed are felbamate, gabapentin, and lamotrigine.

Drugs Used in Anesthesia

4

GENERAL ANESTHETICS

Inhaled Anesthetics

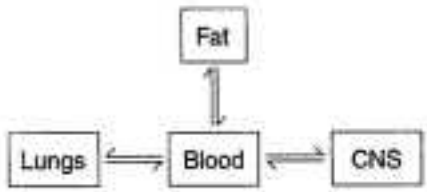


Figure IV-4-1. Compartmentalization of Anesthetics in the Body

Table IV-4-1. Properties of Specific Inhaled Anesthetics

Anesthetic	MAC Value	Blood-Gas Ratio	CVEffects	Specific Characteristics
Nitrous oxide	104%	0.5	Minimal	Rapid onset and recovery, no metabolism Diffusional hypoxia Spontaneous abortions
Halothane	0.8%	2.3	Sensitizes heart to catecholamines	Malignant hyperthermia, hepatitis, cardiac arrhythmias

- Anesthesia protocols include several agents in combinations.
- Inhaled anesthetics have varying potency in proportion to their lipid solubility.
- A MAC (minimal alveolar anesthetic concentration) is defined as the concentration of inhaled anesthetic, as a % of inspired air, at which 50% of patients do not respond to a surgical stimulus.
  - MAC is a measure of potency: ED50.
  - The more lipid soluble the anesthetic, the lower the MAC and the greater the potency.
  - MAC values are additive.
  - MAC values are lower in the elderly and in the presence of opiates or sedative-hypnotics.

- Rates of onset and recovery depend on the blood-gas ratio:
  - The more soluble the anesthetic in the blood, the slower the anesthesia.
  - Anesthetics with high blood-gas ratios are associated with slow onset.
  - Anesthetics with high blood-gas ratios are associated with slow recovery.
  - Anesthetics with low blood-gas ratios have fast onset and recovery.

Intravenous Anesthetics

- Thiopental
  - Barbiturate used for induction
  - Highly lipid soluble; rapid onset; short-acting due to redistribution
- Midazolam
  - Benzodiazepine used for:
    - Preoperative sedation
    - Anterograde amnesia
    - Induction
    - Outpatient surgery
  - Depresses respiratory function
- Propofol
  - Used for induction and maintenance of anesthesia
  - Antiemetic
  - CNS and cardiac depressant
- Fentanyl
  - Opiate used for induction and maintenance of anesthesia
  - Depresses respiratory function
  - *See* Opioid Analgesics chapter in this section
- Ketamine
  - Dissociative anesthetic
  - NMDA-receptor antagonist
  - Induction of anesthesia
  - Emergent delirium, hallucinations
  - Cardiovascular stimulation
  - ↑ intracranial pressure

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local Anesthetics

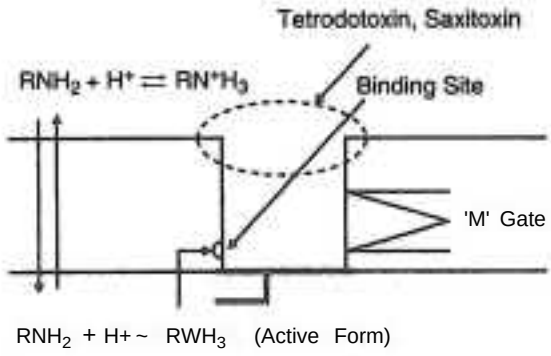

Figure IV-4-2. Mode of Action of Local Anesthetics

- Local anesthetics provide regional anesthesia.
- Drugs:
  - Esters: procaine, cocaine, benzocaine are metabolized by plasma and tissue esterases
  - Amides: lidocaine, bupivacaine, mepivacaine are metabolized by liver amidases
- Mechanisms:
  - Nonionized form crosses axonal membrane
  - From within, ionized form blocks the inactivated Na" channel
  - Slows recovery and prevents propagation of action potentials
- Nerve fiber sensitivity:
  - Nerve fibers most sensitive to blockade are of smaller diameter and have high firing rates
  - The order of sensitivity is:

type Band C > type As> type AI:Iand ~ > type Aa.

  - Recovery is in reverse order
- Absorption:
  - Coadministration of (Xl agonists:
    - o J, local anesthetic absorption into the systemic circulation
    - o Prolong effects and J, toxicity
- Side effects:
  - Neurotoxicity
  - Cardiovascular toxicity
  - Allergies (esters via PABA formation)

Note

Na" Channel Toxins

- Tetrodotoxin (from puffer fish) and saxitoxin (algae toxin, "red tide")
  - Block activated Na" channels
  - J, Na+ influx
- Ciguatoxin (exotic fish) and batrachotoxin (frogs)
  - Bind to activated Na+ channels
  - Cause inactivation
  - Prolong Na+ influx

Note

Esters and Amides

local anesthetics that are esters have just one "i" in their names (e.g., procaine, cocaine); amide local anesthetics have more than one "i" (e.g., lidocaine, bupivacaine).

Note

Cocaine intrinsically causes vasoconstriction by blocking norepinephrine uptake.

Skeletal Muscle Relaxants



Figure IV-4-3. Nicotinic ACh Receptor of the Neuromuscular Junction

- Nicotinic receptors have five subunits.
- Two ACh bind each to two a subunits in order to open the Na+ channel.
- This depolarizes the muscle.
- Used mainly in anesthesia protocols or in the ICU to afford muscle relaxation and/or immobility.
- Muscle relaxants interact with nicotinic ACh receptors at the neuromuscular junction.
- Drugs:
  - **Nondepolarizing (competitive)**
    - Nicotinic antagonists
    - D-Tubocurarine prototype
    - Reversible with AChE inhibitors
    - Progressive paralysis (face, limbs, respiratory muscle)
    - No effects on cardiac and smooth muscle
    - No CNS effects
    - Specific drugs:

      Atracurium
      - Rapid recovery
      - Safe in hepatic or renal impairment
      - Spontaneous inactivation to laudanosine
      - Laudanosine can cause seizures

      Mivacurium
      - Very short duration
      - Metabolized by plasma cholinesterases
  - **Depolarizing (noncompetitive)**
    - Nicotinic agonist
    - Specific drug: **succinylcholine**
    - Two phases:

      Phase I: depolarization, fasciculation, prolong depolarization, flaccid paralysis

      Phase II: desensitization
    - AChE inhibitors t phase I; have no effect on phase II
    - Rapidly hydrolyzed by pseudocholinesterase: short duration

- Cautions:
  - Atypical pseudocholinesterase
  - Hyperkalemia
  - Malignant hyperthermia

Centrally Acting Skeletal Muscle Relaxants

- Benzodiazepines through $GABA_A$ receptors
- Baclofen through $GABA_B$ receptors
- Use: spasticity

Chapter Summary

Drugs Used in Anesthesia

The more lipid soluble the inhalation anesthetic, the greater its potency (lower MACvalue). The more soluble an inhalation anesthetic in the blood (higher blood:gas ratio), the slower will be the onset to anesthesia and the slower will be the recovery.

Thiopental, midazolam, propofol, fentanyl, and ketamine are intravenous anesthetics that are discussed.

Local anesthetics (weak bases) infiltrate and anesthetize nerve bundles near sites of injection by binding to inactive Na+ channels in their ionized forms. However, to get to the channel they must diffuse though the lipid bilayer in an unionized form. Thus, their effects are influenced by pH.

The smaller and most rapidly firing nerve fibers are the most sensitive to blockade.

The coadministration of alpha adrenoceptor agonists decreases local anesthetic absorption into the systemic circulation, prolonging their effects and potentially decreasing their toxicity.

The adverse effects of local anesthetics are given.

Sodium Channel Toxins

Tetrodotoxin, saxitoxin, ciguatoxin, and batrachotoxin are sodium-channel toxins found in various fish, frogs, or dinoflagellates.

Skeletal Muscle Relaxants

The skeletal muscle relaxants provide muscle relaxation and/or immobility via N-receptor interactions. Most, including o-tubocurarine, atracurium, and mivacurium, are cornpetitse and nondepolanzing and can be reversed by AChEinhib~ors. Succin~choline is a depolarizing, noncornpetsve agonist.

Spasmolytics reduce excess muscle tone or spasm in injury or CNS dysfunction. They may act in the CNS, the spinal cord, or directly on the muscle. Benzodiazepines and baclofen reduce the tonic output of spinal motor neurons. Dantrolene blocks Ca^{2+} release from the muscle sarcoplasm reticulum.

Bridge to Pathology/ Genetics

Malignant Hyperthermia

A life-threatening syndrome characterized by muscle rigidity, hyperthermia, hypertension, acidosis, and hyperkalemia. Associated with the use of skeletal muscle relaxants, especially succinylcholine, used in anesthesia regimens. Genotypic susceptibility may be related to mutations in the genes encoding ryanodine receptors and/or a protein component of the L-type calcium channel in skeletal muscle.

Treatment

Dantrolene acts directly on skeletal muscle to decrease contractility by blocking Ca^{2+} release from the sarcoplasmic reticulum. It is used in states that include extreme muscle rigidity, such as malignant hyperthermia associated with inhaled anesthetics and skeletal muscle relaxants or neuroleptic malignant syndrome associated with antipsychotics.

Opioid Analgesics

5

- Endogenous opiate peptides represented by endorphins, enkephalins, and dynorphins
- Three receptor families: μ, κ, and ()
- Presynaptic and postsynaptic inhibition through G_i coupling
- Mu pharmacology most important
- Morphine is the prototype ~ agonist
- Pharmacology of **morphine:**
  - Analgesia: ↑ pain tolerance and ↑ perception and reaction to pain
  - Sedation
  - Respiratory depression: ↓ response to ↑ PCO_2 (do not give O_2; give naloxone)
  - Cardiovascular: minimal effects on heart, but vasodilation (avoid in head trauma)
  - Smooth muscle
    - Longitudinal relaxes
    - Circular constricts
      - GI: ↓ peristalsis, constipation, cramping
      - GU: urinary retention, urgency to void
      - Biliary: ↑ pressure
      - Pupils: miosis
  - Cough suppression: antitussive action, independent of analgesia and respiratory depression
  - Nausea and vomiting: stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema
  - ↑ histamine release
- Pharmacokinetics of morphine:
  - Glucuronidation
  - Morphine-6-glucuronide is highly active
  - Caution in renal dysfunction
- Other opioids and analgesics *(see* Table IV-S-l).

Clinical Correlate

Contraindications and Cautions for Opioids

- Head injuries (possible increased intracranial pressure)
- Pulmonary dysfunction (except pulmonary edema)
- Hepatic/renal dysfunction (possible accumulation)
- Adrenal or thyroid deficiencies (exaggerated responses)
- Pregnancy (possible neonatal depression or dependence), except meperidine

Table IV-5-1. Other Opioids and Analgesics

Receptor Action	Drug	Characteristics
Full agonists	Meperidine	• Also antimuscarinic No miosis Tachycardia No spasm GI/GU/gallbladder • Metabolized by cytochrome P450 to normeperidine, a serotonin reuptake inhibitor, which can cause seizures
	Methadone	• Used in maintenance of opiate addicts
Partial agonists	Codeine	• Cough suppressant • Analgesia • Used in combination with NSAIDs
	Buprenorphine	• Precipation of withdrawal
Mixed agonists	Nalbuphine, pentazocine	• κ agonist spinal analgesia dysphoria • f.1 antagonist precipitation of withdrawal
Antagonists	Naloxone	• IV, reversal for respiratory depression
	Naltrexone	• PO, -1, craving for alcohol and used in opiate addiction

- Side effects of opioid analgesics:
  - Acute toxicity: classic triad
    - Pinpoint pupils
    - Respiratory depression
    - Coma
  - Management of acute toxicity:
    - Supportive
    - IV naloxone
- Abuse liability of opioid analgesics:
  - Tolerance: pharmacodynamic; occurs to all effects, except miosis and constipation
  - Dependence: physical and psychologic
  - Withdrawal:
    - Yawning
    - Lacrimation, rhinorrhea, salivation
    - Anxiety, sweating, goose bumps
    - Muscle cramps, spasms, CNS-originating pain
  - Management of withdrawal:
    - Supportive
    - Methadone
    - Clonidine

- Opiate-related drugs with specific indications
  - Loperamide: diarrhea
  - Dextromethorphan: cough

Chapter Summary

Opioid agonists and/or antagonists act in part by binding to the receptors for the endogenous opiopeptides. These are G-protein-linked, multisubunit structures to which the various opioids bind as full or partial agonists or as antagonists. The resultant complex array of potential mechanisms, sites of action, types of effects, kinetics, and contra indications are discussed. Table IV-5-1summarizes the receptor actions and other relevant characteristics of eight opioid drugs.

Drugs Used in Parkinson Disease and Psychosis

6

DOPAMINERGIC NEURAL PATHWAYS

In the CNS, dopamine (DA) is a precursor to NE in diffuse noradrenergic pathways and is an inhibitory neurotransmitter in the following major dopaminergic pathways:

- Nigrostriatal tract
  - Cell bodies in the substantia nigra project to the striatum, where they release DA, which inhibits GABA-ergic neurons. In Parkinson disease, the loss of DA neurons in this tract leads to excessive ACh activity → extrapyramidal dysfunction.
  - DA receptor antagonists → pseudo-Parkinsonism (reversible).
  - DA agonists may cause dyskinesias.
- Mesolimbic-mesocortical tracts—cell bodies in midbrain project to cerebrocortical and limbic structures.
  - Functions include regulation of affect, reinforcement, cognitive functions, and sensory perception. Psychotic disorders and addiction are partly explained by ↑ DA in these pathways.
  - Drugs that ↑ DA functions → ↑ reinforcement and, at high doses, may cause psychoses.
  - DA antagonists → ↓ cognitive function.
- Tuberoinfundibular
  - Cell bodies in hypothalamus project to anterior pituitary and release DA → ↓ prolactin.
  - DA agonists (e.g., pergolide) are used in hyperprolactinemic states.
  - DA antagonists may cause endocrine dysfunction, including gynecomastia and amenorrheal galactorrhea.
- Chemoreceptor trigger zone
  - Activation of DA receptors → ↑ emesis.
  - DA agonists (e.g., apomorphine) are emetic, and DA antagonists are antiemetic.
- Dopamine receptors
  - D1-like: G_s coupled
  - Dz-like: G_j coupled
    - D_{ZA}: nigrostriatal
    - D_{ZC}: mesolimbic

DRUGS USED IN PARKINSON DISEASE

- Signs and symptoms of Parkinson disease include:
  - Bradykinesia
  - Muscle rigidity
  - Resting tremor
- Pathology: degeneration of nigrostriatal dopamine tracts with imbalance between dopamine (J,) and ACh (i)

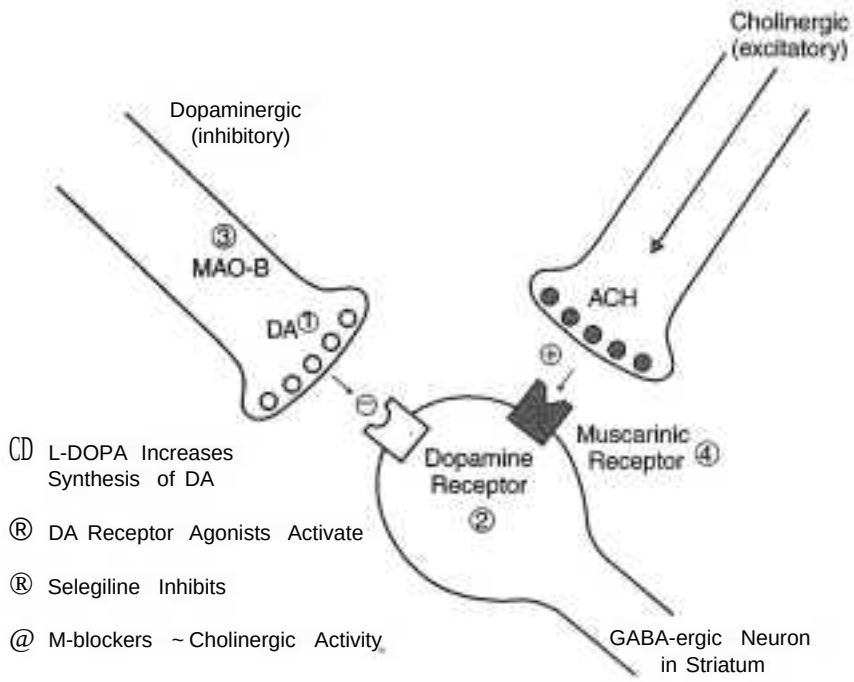

Figure IV-6-1. eNS Targets for Antiparkinsonian Drugs

- Pharmacologic strategy: restore normal dopamine and J, ACh activity at muscarinic receptors in the striatum
- Drugs increasing dopamine function:
  - Levodopa
    - Precursor, converted to dopamine by aromatic amino acid decarboxylase (AAAD)
    - Usually given with carbidopa
    - Side effects:
      - Dyskinesias
      - "On-off" effects
      - Psychosis
      - Hypotension
      - Vomiting

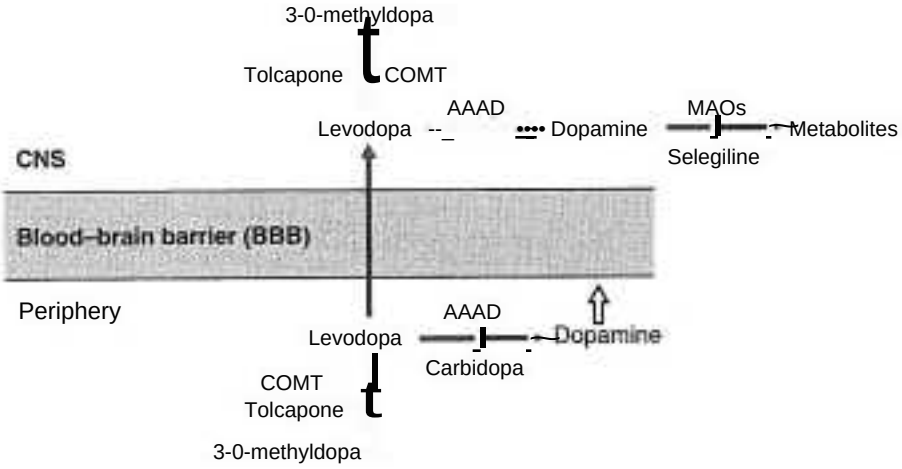

Figure IV-6-2. Inhibitors of Levodopa Metabolism

- Tolcapone and entacapone
  - COMT converts dopamine to 3-0-methyldopa, a partial agonist at dopamine receptors.
  - These drugs inhibit COMT and enhance levodopa uptake and efficacy.
  - Tolcapone is hepatotoxic.
- Selegiline
  - MAOB-selective inhibitor (no tyramine interactions)
  - Initial treatment and adjunct to levodopa
  - Side effects: dyskinesias and psychosis

- Dopamine-receptor agonists:
  - Brornocriptine.
    - Use: hyperprolactinemia and acromegaly
    - Side effects: dyskinesias and psychosis
  - Other dopamine agonists: pergolide and prarnipexole
- Drugs decreasing ACh function:
  - Include benztropine, trihexyphenidyl, and diphenhydramine, which are muscarinic blockers
  - Actions: ↓ tremor and rigidity but have little effects on bradykinesia
  - Side effects: atropine-like
- Amantadine.
  - Antiviral, which block muscarinic receptors and ↑ dopamine function
  - Side effects: atropine-like and livedo reticularis

ANTIPSYCHOTIC DRUGS

Schizophrenia

- Positive symptoms:
  - Thought disorders
  - Delusions
  - Hallucinations
  - Paranoia
- Negative symptoms:
  - Amotivation
  - Social withdrawal
  - Flat affect
  - Poor speech
- "Dopamine hypothesis":
  - Symptoms arise because of excessive dopaminergic activity in mesolimbic system.
  - Dopamine agonists cause psychosis.
  - Dopamine antagonists have antipsychotic actions.
- Serotonin is increasingly seen as a part of the etiology of schizophrenia.
- Mechanism: blockade of dopamine and/or $5HT_2$ receptors
- Uses
  - Schizophrenia
  - Schizoaffective states
  - Bipolar disorder
  - Tourette syndrome
  - Drug or radiation emesis
- Side effects from dopamine blockade:
  - Dyskinesias (extrapyramidal symptoms [EPS])
    - Acute EPS:
      Pseudoparkinsonism, dystonia, akathisia
      Management: antimuscarinic drugs (benztropine or diphenhydramine)
    - Chronic EPS:
      Tardive dyskinesia (TD)
      Management: discontinuation/switch to atypical
  - Dysphoria
  - Endocrine dysfunction:
    - Temperature regulation problems (neuroleptic malignant syndrome [NMS], treated with dantrolene and bromocriptine)
    - t prolactin (galactorrhea, amenorrhea, gynecomastia)
    - t eating behaviors (weight gain)
- Side effects from muscarinic blockade (particularly tachycardia and J. seizure threshold)
- Side effects from alpha blockade (particularly hypotension)

Summary of Antipsychotic Drug Pharmacology

Table IV-6-1. Characteristic Properties of Antipsychotic Drugs

Drug Group **Examples**	EPS*	M **Block**	**Sedation**	**Alpha Block**	**Other Characteristics**
l'YPICALS					
Chlorpromazine	++	++	+++	+++	NA
Thioridazine	+	+++	+++	+++	• Cardiotoxicity (torsades-"quinidine-like") • Retinal deposits
Fluphenazine	+++	+	+	-+	NA
Haloperidol	+++	+	+	+	*ost likely cause of neuroleptic malignant syndrome (NMS) and TD
ATYPICALS					
Clozapine	+1-	++	+	+++	• Blocks D_{2C} and $5HT_2$ receptors • NoTD • Agranulocytosis-(weekly WBC count) requirement for weekly blood test, weight gain • Increased salivation ("wet pillow" syndrome) • Seizures
Olanzapine	+1-	+	+	++	Blocks 5HT z receptors, improves negative symptoms
Risperidone	+	+1-	++	++	Blocks $5HT_2$ receptors, improves negative symptoms
Aripiprazole	+	+1-	+1-	+1-	Partial agonist of D_2 receptor; blocks $5HT_2$ receptors

*Extrapyramidal symptoms

Clinical Correlate

Parenteral Forms

Parenteral formulations of certain antipsychotic drugs (e.g, fluphenazine, haloperidol) are available for rapid initiation of treatment and for maintenance therapy in noncompliant patients. Depot forms of both drugs exist.

Chapter Summary

Dopaminergic Neural Pathways

Dopamine (DA) in the nigrostriatal tract helps regulate kinesis by inhibiting GABA-ergic and cholinergic neurons. The loss of DA neurons in this tract leads to excessive ACh activity and Parkinsonism. DA receptor antagonists cause a reversible pseudo-Parkinsonism; agonists may cause dyskinesis.

DA neurons in the midbrain projecting into the cerebrocortical and limbic regions regulate affect, reinforcement, psychomotor function, and sensory perception. DA agonists enhance psychomotor activity and reinforcement and at high doses may cause psychoses. DA antagonists decrease psychomotor function.

In the hypothalamus, DA released into the pituitary decreases prolactin release. DA agonists (e.g., pergolide) are used to treat hyperprolactinemia; antagonists may cause endocrine dysfunction.

The activation of DA receptors in the chemoreceptor trigger zone increases emesis; thus, DA agonists are emetic, and antagonists are antiemetic.

Antiparkinsonian Drugs

Parkinsonism is due to an imbalance between DA and ACh activity in the nigrostriatal tract. Drugs attempt to restore this balance either by increasing DA or decreasing ACh levels. Figure IV-6-1 illustrates the CNS sites targeted in antiparkinsonism therapy.

Drugs used to increase DA function are levodopa, tolcapone, entacapone, bromocriptine, pramipexole, and selegiline. Drugs that decrease ACh function are benztropine, trihexyphenidyl, diphenhydramine, and amantadine. The properties of each are described.

Antipsychotic Drugs

Although the prevailing concept is that schizophrenia is due to hyperdopaminergic activity in the CNS, not all antischizophrenic drugs act as DA antagonists; some instead modify serotonin function.

The typical antipsychotic drugs (e.g., chlorpromazine, thioridazine, fluphenazine, and haloperidol) act primarily as DA antagonists, blocking D_{1A} receptors. Side effects include the induction of pseudo-Parkinsonism, akathisia, and/or acute dystonic effects. Their use and symptom management are discussed, as are other adverse effects including toxicity, tardive dyskinesia, and neuroleptic malignant syndrome.

Atypical antipsychotics (e.g., c1ozapine, risperidone, and olanzapine) act as antagonists at SHT_2 receptors and seem to have fewer adverse effects. Aripiprazole is a D_2 partial agonist.

Table IV-6-1 summarizes the characteristics of the antipsychotic drugs.

Drugs Used for Depression, Bipolar Disorders, and Attention Deficit Hyperactivity Disorder (ADHD)

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- "Amine hypothesis" of depression:
  - Reserpine: depletes NE, SHT, DA, and causes severe depression
  - Acute mechanism of antidepressants: ↓ NE, ↓ SHT
  - However, antidepressant effect takes several weeks to occur.

DRUGS USED IN DEPRESSION

MAO Inhibitors

- Drugs: phenelzine and tranylcypromine
- Mechanism: inhibition of MAO_A and MAO_B
- Use: atypical depressions
- Drug interactions
  - ↑ NE: hypertensive crisis
    - Symptoms: ↑ BP, arrhythmias, excitation, hyperthermia
    - Drugs: releasers (i.e., tyramine), tricyclic antidepressants (TCAs), α_1 agonists, levodopa
  - ↓ SHT: serotonin syndrome
    - Symptoms: sweating, rigidity, myoclonus, hyperthermia, ANS instability, seizures
    - Drugs: SSRIs, TCAs, meperidine, dextromethorphan

Tricyclic Antidepressants (TCAs)

- Drugs: amitriptyline, imipramine, and clomipramine
- Mechanism: nonspecific blockade of SHT and NE reuptake
- Uses:
  - Major depressions
  - Phobic and panic anxiety states
  - Obsessive-compulsive disorders (OCDs)
  - Neuropathic pain
  - Enuresis
- Side effects: muscarinic and α_1 blockade
- Toxicity: the "3 Cs": coma, convulsions, and cardiotoxicity
- Drug interactions:
  - Hypertensive crisis with MAO inhibitors
  - Serotonin syndrome with SSRIs and MAO inhibitors
  - Prevent antihypertensive action of α_2 agonists and guanethidine

Selective Serotonin Reuptake Inhibitors (SSRIs)

- I>rugs:fluoxetble,paroxetUne,sertralUne
- Mechanism: selective blockade of 5HT reuptake
- Uses:
  - Major depression
  - OCI>
  - Bulimia
  - Anxiety disorders
  - Premenstrual dysphoric disorder (PMI>I»)
- Side effects: anxiety, agitation, bruxism, sexual dysfunction, weight loss
- Toxicity: serotonin syndrome
- Drug interactions: serotonin syndrome with MAO inhibitors, TCAs, meperidine and dextromethorphan

Other Antidepressants

- Trazodone: associated with cardiac arrhythmias and priapism
- Venlafaxine: nonselective reuptake blocker devoid of ANS side effects
- Bupropion: dopamine reuptake blocker; used in smoking cessation
- Mirtazapine: (X2 antagonist, associated with weight gain

LITHIUM AND BIPOLAR DISORDER

- Lithium remains I>OC for bipolar disorders.
- Usually antidepressants/antipsychotics also required
- Mechanism:
  - Prevents recycling of inositol (J- PIP 2)
  - J- cAMP
- Side effects:
  - Narrow therapeutic index; requires therapeutic monitoring
  - Tremor, flu-like symptoms, life-threatening seizures
  - Hypothyroidism with goiter (J- TSH effects and inhibition of 5'-deiodinase)
  - Nephrogenic diabetes insipidus (J- AI>H effect); manage with amiloride
- Teratogenicity: in case of pregnancy, use clonazepam or gabapentin
- Other drugs used in bipolar disorders: valproate

DRUGS USED IN ADHD

- Methylphenidate: amphetamine-like
  - Side effects: agitation, restlessness, insomnia, cardiovascular toxicity
- Atomoxetinei selective NE reuptake inhibitor
  - Side effects: *See* TCA section, above.

Chapter Summary

The amine hypothesis of depression postulates that symptoms are caused by a functional deficiency of CNS NE and/or 5HT. This is based on the observation that most antidepressants affect the metabolism of these amines. Again, there are exceptions.

The uses, drug interactions, and adverse effects of the monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitdrs, and other antidepressants are discussed.

Lithium, the mainstay for bipolar disorder treatment, often needs supplementation with antidepressant and/or sedative drugs. The uses, mechanisms of action, and adverse effects of lithium therapy as well as backup drugs used for treatment of bipolar disorder are considered.

Atomoxetine and methylphenydate are used in the treatment of ADHD.

Drugs of Abuse

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DRUGS OF ABUSE

Table IV-8-1. Properties of Drugs of Abuse

CNS Stimulants	Cocaine	Amphetamines
Neurotransmitters involved	NE,DA,5HT	
Mechanism(s) of action	Blocks DA, NE, and 5HT reuptake in CNS; local anesthetic action from Na+ channel blockade	Blockade of reuptake of NE and DA, release amines from mobile pool, weak MAO inhibitors
Effects	1. Increase NE: sympathomimetic effect with increased heart rate and contractility, blood pressure changes, mydriasis, and central excitation, hyperactivity 2. Increase DA: psychotic episodes, paranoia, hallucinations, possible dyskinesias, and endocrine disturbances 3. Increase 5HT: behavioral changes, aggressiveness, dyskinesias, and decreased appetite	
Toxicity	1. Excess NE: cardiac arrhythmias, generalized ischemia with possible MI and strokes; acute renal and hepatic failures 2. Excess DA: major psychosis, cocaine delirium 3. Excess 5HT: possible serotonin syndrome 4. All of the above: convulsion, hyperpyrexia, and death	
Withdrawal	Craving, severe depression, anhedonia, anxiety; manage with antidepressants	

CNS Depressants	Benzodiazepines	Barbiturates and Ethanol
Neurotransmitters involved	GABA	
Mechanism of action	Potentiation of GABA interaction with $GABA_A$ receptors involves BZ_1 and BZ_2 binding sites	Prolongation of GABA, GABA mimetic at high doses, on $GABA_A$ receptors
Effects	Light to moderate CNS depression	Any plane of CNS depression

(Continued)

Table IV-8-1. Properties of Drugs of Abuse *(continued)*

Toxicity	Sedation, anterograde amnesia; in severe OD (or IV use), reverse with flumazenil	Severe CNS depression, respiratory depression, and death
Withdrawal	Rebound insomnia, rebound anxiety	Agitation, anxiety, hyperreflexia, and life-threatening seizures + in ethanol withdrawal delusions/ hallucinations-delirium tremens (DTs)
Opioids	**Morphine, Heroin, Methadone, Fentanyls, Other Opioids**	
Neurotransmitters involved	NE, DA, 5HT, GABA, and many others	
Mechanism of action	Activate opioid μ, κ, and δ receptors. Potent μ receptor activators have the most intense abuse and dependence liability, possibly effected via an increase in dopaminergic transmission in the mesolimbic tracts	
Effects	Euphoria, analgesia, sedation, cough suppression, and constipation; strong miosis (except meperidine)	
Toxicity	Severe respiratory depression (reverse with naloxone), nausea, vomiting	
Withdrawal	Lacrimation, yawning, sweating, and restlessness, rapidly followed with centrally originating pain, muscle cramping, and diarrhea; not life-threatening	
Hallucinogens	**Marijuana**	**Hallucinogens**
Neurotransmitters involved	Many	5HT
Mechanism of action	Interaction of THC with CB_1 and CB_2 cannabinoid receptors in CNS and periphery	Interaction with several subtypes of 5HT receptors
Effects	Sedation, euphoria, ↑ HR, conjunctiva, delusions, hallucinations	Hallucinogen, sympathomimetic, causes dysesthesias
Toxicity	Associated with smoking, possible flashbacks	Poorly described, flashbacks likely
Withdrawal	Irritability, anxiety	Poorly characterized

Miscellaneous Abused Drugs

1. PCP: extremely toxic, horizontal and vertical nystagmus, paranoia, rhabdomyolysis; overdose is common, with convulsions and death
2. Ketamine: similar to but milder than PCP, with hallucinations, glutamate-receptor antagonist
3. Anticholinergics: scopolamine, atropine-like
4. MDMA ("Ecstasy"), MDA, MDEA: amphetamine-like with strong 5HT pharmacology and therefore hallucinogenic; generally neurotoxic
5. Inhalants: solvent abuse, multiple organ damage; *see* Toxicology section

Chapter Summary

Table IV-8-1 summarizes the properties of drugs of abuse. These include the CNS stimulants (cocaine and amphetamines), the CNS depressants (benzodiazepines, barbiturates, and ethanol), the opioids (morphine, heroin, methadone, fentanyl, and others), the hallucinogens (marijuana and other hallucinogens), PCP, ketamine, anticholinergics (scopolamine), MDMA-MDA-MDEA (all amphetamine-like), and inhalants.

CNS Drug List and Practice Questions

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Table IV-9-1. eNS Drug List

Sedative-Hypnotics	Anticonvulsants
Barbiturates: phenobarbital Benzodiazepines: alprazolam, diazepam, lorazepam,oxazepam Others: buspirone, zolpidem, zaleplon BZ receptor antagonist: flumazenil	Carbamazepine,ethosuximide,valproic acid, phenytoin, diazepam, lorazepam, gabapentin, lamotrigine, felbamate, topiramate, tiagabin, vigabatrin
	Anesthetics (Inhaled)
	Halothane, nitrous oxide
Anesthetics (IV)	**Neuromuscular Blocking Agents**
Fentanyl, ketamine, midazolam, propofol, thiopental	Depolarizing: succinylcholine Nondepolarizing: atracurium, mivacurium, tubocurarine
Local Anesthetics	**Skeletal Muscle Relaxants**
Lidocaine, bupivacaine, mepivacaine, procaine, cocaine	Depolarizing: succinylcholine Nondepolarizing: D-tubocurarine, atracurium, mivacurium
Opioid Analgesics	**Antipsychotics**
Full agonists: morphine, meperidine, methadone, fentanyl, and heroin Partial agonists: buprenorphine, codeine Mixed agonist-antagonists: nalbuphine Antagonists: naloxone, naltrexone	Chlorpromazine, fluphenazine, thioridazine, haloperidol, clozapine, risperidone, olanzapine, aripiprazole
Antiparldnsonian Drugs	**Antidepressants**
DA agonists: levodopa, bromocriptine, pergolide, pramipexole MAO-B inhibitor: selegiline AAAD inhibitor: carbidopa M blockers: benztropine, trihexiphenidyl COMT inhibitor: tolcapone Amantadine	MAOIs: phenelzine, tranylcypromine TCAs: amitriptyline, imipramine, clomipramine SSRIs: fluoxetine, paroxetine, sertraline Others: bupropion, mirtazapine, trazodone, venlafaxine
Bipolar Disorder	**ADHD**
Lithium	Methylphenydate Atomoxetine

CNS DR.UGS

Review Questions

1. Which one of the following CNS receptors is directly coupled to an ion channel so that the effects of its activation do not involve second messenger systems?

   A. N(ACh)
   B. a (NE)
   C. D_{2A} (DA)
   D. JJ. (beta endorphin)
   E. $5HT_2$ (serotonin)

2. Lorazepam can be safely used as a preanesthetic medication in a patient undergoing liver transplantation without fear of excessive CNS depression because the drug is

   A. excreted in unchanged form
   B. actively secreted into the GI tract
   C. conjugated extrahepatically
   D. a selective anxiolytic devoid of CNS depressant actions
   E. reversible by naloxone

3. Benzodiazepines are thought to cause sedative and/or anxiolytic effects by

   A. increasing functional activity at $GABA_B$ receptors
   B. enhancing the actions of dopamine
   C. blocking the NMDA glutamate receptor subtype
   D. acting as a partial agonist at 5HT receptors
   E. facilitating GABA-mediated increases in chloride ion conductance

4. Which one of the following is an established clinical use of morphine?

   A. Management of generalized anxiety disorders
   B. Relief of pain associated with biliary colic
   C. Pulmonary congestion
   D. Treatment of cough associated with use of ACE inhibitors
   E. Suppression of the ethanol withdrawal syndrome

5. A 40-year-old man was brought to the ER after ingesting an unknown quantity of phenobarbital, the plasma level of which was 50 mg/L on admission. Pharmacokinetic parameters for phenobarbital are: V_d = 40 L, CL = 6 L'day, half-life = 4 days, oral bioavailability f = 1. The quantity of the drug that the patient ingested must have been close to

   A. 100mg
   B. 500 mg
   C. 1 g
   D. 2g
   E. 5 g

6. Which one of the following is characteristic of phenytoin?

   A. Inhibition of hepatic cytochrome P450
   B. First-order elimination at high therapeutic doses
   C. Enhances the effects of estrogenic steroids
   D. The drug is safe to use in pregnancy
   E. Delays recovery of voltage-dependent sodium channel

7. A patient known to be a heroin abuser comes to the ER with a painful stab wound. The ER resident administers nalbuphine for the pain. Why is this not a good idea?

   A. The patient is probably tolerant to nalbuphine.
   B. The drug may precipitate a withdrawal state.
   C. Nalbuphine is a weaker analgesic than codeine.
   D. Vasodilating effects of nalbuphine increase blood loss.
   E. Nalbuphine is a strong ~ receptor agonist.

8. The data shown in the table below concern the effects of drugs on transmitter function in the eNS. Which one of the drugs is most likely to alleviate extrapyramidal dysfunction caused by neuroleptics? (The + signs denote intensity of drug actions.)

Drug	Activation of DA Receptors	Activation of GABA Receptors	BlockofACh MReceptors
A.	++++	0	0
B.	++	++	0
C.	0	0	++++
D.	0	+++++	0
E.	+	+	0

9. Tricyclic antidepressants

   A. increase the antihypertensive effect of guanethidine
   B. have anticonvulsant activity
   C. should not be used in patients with glaucoma
   D. may increase oral absorption of levodopa
   E. are sometimes used as antiarrhythmics

10. Which one of the following statements about lithium is accurate?

    A. It causes symptoms of mild hyperthyroidism in up to 25% of patients.
    B. Plasma levels are increased by a high-Na diet.
    C. Adverse effects include acne, polydipsia, and polyuria.
    D. Spina bifida is major concern in fetal development.
    E. Sedative actions calm manic patients within 24 h.

11. **In** the management of toxicity caused by ingestion of methanol in wood spirits, which one of the following statements is most accurate?

A. Treatment should involve the administration of disulfiram in the ER.
B. Naltrexone is a suitable antidote in poisoning due to alcohols.
C. Ethanol will prevent formation of formaldehyde in methanol poisoning.
D. Hemodialysis will not remove methanol from the blood.
E. Delirium tremens is characteristic of methanol poisoning.

12. Regarding the management of Parkinson disease, which one of the following statements is most accurate?

A. Selegiline is a direct activator of striatal DA receptors.
B. Carbidopa increases levodopa entry into the CNS by inhibiting peripheral COMT.
C. Levodopa causes a rapid development of tardive dyskinesia.
D. Pramipexole is an inhibitor of MAO type B.
E. Bradykinesia is not improved significantly by benztropine.

13. A 29-year-old male patient is being treated with an antidepressant drug, and his mood is improving. However, he complains of feeling "jittery" and agitated at times, and if he takes his medication in the afternoon he finds it difficult to get to sleep at night. He seems to have lost weight during the 6 months that he has been taking the drug. He has been warned not to take other drugs without consultation because severe reactions have occurred with opioid analgesics, and With dextromethorphan (in cough syrup). This patient is probably taking

A. alprazolam
B. chlorpromazine
C. paroxetine
D. amitriptyline
E. trazodone

14. The ability of several drugs to inhibit the reuptake of CNS amine neurotransmitters is shown in the table below (number of arrows ↓ indicates the intensity of inhibitory actions). Which one of the drugs is most likely to have therapeutic effectiveness in the management of both obsessive-compulsive disorders (OCD) and major depressive disorders?

Drug	DA Reuptake	NE Reuptake	SHT Reuptake	GABA Reuptake
A.	↓↓	0	0	↓↓
B.	0	↓↓↓↓	↓	0
C.	0	0	↓↓↓↓	0
D.	0	0	↓	↓↓↓↓
E.	↓↓↓↓	↓↓	0	0

15. A patient suffering from bipolar disorder (BD) becomes pregnant. A drug that has been shown to have some clinical value in alleviating symptoms of BD and that is unlikely to cause problems regarding fetal development is

A. carbamazepine
B. clonazepam
C. methylphenidate
D. phenytoin
E. valproic acid

16. A patient suffering from generalized anxiety disorder (GAD) has a history of drug dependence that includes the illicit use of secobarbital ("reds") and a variety of other drugs. Psychotherapy is indicated, but the physician also prescribes a drug that can be helpful in GAD and that has the advantage of no abuse liability. The drug prescribed was most likely to have been

A. bupropion
B. buspirone
C. baclofen
D. buprenorphine
E. phenobarbital

17. A patient has been diagnosed has having "long QT syndrome." Which one of the following drugs used in the management of eNS dysfunction is most likely to cause problems in this patient?

A. Diazepam
B. Ethosuximide
C. Fluoxetine
D. Buspirone
E. Thioridazine

18. A habitual user of a schedule-controlled drug abruptly stops using it. Within 8 h, she becomes anxious, starts to sweat, and gets severe abdominal pain with diarrhea. These symptoms intensify over the next 12 h, during which time she has a runny nose, is lacrimating, and has uncontrollable yawning and intensification of muscle cramping and jerking. Assuming that these are withdrawal symptoms in the patient due to her physical dependence, the drug most likely to be involved is

A. alprazolam
B. amphetamine
C. ethanol
D. meperidine
E. secobarbital

19. A hospital nurse is taking imipramine for a phobic anxiety disorder, and her patient is being treated with chlorpromazine for a psychotic disorder. Which of the following adverse effects is likely to occur in both of these individuals?

A. Excessive salivation
B. Pupillary constriction
C. Orthostatic hypotension
D. t Seizure threshold
E. Weight loss

20. A 30-year-old male patient is brought to the ER with the following symptoms attributed to a drug overdose: t HR and BP, mydriasis, behavioral excitation, aggressiveness, paranoia, and hallucinations. Of the following drugs, which one is most likely to be responsible for these symptoms?

A. Amphetamine
B. Ethanol
C. Fentanyl
D. Flunitrazepam
E. Marijuana

21. Which one of the following pairs of "drug/mechanism of action" is most accurate?

A. Carbamazepine/facilitation of the actions of GABA
B. Ethosuximide/blocks Na channels in axonal membranes
C. Phenelzine/inhibits dopa decarboxylase
D. Procainelblocks Ca channels (type T) in thalamic neurons
E. Lithium/inhibits recycling of inositol

22. A 57-year-old patient, living at home, has severe pain due to a metastatic carcinoma that is being managed with fentanyl, delivered transdermally from a patch. He should also be taking, or at least have on hand

A. apomorphine
B. docusate
C. loperamide
D. morphine
E. naloxone

Answers

1. **Answer: A.** ACh receptors in the eNS are present on less than 5% of the neuronal population. Most of them are of the muscarinic subtype, M_1 (excitatory) and M_2 (inhibitory), via G-protein coupled changes in cAMP. Nicotinic receptors are excitatory via direct coupling to cation channels (Na/K), and their activation does not initiate second messenger pathways. Other CNS transmitter receptors that are directly coupled to ion channels include those for GABA and glutamic acid. Almost all CNS receptors for DA, NE, 5HT, and opioid peptides are coupled to ion channels via second messenger systems.

2. **Answer:** C. Most benzodiazepines are metabolized by liver cytochrome P450. In a patient lacking liver function, benzodiazepines that are metabolized via extrahepatic conjugation (e.g., lorazepam, oxazepam) are safer in terms of the possibility of excessive CNS depression. Lorazepam is metabolized, probably in the lungs, via glucuronidation. Although benzodiazepine actions can be reversed, the drug that acts as an antagonist is tlumazenil, not naloxone.

3. **Answer: E.** Benzodiazepines interact with components of the GABA receptor-ehloride ion channel macromolecular complex. Binding of BZs leads to an increase in the frequency of chloride ion channel opening elicited by the inhibitory transmitter GABA. Benzodiazepines do not act on $GABA_B$ receptors; baclofen, a centrally acting muscle relaxant, is an agonist at these receptors. Buspirone, the selective anxiolytic, may be a partial agonist at 5HT receptors.

4. **Answer:** C. Morphine continues to be used in pulmonary congestion, in part because of its sedative (calming) and analgesic effects and also because of its vasodilating actions, which result in favorable hemodynamics in terms of cardiac and pulmonary function. Similarly, morphine is of value in an acute MI, especially its ability to relieve pain. However, morphine is not suitable for pain of biliary origin because it causes contraction of the sphincters of Oddi, leading to spasms. None of the other proposed indications are appropriate.

5. **Answer: D.** Although there is no information regarding the time lapse between phenobarbital ingestion and ER admission, we might "guess" that the blood level approximates COand is certainly no higher. With such an assumption, the dose ingested is given by:

$$\text{Dose} = CO \times V_d \div f = 50\ \text{mg/L} \times 40\ \text{L} \div 1$$

$$= 2{,}000\ \text{mg}$$

$$= 2\text{g}$$

6. **Answer:** E. Phenytoin has the unusual characteristic of following first-order elimination kinetics at low doses but zero-order kinetics at high doses because of saturation of the liver enzymes involved in its metabolism. It does not inhibit P450 but is an inducer of such drug-metabolizing enzymes, increasing their activities including those responsible for the inactivation of estrogenic steroids such as those used in oral contraceptives. Phenytoin is teratogenic, causing structural abnormalities during fetal development including cleft palate. Phenytoin blocks inactivated sodium channels, thereby prolonging the time to recovery.

7. **Answer: B.** Nalbuphine is an agonist at κ (kappa) opioid receptors and an antagonist at μ opioid receptors. Mixed agonist-antagonists can displace μ receptor agonists such as heroin from receptors, resulting in the rapid development of symptoms of withdrawal in patients who are physically dependent on such drugs-"precipitated withdrawal." Although cross-tolerance does occur between opioids, in the relief of pain this is overcome by increased dosage. Nalbuphine is superior to codeine as an analgesic, and any vasodilation that results would probably decrease blood loss.

8. **Answer:** C. Muscarinic receptor antagonists such as benztropine, trihexyphenidyl, and diphenhydramine are used to manage the reversible extrapyramidal dysfunction (e.g., pseudo-Parkinsonism) that results from treatment with drugs that block DA receptors in the striatum. Drugs that activate DA receptors, although theoretically possible, require doses that are toxic and exacerbate psychoses. Because the actions of DA in the striatum lead to inhibition of GABA-ergic neurons, drugs that activate GABA receptors are unlikely to be effective in this situation, although they may well have both anxiolytic and anticonvulsant properties.

9. **Answer:** C. In addition to blocking reuptake of NE and 5HT, pharmacodynamic actions of the tricyclic antidepressants include block of peripheral adrenergic and muscarinic receptors-the former resulting in postural hypotension and the latter, via mydriasis, exacerbating glaucoma. TCAs block the uptake of guanethidine into sympathetic nerve endings, decreasing its antihypertensive effects, and they may cause arrhythmias in overdose. They have no effect on the absorption of levodopa.

10. **Answer: C.** Lithium causes goiter in a significant number of patients; however, thyroid dysfunction does not occur in all such patients, and when it does it presents as hypothyroidism (not hyper-T), High-Na diets increase lithium elimination; low Na increases lithium plasma levels. Uncoupling of vasopressin receptors is characteristic of lithium, leading to a nephrogenic diabetes insipidus. Although potential teratogenicity is a concern during pregnancy, lithium does not cause neural tube defects but may cause abnormalities in heart valves. Lithium takes 10 to 20 days for effectiveness, and in acute mania it is often necessary to calm the patient with parenteral antipsychotic drugs such as fluphenazine or haloperidol.

11. **Answer:** C. Ethanol saturates alcohol dehydrogenase (ADH) at very low blood levels (zero-order elimination), preventing the conversion of methanol to formaldehyde, a toxic compound that can result in blindness. Ethanol (IV) continues to be used as an antidote in poisoning due to the ingestion of liquids containing methanol or ethylene glycol (antifreeze). Hemodialysis is also employed in management of methanol intoxication. Disulfiram (Antabuse) is an inhibitor of aldehyde dehydrogenase used in some alcohol rehabilitation programs, and naltrexone (an opioid antagonist) is approved for use in alcoholism because it decreases "craving." Delirium tremens is a characteristic of the withdrawal or abstinence syndrome in patients who have become physically dependent on ethanol.

12. **Answer: E.** Muscarinic receptor blockers may improve muscle rigidity and tremor in Parkinson disease but result in very little improvement in bradykinesia; thus, they are mainly considered as adjunctive to the use of drugs that improve dopaminergic function. Selegiline is the inhibitor of MAO type B, and pramipexole is a non-ergot DA receptor agonist. Carbidopa inhibits peripheral AAAD (dopa decarboxylase); tolcapone is an inhibitor of COMT. Levodopa causes a high incidence of dose-dependent dyskinesias that are not slow in onset, like tardive dyskinesia that results from chronic administration of DA receptor blockers.

13. **Answer: C.** The patient is probably taking an SSRI such as paroxetine. SSRIs rarely cause sedation and commonly cause agitation and the "jitters," which sometimes necessitates concomitant use of drugs that are strongly sedating, such as trazodone. SSRIs are best taken in the morning to avoid problems of .insornnia, and they appear to cause weight loss, at least during the first 12 months of treatment, Severe drug interactions leading to the "serotonin syndrome" have been reported when SSRIs have been used together with MAO inhibitors, tricyclics, certain opioids, and even recreational or illicit drugs.

14. **Answer:** C. Drug C appears to be a selective inhibitor of the reuptake of serotonin, and existing drugs of this class (SSRIs) are approved for use in both major depressive and obsessive-compulsive disorders. The tricyclic antidepressant clomipramine, a potent inhibitor of 5HT reuptake, was formerly the drug of choice for OCD until replaced by the SSRIs. Drugs A and C may have value in the treatment of Parkinson disease because they block the reuptake of DA. Drug D may be effective in anxiety and seizure states because it is an effective blocker of *GABA* reuptake.

15. **Answer: B.** Symptoms of bipolar disorder, particularly those related to the manic phase, can be suppressed by several drugs that are commonly used for seizure disorders. Some of these drugs are teratogenic, including carbamazepine, phenytoin, and valproic acid, and are contraindicated in pregnancy. Clonazepam, a benzodiazepine, has not been reported to be teratogenic. Methylphenidate is used in attention deficit disorder and has not been shown to have value in bipolar disorder. Recently, the anticonvulsant gabapentin has been shown to be effective in bipolar disorders.

16. **Answer: B.** Buspirone has selective anxiolytic activity that is slow in onset. The drug has no abuse liability and will not suppress withdrawal symptoms in patients who have become physically dependent on barbiturates, benzodiazepines, or ethanol. Bupropion is an antidepressant, also approved for management of dependence on nicotine. Baclofen is a spinal cord muscle relaxant that activates $GABA_B$ receptors. Buprenorphine is a long-acting opioid analgesic with no effectiveness in GAD, and phenobarbital is a barbiturate that may cause dependence.

17. **Answer: E.** Thioridazine is distinctive because it is the only phenothiazine that has significant cardiotoxic potential. In high or toxic dose, it exerts a "quinidine-like" action on the heart, increasing APD and ERP, effects that have resulted in cardiac arrhythmias. Patients with long QT syndrome have a genetic flaw in cardiac inward rectifying K current, leading to increased APD. Drugs that accentuate this by inhibiting the repolarizing K current (phase 3), which include thioridazine and the tricyclic antidepressants, are likely to have enhanced cardiotoxic potential in such patients.

18. **Answer: D.** The signs and symptoms described are typical of withdrawal from physical dependency on an opioid that has efficacy equivalent to a full agonist-in this case, meperidine. Although anxiety, agitation, and even muscle jerking may occur in withdrawal from dependence on sedative-hypnotics such as alprazolam and secobarbital, the symptoms of GI distress, rhinorrhea, lacrimation, and yawning are not characteristic (seizures are more typical). Symptoms of withdrawal from high-dose use of CNS stimulants such as amphetamine or cocaine include lassitude and severe depression of mood. The phrase "schedule-controlled" refers to FDA classifications of drugs that have abuse liability, including both licit and illicit drugs.

19. **Answer:** C. Orthostatic hypotension occurs with both tricyclic antidepressants and phenothiazines because both types of drug can block alpha-adrenergic receptors in venous beds. Their ability to block M receptors leads to xerostomia (not salivation) and mydriasis (not miosis). Tricyclics and phenothiazines also share a common tendency to decrease seizure threshold and cause weight gain (not loss).

20. Answer: A. The signs and symptoms are characteristic of a CNS stimulant that facilitates the activity of amines in both the CNS and the periphery. Amphetamines promote the release of NE from sympathetic nerve endings, causing CV stimulation and pupillary dilation. In the CNS, they enhance the actions of DA, NE, and 5HT, causing behavioral excitation and a psychotic state that may be difficult to distinguish from schizophrenia. Ethanol, marijuana, fentanyl, and tlunitrazepam (a benzodiazepine that has been used in "date rape") are all CNS depressants.

21. Answer: E. Lithium inhibits the dephosphorylation of IP_z (needed for the recycling of inositol), leading to depletion of membrane PIPz' Consequently, the activation of receptors by neurotransmitters such as ACh, NE, and 5HT fails to release the second messengers IP3 and DAG. Carbamazepine and the local anesthetic procaine block axonal Na channels; ethosuximide may block Ca channels in thalamic neurons. Phenelzine is a nonselective inhibitor of MAO.

22. Answer: B. Fentanyl is a full agonist at opioid receptors and provides analgesia in cancer pain equivalent to morphine, so there is no good reason to have morphine on hand, and it would be a danger to the patient in terms of accidental overdose. Apomorphine is an emetic, hardly appropriate given the stimulatory effects of opioids on the emetic center. Likewise, loperamide is used in diarrheal states, and patients on strong opioids are almost certain to be constipated; for this reason, a stool softener like docusate should be available to the patient. The opioid antagonist naloxone is used IV in overdose situations but would not be provided to the patient for use PRN.

SECTION V

Antimicrobial Agents

1 Antibacterial Agents

PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

- Bactericidal
- Bacteriostatic
- Combinations:
  - Additive
  - Synergistic (penicillins plus aminoglycosides)
  - Antagonistic (penicillin plus tetracyclines)
- Mechanisms:

Table V-I-I. Mechanism of Action of Antimicrobial Agents

Mechanism of Action	Antimicrobial Agents
Inhibition of bacterial cell-wall synthesis	Penicillins. cephalosporins, imipeneml meropenem, aztreonam, vancomycin
Inhibition of bacterial protein synthesis	Aminoglycosides, chloramphenicol, macrolides, tetracyclines, streptogramins, linezolid
Inhibition of nucleic synthesis	Fluoroquinolones, rifampin
Inhibition of folic acid synthesis	Sulfonamides, trimethoprim, pyrimethamine

- Resistance:

Table V-I-2. Mechanisms of Resistance to Antimicrobial Agents

Antimicrobial Agents	Primary Mechanism(s) of Resistance
Penicillins and cephalosporins	Production of beta-lactamases, which cleave the beta-lactam ring structure; change in penicillin-binding proteins; change in porins
Aminoglycosides (gentamicin, streptomycin, amikacin, etc.)	Formation of enzymes that inactivate drugs via conjugation reactions that transfer acetyl, phosphoryl, or adenylyl groups
Macrolides (erythromycin, azithromycin, clarithromycin, etc.) and clindamycin	Formation of methyltransferases that alter drug binding sites on the 50S ribosomal subunit Active transport out of cells
Tetracyclines	Increased activity of transport systems that "pump" drugs out of the cell
Sulfonamides	Change in sensitivity to inhibition of target enzyme; increased formation of PABA;use of exogenous folic acid
Fluoroquinolones	Change in sensitivity to inhibition of target enzymes; increased activity of transport systems that promote drug efflux
Chloramphenicol	Formation of inactivating acetyltransferases

INHIBITORS OF CELL-WALL SYNTHESIS

- All cell-wall synthesis inhibitors are bactericidal.

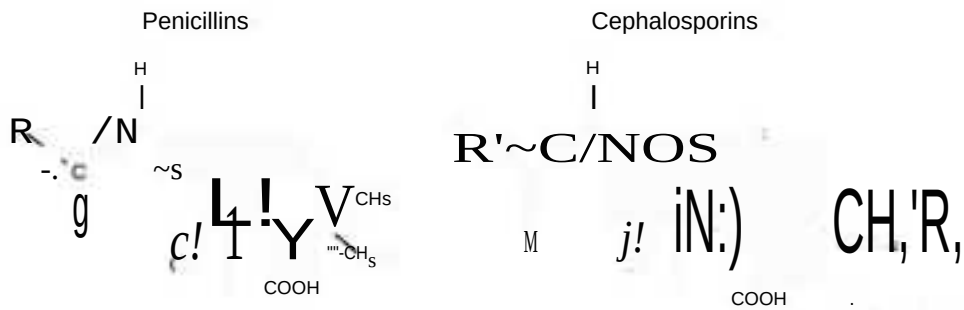

Figure V-1-1. Beta-Lactam Antibiotics

Penicillins

- Mechanisms of action:
  - Bacterial cell wall is cross-linked polymer of polysaccharides and pentapeptides
  - Penicillins interact with cytoplasmic membrane-binding proteins (PBPs) to inhibit transpeptidation reactions involved in cross-linking, the final steps in cell-wall synthesis
- Mechanisms of resistance:
  - Penicillinases (beta-lactamases) break lactam ring structure (e.g., staphylococci)
  - Structural change in PBPs (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA], penicillin-resistant pneumococci)
  - Change in porin structure (e.g., *Pseudomonas)*
- Subgroups and antimicrobial activity:
  - Narrow spectrum, beta-lactamase sensitive: penicillin G and penicillin V
    - Spectrum: streptococci, pneumococci, meningococci, *Treponema pallidum*
  - Very narrow spectrum, beta-lactamase resistant: nafcillin, methicillin, oxacillin
    - Spectrum: known or suspected staphylococci (not MRSA)
  - Broad spectrum, aminopenicillins, beta-lactamase sensitive: ampicillin and amoxicillin
    - Spectrum: gram-positive cocci (not staph), *E. coli,* H. *influenzae, Listeria monocytogenes* (ampicillin), *Borrelia burgdorferi* (amoxicillin), H. *pylori* (amoxicillin)
    - Activity enhanced if used in combination with inhibitors of beta lactamase: clavulanic acid, sulbactam
    - Synergy with aminoglycosides against enterococcal species
  - Extended spectrum, antipseudomonal, beta-lactamase sensitive: ticarcillin, piperacillin, azlocillin
    - Spectrum: increased activity against gram-negative rods, including *Pseudomonas aeruginosa*
    - Activity enhanced if used in combination with beta-lactamase inhibitors
    - Synergy with aminoglycosides against pseudomonal species
- Pharmacokinetics:
  - Most are eliminated via active tubular secretion with half-life <60 min; dose reduction needed only in major renal dysfunction
  - Nafcillin and oxacillin eliminated largely in bile; ampicillin undergoes enterohepatic cycling, but excreted by the kidney
  - Benzathine penicillin G-repository form (half-life of 2 weeks)
- Side effects:
  - Hypersensitivity
    - Incidence 5 to 7% with wide range of reactions (types I-IV). Urticarial skin rash common, but severe reactions, including anaphylaxis, are possible.
    - Interstitial nephritis with methicillin
    - Assume complete cross-allergenicity between individual penicillins
  - Other:
    - GI distress (NVD), especially ampicillin
    - Jarisch-Herxheimer reaction in Rx of syphilis

Suicide Inhibitors

Metabolism of a substrate by an enzyme to form a compound that irreversibly inhibits that enzyme. Penicillinase inhibitors, such as clavulanic acid and sulbactam, are suicide inhibitors.

Drug Hypersensitivity Reactions

I. IgE mediated-rapid onset; anaphylaxis, angioedema, laryngospasm

II. IgM and IgG antibodies fixed to cells-vasculitis, neutropenia, positive Coombs test

III. Immune complex formation-vasculitis, serum sickness, interstitial nephritis

IV. T-cell mediated-urticarial and maculopapular rashes, Stevens-Johnson syndrome

Cephalosporins

- Mechanisms of action and resistance: identical to penicillins
- Subgroups and antimicrobial activity:
  - First generation: cefazolin, cephalexin
    - Spectrum: gram-positive cocci (not MRSA), *E. coli*, *Klebsiella pneumoniae*, and some *Proteus* species
    - Common use in surgical prophylaxis
    - Pharmacokinetics: none enter CNS
  - Second generation: cefotetan, cefaclor, cefuroxime
    - Spectrum: ↑ gram-negative coverage, including some anaerobes
    - Pharmacokinetics: no drugs enter the CNS, except cefuroxime
  - Third generation: ceftriaxone (IM) and cefotaxime (parenteral), cefdinir and cefixime (oral)
    - Spectrum: gram-positive and gram-negative cocci, plus many gram-negative rods
    - Pharmacokinetics: most enter CNS (not cefoperazone); important in empiric management of meningitis and sepsis
  - Fourth generation: cefepime (IV)
    - Even wider spectrum
    - Resistant to most beta-lactamases
    - Enters CNS
- Pharmacokinetics:
  - Renal clearance similar to penicillins, with active tubular secretion blocked by probenecid
  - Dose modification in renal dysfunction
  - Cefoperazone and ceftriaxone are largely eliminated in the bile
- Side effects:
  - Hypersensitivity:
    - Incidence: 2%
    - Wide range, but rashes and drug fever most common
    - Positive Coombs test, but rarely hemolysis
    - Assume complete cross-allergenicity between individual cephalosporins and partial cross-allergenicity with penicillins (about 5%)
    - Most authorities recommend avoiding cephalosporins in patients allergic to penicillins (for gram-positive organisms, consider macrolides; for gram-negative rods, consider aztreonam)
  - Other:
    - Disulfiram-like effect: cefotetan, cefoperazone, and cefamandole
    - Hypoprothrombinemia

Classic Clues

Organisms *not* covered by cephalosporins are "LAME":

Listeria monocytogenes

Atypicals (e.g., *Chlamydia, Mycoplasma)*

MRSA

Enterococci

Imipenem and Meropenem

- Mechanism of action:
  - Same as penicillins and cephalosporins
  - Resistant to beta-lactamases
- Spectrum:
  - Gram-positive cocci, gram-negative rods (e.g., *Enterobaaer; Pseudomonas* spp.), and anaerobes
  - Important in-hospital agents for empiric use in severe life-threatening infections
- Pharmacokinetics:
  - Both drugs are only used IV
  - Imipenem is given with cilastatin, which inhibits its rapid metabolism by renal dehydropeptidase
  - Both drugs undergo renal elimination- J, dose in renal dysfunction
- Side effects:
  - GI distress
  - Drug fever (partial cross-allergenicity with penicillins)
  - CNS effects, including seizures with imipenem in overdose or renal dysfunction

Aztreonam

- Mechanism of action:
  - Same as for penicillins and cephalosporins
  - Resistant to beta-lactamases
- Uses:
  - IV drug mainly active versus gram-negative rods
  - No cross-allergenicity with penicillins or cephalosporins

Vancomycin

- Mechanism of action:
  - Binding at the D-ala-D-ala muramyl pentapeptide to sterically hinder the transglycosylation reactions involved in elongation of peptidoglycan chains
  - Does not interfere with PBPs
- Spectrum:
  - MRSA
  - Enterococci
  - *Clostridium difficile* (backup drug)
- Resistance:
  - Vancomycin-resistant staphylococcal (VRSA) and enterococcal (VRE) strains emerging
  - Enterococcal resistance involves change in the muramyl pentapeptide "target," such that the terminal D-ala is replaced by D-Iactate
- Pharmacokinetics:
  - Used IV and orally (not absorbed) in colitis
  - Enters most tissues (e.g., bone), but not CNS

- Eliminated by renal filtration (important to decrease dose in renal dysfunction)
- Has a long half-life

• Side effects:

- "Red man syndrome" (histamine release)
- Ototoxicity (usually permanent, additive with other drugs)
- Nephrotoxicity (mild, but additive with other drugs)

INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

• Site of action:

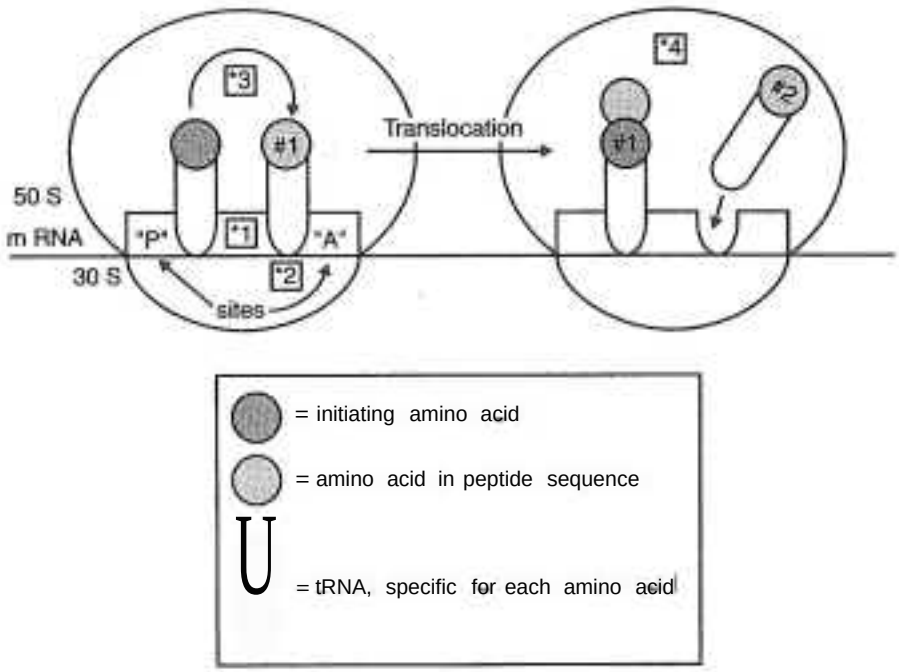

Figure V-1-2. **Bacterial Protein Synthesis**

- Mechanisms:

Table V-I-3. Summary of Mechanisms of Protein Synthesis Inhibition

Event	Antibiotic(s) and Binding Site(s)	Mechanism(s)
1. Formation of initiation complex	Aminoglycosides (30S) Linezolid (50S)	Interfere with initiation codon functions-block association of 50S ribosomal subunit with mRNA-30S (static); misreading of code (aminoglycosides only)-incorporation of wrong amino acid (-cidal)
2. Amino-acid incorporation	Tetracyclines (30S) Dalfopristin/ quinupristin (50S)	Block the attachment of aminoacyl tRNA to acceptor site (-static)
3. Formation of peptide bond	Chloramphenicol (50S)	Inhibit the activity of peptidyltransferase (-static)
4. Translocation	Macrolides and clindamycin (50S)	Inhibit translocation of peptidyl-tRNA from acceptor to donor site (-static)

- For mechanisms of resistance of antibiotics, see Table V-1-2 on page 182.

Aminoglycosides

- Activity and clinical uses:
  - Bactericidal, accumulated intracellularly in microorganisms via an 02-dependent uptake -7 anaerobes are innately resistant
  - Useful spectrum includes gram-negative rods; gentamicin, tobramycin, and amikacin, often used in combinations
  - Synergistic actions occur for infections caused by enterococci (with penicillin G or ampicillin) and *P. aeruginosa* (with an extended-spectrum penicillin or third-generation cephalosporin)
  - Streptomycin, used in tuberculosis; is the DOC for bubonic plague and tularemia
  - Neomycin too toxic for systemic use; used topically
- Pharmacokinetics:
  - Are polar compounds, not absorbed orally or widely distributed into tissues
  - Renal elimination proportional to GFR, and major dose reduction needed in renal dysfunction
- Side effects:
  - Nephrotoxicity (6 to 7% incidence) includes proteinuria, hypokalemia, acidosis, and acute tubular necrosis-usually reversible, but enhanced by vancomycin, amphotericin B, cisplatin, and cyclosporine
  - Ototoxicity (2% incidence) from hair cell damage; includes deafness (irreversible) and vestibular dysfunction (reversible); toxicity may be enhanced by loop diuretics

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Once-Daily Dosing of Aminoglycosides

Antibacterial effects depend mainly on peak drug level (rather than time) and continue with blood levels < MIC-a postantibiotic effect (PAE).

Toxicity depends both on blood level and the time that such levels are> than a specific threshold (i.e., total dose).

- Neuromuscular blockade with ↓ release of ACh-may enhance effects of skeletal muscle relaxants
- Contact dermatitis (neomycin)

Tetracyclines

- Activity and clinical uses:
  - Bacteriostatic drugs, actively taken up by susceptible bacteria
  - "Broad-spectrum" antibiotics, with good activity versus chlamydial and mycoplasmal species, H. *pylori* (GI ulcers), *Rickettsia, Borrelia burgdorferi; Brucella,* and *Vibrio*
  - Continued use prophylactically in chronic bronchitis and for acne
  - Backup to penicillin G in syphilis
- Specific drugs:
  - **Doxycycline:** more activity overall than tetracycline HCl and has particular usefulness in prostatitis because it reaches high levels in prostatic fluid
  - **Minocycline:** in saliva and tears at high concentrations and used in the meningococcal carrier state
  - **Demeclocycline:** used in syndrome of inappropriate secretion of ADH (SIADH; blocks ADH receptor function in collecting ducts)
- Pharmacokinetics:
  - Kidney for most (↓ dose in renal dysfunction)
  - Liver for doxycycline
  - Chelators: tetracyclines bind divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}), which ↓ their absorption
- Side effects:
  - Tooth enamel dysplasia and possible ↓ bone growth in children (avoid)
  - Phototoxicity (demeclocycline, doxycycline)
  - GI distress (NVD), superinfections leading to candidiasis or colitis
  - Vestibular dysfunction (minocycline)
  - Have caused liver dysfunction during pregnancy at very high doses (contraindicated)

Classic Clues

Phototoxicity

- Tetracyclines
- Sulfonamides
- Quinolones

Chloramphenicol

- Activity and clinical uses:
  - Bacteriostatic with a wide spectrum of activity
  - Currently a backup drug for infections due to *Salmonella typhi, B. fragilis, Rickettsia,* and possibly in bacterial meningitis
- Pharmacokinetics:
  - Orally effective, with good tissue distribution, including CSF
  - Metabolized by hepatic glucuronidation, and dose reductions are needed in liver dysfunction and in neonates
  - Inhibition of cytochrome P450
- Side effects:
  - Dose-dependent bone marrow suppression common; aplastic anemia rare (1 in 35,000)
  - "Gray baby" syndrome in neonates (↓ glucuronosyl transferase)

Macrolides

- Drugs: erythromycin, azithromycin, clarithromycin
- Activity and clinical uses:
  - Macrolides are wide-spectrum antibiotics
  - Erythromycin:
    - Gram-positive cocci (not MRSA)
    - Atypical organisms *(Chlamydia, Mycoplasma, and Ureaplasma* species)
    - *Legionella pneumophila*
    - *Campylobacter jejuni*
  - Azithromycin:
    - Similar spectrum, but is more active in respiratory infections, including *Mycobacterium avium-intracellulare*
  - Clarithromycin:
    - Has > activity against M. *avium* and H. *pylori*
- Pharmacokinetics:
  - Erythromycin and clarithromycin are metabolized by the liver and excreted through the bile
  - They inhibit cytochrome P450s
  - They are not safe in pregnancy
  - Azithromycin is excreted by the kidney
  - It does not inhibit cytochrome P450
  - It is safer in pregnancy
- Side effects:
  - Macrolides stimulate motilin receptors and cause gastrointestinal distress (erythromycin, azithromycin > clarithromycin)
  - Macrolides cause reversible deafness at high doses
  - Erythromycin estolate causes cholestasis, jaundice

Community-Acquired Pneumonia

With **no** comorbidity, the most common organisms associated with community-acquired pneumonia are *M. pneumoniae,* C *pneumoniae,* and viruses. In smokers, the pneumococcus is a more frequent pathogen. Macrolide antibiotics have activity against most strains of these organisms (other than viruses) and are therefore commonly used in the treatment of a community-acquired pneumonia.

Clindamycin

- Not a macrolide, but has the same mechanisms of action and resistance
- Narrow spectrum: gram-positive cocci (not MRSA) and anaerobes, including *B. fragilis* (backup drug); has also been used in toxoplasmosis
- Concentration in bone has clinical value in osteomyelitis due to gram-positive cocci
- First known drug to cause pseudomembranous colitis

Clinical Correlate

Don't Use in Pregnancy

Aminoglycosides, erythromycin estolate, c1arithromycin, fluoroquinolones, sulfonamides, tetracyclines

linezolid

- Mechanism of action:
  - Inhibits the formation of the initiation complex in bacterial translation systems by preventing formation of the N-formylmethionyl-tRNA-ribosome-mRNA ternary complex
- Spectrum:
  - Treatment ofVRSA, VRE, and drug-resistant pneumococci
- Side effects: bone marrow suppression (platelets)

Note

- Streptogramins for *E faecium*, including VRE faecium, but not for *E faecalis*
- Linezolid for both types of enterococci

Quinupristin-Dalfopristin

- Mechanism of action:
  - Quinupristin and dalfopristin--streptogramins that act in concert via several mechanisms
  - Binding to sites on 50S ribosomal subunit, they prevent the interaction of amino-acyl-tRNA with acceptor site and stimulate its dissociation from ternary complex
  - May also decrease the release of completed polypeptide by blocking its extrusion
- Spectrum:
  - Used parenterally in severe infections caused by vancomycin-resistant staphylococci (VRSA) and enterococci (VRE), as well as other drug-resistant, gram-positive cocci
- Side effects:
  - Toxic potential remains to be established

!!td,j~~,,!!~~'~!~INHIBITORS OF NUCLEIC ACID SYNTHESIS

Antimetabolites

Definftmn:asub~ance inhibiting cell growth by competing with, or sub~ituting for, a natural substrate in an enzymatic process

Sulfonamides and trimethoprim are antimetabolites, as are many antiviral agents and drugs used in cancer chemotherapy.

Inhibitors of Folic Acid Synthesis

- Drugs: sulfonamides, trimethoprim, and pyrimethamine

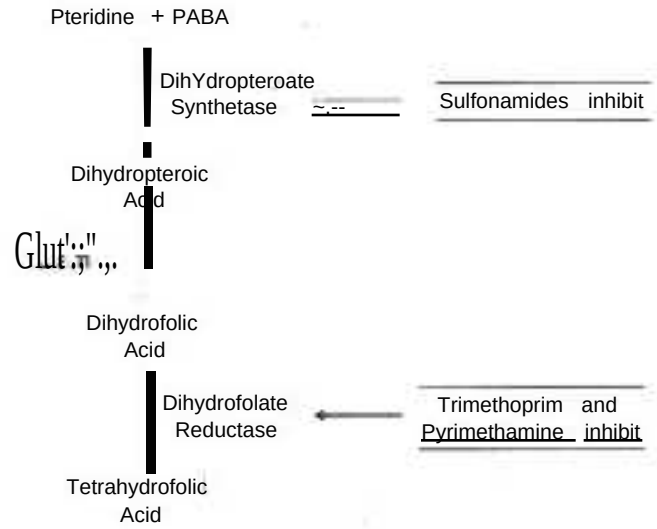


Figure V-1-3.Inhibitors of Folic Acid Synthesis

- Activity and clinical uses:
  - Sulfonamides alone are limited in use because of multiple resistance
  - Sulfasalazine used as prodrug of salicylate in ulcerative colitis and rheumatoid arthritis
  - Ag sulfadiazine used in burns

- Combination with dihydrofolate reductase inhibitors:
  - ↓ resistance
  - Synergy
- Uses of trimethoprim-sulfamethoxazole (cotrimoxazole):
  - Bacteria:
    - DOC in *Nocardia*
    - Mycobacteria
    - Gram-negative infections *(E. coli, Salmonella, Shigella,* H. *influenzae)*
    - Gram-positive infections *(Staph., Strep.)*
  - Fungus: *Pneumocystis carinii*
  - Protozoa: *Toxoplasma gondii* (sulfadiazine + pyrimethamine)

- Pharmacokinetics:
  - Sulfonamides are hepatically acetylated (conjugation)
  - Renally excreted metabolites cause crystalluria (older drugs)
  - High protein binding
    - Drug interaction
    - Kernicterus in neonates (avoid in third trimester)
- Side effects:
  - Sulfonamides
    - Hypersensitivity (rashes, Stevens-Johnson syndrome)
    - Phototoxicity
    - Gastrointestinal distress
    - Hemolysis in G6PD deficiency
  - Trimethoprim, or pyrimethamine
    - Bone marrow suppression
    - Enterocolitis

Direct Inhibitors of Nucleic Acid Synthesis: Quinolones

- Drugs: norfloxacin, ciprofloxacin, ofloxacin, and other "-oxacins"
- Mechanisms of action:
  - Quinolones are bactericidal and interfere with DNA synthesis
  - Inhibit topoisomerase II (DNA gyrase) and topoisomerase IV (responsible for separation of replicated DNA during cell division)
  - Resistance is increasing
- Activity and clinical uses:
  - Urinary tract infections (UTIs), particularly when resistant to cotrimoxazole
  - Sexually transmitted diseases (STDs)/pelvic inflammatory diseases (PIDs): chlamydia (ofloxacin), gonorrhea (ciprofloxacin,ofloxacin)
  - Skin, soft tissue, and bone infections by gram-negative organisms (all, except norfloxacin)
  - Diarrhea to *Shigella, Salmonella,* E. *coli, Campylobacter* (any quinolone)
  - Drug-resistant pneumococci (levofloxacin)

Note

The activity of quinolones includes *Bacillus anthracis.* Anthrax can also be treated with penicillins or tetracyclines.

- Pharmacokinetics:
  - Iron, calcium limit their absorption
  - Eliminated mainly by kidney by filtration and active secretion (inhibited by probenecid)
  - Reduce dose in renal dysfunction
- Side effects:
  - Gastrointestinal distress
  - Phototoxicity, rashes
  - Tendonitis, tendon rupture
  - CNS effects (insomnia, dizziness, headache)
  - All quinolones ↑ QT interval
  - Contraindicated in pregnancy and in children (inhibition of chondrogenesis)

UNCLASSIFIED ANTIBIOTIC: METRONIDAZOLE

- Possibly producing free radicals, bactericidal
- Antiprotozoal: *Giardia, Trichomonas, Entamoeba*
- Antibacterial: strong activity against most anaerobic gram-negative *Bacteroides* species and *Clostridium* species (DOC in pseudomembranous colitis)
- Side effects:
  - Stomatitis, metallic taste, cystitis
  - Nausea, diarrhea
  - Disulfiram-like effect
  - Reversible peripheral neuropathy

Clinical Correlate

Antibiotics for *H. pylori* Gastrointestinal Ulcers

- "BMT" regimen: bismuth, metronidazole, and tetracycline
- Clarithromycin, amoxillin, omeprazole

ANTITUBERCULAR DRUGS

- Combination drug therapy is the rule to delay or prevent the emergence of resistance and to provide additive (possibly synergistic) effects against *Mycobacterium tuberculosis.*
- The primary drugs in combination regimens are isoniazid (INH), rifampin, ethambutol, and pyrazinamide. Regimens may include two to four of these drugs, but in the case of highly resistant organisms, other agents may also be required. Backup drugs include aminoglycosides (streptomycin, amikacin, kanamycin), fluoroquinolones, capreomycin (marked hearing loss), and cycloserine (neurotoxic).
- Prophylaxis: usually INH, but rifampin if intolerant. In suspected multidrug resistance, both drugs may be used in combination.

Note

Mycobacterium avium-intracellulare (MAC)

- *Prophylaxis:* azithromycin (1 x week) or clarithromycin (daily)
- *Treatment:* clarithromycin + ethambutol ± rifabutin

- Mechanisms of action, resistance, and side effects:

Table V-I-4. Sununary of the Actions, Resistance, and Side Effects of the Antitubercular Drugs

Drug	Mechanisms of Action and Resistance	Side Effects
Isoniazid (INH)	▪ Inhibits mycolic acid synthesis ▪ Prodrug requiring conversion by catalase ▪ High level resistance--deletions in *katG* gene (encodes catalase needed for INH bioactivation) ▪ Low-level resistance--deletions in *inhA* gene (encodes acyl carrier protein, the "target")	▪ Hepatitis (age-dependent) ▪ Peripheral neuritis (use vitamin B_6) ▪ Sideroblastic anemia (use vitamin B_6) ▪ Hemolysis in G6PD deficiency ▪ SLE in slowacetylators (rare)
Rifampin	▪ Inhibits DNA-dependent RNA polymerase (nucleic acid synthesis inhibitor) ▪ Resistance via change in enzyme	▪ Hepatitis ▪ Induction of P450 ▪ Red-orange metabolites
Ethambutol	▪ Inhibits synthesis of arabingalactan (cell-wall component)	▪ Dose-dependent retrobulbar neuritis → ↓ visual acuity and red-green discrimination
Pyrazinamide	▪ Unknown, but metabolically activated by bacteria-strains lacking the bioactivating enzyme are resistant	▪ Hepatitis ▪ Polyarthralgia ▪ Myalgia ▪ Rash ▪ Hyperuricemia ▪ Phototoxicity ▪ ↓ Porphyrin synthesis
Streptomycin	▪ Protein synthesis inhibition *(see* Aminoglycoside, pages 187-188)	▪ Deafness ▪ Vestibular dysfunction ▪ Nephrotoxicity

Clinical Correlate

INH Prophylaxis

- Exposure, TST-negative, young children
- TST conversion in past 2 years
- Tuberculin reactors with high risk: e.g., diabetes, immunosuppressive Rx, prolonged glucocorticoid Rx, HIV-positive, leukemia

Chapter Summary

Basic Principles

Antibacterial drugs can be enher bactericidal or baderiostatc The effectiveness of bacteriostatic drugs depends on an intact host immune system. Antimicrobial agents may be administered singly or in combination. Some combinations induce synergy and/or delay emergence of resistance.

An antimicrobial agent should have maximal toxicity toward the infecting agent and minimal toxic~ for the host Table V-l-l summarizes the five basic antibacterial actions demonstrated by antibiotics and the agents working by each of these mechanisms.

Microbial resistance can occur by the gradual selection of resistant mutants or more usually by R-factor transmission between bacteria. Table V-1-2 summarizes the common modes of resistance exhibited by microorganisms against the various classes of antimicrobial agents.

Inhibitors of Bacterial Cell-Wall Synthesis

The inhib~ors of bacterial cell-wall synthesis are the beta-Iactam antibiotics (the penicillins and cephalosporins; Figure V-l-l), the carbapenems, vancomycin, and aztreonam.

The mechanisms of action of penicillins, the bacterial modes of resistance to penicillins, the penicillin subgroups, their biodisposition, and side effects are provided. The subgroups discussed are the penicillins that are ~-Iactamase susceptible with a narrow spectrum of activity; ~-Iactamase-resistant penicillins that have a very narrow spectrum of activity; and ~-Iactamase-susceptible penicillins that have a wider spectrum of activity. The common penicillins and their susceptible organisms are listed for each subgroup.

The same parameters are considered for the cephalosporins. These have the same mode of action as the penicillins and also require an intact ~-Iactam ring structure for activ~. There are four generations of cephalosporins. Each is considered in terms of range of activity, susceptibility to resistance, clinical usage, and specific antibiotics in that class.

Imipenem and meropenem have the same mode of antibacterial action as the penicillins and cephalosporins but structurally are carbapenems that have the ~-Iactam ring. Their clinical uses, routes of elimination, and side affects are considered.

Aztreonam is a monobactam inhibitor of early cell-wall synthesis. It is used primarily as an intravenous drug against gram-negative rods.

Vancomycin inhib~ an early stage of cell-wall synthesis. It has a relatively narrow range of activity, but as yet, resistance is uncommon. Its use, excretion, and side effects are considered.

Inhibitors of Bacterial Protein Synthesis

Figure V-1-2 illustrates the mechanisms of bacterial protein synthesis, and Table V-1-3 summarizes the places in the translatory sequence, as well as the mechanisms by which antibiotics operate to disrupt protein synthesis.

The aminoglycosides (e.g., gentamicin and tobramycin) inhibit initiation complex formation. Their uses and properties are discussed. Streptomycin is particularly useful in the treatment of tuberculosis and is the drug of choice for treating bubonic plague and tularemia. Neomycin is toxic and can only be used topically.

(Continued)

Chapter Summary *(contd)*

The tetracyclines block the attachment of aminoacyl tRNA to the acceptor site on the bacterial ribosome. They are broad-spectrum drugs with good activity against chlamydial and mycoplasmal species, as well as against other indicated bacteria. Doxycycline is of particular use in the treatment of prostatitis, minocycline is useful for treating meningococcal carrier states, and demeclocycline is useful for treating the syndrome of inappropriate secretion of ADH (SIADH). Their biodisposition and side effects are discussed.

Chloramphenicol inhibits the activity of peptidyltransferase and is currently used primarily as a backup drug. Its activity, clinical use, and side effects are considered.

The macrolides (e.g., erythromycin, c1arithromycin, and azithromycin) are translocation inhibitors. Their spectrums of activity, clinical uses, biodisposition, and side effects are considered. C1indamycin is not a macrolide but shares the same mechanism of action.

Linezolid inhibits initiation by blocking formation of the N-formyl-methionyl-tRNA-ribosome-mRNA ternary complex. The clinical uses and side effects of this new drug are mentioned.

Quinupristin and dalfopristin bind to the 50S ribosomal subunit, where they interfere with the interaction of aminoacyl-tRNA and the acceptor site and also stimulate its dissociation from the ternary complex. Their clinical use and side effects are discussed.

Antibiotics That Inhibit Folic Acid Synthesis and Nucleic Acid Metabolism

The sulfonamides compete with para-aminobenzoic acid (PABA) as shown in Rgure V-1-3. The methods bacteria use to develop resistance to the sulfonamides, their activity and clinical uses, biodisposition, and side effects are considered.

Trimethoprim (TMP), a folate analog and inhibitor of dihydrofolate reductase (Rgure V-1-3), is usually used together with sulfamethoxazole (SMX). The simultaneous inhibition of the tetrahydrofolate synthesis pathway at two steps has a synergistic effect and prevents the rapid generation of resistance. The clinical uses and side effects of TMP-SMX are discussed.

The fluoroquinones (e.g., ciprofloxacin) are nalidixic acid analogs that inhibit topoisomerase II (DNA gyrase) and topoisomerase IV. Their clinical use, the relevant drugs in this class, their biodisposition, and side effects are reported.

The exact mode of metronidazole action is unknown. Its use as an antiprotozoal and antibacterial drug is discussed, as are its side effects.

Antitubercular Drugs

Infections caused by *Mycobacterium tuberculosis* are treated with combination therapy. The primary drugs used are isoniazid, rifampin, ethambutol, , and pyrazinamide. Highly resistant organisms may require the use of additional agents. Backup drugs include streptomycin, fluoroquinolones, capreomycin, and cycloserine.

Table V-1-4 summarizes the actions, resistance, and side effects of the antitubercular drugs.

Antifungal Agents

2

Polyenes (Amphotericin B [Amp B], Nystatin)

- Mechanisms:
  - Amphoteric compounds with both polar and nonpolar structural components—interact with **ergosterol** in fungal membranes to form artificial "pores:' which disrupt membrane permeability
  - Resistant fungal strains appear to have low ergosterol content in their cell membranes
- Activity and clinical uses:
  - Amphotericin B has wide fungicidal spectrum; remains the DOC (or co-DOC) for severe infections caused by *Aspergillus, Candida, Cryptococcus, Histoplasma, Mucor,* and *Sporothrix.*
  - Amphotericin B—synergistic with flucytosine in candidiasis and cryptococcoses
  - Nystatin (too toxic for systemic use)-used topically for localized infections (e.g., candidiasis)
- Pharmacokinetics:
  - Amphotericin B given by slow IV infusion-poor penetration into the CNS (intrathecal possible)
  - Slow clearance (half-life >2 weeks) via both metabolism and renal elimination
- Side effects:
  - Infusion-related
    - Fever, chills, muscle rigor, hypotension (histamine release) occur during IV infusion (a test dose is advisable)
    - Can be alleviated partly by pretreatment with NSAIDs, antihistamines, meperidine, and adrenal steroids
  - Dose dependent
    - Nephrotoxicity includes ↓ GFR, tubular acidosis, ↓ K^+ and Mg^{2+}, and anemia through ↓ erythropoietin
    - Protect by Na^+ loading, use of liposomal amphotericin B, or by drug combinations (e.g., + flucytosine), permitting ↓ in amphotericin B dose

Azoles (Ketoconazole, Fluconazole, Itraconazole)

- Mechanism:
  - "Azoles" are fungicidal and interfere with the synthesis of ergosterol by inhibiting 14-a-demethylase, a fungal P450 enzyme, which converts lanosterol to ergosterol
  - Resistance occurs via decreased intracellular accumulation of azoles

- Activity and clinical uses:
  - Ketoconazole
    - Co-DOC for *Paracoccidioides* and backup for *Blastomyces* and *Histoplasma*
    - Oral use in mucocutaneous candidiasis or dermatophytoses
  - Fluconazole
    - DOC for esophageal and invasive candidiasis and coccidioidomycoses
    - Prophylaxis and suppression in cryptococcal meningitis
  - Itraconazole
    - DOC in blastomycoses and sporotrichoses
    - Backup for several other mycoses and candidiasis
  - Clotrimazole and miconazole
    - Used topically for candidal and dermatophytic infections
- Pharmacokinetics:
  - Effective orally
  - Absorption of ketoconazole ↓ by antacids
  - Absorption of itraconazole ↓ by food
  - Only fluconazole penetrates into the CSF and can be used in meningeal infection. Fluconazole is eliminated in the urine, largely in unchanged form.
  - Ketoconazole and itraconazole are metabolized by liver enzymes.
  - Inhibition of hepatic P*450s*
- Side effects:
  - ↓ synthesis of steroids, including cortisol and testosterone → ↓ libido, gynecomastia, menstrual irregularities
  - ↑ liver function tests and rare hepatotoxicity

Other Antifungals

- Flucytosine
  - Activated by fungal cytosine deaminase to 5-fluorouracil (5-FU), which after triphosphorylation is incorporated into fungal RNA
  - 5-FU also forms 5-fluorodeoxyuridine monophosphate (5-Fd-UMP), which inhibits thymidylate synthase → ↓ thymine.
  - Resistance emerges rapidly if flucytosine is used alone.
  - Use in combination with amphotericin B in severe candidal and cryptococcal infections-↑-enters CSF
  - Toxic to bone marrow *(see* Anticancer Drugs).
- Griseofulvin
  - Active only against dermatophytes (orally, not topically) by depositing in newly formed keratin and disrupting microtubule structure

- Side effects:
  - Headache, thrush, peripheral neuritis, photo toxicity
  - Potentiates ethanol
  - Avoid with history of porphyria
- Terbinafine
  - Active only against dermatophytes by inhibiting squalene epoxidase ~ 1- ergosterol
  - Possibly superior to griseofulvin in onychomycoses
- Side effects: GI distress, rash, headache, i liver function tests ~ possible hepatotoxicity

Chapter Summary

In eukaryotes, fungal metabolism is somewhat similar to that in humans. Thus, most bacterial antibiotics are ineffective, and many otherwise potentially effective drugs are also toxic to their human hosts. A difference between fungi and humans susceptible to exploitation by antibiotics is the high concentration of ergosterol in their membranes.

The polyenes amphotericin (amp B) are amphoteric compounds that bind to ergosterol, forming pores, which results in the leakage of intracellular contents. The activity, clinical uses, biodisposition, and side effects of these polyenes are discussed.

The azoles (ketoconazole, fluconazole, c1otrimazole, miconazole, and itraconazole) kill fungi by interfering with ergosterol synthesis. The mechanisms of action, clinical uses, biodisposition, and side effects are considered.

Flucytosine is activated by fungal cytosine deaminase to form S-fluoruracil (S-FU). It is sometimes used in combination with amp-B. Insomuch as S-FU is a classic anticancer agent, it is not surprising that flucytosine is also toxic to bone marrow.

Griseofulvin and terbinafine are active against dermophytes. Griseofulvin interferes with microtubule function; terbinafine blocks ergosterol synthesis.

Antiviral Agents

3

Many antiviral drugs are antimetabolites that resemble the structure of naturally occurring purine and pyrimidine bases or their nucleoside forms. Antimetabolites are usually prodrugs requiring metabolic activation by host-cell or viral enzymes-eommonly,, such bioactivation involves phosphorylation reactions catalyzed by kinases.

- Site of action:

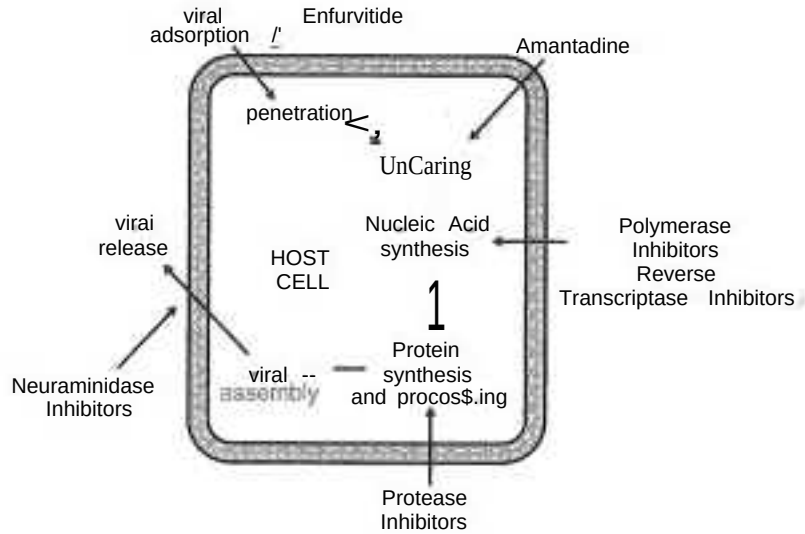


Figure V·3·1. Sites of Antiviral Drug Actions

Table V-3-I. . Mechanism of Action of Antiviral. Drugs

Mechanism of Action	Major Drugs
Block viral penetration/uncoating	Amantadine, enfurvitide
Inhibit viral DNA polymerases	Acyclovir, foscarnet, ganciclovir
Inhibit viral RNA polymerases	Foscarnet, ribavirin
Inhibit viral reverse transcriptase	Zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine, delavirdine, efavirenz
Inhibit viral aspartate protease	Indinavir, ritonavir, saquinavir, nelfinavir
Inhibit viral neuraminidase	Zanamivir, oseltamivir

ANTIHERPETICS

Acyclovir

- Mechanisms of action:
  - Monophosphorylated by viral thymidine kinase (TK), then further bioactivated by host-cell kinases to the triphosphate
  - Acyclovir-triphosphate is both a substrate for and inhibitor of viral DNA polymerase
  - When incorporated into the DNA molecule, acts as a chain terminator because it lacks the equivalent of a ribosyl 3' hydroxyl group
  - Resistance possibly due to changes in DNA polymerase or to decreased activity of TK
  - >50% of HSV strains resistant to acyclovir completely lack thymidine kinase (TK- strains)
- Activity and clinical uses:
  - Activity includes herpes simplex virus (HSV) and varicella-zoster virus (VZV)
  - There are topical, oral, and IV forms; has a short half-life
  - Reduces viral shedding in genital herpes; ↓ acute neuritis in shingles but has no effect on postherpetic neuralgia
  - Reduces symptoms if used early in chickenpox; prophylactic in immunocompromised patients
- Side effects:
  - Minor with oral use, more obvious with IV
  - Crystalluria (maintain full hydration) and neurotoxicity (agitation, headache, confusion-seizures in aD)
  - Is *not* hematotoxic
- Newer drugs--famciclovir and valacyclovir are approved for HSV infection and are similar to acyclovir in mechanism. They may have activity against strains resistant to acyclovir, but not TK- strains. They have a longer $t_{1/2}$ than acyclovir.

Ganddovir

- Mechanisms of action:
  - Similar to that of acyclovir
  - First phosphorylation step is viral-specific; involves thymidine kinase in HSV and a phosphotransferase (UL97) in cytomegalovirus (CMV)
  - Triphosphate form inhibits viral DNA polymerase and causes chain termination
  - Resistance mechanisms similar to acyclovir
- Activity and clinical uses:
  - HSV, VZV, and CMV
  - Mostly used in prophylaxis and treatment of CMV infections, including retinitis, in AIDS and transplant patients-relapses and retinal detachment occur
- Side effects:
  - Dose-limiting hematotoxicity (leukopenia, thrombocytopenia), mucositis, fever, rash, and crystalluria (maintain hydration)
  - Seizures in overdose

Foscarnet

- Mechanisms and clinical uses:
  - Not an antimetabolite, but still inhibits viral DNA and RNA polymerases
  - Uses identical to ganciclovir, plus> activity versus acyclovir-resistant strains of HSV
- Side effects:
  - Dose-limiting nephrotoxicity with acute tubular necrosis, electrolyte imbalance with hypocalcemia (tremors and seizures)
  - Avoid pentamidine IV (-7t nephrotoxicity and hypocalcemia)

REVERSE TRANSCRIPTASE INHIBITORS (RTls)

- The original inhibitors of reverse transcriptases of HIV are nucleoside antimetabolites (e.g., zidovudine, the prototype) that are converted to active forms via phosphorylation reactions.
- Nucleoside reverse transcriptase inhibitors (NRTIs):
  - Are components of most combination drug regimens used in HIV infection
  - Are used together with a protease inhibitor (PI)
  - Highly active antiretroviral therapy (HAART) has often resulted in ,t. viral RNA, reversal of the decline in CD4 cells, and ,t. opportunistic infections
- Nonnucleoside reverse transcriptase (NNRTIs):
  - RTIs that do not require metabolic activation: delavirdine, nevirapine, efavirenz; and a nucleotide RTI, adefovir
  - Are not myelosuppressant
  - Inhibit reverse transcriptase at a site different from the one NRTIs bind to
  - Additive or synergistic if used in combination with NRTIs and/or PIs

Zidovudine (Azidothymidine, ZDV, AZn

- Mechanisms of action:
  - Phosphorylated nonspecifically to a triphosphate that can inhibit reverse transcriptase (RT) by competing with natural nucleotides and can also be incorporated into viral DNA to cause chain termination.
  - Resistance occurs by mutations (multiple) in the gene that codes for RT.
- Drug interactions:
  - t levels of ZDV: azole antifungals, cimetidine, indomethacin, probenecid, and TMP-SMX
  - ,t. levels of ZDV: rifampin.
- Side effects:
  - Hematotoxicity (neutropenia, anemia, granulocytopenia)--dose-limiting and may require transfusions
  - Headache, asthenia
  - Myalgia and myopathy
  - Peripheral neuropathy
  - Rare, but potentially fatal, lactic acidosis (ZDV and other NRTIs)

Other NRTIs

- Mechanism of action identical to that of zidovudine
- Each requires metabolic activation to nucleotide forms that inhibit reverse transcriptase
- Resistance mechanisms are similar
- Not complete cross-resistance between NRTIs
- Drugs differ in their toxicity profiles and are less bone-marrow suppressing than ZVD
- Side effects:

Table V-3-2. Side Effects ofNRTIs

Drug	Side Effects
Zidovudine, AZT	• Hematotoxicity (major and dose-limiting) ▪ Headache, asthenia, myalgia, myopathy, and peripheral neuropathy
Didanosine, DDI	• Pancreatitis (major and dose-limiting) ▪ Peripheral neuropathy, hyperuricemia, liver dysfunction
Zalcitabine, DDC	▪ Peripheral neuropathy (major and dose-limiting) ▪ GI distress, pancreatitis, neutropenia, rash
Stavudine, D4T	▪ Peripheral neuropathy (major and dose-limiting) • Myelosuppression < ZDV
Lamivudine, 3TC	▪ Least toxic of the NRTIs, but some GI effects and neutropenia ▪ Active in hepatitis B

Clinical Correlate

Combinations to Avoid

- 001 + DOC because of additive toxicity
- D4T + AZTbecause of competition for activation

Protease Inhibitors (Pis)

- Mechanisms of action:
  - Aspartate protease *(pol* gene encoded) is a viral enzyme that cleaves precursor polypeptides in HIV buds to form the proteins of the mature virus core.
  - The enzyme contains a dipeptide structure not seen in mammalian proteins. PIs bind to this dipeptide, inhibiting the enzyme.
  - Resistance occurs via specific point mutations in the *pol* gene, such that there is not complete cross-resistance between different PIs.
- Clinical uses:
  - The two PIs used most in the last 5 to 6 years, nearly always in combination regimens with two NRTIs, are indinavir and ritonavir.
  - Saquinavir, one of the least toxic, has very low (and variable) oral bioavailability that predisposes to resistance development.
- Side effects:
  - Indinavir
    - Nephrolithiasis (maintain hydration)
    - GI distress
    - Thrombocytopenia
    - Inhibition of P450 (3A4 isoform)

- Ritonavir
  - GI distress
  - Asthenia and paresthesias
  - Major drug interactions: induces CYP 1A2 and inhibits the major P450 isoforms (3A4 and 2D6) ~ t effects of dronabinol, erythromycin, ketoconazole, and rifampin.
- General: syndrome of disordered lipid and CHO metabolism with central adiposity and insulin resistance

FUSION INHIBITOR: ENFUVIRTIDIE

- Mechanism of action: binds gp41 and inhibits fusion of HIV-1 to CD4+ cells

OTHER ANTIVIRAlS

Amantadine

- Mechanisms of action: blocks attachment, penetration, and uncoating of influenza A virus
- Clinical uses: prophylaxis mainly, but may-l- duration of flu symptoms by 1-2 days
- Side effects:
  - CNS effects: nervousness, insomnia, and seizures in OD
  - Causes atropine-like peripheral effects and livedo reticularis

Zanamivir and Oseltamivir

- Mechanisms of action:
  - Inhibit neuraminidases of influenza A and B (enzymes that prevent clumping of virions, so that more particles are available for infecting host cells)
  - Decreases the likelihood that the virus will penetrate uninfected cells
- Clinical uses: prophylaxis mainly, but may ,t. duration of flu symptoms by 2-3 days
- Side effects:
  - Both cause nausea and vomiting
  - Zanamivir (via inhalation}--nasal and throat irritation

Ribavirin

- Mechanisms:
  - Monophosphorylated form inhibits IMP dehydrogenase
  - Triphosphate inhibits viral RNA polymerase and end-capping of viral RNA
- Clinical uses:
  - Management of respiratory syncytial virus
  - Influenza A and B
  - Lassa fever

Clinical Correlate

HIV Prophylaxis

Needle stick-ZDV+ 3TC, 1 month, but in high risk (e.g., high viral RNA copies), a combination of ZDV + 3TC + indinavir is recommended.

Pregnancy-ZDV full dose, trimester 2 and 3/ plus 6 weeks to neonate, reduces vertical transmission by 80%-possible combination if high maternal viral RNA.

ZDV restricted to intrapartum period, or nevirapine (NNRTI) one dose at onset of delivery + one dose to neonate ~ ,t. transmission by 50 to 60%.

- Hantavirus
- Adjunct to alpha-interferons in hepatitis C

- Side effects:
  - Hematotoxic
  - Upper airway irritation
  - Teratogenic

Human Interferons

- Antiviral: hepatitis B, C, and D
- Antitumor: Kaposi sarcoma, CML, multiple myeloma, renal carcinoma
- Immunoregulatory: multiple sclerosis
- *See* Section VIII, Chapter 2 (Immunopharmacology)

Chapter Summary

General Principles

Antiviral drugs are often antimetabolites that are structural analogs of purine or pyrimidine bases or their nucleoside forms. Many are prodrugs to be activated by host or viral enzymes. The steps in viral replication and the main sites of action of such antiviral drugs are illustrated in Figure V-3-1.

Table V-3-1 summarizes the mechanisms of action of the major antiviral drugs.

Antiherpetics

The antiherpes drugs include acyclovir, ganciclovir, and foscarnet. Famciclovir and valacyclovir are newer drugs very similar to acyclovir. All inhibit viral DNA polymerase. Acyclovir and ganciclovir do so by first being phosphorylated by viral enzymes. As well as acting as a polymerase inhibitor, acyclovir triphosphate is incorporated into the viral DNA, where it acts as a chain terminator. The mechanisms of action, activities, clinical uses, and adverse effects are discussed.

Reverse Transcriptase Inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs) are used in most drug regimes to treat HIV infections. Commonly two NRTIs are used together with a protease inhibitor.

The mechanisms, biodisposition, and adverse effects associated with zidovudine (AZT) use are described. The other nucleotide RTIs act almost identically. The NRTIs and their adverse effects are summarized in Table V-3-2.

Nonnucleoside inhibitors of reverse transcriptase (NNRTIs) and a nucleotide RTI are also used in combinations for treatment in an HIV-positive patient.

Protease Inhibitors (PIs)

HIV aspartate protease has a unique dipeptide structure that has been used as a target for protease inhibitory drugs.

The two protease inhibitors most used are indinavir and ritonavir. Their adverse effects are discussed. A new class of drug is represented by enfuvirtide, a fusion inhibitor.

Other Antivirals

Amantadine blocks the attachment, penetration, and uncoating of influenza virus A; zanamivir and oseltamivir inhibit influenza viruses A and B neuraminidase, promoting viral clumping and decreasing the chance of penetration. Ribavirin becomes phosphorylated and inhibits IMP dehydrogenase and RNA polymerase. It is used to treat respiratory syncytial virus, influenza A and B, Lassa fever, Hantavirus, and as an adjunct to alpha-interferons in hepatitis C. The mechanisms, clinical uses, and side effects of these drugs are considered.

Antiprotoloal Agents

4

OVERVIEW

Table V-4-1. Major Protozoal Infections and the Drugs of Choice

Infection	Drug of Choice	Comments
Amebiasis	Metronidazole	Diloxanide for noninvasive intestinal amebiasis
Giardiasis	Metronidazole	"Backpacker's diarrhea" from contaminated water or food
Trichomoniasis	Metronidazole	Treat both partners
Pneumocystosis	TMP-SMX	Atovaquone or pentamidine IV are backups
Toxoplasmosis	Pyrimethamine + sulfadiazine	TMP-SMX is also prophylactic against *Pneumocystis carinii* in AIDS
Leishmaniasis	Stibogluconate	-
Trypanosomiasis	Nifurtimox (Chagas disease) Arsenicals (African)	—

ANTIMALARIAL DRUGS

- Clinical uses:
  - Chloroquine-sensitive regions
    - Prophylaxis: chloroquine +/- primaquine
    - Backup drugs: hydroxychloroquine, primaquine, pyrimethamine-sulfadoxine

- Specific treatment:

Table V-4-2. Treatment of Chloroquine-Sensitive Malaria

P. falciparum	Chloroquine
P. malariae	Chloroquine
P. vivax	Chloroquine + primaquine
P. ovale	Chloroquine + primaquine

  - Chloroquine-resistant regions
    - Prophylaxis: mefloquine; backup drugs: doxycycline, atovaquone-proguanil
    - Treatment: quinine +/- either doxycycline or clindamycin or pyrimethamine

Table V-4-3. Adverse Effects of Antimalarial Drugs

Drug	Side Effects	Contraindications and Cautions
Chloroquine, Hydroxychloroquine	GI distress, pruritus, headache, dizziness, hemolysis, ocular dysfunction.	Avoid in psoriasis
Mefloquine	NVD, dizziness, syncope, extrasystoles, CNS effects (rare)	Avoid in seizures, psychiatric disorders, and cardiac conduction defects
Primaquine	GI distress, headache, dizziness, neutropenia, hemolysis	Avoid in pregnancy, G6PD deficiency, and autoimmune disorders
Quinine	GI distress, cinchonism, CNS effects, hemolysis, hematotoxicity	Avoid in pregnancy

Definition of abbreviation: NVD: nausea, vomiting, and diarrhea.

DRUGS FOR HELMINTHIC INFECTIONS

- Most intestinal nematodes (worms)
  - Mebendazole (↓ glucose uptake and ↓ microtubular structure)
  - Pyrantel pamoate (NM agonist ~ spastic paralysis)
- Most cestodes (tapeworms) and trematodes (flukes)
  - Praziquantel (↑ Ca^{2+} influx, ↑ vacuolization)

Chapter Summary

Table V-4-1 lists the major types of protozoal infections and the drugs of choice for their treatment, with various relevant comments.

Table V-4-2 lists the drugs of choice used against the various forms of malaria, and information is given about treatment and prophylaxis of malaria. Chloroquine-sensitive or -resistant areas are listed separately.

The drugs used to treat helminthic infections are listed, and their mechanisms of action are noted.

Antimicrobial Drug List and Practice Questions

5

Table V-5-1. Antimicrobial Drug List

Penicillins	Cephalosporins	Other Cell Wall Inhibitors	
Penicillin G	Cefazolin (Ist)	Imipenem, meropenem	
Nafcillin, oxacillin	Cefaclor (2nd)	Vancomycin	
Amoxicillin, ampicillin	Ceftriaxone (3rd)		
Ticarcillin, piperacillin, azlocillin			
Macrolides	**Aminoglycosides**	**Tetracyclines**	**Others**
Erythromycin	Gentamicin	Tetracycline HCl	Metronidazole
Azithromycin	Tobramycin	Doxycycline	
Clarithromycin	Streptomycin		
Pluoroquinolones	**Antifolates**	**Antimycobacterials**	
Ciprofloxacin	Sulfamethoxazole	Isoniazid, rifampin	
Ofloxacin	Trimethoprim	Ethambutol, pyrazinamide	
Antifungals	**Anti-Herpes**	**Anti-HIV**	
Amphotericin B	Acyclovir	Zidovudine (NRTI), didanosine (NRTI)	
Ketoconazole	Ganciclovir	Zalcitabine (NRTI)	
Fluconazole	Foscarnet	Indinavir (PI), ritonavir (PI) Enfuvirtide	

Review Questions

1. Which of the following is a mechanism underlying the resistance of strains of *S. pneumoniae* to the widely used antibiotic ciprofloxacini

   (A) Reduced topoisomerase sensitivity to inhibitors
   (B) Increased synthesis of PABA
   (C) Formation of methyltransferases that change receptor structure
   (D) Structural changes in porins
   (E) Formation of drug-inactivating hydrolases

2. An 82-year-old hospitalized patient with creatinine clearance of 25 mL/min has a microbial infection requiring treatment with antibiotics. Which of the following drugs is least likely to require a dosage adjustment, either a smaller dose than usual or an increased interval between doses?

   (A) Amphotericin B
   (B) Erythromycin
   (C) Gentamicin
   (D) Imipenem-cilastatin
   (E) Vancomycin

3. A 7-year-old child presents with pharyngitis and fever of 2 days' duration, and microbiology reveals small, translucent, beta-hemolytic colonies sensitive in vitro to bacitracin. Past history includes a severe allergic reaction to amoxicillin when used for an ear infection. The physician needs to treat this infection, but prefers not to use a drug that needs parenteral administration. Which one of the following agents is most likely to be appropriate in terms of both effectiveness and safety?

   (A) Azithromycin
   (B) Cefaclor
   (C) Doxycycline
   (D) Penicillin G
   (E) Vancomycin

4. What does high-level resistance of *Mycobacterium tuberculosis* to isoniazid (INH) involve?

   (A) Decreased intracellular accumulation of the drug
   (B) Inactivation of the drug via N-acetyltransferases
   (C) Increased synthesis of mycolic acids
   (D) Mutations in the gene coding for DNA-dependent RNA polymerase
   (E) Reduced expression of the gene that encodes a catalase

5. A woman has pelvic inflammatory disease, and the decision is made to treat her with antibiotics as an outpatient. One of the drugs to be used is a cell-wall synthesis inhibitor with activity against anaerobic gram-negative rods, including *Bacteroides fragilis.* She is warned that unpleasant reactions may occur if she consumes alcoholic beverages while taking this drug. If the antibiotic may cause hypoprothrombinemia, it can be identified as which of the following?

   (A) Ceftriaxone
   (B) Doxycycline
   (C) Metronidazole
   (D) Ofloxacin
   (E) Cefotetan

6. A patient suffering from invasive aspergillosis is first administered NSAIDs, antihistamines, and adrenal glucocorticoids. Which of the following drugs should be administered next?

   (A) Amphotericin B
   (B) Ketoconazole
   (C) Flucytosine
   (D) Itraconazole
   (E) Terfenadine

7. What is the drug most likely to be effective in diseases caused by cestodes and trematodes?

   (A) Chloroquine
   (B) Mebendazole
   (C) Metronidazole
   (D) Praziquantel
   (E) Pyrimethamine

8. Several antibiotics are effective in single doses for the treatment of uncomplicated gonorrhea. Which one of the following drugs necessitates a 7-day course of treatment to be effective?

   (A) Azithromycin
   (B) Ceftriaxone
   (C) Doxycycline
   (D) Ofloxacin
   (E) Spectinomycin

9. In bacterial meningitis, third-generation cephalosporins are commonly drugs of choice. However, in neonatal meningitis they would not provide coverage if the infection was due to which of the following organisms?

   (A) Meningococci
   (B) *L. monocytogenes*
   (C) Pneumococci
   (D) *E. coli*
   (E) Group B streptococci

10. Which one of the following drugs inhibits bacterial protein synthesis, preventing the translocation step via its interaction with the 50S ribosomal subunit?

   (A) Clindamycin
   (B) Gentamicin
   (C) Chloramphenicol
   (D) Imipenem
   (E) Tetracycline

11. Despite its short elimination half-life, gentamicin may be administered once daily (at high dose) in the treatment of hospitalized patients with infections caused by aerobic gram-negative rods. What are once-daily dosing regimens with gentamicin likely to result in?

   (A) A decrease in cure rate
   (B) A higher incidence of deafness
   (C) The rapid emergence of resistance
   (D) Less nephrotoxicity
   (E) Higher cost

12. In the treatment of a urinary tract infection in a patient known to have a deficiency of glucose-e-phosphate dehydrogenase, it would not be advisable to prescribe which of the following?

   (A) Ciprotloxacin
   (B) Amoxicillin
   (C) Cephalexin
   (D) Doxycycline
   (E) Sulfamethoxazole

13. Beta-lactamase production is a mechanism of resistance common to strains of H. *influenzae*, M. *catarrhalis*, and *Neisseria gonorrhoeae*. Which one of the following drugs is most likely to be effective against *all* strains of the above-mentioned organisms?

(A) Amoxicillin
(B) Ceftriaxone
(C) Clindamycin
(D) TMP-SMX
(E) Ticarcillin

14. Which one of the following drugs is most likely to be equally effective in the treatment of amebic dysentery and "backpacker's diarrhea"?

(A) Ciprofloxacin
(B) Diloxanide
(C) Metronidazole
(D) Quinacrine
(E) Trimethoprim-sulfamethoxazole

15. Oseltamivir and zanamivir are available for treatment of infections due to influenza A and B. The mechanism of their antiviral action is inhibition of which of the following?

(A) RNA polymerase
(B) Reverse transcriptase
(C) Thymidine kinase
(D) Neuraminidase
(E) Aspartate protease

16. The major mechanism of HSV resistance to acyclovir is

(A) a structural change in viral thymidine kinase
(B) a mutation in the gene that encodes DNA polymerase
(C) the loss of ability to produce viral thymidine kinase
(D) changes in reverse transcriptase
(E) mutations in the gene that codes for phosphotransferase

17. An AIDS patient who is being treated with multiple drugs, including AZT, lamivudine, indinavir, ketoconazole, and cotrimoxazole, develops breast hypertrophy, central adiposity, hyperlipidemia, insulin resistance, and nephrolithiasis. If these changes are related to his drug treatment, which of the following is the most likely cause?

(A) Azidothymidine
(B) Indinavir
(C) Ketoconazole
(D) Sulfamethoxazole
(E) Trimethoprim

18. Which one of the following drugs is most suitable in an immunocompromised patient for prophylaxis against infection due to *Cryptococcus neoformans?*

(A) Amphotericin B
(B) Ampicillin
(C) Fluconazole
(D) Nystatin
(E) Flucytosine

19. Which one of the following drugs is most likely to be associated with elevations of pancreatic enzymes, including amylase and lipase?

(A) Erythromycin
(B) Didanosine
(C) Isoniazid
(D) Zidovudine
(E) Pyrazinamide

20. Which one of the following pairs of "drug: mechanism" is most accurate?

(A) Streptomycin: misreading in bacterial protein synthesis
(B) Ritonavir: inhibition of reverse transcriptase in HIV
(C) Nystatin: decreased synthesis of ergosterol in fungal cell membranes
(D) Tetracycline: inhibits the activity of peptidyltransferase in bacterial protein synthesis
(E) Vancomycin: inhibits cross-linking of peptidoglycan chains in cell-wall synthesis

21. In community-acquired pneumonia, pathogens responsible for infection include pneumococci, gram-negative rods, and atypicals, such as M. *pneumoniae* and C. *pneumoniae.* Which one of the following drugs used as monotherapy is most likely to be both effective and safe if your patient is pregnant?

(A) Amoxicillin
(B) Erythromycin estolate
(C) Clarithromycin
(D) Ofloxacin
(E) Azithromycin

22. A mother is breast-feeding her 2-month-old infant. Which one of the following drug situations involving the mother is unlikely to cause effects in the nursing infant?

(A) Ciprofloxacin for a urinary tract infection
(B) Amphetamine for weight loss
(C) Nystatin for a yeast infection
(D) Temazepam as a "sleeping pill"
(E) Two glasses of red wine

23. In a patient who has an established hypersensitivity to metronidazole, what is the most appropriate drug to use for the management of pseudomembranous colitis?

(A) Ampicillin
(B) Clindamycin
(C) Doxycycline
(D) Ofloxacin
(E) Vancomycin

24. Despite its "age:' penicillin G remains the drug of choice in the treatment of infections caused by which of the following organisms?

(A) *B. fragilis*
(B) *T. pallidum*
(C) H. *influenzae*
(D) *E. coli*
(E) S. *aureus*

25. Highly active antiretroviral therapy (HAART) in HIV infection is associated with which of the following?

(A) A decrease in viral mRNA copies/mL of blood
(B) A decrease in the rate of emergence of drug resistance
(C) A possible increase in CD4 cell count
(D) A reduced incidence of opportunistic infections
(E) All of the above

Answers

1. **Answer:** A. Microbial resistance to fluoroquinolones is increasing, and some strains of *Streptococcus pneumoniae* are now resistant to ciprofloxacin. The mechanism can involve changes in the structure of topoisomerase IV, one of the "targets" of fluoroquinolones, which inhibit nucleic acid synthesis. Pneumococcal resistance to penicillins is also increasing via changes in penicillin-binding proteins (PBPs). The other mechanisms listed underlie microbial resistance to other antibiotics as follows: sulfonamides **(choice** B), macrolides **(choice** C), extended-spectrum penicillins **(choice** D), and beta-lactams **(choice** E).

2. **Answer: B.** Erythromycin is eliminated largely via biliary excretion, and decreases in renal function do not usually require a dose reduction, unless creatinine clearance is <10 mUmin. All of the other antimicrobial drugs listed are eliminated by the kidney, at rates proportional to creatinine clearance, so major dose reductions would be needed in patients with renal dysfunction to avoid toxicity.

3. **Answer:** A. Azithromycin is highly effective as an oral agent in the management of pharyngitis caused by gram-positive cocci and may necessitate only a short course of therapy. In patients who have marked hypersensitivity to penicillins, it is inappropriate to use a cephalosporin, even though cefaclor is active against common oropharyngeal pathogens. Doxycycline should not be used in children. One must assume that complete cross-allergenicity exists between different members of the penicillin class of antibiotics, and, in any case, penicillin G is not usually given orally because of its lability in gastric acid. Vancomycin would need parenteral administration, and this antibiotic should be reserved for more serious bacterial infections.

4. **Answer: E.** For antitubercular activity, isoniazid (INH) must first be metabolically activated via a catalase present in mycobacteria. A decrease in expression of the *cat* G gene that encodes this enzyme is the mechanism of high-level resistance to INH. Low-level resistance occurs via mutations in the *inh* A gene, which codes for an enzyme involved in synthesis of mycolic acids. Mutations in the gene that codes for DNA-dependent RNA polymerase is an important mechanism of resistance to rifampin and related antibiotics.

5. **Answer: E.** Organisms associated with pelvic inflammatory disease (PID) include chlamydia, gonococci, and anaerobic gram-negative rods. Effective treatment often requires hospitalization, but some patients are treated on an outpatient basis. Drug regimens for PID have included each of the drugs listed in the question because they are all active. However, only the cephalosporins are cell-wall synthesis inhibitors. Several cephalosporins, including cefotetan (but not ceftriaxone), have a chemical structure that results in a disulfiram-like effect on aldehyde dehydrogenase and also causes inhibition of prothrombin synthesis. Metronidazole is also an inhibitor of aldehyde dehydrogenase, causing reactions with ethanol, but the drug does not cause hypoprothrombinemia.

6. **Answer:** A. Life-threatening invasive aspergillosis, with necrotizing pneumonia, most commonly occurs in severely immunocompromised patients. The mortality rate approaches 50%, but high intravenous doses of amphotericin B may be lifesaving. Intravenous amphotericin B causes infusion-related hypotension (via histamine release), Jever,and chills, which may be attenuated by the prior administration of NSAIDs and antihistamines. Adrenal steroids may provide supplementary stress support. Oral itraconazole is effective in less severe aspergillosis, but its efficacy in the invasive forms of the infection has not been established. The other antifungal drugs listed have minimal effectiveness in aspergillosis.

7. Answer: D. Praziquantel is the drug of choice for treatment of all fluke (trematode) infections and most tapeworm (cestode) infections. Its antihelminthic action derives from an increase in membrane permeability to Ca^{2+}, which results in contraction, followed by paralysis, of worm musculature. Mebendazole also has antihelminthic activity, but it is restricted to the nematodes. The other drugs listed are antiprotozoals.

8. Answer: C. Doxycycline (or tetracycline) takes at least a 7-day course of treatment in gonorrhea, raising the possibility of patient noncompliance. The quinolones (e.g., ciprofloxacin and ofloxacin) and the third-generation cephalosporin ceftriaxone (1M) is effective in single doses and are the drugs of choice in most situations. Spectinomycin (IM) in a single dose is a backup drug; its only use is for uncomplicated gonorrhea.

9. Answer: B. The most common pathogens implicated in bacterial meningitis in a neonate (age <1 month) are group B streptococci, followed by *E. coli*. Meningococci and pneumococci become prevalent after 1 month of age, and H. *influenzae* is becoming rarer since the availability of a vaccine. A third-generation cephalosporin (e.g., cefotaxime) would be administered because it provides coverage for most of the organisms mentioned. However, ampicillin is also needed to cover for *Listeria monocytogenes*, which occurs with an incidence of 7 to 8% in neonatal meningitis.

10. Answer: A. Clindamycin has a mechanism of action similar to, if not identical with, erythromycin and related macrolides. They bind to rRNA bases on the 50S subunit to prevent translocation of peptidyl-mRNA from the acceptor to the donor site. Chloramphenicol also binds to the 50S subunit but interferes with the activity of peptidyltransferase. Gentamicin and tetracyclines bind to the 30S ribosomal subunit. Imipenem is a cell-wall synthesis inhibitor, acting similarly to beta-lactams.

11. Answer: D. Once-daily aminoglycoside dosing regimens in the treatment of bacterial infections have similar effectiveness to the conventional dosing regimens and do not appear to increase the risk of ototoxicity. They are less likely to result in toxicity to the kidney, and the impact on cost favors once-daily dosing. There is no difference in resistance emergence rate from that of conventional dosing regimens.

12. Answer: E. Drugs that cause oxidative stress may precipitate acute hemolysis in patients who lack G6PD because they have a limited ability to generate NADPH, which restricts the formation of glutathione. Drugs in this category include primaquine, quinine, nitrofurantoin, sulfonamides, and TMP-SMX.

13. Answer: B. Ceftriaxone (1M) is a drug of choice in gonorrhea and is also highly effective in otitis media, infections in which beta-lactamase-producing strains of H. *influenzae* and M. *catarrhalis* are commonly implicated. The fourth-generation drug, cefepime, also has activity against these organisms. Amoxicillin and ticarcillin are susceptible to beta-lactamases, TMP-SMX does not cover all strains of the organisms listed, and the activity of clindamycin is restricted to gram-positive cocci and anaerobes.

14. Answer: C. In amebic dysentery caused by *Entamoeba histolytica* and gastrointestinal infections with diarrhea ("backpacker's diarrhea") due to *Giardia lamblia*, metronidazole is the drug of choice. Diloxanide is a backup drug for noninvasive intestinal amebiasis, but it has minimal activity in *Giardia* infections. Quinacrine has effectiveness in giardiasis but not amebiasis. TMP-SMX has antiprotozoal effectiveness in *Pneumocystis carinii* pneumonia. Ciprofloxacin is devoid of antiprotozoal activity.

15. **Answer: D.** Neuraminidase is an enzyme on the lipid envelope of influenza A and B virions that prevents their clumping together and also their binding to the surface of cells that have been already infected. Neuraminidase inhibitors interfere with this activity and reduce the availability of virions for entry into noninfected cells. Oseltamivir and zanamivir decrease the severity and duration of symptoms if given within a day or two of onset.

16. **Answer: C.** To inhibit DNA polymerases in HSV, acyclovir must undergo initial monophosphorylation by a viral specific thymidine kinase (TK). Most HSV strains resistant to acyclovir lack this enzyme and are thus TK- strains. A few strains of HSV are resistant to acyclovir by structural changes in TK that lower substrate affinity or by mutations in the gene that encode viral DNA polymerases.

17. **Answer: B.** AIDS patients being treated with protease inhibitors (e.g., indinavir) have developed a syndrome involving derangement of lipid and CHO metabolism. Changes in lipid metabolism and distribution occur quite commonly, and type 2 diabetes has also been reported. Indinavir is also notable for its tendency to precipitate in the urinary tract, causing nephrolithiasis, unless the patient is maintained in a high state of hydration.

18. **Answer: C.** Fluconazole is distinctive in terms of its ability to penetrate into the cerebrospinal fluid, reaching levels similar to those in the blood. It is effective against C. *neoformans* and has become the most appropriate drug to use in both prophylaxis and suppression because of its oral efficacy and low toxicity compared with amphotericin B. Flucytosine is also active against C. *neoformans* but is not used alone because of rapid emergence of resistance. Nystatin is too toxic for systemic use.

19. **Answer: B.** Pancreatic dysfunction, heralded by large increases in serum amylase and lipase, is associated with the use of several reverse-transcriptase inhibitors (RTIs). Didanosine appears to be the worst offender, and pancreatitis is the most characteristic adverse effect of this particular NRTI. Conditions enhancing susceptibility to drug-induced pancreatic dysfunction include hypertriglyceridernia, hypercalcemia, and history of excessive ethanol use. Liver dysfunction including hepatitis may occur with the antitubercular drugs, isoniazid, and pyrazinamide. Cholestasis is associated with the estolate form of erythromycin.

20. **Answer: A.** Aminoglycosides (gentamicin, streptomycin) are bactericidal inhibitors of protein synthesis. They bind to the 30S ribosomal subunit to block initiation, cause misreading, and may prevent elongation. Ritonavir inhibits HIV protease (not reverse transcriptase). Nystatin interacts with ergosterol to form artificial membrane "pores" (azole antifungals inhibit ergosterol synthesis). Tetracyclines prevent binding of aminoacyl-tRNA (chloramphenicol inhibits peptidyltransferase), and beta-lactams inhibit cross-linking of peptidoglycan chains in bacterial cell-wall synthesis.

21. **Answer: E.** Penicillins (and most cephalosporins) have minimal activity against the atypical organisms associated with community-acquired pneumonia, although they may be effective against S. *pneumoniae*, H. *influenzae*, and M. *catarrhalis*. Erythromycin has been used, but the estolate form is contraindicated in pregnancy because of an increased risk of cholestasis. Likewise, clarithromycin and ofloxacin are both effective in community-acquired pneumonia, but neither of these drugs can be used in pregnancy because animal studies have shown detrimental effects on fetal development. Fortunately, azithrornycinis both effective and safe in pregnancy .

22. **Answer:** C. Drugs that are capable of crossing the blood-brain barrier penetrate most body tissues and can appear in the milk of the lactating mother. Although concentrations of such drugs may be low in breast milk, they may cause effects in an infant who perhaps weighs just a few kilograms. Fluoroquinolones also penetrate tissues, and because they are contraindicated in children, it seems appropriate not to risk infant exposure via breast milk. The "safest" drug situation concerns nystatin, which is used only via the topical route and, as a polyene, does not cross membrane barriers.

23. **Answer: E.** Vancomycin is usually considered to be a backup drug to metronidazole in colitis due to *Clostridium difficile* on the grounds that it is no more effective, is more costly, and should be reserved for treatment of resistant gram-positive coccal infections. None of the other drugs has activity in pseudomembranous colitis-indeed, they may cause it!

24. **Answer: B.** Indications for the use of penicillin G are currently limited for a number of reasons. The drug has a narrow spectrum, is susceptible to beta-lactamases, and may cause hypersensitivity. Also, alternative antibiotics are available. However, penicillin G remains the drug of choice in syphilis, usually given 1M as benzathine penicillin G, but as the Na+ or K+ salt IV in neurosyphilis. What would you do for patients who are highly allergic to penicillins? (Consider tetracyclines, or possibly desensitization.)

25. **Answer: E.** HAART in the management of HIV infection is reported in many but not all patients to decrease viral load, increase CD4 cells, slow disease progression, and reduce opportunistic infections. However, in terms of the chemotherapy of AIDS, the word *cure* has little meaning. Discontinuance of HAART, after suppression of viral RNA copies below the sensitivity of the best current methods of analysis, is followed by the reemergence of detectable viral RNA in the blood within a few months.

SECTION VI

Drugs for Inflammatory and Related Disorders

Histamine and Antihistamines

1

HISTAMINE

- Histamine is an autacoid present at high levels in the lungs, skin, and the gastrointestinal tract and is released from mast cells and basophils by type I hypersensitivity reactions, drugs, venoms, and trauma.
- Histamine receptors are of the serpentine family, with seven transmembrane-spanning domains with G-protein-coupled second messenger effectors.
  - H_1 activation
    - ↑ capillary dilation (via NO) → ↓ BP
    - ↑ capillary permeability → ↑ edema
    - ↑ bronchiolar smooth muscle contraction (via IP_3 and DAG release)
    - ↑ activation of peripheral nociceptive receptors → ↑ pain and pruritus
    - ↓ AV nodal conduction
  - H_2 activation
    - ↑ gastric acid secretion → ↑ gastrointestinal ulcers
    - ↑ SA nodal rate, positive inotropism, and automaticity

H. ANTAGONISTS

- Mechanism of action:
  - H_1 antagonists act as competitive antagonists of histamine and therefore may be ineffective at high levels of histamine.
  - Vary in terms of both pharmacologic and kinetic properties, but all require hepatic metabolism and most cross the placental barrier.

Table VI-I-I. Properties of Major Antihistamines

Drug	MBlock	Sedation	Antimotion	Other Characteristics
Diphenhydramine	+++	+++	+++	Widely used *GTC* drug
Promethazine	+++	+++	++	Some *ex* block and local anesthetic action
Chlorpheniramine	++	++	++	Possible CNS stimulation
Meclizine	++	++	++++	Highly effective in motion sickness
Hydroxyzine	++	+++	++	Commonly used as a sedative
Loratadine	+/-	0	0	No CNS entry
Fexofenadine	+/-	0	0	No CNS entry

- Uses:
  - Allergic reactions: hay fever, rhinitis, urticaria
  - Motion sickness, vertigo
  - Nausea and vomiting with pregnancy
  - Preoperative sedation
  - *GTC:* sleep aids and cold medications
  - Parkinson disease
  - Acute EPSs
- Adverse effects:
  - Extensions of M block and sedation (additive with other CNS depressants), gastrointestinal distress, allergic reactions. H_2 antagonists are discussed in the next chapter.

Chapter Summary

Histamine is an autacoid released from mast cells and basophils by type I hypersensitivity reactions or under the influence of drugs, venoms, or trauma. Histamine receptors are the G-protein-coupled, seven-transmembrane type. Three different receptors are recognized: the well-characterized H] and H_2 types and an H_3 variant.

The sequence of reactions leading to H] and H_2 activation is presented.

H] antagonists are competitive inhibitors with varying pharmacologic and kinetic properties. All require hepatic metabolism and cross the placental barrier.

The H] antagonists are used to treat allergic reactions, motion sickness, vertigo, nausea and vomiting in pregnancy, and preoperative sedation, and are in over-the-counter sleeping pills.

The adverse effects are excess M block and sedation, gastrointestinal distress, and allergic reactions. Table VI-l-l summarizes the properties of some of the major type 1 antihistamines.

Drugs Used in Gastrointestinal Dysfunction

2

DRUGS USED IN PEPTIC ULCER DISEASE (PUll)

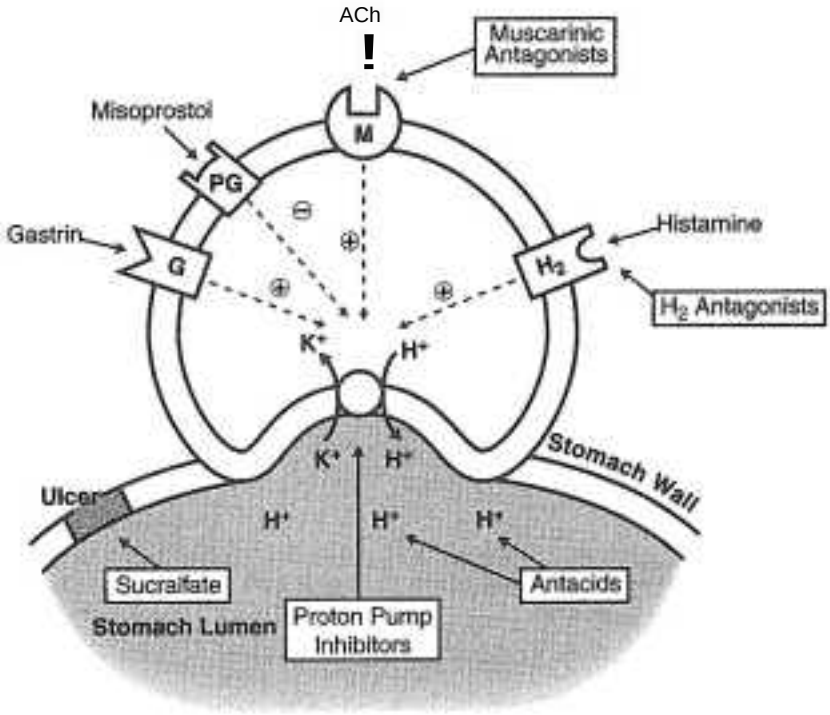


Figure VI-2-1. Drug Actions in PUD

H_2 Antagonists (e.g., Cimetidine, Ranitidine)

- Mechanisms of action:
  - Suppress secretory responses to food stimulation and nocturnal secretion of gastric acid via their ability to decrease (indirectly) the activity of the proton pump.
  - Also partially antagonize HCl secretion caused by vagally or gastrin-induced release of histamine from ECL-like cells (GI mast cells)
  - No effects on gastric emptying time

- Uses:
  - PUD (overall less effective than proton pump inhibitors)
  - Gastroesophageal reflux disease (GERD)
  - Zollinger-Ellison syndrome
- Side effects:
  - Gastrointestinal distress
  - Dizziness, somnolence; slurred speech and delirium possible in elderly
  - Cimetidine is a major inhibitor of P450 isoforms ~ drug interaction via ↑ effects of quinidine, phenytoin, tricyclic antidepressants, and warfarin
  - Cimetidine ~↓ androgens ~ gynecomastia and ↓libido

Proton Pump Inhibitors

- Mechanism of action:
  - **Omeprazole** and related "-prazoles" are irreversible, direct inhibitors of the proton pump (K+/H+ antiport) in the gastric parietal cell
- Uses:
  - More effective than H_2 blockers in peptic ulcer disease (PUD)
  - Also effective in GERD and Zollinger-Ellison syndrome
  - Eradication regimen for H. *pylori*
- Side effects:
  - May cause mild CNS and gastrointestinal effects and ↓bioavailability of drugs that require acidity for oral absorption (e.g., fluoroquinolones, ketoconazole)
  - Inhibit P450 ~↓ elimination of diazepam, phenytoin, and warfarin

Misoprostol

- Mechanism of action: PGE_1 analog, which is cytoprotective ~ ↑ mucus and bicarbonate secretion and↓ HCl secretion
- Uses: Selective use in NSAID-induced gastrointestinal ulcers

Sucralfate

- Mechanism of action: polymerizes on gastrointestinal luminal surface to form a protective gel-like coating of ulcer beds. Requires acid pH (antacids may interfere)
- Uses: ↑ healing and ↓ulcer recurrence

Bismuth Subsalicylate

- Mechanism of action: like sucralfate, binds selectively to ulcer, coating it, and protecting it from acid and pepsin
- Combined with metronidazole and tetracycline to eradicate H. *pylori* (BMT regimen)

Antacids

- Mechanism of action: bases that neutralize protons in the gut lumen
- Side effects: May j, oral absorption of azoles, fluoroquinolones, and tetracyclines

Table VI-2-1. Side Effects of Various **Antacids**

Antacid	Alkalosis	Acid Rebound	Diarrhea	Constipation	Other Toxicity
Al(OH)3	–	–	–	++	Hypophosphatemia, osteodystrophy, dementia
$CaC0_3$	+	++	–	++	Hypercalcemia
Mg(OH)2	–	++	++	–	Hypermagnesemia ~ loss of deep tendon reflexes, respiratory paralysis
$NaHC0_3$	++	++	–	–	"Gas"

Clinical Correlate

Antacids and Drug Absorption

i Oral absorption of weak bases (e.g., quinidine)

J. Oral absorption of weak acids (e.g., warfarin)

J. Oral absorption of tetracyclines (via chelation)

laxatives

- $MgS0_4$: water-retaining ~ i intraluminal pressure
- Bisacodyl: direct intestinal wall stimulant
- Methykellulose: collects water and swells ~ i bulk
- Docusate: detergent ~. stool softener
- Mineral oil: lubricant
- Lactulose: hyperosmotic (also indicated for systemic encephalopathy)

Antidiarrheals

- Loperamide and diphenoxylate (with atropine) are opioids that are poorly absorbed *(see* Opioid Analgesics, Chapter 5, Section IV [CNS])
- Adsorbants: kaolin, pectin

ANTIEMETICS

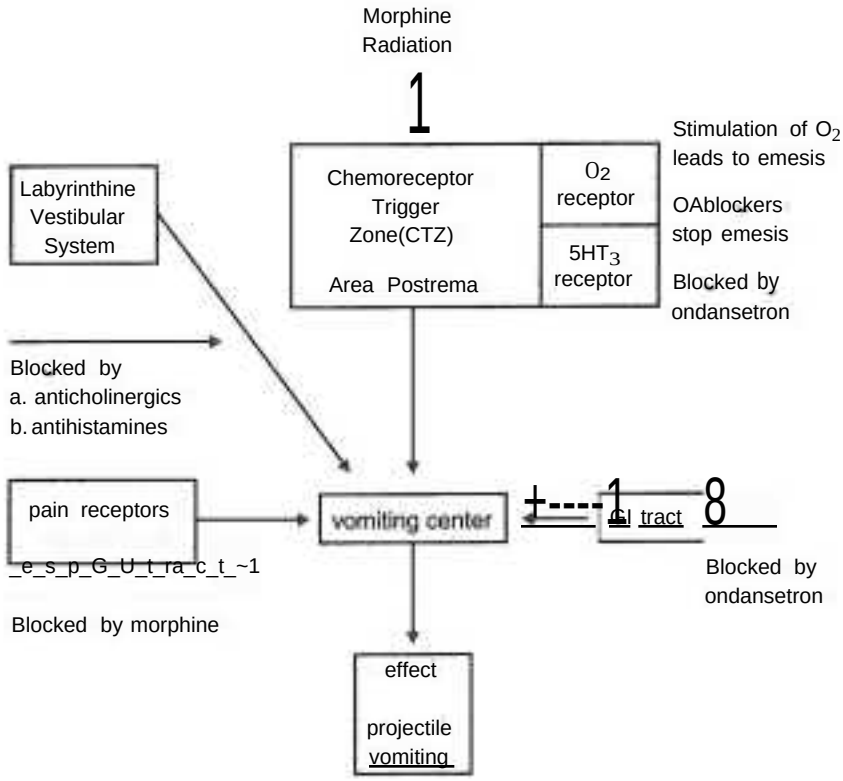


Figure VI-2-2. The Emetic Pathways and Drug Actions

Figure VI-2-2 shows the complexity of the emetic pathways with an impact on the vomiting center and reveals the multiplicity of receptor types involved, including those activated by ACh, DA, SHT, histamine, and endogenous opiopeptides.

Clinical Correlate

Opioid analgesics (e.g., morphine) have duality of action: **t** emesis by activating receptors that decrease pain transmission and **i** emesis by activating receptors in the CTZ.

Drugs for nausea and vomiting include:

- SHT_3 (a serotonin *receptor-see* following chapter) antagonists: ondansetron (commonly used in cancer chemotherapy), granisetron
- DA antagonists: prochlorperazine, metoclopramide (also used in cancer chemotherapy; also prokinetic in GERD)
- HI antagonists: diphenhydramine, meclizine, promethazine
- Muscarinic antagonists: scopolamine
- Cannabinoids: dronabinol
- NKI-receptor antagonist: aprepitant (NK_I is a receptor to substance P)

Chapter Summary

The H_2 histamine antagonists (e.g., cimetidine and ranitidine) are used to suppress the secretion of gastric acid. The mechanism of action is illustrated in Figure VI-2-1. The clinical uses and adverse effects are discussed.

Omeprazole and the other "-prazole" proton-pump inhibitors are more powerful inhibitors of gastric secretion than are the antagonists. Their clinical uses and adverse reactions are considered.

Misoprostol is a cytoprotective prostaglandin E_j analog.

Sucralfate forms a protective gel, covering gastrointestinal ulcers. Bismuth subsalicylate behaves similarly.

Antacids neutralize preformed protons. Their mechanisms of action and side reactions are summarized in Table VI-2-1.

The modes of action of various laxatives are also discussed.

Figure VI-2-2 illustrates the complex number of factors impinging upon the emetic (vomiting) center. The antiemetic drugs are listed.

Drugs Acting on Serotonergic Systems

3

- Serotonin (5-hydroxytryptarnine, 5HT) is an autacoid synthesized and stored in gastrointestinal cells, neurons, and platelets. Metabolized by MAO type A, its metabolite 5-hydroxyinolacetic acid (5HIAA) is a marker for carcinoid.
- Of the seven receptor subtype families, all are G-protein coupled, except $5HT_3$, which is coupled directly to an ion channel.

DRUG ACTIONS ON 5HT RECEPTORS

$5HT_{1(a_h)}$

- Found in the CNS (usually inhibitory) and smooth muscle (excitatory or inhibitory)
- Drug: buspirone
  - Partial agonist at $5HT_{1a}$ receptors ~ anxiolytic (generalized anxiety disorder [GAD])
- Drug: sumatriptan
  - Agonist at $5HT_{1d}$ receptors in cerebral vessels ~t migraine pain
  - Side effects of "-triptans": possible asthenia, chest or throat pressure or pain

$5HT_{2(a_c)}$

- Found in CNS (excitatory)
- In periphery, activation ~ vasodilation, contraction of gastrointestinal, bronchial, and uterine smooth muscle, and platelet aggregation
- Drugs:
  - Olanzapine and other atypical antipsychotics: antagonist at $5HT_{2a}$ receptors in CNS ~t symptoms of psychosis
  - Cyproheptadine
    - $5HT_2$ antagonist used in carcinoid, other gastrointestinal tumors, and postgastrectomy; also used for anorexia nervosa
    - Has marked HI-blocking action: used in seasonal allergies

$5HT_3$

- Found in area postrema, peripheral sensory and enteric nerves
- Mechanism of action: activation opens ion channels (no second messengers)
- Drugs: ondansetron and "-setrons"
  - Antagonists ~t emesis in chemotherapy and radiation and postoperatively

$5HT_4$

- Found in gastrointestinal smooth muscle and myenteric nerves
- Drug: **tegaserod**
  - Agonist used in irritable bowel syndrome when associated with constipation

$5HT_S$-$5HT_7$

- Many future antipsychotic and antidepressant medications

DRUGS USED IN MIGRAINE HEADACHES

- Ergot alkaloids
  - **Ergotamine**
    - Mechanism of action:

      Ergotamine acts as partial agonists at both a and SHT_2 receptors in the vasculature and possibly in the eNS.

      Vasoconstrictive actions to decrease pulsation in cerebral vessels may be relevant to acute actions of ergotamine during migraine attack.
    - Uses: ergotamine used in acute attacks
    - Side effects: gastrointestinal distress, prolonged vasoconstriction ~ ischemia and gangrene, abortion near term
- In addition to the "-triptans" and ergots:
  - Analgesics: ASA (+/- caffeine, or butabarbital), other NSAIDs, acetaminophen (+/- caffeine), oral or injectable opioid-analgesics, and butorphanol (spray)
  - Prophylaxis: propranolol, verapamil, amitriptyline, valproic acid

Note

Ergonovine

- Mechanism of action: uterine smooth muscle contraction
- Use: given intramuscularly after placental delivery

Chapter Summary

Serotonin (5H1) is an autacoid synthesized and stored in gastrointestinal cells, neurons, and platelets. Monoamine oxidase (MAO) type A degrades it, forming 5-hydroxyindoleacetic acid (SHIM), a carcinoid marker.

There are seven receptor subtypes, six of which are G-protein coupled. The seventh type, 5HT3' is directly coupled to an ion channel.

The locations and normal functions of different types of SHT receptors, as well as drugs acting on them, are described.

There are approximately 20 natural ergot alkaloids. A few of these, plus some derivatives, are used pharmacologically. Several act via 5HT receptors, but a- and O_2 receptors are also utilized. The clinical uses and properties of specific ergots are indicated.

Drugs (in addition to the "-triptans" and ergots) used to treat migraines are mentioned, as are other drugs affecting serotonergic neurotransmission.

Eicosa"oid Pharmacology

4

- Eicosanoids are cell-regulating polyunsaturated fatty acids primarily synthesized from arachidonic acid and released by the action of phospholipase A_2 from lipids in cell membranes.
- Eicosanoids are present in low concentrations in most cells but are synthesized and released "on demand" in response to stimuli, including IgE-mediated reactions, inflammatory mediators, trauma, heat, and toxins.
- Eicosanoids interact with specific receptors, which are G-proteins coupled to second messenger effector systems.

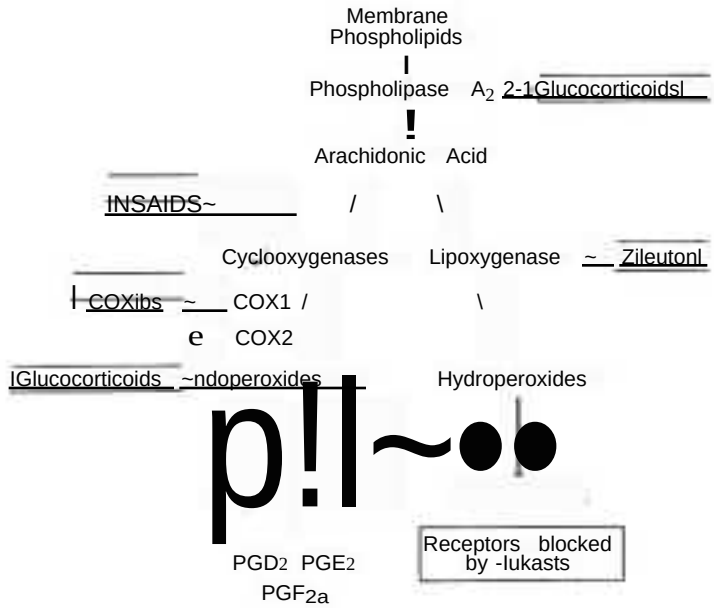


Figure VI-4-1. Drugs Acting on Elcosanoids

!~!~J~,~!~,~|~¡~!

Prostaglandins (PGs) are cytoprotective in the stomach, dilate renal vasculature, contract the uterus, and maintain the ductus arteriosus. Thrombaxane (T~) causes platelet aggregation. GI PGs and platelets T~s are synthesized by COX1 (const~utive). COX2 (inducible) synthesizes PGs involved in inflammation, fever, and pain. Both enzymes synthesize renal PGs –4 RBF.

LEUKOTRIENES (Lis)

- Formed (via hydroperoxides) from the action oflipoxygenases on arachidonic acid
  - LTB_4:
    - Mechanism of action: inflammatory mediator ~ neutrophil chemoattractant; activates PMNs; i free radical formation ~ cell damage
  - LTA_4, LTC_4, and LTD_4
    - Cause anaphylaxis and bronchoconstriction (role in asthma)
- Leukotrienes are "targets" for the following:
  - Glucocorticoids: ~J- phospholipase A_2 activity ~ contributes to both antiinflammatory and immunosuppressive actions
  - Zileuton: inhibits lipoxygenase ~J- LTsand is used in treatment of asthma
  - Zafirlukast and "-lukasts": LT-receptor antagonists used in treatment of asthma

PROSTAGLANDINS (PGs)

- PGs are formed (via endoperoxides) from the actions of cyclooxygenases (COXs).
- COX 1 is expressed in most tissues, including platelets and stomach, where it acts to synthesize thromboxane and cytoprotective prostaglandins, respectively.
- COX 2 is expressed in the brain and kidney and at sites of inflammation.

Note

Indomethacin is used to close a patent ductus arteriosus.

PGE_1

- Drugs:
  - Misoprostol (analog) used in treatment of NSAID-induced ulcers (protective action on gastric mucosa)
  - Alprostadil
    - Maintains patency of ductus arteriosus
    - Vasodilation; used in male impotence
- Contraindicated in pregnancy, unless used as an abortifacient (misoprostol in combination with mifepristone)

PGE_2

- Mechanism of action: uterine smooth muscle contraction
- Uses: dinoprostone can be used for "cervical ripening" and as abortifacient

PGF_{2a}

- Mechanism of action: uterine and bronchiolar smooth muscle contraction
- Drugs:
  - Carboprost used as abortifacient
  - Latanoprost for treatment of glaucoma (J- intraocular pressure)

PGI_2 (Prostacyclin)

- Platelet stabilizer and vasodilator
- **Drug: epoprostenol**
- Uses: pulmonary hypertension

PGE_2 and $PGF_{2\alpha}$

- Both ↑ in primary dysmenorrhea
- Therapeutic effects of NSAIDs may be due to inhibition of their synthesis

THROMBOXANES (TXAs)

TXA_2

- Platelet aggregator (inhibition of synthesis underlies protective role of acetylsalicylic acid [ASA] post-MI) and causes marked bronchoconstriction and vasoconstriction

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

- Most NSAIDs are nonselective inhibitors of cyclooxygenases, acting on both COX 1 and COX 2 isoforms to decrease formation of PGs and thromboxanes.
- They are analgesic, antipyretic, and antiinflammatory and have antiplatelet effects.
- Acetylsalicylic acid (ASA) is the prototype of the group, which includes more than 20 individual drugs.

Acetylsalicylic Acid (ASA; Aspirin)

- Causes irreversible inhibition of COX
- Covalent bond via acetylation of a serine hydroxyl group near the active site
- Actions are dose dependent:
  - *Antiplatelet aggregation.* Low dose, the basis for post-MI prophylaxis and to reduce the risk of recurrent TIAs
  - *Analgesia and antipyresis.* Moderate dose
  - *Antiinflammatory.* High doses
  - *Uric acid elimination*
    - Low to moderate doses: ↑ tubular secretion → hyperuricemia
    - High doses: ↑ tubular reabsorption → uricosuria
  - *Acid-base and electrolyte balance*
    - Dose-dependent actions
    - High therapeutic: mild uncoupling of oxidative phosphorylation → ↑ respiration → ↑ pCO_2 → *respiratory alkalosis* → renal compensation → ↑ HCO_3^- elimination → *compensated* respiratory alkalosis (pH = normal, ↑ HCO_3^-, ↑ pCO_2)
    - In adults, this can be a stable condition; in children → ↑ toxicity.
    - Toxic doses: inhibits respiratory center → ↑ respiration → ↑ pCO_2 → *respiratory acidosis* (↓ pH, ↑ HCO_3^-, normalization of pCO_2) plus inhibition of Krebs cycle and severe uncoupling of oxidative phosphorylation (↓ ATP) → *metabolic acidosis*, hyperthermia, and hypokalemia (↓ K^+).

Bridge to Physiology

Platelet Stability and Eicosanoids

Activation of TxA_2 receptors → stimulation of phospholipase C → ↑ PIP_2 hydrolysis → ↑ IP_3 → mobilization of bound Ca^{2+} → ↑ free Ca^{2+} → platelet aggregation.

Activation of PGI_2 receptors → stimulation of adenylyl cyclase → ↑ cAMP → ↑ activity of internal Ca^{2+} "pumps" → ↓ free Ca^{2+} → platelet stabilization.

- Side effects:
  - Gastrointestinal irritation: gastritis, ulcers, bleeding
  - Salicylism: tinnitus, vertigo, ↓ hearing-often first signs of toxicity
  - Bronchoconstriction: exacerbation of asthma
  - Hypersensitivity, especially the "triad" of asthma, nasal polyps, rhinitis
  - Reye syndrome: encephalopathy
  - ↑ bleeding time (antiplatelet): ↑ prothrombin time (high dose)
  - Chronic use: associated with renal dysfunction
  - Many drug interactions (ethanol ↑ gastrointestinal bleeding, ↑ effects of sulfonylurea and warfarin, ↓ effects of uricosurics)
- Aspirin overdose and management:
  - Extensions of the toxic actions described above, plus at high doses vasomotor collapse occurs, with both respiratory and renal failure.
  - No specific antidote, Management includes gastric lavage (+/- activated charcoal) plus ventilatory support and symptomatic management of acid-base and electrolyte imbalance, and the hyperthermia and resulting dehydration. ↑ urine volume and its alkalinization facilitate salicylate renal elimination. (Note: ASA follows zero-order elimination kinetics at toxic doses.)

Other NSAIDs

Types

- Reversible inhibitors of COX 1 and COX 2, with analgesic, antipyretic, and antiinflammatory actions, include:
  - Ibuprofen
  - Naproxen
  - Indomethacin
  - Ketorolac
  - Sulindac
- Comparisons with ASA:
  - Analgesia: ketorolac > ibuprofen/naproxen > ASA
  - Gastrointestinal irritation: < ASA, but still occurs (consider misoprostol)
  - Minimal effects on acid-base balance; no effects on uric acid elimination
  - Allergy: common, possible cross-hypersensitivity with ASA
  - Renal: chronic use may cause nephritis, nephritic syndrome, acute failure (via ↓ formation of PGE_2 and PGI_2, which normally maintain GFR and RBF)-does not occur with sulindac
- Drug interactions:
  - ↑ activity of sulfonylurea hypoglycemics, methotrexate, and lithium (not ASA)
  - In treatment of hypertension, may ↓ activity of ACE inhibitors, loop diuretics, and ~ blockers
- Specific toxicities:
  - Indomethacin: thrombocytopenia, agranulocytosis, and > CNS effects
  - Sulindac: Stevens-Johnson syndrome, hematotoxicity

Selective COX 2 Inhibitors: Celecoxib

- Compared with conventional NSAIDs, it is no more effective as an antiinflammatory agent.
- Primary differences are:
  - Less gastrointestinal toxicity
  - Less antiplatelet action
- However, it ↑ prothrombin time (PT) when used with warfarin and may possibly exert prothombotic effects via inhibition of endothelial cell function.
- Cross-hypersensitivity between celecoxib and sulfonamides
- Potential cardiotoxicity resulted in a withdrawal of rofecoxib from the market in October 2004.

Acetaminophen

- Mechanisms
  - No inhibition of COX in peripheral tissues and lacks significant antiinflammatory effects
  - Equivalent analgesic and antipyretic activity to ASA due to inhibition of cyclooxygenases in the CNS .
- Comparisons with ASA:
  - No antiplatelet action
  - Not implicated in Reye syndrome
  - No effects on uric acid
  - Not bronchospastic
  - Gastrointestinal distress is minimal at low to moderate doses
- Overdose and management:
  - Hepatotoxicity-Acetaminophen is metabolized mainly by liver glucuronyl transferase to form the inactive conjugate. A minor pathway (via P450) results in formation of a reactive metabolite (N-acetylbenzoquinoneimine), which is inactivated by glutathione (GSH). In overdose situations, the finite stores of GSH are depleted. Once this happens, the metabolite reacts with hepatocytes, causing nausea and vomiting, abdominal pain, and ultimately liver failure due to centrilobular necrosis. Chronic use of ethanol enhances liver toxicity via induction of P450.
  - Management of the hepatotoxicity: N-acetylcysteine (supplies -SH groups), preferably within the first 12 hours

Clinical Correlate

"Tot" Toxicity

Young children are gustatory explorers. Among the compounds responsible for toxicity in youngsters under the age of 3 years are three items commonly found in households with "tots": aspirin, acetaminophen (people know about Reye syndrome!), and supplementary iron tablets.

Chapter Summary

Eicosanoid Pharmacology

Eicosanoids are synthesized and released on demand to interact with specific G-protein-coupled receptors. They include the leukotrienes (LTs), prostaglandins (PGs), and thromboxanes (TxAs).

Figure VI-4-1 presents the pathways for the synthesis of PGI_2, PGE_2, PGF_{2a}, TXA_2, and the leukotrienes from the membrane phospholipids. It also shows the sites of action of the glucocorticoids, NSAIDs, COX 2 inhibitors, zileuton, and zafirlukast.

The physiologic functions of relevant eicosanoids interacting with specific receptor types and the clinical aspects of the drugs affecting these actions are considered.

Nonsteroidal Antiinflammatory Drugs

There are more than 20 nonsteroidal antiinflammatory drugs (NSAIDs) in use. Acetylsalicylic acid (ASA), the prototype, like most other NSAIDS, is a nonselective inhibitor of the cyclooxygenases; however, it binds in an irreversible fashion, whereas the others do so in a reversible manner.

Progressively higher doses of ASA cause antiplatelet aggregation, analgesia, antipyresis, and antiinflammation. The mechanisms responsible for each of these responses, modes of excretion, effects on the acid-base balance, and side effects are discussed.

Aspirin overdoses can cause vasomotor collapse and renal failure. The management of such toxic overdose cases is considered, as are the doses required to elicit such dangerous effects in adults and children.

Other NSAIDs, including ibuprofen, naproxen, indomethacin, ketorolac, and sulindac, also have analgesic, antipyretic, and antiinflammatory properties. The properties of these NSAIDs are compared with those of ASA.

Celecoxib is a selective inhibitor of cyclooxygenase 2 (COX 2), providing less gastrointestinal and antiplatelet activity than are imparted by the nonselective COX inhibitors.

Acetaminophen is not an NSAID but an analgesic and antipyretic. Its properties are compared with those of ASA. It has the potential for creating severe liver damage.

Drugs Used for Treatment of Rheumatoid Arthritis

5

Table VI-5-1. Disease-Modifying Antirheumatic Drugs (DMARDs)

Drug	Mechanism(s)	Side Effects
Hydroxychloroquine	Stabilizes lysosomes and ↓ chemotaxis	GI distress and visual dysfunction (cinchonism), hemolysis in G6PD deficiency
Methotrexate	Cytotoxic to lymphocytes	Hematotoxicity, mucositis, crystalluria
Sulfasalazine	Sulfapyridine ~↓ B-cell functions; 5-ASA possibly inhibits COX	GI distress, rash, hemolysis in G6PD deficiency, SLE-like syndrome
Glucocorticoids	↓ LTs,ILs, and platelet-activating factor (PAF)	ACTH suppression, cushingoid state, osteoporosis, GI distress, glaucoma
Gold salts	↓ Lysosomal and macrophage functions	Dermatitis, hematotoxicity, nephrotoxicity
Penicillamine	Suppresses T cells and circulating rheumatoid factor	Proteinuria, hematotoxicity, autoimmune disease
Etanercept	Binds tumor necrosis factor (TNF); is a recombinant form of TNF receptor	Hypersensitivity, injection-site reactions, infections
Infliximab	Monoclonal antibody to TNF	Infusion reactions, infections
Leflunomide	Inhibits dihydro-orotic acid dehydrogenase (DHOD) ~↓ UMP~ ↓ ribonucleotides ~ arrests lymphocytes in G_1	Alopecia, rash, diarrhea, hepatotoxicity
Anakinra	IL-l receptor antagonist	Infection, injection-site reaction

- NSAIDs are commonly used for initial management of rheumatoid arthritis (RA), but the doses required generally result in marked adverse effects.
- NSAIDs decrease pain and swelling but have no beneficial effects on the course of the disease or on bone deterioration.
- DMARDs are thought to slow disease progression.
- DMARDs may be started with NSAIDs at the time of initial diagnosis if symptoms are severe because DMARDs take 2 weeks to 6 months to work.
- Hydroxychloroquine is often recommended for mild arthritis and methotrexate (MTX) for moderate to severe RA.
- Other DMARDs are used less frequently, sometimes in combination regimens for refractory cases.

Chapter Summary

NSAIDs are commonly used to help alleviate the pain and inflammation associated with rheumatoid arthritis. However, they have no effect on the progress of the disease. Disease-modifying antirheumatic drugs (DMARDs) are used with the hope of slowing the disease progress. Table VI-5-1 summarizes the mechanisms of action and the adverse effects of the DMARDs.

Drugs Used for Treatment of Gout

6

TREATMENT Of ACUTE INfLAMMATORY EPISODES

- **Colchicine,** indomethacin, other NSAIDs (naproxen, sulindac), and intra-articular steroids
- Colchicine
  - Mechanism of action: binds to tubulin -+1. microtubular polymerization, ↓ LTB_4, and ↓ leukocyte and granulocyte migration
  - Side effects:
    - Acute: include diarrhea and gastrointestinal pain
    - Longer use: hematuria, alopecia, myelosuppression, gastritis, and peripheral neuropathy

PROPHYLAXIS OF CHRONIC GOUT

- Drug strategy: reduction of the uric acid pool
- Drugs: **allopurinol** and **probenecid**
- Action of allopurinol:
  - Prodrug (a suicide substrate) converted by xanthine oxidase, forming alloxanthine, which inhibits the enzyme ~J.,purine metabolism ~J.,uric acid.
  - Also used in cancer chemotherapy and radiation therapy
- Side effects of allopurinol:
  - Include gastrointestinal distress, peripheral neuropathy, rash, vasculitis, and stone formation
  - Inhibits 6-mercaptopurine (6-MP) metabolism
- Action of probenecid:
  - Inhibits proximal tubular reabsorption of urate, but ineffective if GFR <50 mLimin
  - Also inhibits secretion of many acidic drugs, e.g., cephalosporins, fluoroquinolones
- Side effects of probenecid:
  - Include GI distress, rash, nephrotic syndrome, crystallization if high excretion of uric acid
  - ASA may ↓ effects

Chapter Summary

Acute inflammatory episodes are treated with colchicine, NSAIDs, and intraarticular steroids. The mode of colchicine's action and its adverse effects are considered.

Chronic gout is treated with allopurinol, a suicide inhibitor of xanthine oxidase. The goal is to reduce the uric acid pool by inhibiting its formation from purines. The adverse effects of allopurinol are considered.

Probenecid decreases the uric acid pool by inhibiting the proximal tubular reabsorption of urate. Its use and side effects are also discussed.

Glucocorticoids

7

Table VI-7-1. Synthetic Derivatives of Cortisol

Drugs	Glucocorticoid Activity	Mineralocorticoid Activity	Duration
Cortisol	1	1	Short
Prednisone	4	03	Medium
Triamcinolone	5	0	Intermediate
Betamethasone	25	0	Long-acting
Dexamethasone	30	0	Long-acting

- Mechanisms of action:
  - Cellular effects
    - ↓ leukocyte migration
    - ↑ lysosomal membrane stability ~ ↓ phagocytosis
    - ↓ capillary permeability
  - Biochemical actions
    - Inhibit PL~ (via lipocortin expression) ~ ↓ PGs and ↓ LTs
    - ↓ expression of COX 2
    - ↓ platelet-activating factor
    - ↓ interleukins (e.g., IL-2)
- Uses: antiinflammatory and immunosuppressive
- Side effects:
  - Suppression of ACTH: cortical atrophy, malaise, myalgia, arthralgia, and fever- may result in a shock state with abrupt withdrawal
  - Iatrogenic cushingoid syndrome ~ fat deposition, muscle weakness/atrophy, bruising, acne
  - Hyperglycemia due to ↑ gluconeogenesis ~ increased insulin demand and other adverse effects
  - Osteoporosis: vertebral fractures-aseptic hip necrosis
  - ↑ gastrointestinal acid and pepsin release ~ ulcers, gastrointestinal bleeding
  - Electrolyte imbalance: Nat/water retention ~ edema and hypertension, hypokalemic alkalosis, hypocalcemia

Clinical Correlate

Minimize Steroidal Toxicity

- Alternate-day therapy; **local** application (e.g., aerosols)
- Dose-tapering to avoid cortical suppression

- ↓ skeletal growth in children
- ↓ wound healing, ↑ infections (e.g., thrush)
- ↑ glaucoma, ↑ cataracts (via ↑ sorbitol)
- ↑ mental dysfunction

Chapter Summary

Synthetic derivatives of cortisol are often used to manage inflammatory conditions or to promote immunosuppression. This chapter discusses the duration of action of several antiinflammatory steroids, their cellular effects and biochemical actions, as well as the many and severe adverse effects.

Drugs Used for Treatmentot Asthma

8

- Asthma is an inflammatory disease associated with bronchial hyperactivity (BHR), bronchospasm, t mucus secretion, edema, and cellular infiltration.
- Early asthmatic responses (EAR) lasting from 30 to 60 minutes are associated with bronchospasm from the actions of released histamine and leukotrienes.
- Late asthmatic responses (LAR) involve infiltration of eosinophils and lymphocytes into airways -7 bronchoconstriction and inflammation with mucous plugging. .
- Management of asthma includes bronchodilators to provide short-term relief and antiinflammatory agents that reduce bronchial hyperactivity and protect against cellular infiltration.

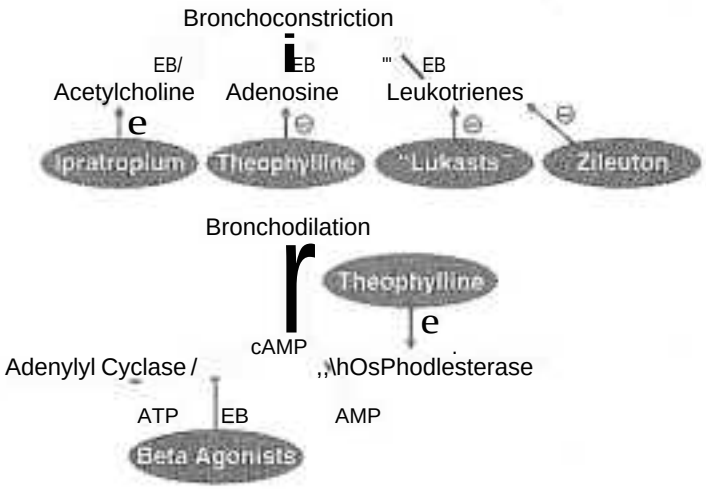


Figure VI-8-1. Drug Actions on Bronchiolar Smooth Muscle

BETA-RECEPTOR AGONISTS

- Beta-2 selective drugs (albuterol,, metaproterenol, terbutaline) are widely used for relief of acute bronchoconstriction and in prophylaxis of exercise-induced asthma *(see* Figure VI-8-1).
- Longer-acting drugs (e.g., salmeterol) may decrease nighttime attacks (prophylaxis only) and permit dosage reduction of other agents.
- Aerosolic forms have low potential for systemic toxicity but may cause anxiety, muscle tremors, and cardiovascular toxicity with overuse.

MUSCARINIC-RECEPTOR BLOCKERS

- Ipratropium and other M blockers used via inhalation cause bronchodilation in acute asthma, especially in COPD patients, and they may be safer than P agonists are in patients with cardiovascular disease.
- They are the drugs of choice in bronchospasm caused by P blockers.
- There are minor atropine-like effects.

THEOPHYLLINE

- Bronchodilates via inhibition of phosphodiesterase (PDE) ~ i cAMP and also by antagonism of adenosine (a bronchoconstrictor)
- Mainly adjunctive; regular use may decrease symptoms, but narrow therapeutic window predisposes to toxicity ~ nausea, diarrhea, CV (i HR, arrhythmias) and CNS excitation
- Many drug interactions; toxicity i by erythromycin, cimetidine, and fluoroquinolones
- Aminophylline IV sometimes used in bronchospasm or status asthmaticus

CROMOLYN AND NEDOCROMIL

- Prevent degranulation of pulmonary mast cells and J.. release of histamine, PAF, and LTC_4 from inflammatory cells
- Prophylactic use:
  - J.. symptoms and bronchial hyperactivity (BHR), especially responses to allergens
  - Minimal systemic toxicity but may cause throat irritation and cough
  - Relieved by a P_2 agonist

GUJCOCORTICOIDS

- Block mediator release and J.. BHR via J.. PGs, LTs, and inflammatory interleukins (ILs)
- Surface-active drugs (beclomethasone, flunisolide) used via inhalation for both acute attacks and for prophylaxis
- May cause oropharyngeal candidiasis and systemic effects with excessive use, including J.. long bone growth in children
- Low dosage may also prevent the desensitization of P receptors that can occur with overuse of P_2 agonist
- Prednisone (oral) and IV steroids generally reserved for severe acute attacks

Antileukotrienes

- Zafirlukast and montelukast are antagonists at LTD_4 receptors with slow onset of activity used prophylactically for many forms of asthma, including antigen, exercise, or drug-induced (e.g., ASA).
- Side effects include diarrhea, headache, and ↑ infections.
- Zileuton is a selective inhibitor of lipoxygenases (LOX), ↓ formation of all LTs. It has a more rapid onset (1-3 hours) and is adjunctive to steroids. Side effects include asthenia, headache, and ↑ LFTs.

Chapter Summary

The management of asthma involves the use of bronchodilators to relieve short-term effects and antiinflammatories to reduce bronchial hyperactivity and protect against cellular infiltration.

~fselective agonists are used for the relief of acute bronchoconstriction and as a prophylaxis in exercise-induced asthma. longer-acting ~-adrenoceptor agonists can be used prophylactically to decrease nighttime attacks. The mechanisms responsible for their effects are shown in Figure VI-8-1, which illustrates the action of antiasthmatic drugs.

The roles of muscarinic receptor blockers, theophylline, cromolyn, and nedocromil, glucocorticoids, and antileukotrienes in the treatment of asthma are discussed. Their modes of action are also illustrated in Figure VI-8-1.

List of Drugs for Inflammatory Disorders and Pradice Questiens

9

Histamine and Antihistamines

- H_1 antagonists: diphenhydramine, promethazine, meclizine, hydroxyzine, loratadine
- H_2 antagonists: cimetidine, ranitidine

Drugs Used in Gastrointestinal Dysfunction

- Proton pump inhibitor: omeprazole
- PGE_1 analog: misoprostol
- Polymer: sucralfate

Drugs Acting on Serotonergic Systems

- SHT_{1a} partial agonist: buspirone
- SHT_{1d} agonist: sumatriptan
- SHT_2 antagonist: cyproheptadine, atypical antipsychotics
- SHT_3 antagonist: ondansetron
- SHT_4 agonist: tegaserod

Antiemetics

- DA antagonist: metoclopramide, prochlorperazine
- HI antagonist: meclizine, promethazine
- Muscarinic antagonist: scopolamine
- Cannabinoid: dronabinol
- SHT_3 antagonist: ondansetron
- NK_1 antagonist: aprepitant

NSAIDs

- Aspirin, indomethacin, ibuprofen, naproxen, sulindac
- COX 2 inhibitor: celecoxib
- Acetaminophen

Glucocorticoids

- Prednisone, triamcinolone, dexamethasone

Drugs Used for Treatment of Gout

- Acute: colchicine, indomethacin
- Chronic: allopurinol, probenecid

Drugs Used for Treatment of RA

- NSAIDs
- DMARDs: methotrexate, etanercept, infliximab, anakinra, and others

Drugs Used for Treatment of Asthma

- ~2 agonists: albuterol, terbutaline
- M-blocker: ipratropium
- Methylxanthine: theophylline
- Mast-cell stabilizer: cromolyn
- Steroids: flunisolide
- LT modifiers: zafirlukast, zileuton

QUESTIONS

1. A patient using NSAIDs for chronic pain develops a bleeding ulcer and suffers considerable pain and blood loss. Which one of the following is most likely to occur if the patient stands up quickly?

   (A) Bradycardia
   (B) Bronchospasm
   (C) Miosis
   (D) Salivation
   (E) Sweating

2. A 2-year-old child is brought into the emergency department in convulsions. According to her mother, she had ingested most of a bottle of "sleeping pills;' an over-the-counter preparation. What do the sleeping pills she ingested probably contain?

   (A) Caffeine
   (B) Chlorpromazine
   (C) Diphenhydramine
   (D) Meperidine
   (E) Temazepam

3. Which of the following statements about the management of patients with gastrointestinal ulcers is accurate?

   (A) Overall, Hz-receptor blockers are as effective as proton pump inhibitors.
   (B) Antimicrobial regimens that eradicate *Helicobacter pylori* are >98% effective in gastrointestinal ulcers.
   (C) Omeprazole is effective because it activates PGE_1 receptors.
   (D) Sucralfate polymerizes in the gut, forming a protective coat over ulcer beds.
   (E) Steroids provide useful antiinflammatory effects in gastrointestinal ulcers.

4. Which one of the following statements regarding drug effects on serotonin receptor systems is accurate?

   (A) SHTz-receptor blockers counteract bronchoconstriction and diarrhea of carcinoid.
   (B) Sumatriptan is an antiemetic because it blocks SHT_3 receptors.
   (C) MAO type B inhibitors lead to increased levels of serotonin in the CNS.
   (D) Ondansetron is used in migraine because it activates SHT Id receptors.
   (E) Inhibitors of SHT reuptake into nerve endings in the CNS have antipsychotic effects.

5. A patient with RA is being treated with ibuprofen, but joint pain and stiffness are increasing. His physician prescribes another drug to be used with ibuprofen that may slow progression of the disease. Unfortunately, side effects develop, including dizziness, tinnitus, blurred vision, and pruritus. Ocular examination reveals corneal deposits and slight retinal pigmentation. What is the drug more recently prescribed likely to be?

   (A) Auranofin
   (B) Etanercept
   (C) Hydroxychloroquine
   (D) Methotrexate
   (E) Thioridazine

6. A patient suffers from troublesome allergic rhinitis due to pollen, and you want to prescribe a drug for her that is least likely to cause sedation. What would your best choice be?

   (A) Betamethasone
   (B) Cimetidine
   (C) Hydroxyzine
   (D) Loratadine
   (E) Metoclopramide

7. The widely used anticonvulsant phenytoin is often implicated in drug interactions. If a patient takes phenytoin but also cimetidine for a gastrointestinal ulcer, which one of the following is likely to occur?

   (A) J, half-life of phenytoin
   (B) i half-life of cimetidine
   (C) i clearance of phenytoin
   (D) Displacement of cimetidine from plasma proteins
   (E) i half-life of phenytoin

8. Which one of the following pairs of "drug; mechanism of action" is accurate?

   (A) Dexamethasone: J, expression of lipoxygenase
   (B) Leflunomide: inhibition of dihydro-orotic acid dehydrogenase
   (C) Misoprostol: activates PGF_{2a} receptors
   (D) Colchicine: i microtubular polymerization
   (E) Ketorolac: selective inhibition of COX 2

9. A child suffering from acute asthma with intermittent bronchospasm is brought to a hospital ER, and oxygen is administered to establish a $Pa0_2$ >60 mm Hg. Which of the following statements about the further management of this patient is most accurate?

   (A) Benzodiazepines should be given for sedation.
   (B) Inhaled steroids are drugs of choice in acute asthma.
   (C) Frequent high-dose delivery of an inhaled ~2 agonist is indicated.
   (D) Aminophylline is always used if bronchospasm is present.
   (E) Zafirlukast should be administered parenterally.

10. Which one of the following is LEAST likely to be an effect of histamine?

(A) Bronchiolar constriction
(B) Hypotension
(C) Increased gastric secretion
(D) Activation of type C pain fibers
(E) Decreased capillary permeability

11. For temporary maintenance of a patent ductus arteriosus prior to cardiac surgery in an infant; what is the drug of choice?

(A) Alprostadil
(B) Indomethacin
(C) Epoprostenol
(D) Celecoxib
(E) Zileuton

12. Following an overdose of an over-the-counter drug, a young college student has marked gastrointestinal distress and is lethargic and confused, with an elevated body temperature. Lab analysis of blood reveals: t pCO_2' ·|· HC03~' ·|· K+, and an anion gap acidosis. The most likely cause of these signs and symptoms is a toxic dose of

(A) acetaminophen
(B) acetylsalicylic acid
(C) diphenhydramine
(D) pseudoephedrine
(E) naproxen

13. In an overdose situation, the elimination of aspirin follows zero-order kinetics. What does this mean?

(A) No drug appears in the urine.
(B) The metabolism rate of aspirin is zero.
(C) Elimination rate is directly proportional to plasma concentration.
(D) Manipulations of urinary pH have zero effect.
(E) Plasma concentrations decrease linearly with time.

14. Which one of the following antiinflammatory drugs used in rheumatoid arthritis has a mechanism of action that leads to a decrease in the activity of tumor necrosis factor?

(A) Etanercept
(B) Sulfasalazine
(C) Prednisone
(D) Celecoxib
(E) Penicillamine

15. When used in the management of inflammatory disorders, glucocorticoids are likely to cause

(A) hypoglycemia
(B) decreases in blood pressure
(C) anabolic actions in wound healing
(D) increases in intraocular pressure
(E) sedation

16. A reasonable explanation for the therapeutic effects of ibuprofen or naproxen in primary dysmenorrhea is that these drugs

(A) ↓ PGE_2 and $PGF_{2\alpha}$
(B) selectively inhibit COX 2
(C) ↓ LTB_4
(D) inhibit PLA_2
(E) ↑ PI_2

17. A patient suffering from chronic gout has renal calculi and is a "high excretor" of uric acid. Past drug history includes severe hypersensitivity to antibacterial sulfonamides. What is the most appropriate drug for treatment of this patient?

(A) Allopurinol
(B) Acetylsalicylic acid
(C) Indomethacin
(D) Colchicine
(E) Probenecid

18. The plasma levels of ketoconazole are lower than normal following its oral absorption in patients treated with ranitidine. What is the reason for this?

(A) The induction of enzymes that metabolize ketoconazole
(B) Ketoconazole requires an acid environment for its oral absorption
(C) Ranitidine binds acidic drugs in the gastrointestinal tract
(D) Increased gastrointestinal transit time because of the prokinetic effects of ranitidine
(E) Competition for transport mechanisms in the gastrointestinal tract

19. Why is cromolyn useful in many patients with asthma?

(A) It inhibits COX 2
(B) It blocks adenosine receptors in bronchiolar smooth muscle
(C) It prevents antigen-induced degranulation of mast cells
(D) It inhibits phosphodiesterase
(E) It ↓ mRNA for IL-2

20. Which one of the following is approved for "ripening" of an unfavorable cervix at or near term in a pregnant patient?

(A) Alprostadil
(B) Ergonovine
(C) Dinoprostone
(D) Terbutaline
(E) Morphine

21. 6-Mercaptopurine (6-MP), frequently used in drug regimens for neoplastic disease, is metabolized by xanthine oxidase. Major dose reductions are advised in patients who are being treated with which of the following?

(A) Cimetidine
(B) Sulfinpyrazone
(C) Allopurinol
(D) Indomethacin
(E) Acetylsalicylic acid

22. Constipation is a possible side effect of drugs taken by the oral route, but it is highly unlikely to occur with the use of which of the following?

(A) Diphenhydramine
(B) Docusate
(C) Promethazine
(D) Loperamide
(E) Scopolamine

Questions 23 and 24

According to the *Handbook of Poisoning and Toxicology* published by the American Pharmaceutical Association, the dose of acetaminophen causing hepatotoxicity is 150 mg/kg. In an adult weighing 70 kg, this would represent the ingestion of about 10.5 g, or 21 acetaminophen caplets, each containing 500 mg.

23. In an overdose of acetaminophen, protection may be afforded by the administration of acetylcysteine because this compound

(A) increases the activity of hepatic cytochrome P450 isozymes

(B) acts on the kidney to decrease tubular reabsorption of a toxic metabolite

(C) enhances metabolic inactivation of N-acetyl-benzoquinoneimine

(D) acts as a chelating agent in the gastrointestinal tract

(E) increases hepatic blood flow

24. In a person who regularly consumes greater than average quantities of ethanol daily (e.g., two bottles of wine), the potential for hepatotoxicity due to acetaminophen is greater than normal. What is the most likely explanation for this?

(A) Cirrhosis of the liver

(B) Ethanol inhibits the metabolism of acetaminophen

(C) Most beer drinkers are smokers, and nicotine sensitizes the liver to toxins

(D) Nutritional deficiency

(E) Ethanol induces a P450 that forms a toxic metabolite

ANSWERS

1. Answer: E. Back to basics! Blood loss from any cause elicits increased sympathetic outflow, as does pain. In a patient hypotensive because of blood loss, the act of standing causes further activation of SANS. Anticipate signs and symptoms of sympathetic stimulation, including tachycardia, bronchiolar dilation, mydriasis, dry mouth, and sweating.

2. Answer: C. Over-the-counter (OTe) sleep aids invariably contain sedating antihistamines such as diphenhydramine. Sometimes called sedative-autonomies, overdoses of such drugs are dangerous, especially in small children. They usually have muscarinic-blocking (atropine-like) effects causing hyperthermia, and they lower the seizure threshold, leading to convulsions. Chlorpromazine is very similar in its pharmacology but is not available OTC and would not be appropriate as a sleeping aid because of its autonomic side effects. Temazepam, a benzodiazepine, is used as a sleeping pill but requires a prescription and raises the seizure threshold. Meperidine is an opioid-analgesic that can cause seizures in OD, but it is not used as a sleeping aid or available OTe. Caffeine is a CNS stimulant.

3. Answer: D. Sucralfate polymerizes in the gastrointestinal tract, forming a protective gel-like coating of ulcer beds -7 t healing and J, ulcer recurrence. Overall, proton pump inhibitors such as omeprazole provide more rapid pain relief and faster healing than do antihistamines for ulcers caused by acid secretion. Misoprostol, not omeprazole, activates PGE_1 receptors. Not all gastrointestinal ulcers are associated with *Helicobacter pylori,* so a cure rate of 98% is not feasible in principle and (at best) is only in the 95% range in treatment of ulcers established to be associated with the bacterium. Antiinflammatory steroids cause gastrointestinal ulcers and would be contraindicated.

4. Answer: A. Cyproheptadine and ketanserin are $5HT_2$ receptor blockers used in the management of carcinoid and related states; cyproheptadine also has HI-receptor blocking effects. Sumatriptan is used in migraine (not for emesis) and exerts its effects on cerebral vasculature via activation of 5HT ld receptors. Ondansetron is the antiemetic, a blocker of 5HT3 receptors. Because serotonin is metabolized by MAO type A (which also metabolizes NE and tyramine), drugs like selegiline have no effects on 5HT levels in the brain. Newer antipsychotic drugs (e.g., olanzapine) are $5HT_2$-receptor antagonists, so it does not appear likely that inhibition of 5HT reuptake would have value in psychotic disorders-such an action may actually cause an exacerbation.

5. Answer: C. Ocular toxicity is characteristic of chloroquine and hydroxychloroquine. Corneal deposits are reversible, but retinal pigmentation can ultimately lead to blindness. Patients will complain about gastrointestinal distress, visual dysfunction, ringing in the ears (note that tinnitus also occurs in salicylism), and "itchy skin." Hydroxychloroquine also promotes oxidative stress that can lead to hemolysis in G6PD deficiency. DMARDs include gold salts (e.g., auranofin), methotrexate, and etanercept, but thioridazine is a phenothiazine used as an antipsychotic; it lacks an antiinflammatory effect, but does cause retinal pigmentation.

6. Answer: D. The usual choice for pollen-induced allergies would be an HI antagonist. Of the two listed, loratadine would be the best choice in this case because it does not cross the blood-brain barrier and is nonsedating; hydroxyzine is an effective CNS depressant used for preoperative sedation. Cromolyn (not listed) can also be used in allergic rhinitis and is also nonsedating. Betamethasone, a potent antiinflammatory steroid, is less effective than antihistamines in this situation and would cause more serious side effects. Metoclopramide is a DA-receptor antagonist and prokinetic used as an antiemetic and in GERD. Cimetidine is the prototype Hz antagonist used in gastrointestinal ulcers.

7. **Answer: E.** Cimetidine is an inhibitor of the hepatic cytochrome P450 isoform that metabolizes phenytoin, consequently ↓ its clearance and thus ↑ its elimination half-life. The hepatic metabolism of many other drugs can be inhibited by cimetidine, possibly necessitating dose reductions to avoid toxicity, including beta blockers, isoniazid, procainamide, metronidazole, tricyclic antidepressants, and warfarin.

8. **Answer: B.** Leflunomide, used in rheumatoid arthritis, inhibits dihydro-orotic acid dehydrogenase ~↓, formation of UMP ~↓, de novo synthesis of ribonucleotides ~ arrest of lymphocytes in the G_1 phase. Glucocorticoids do not decrease expression of lipoxygenase, but by preventing arachidonate formation, they ↓ activity of the pathway. Misoprostol, used in NSAID-induced gastrointestinal ulcers, activates receptors; colchicine ↓ microtubular polymerization; ketorolac is a potent NSAID, but a nonselective inhibitor of cyclooxygenases.

9. **Answer:** C. Inhaled ~2-selective agonists are preferred in most cases of acute asthma. Intravenous steroids are also helpful, but inhaled steroids should be avoided because they may cause bronchospasm. Despite anxiety and agitation that frequently accompany acute attacks of asthma, sedatives are not generally recommended because they exert respiratory depressant actions. Zafirlukast, a leukotriene-receptor antagonist, is of minimal value in acute asthma. (Avoid answers with the word *always.)*

10. **Answer: E.** The activation of HI receptors in bronchiolar smooth muscle leads to contraction ~ bronchoconstriction, but in vascular smooth muscle relaxation (via release of NO) ~ hypotension. HI receptor activation increases firing rate of type C afferent pain fibers in the periphery, and activation of H_2 receptors leads to increased gastric acid secretion. However, the release of histamine is associated with urticaria and edema because of *increases* in capillary permeability.

11. **Answer: A.** During fetal development, the ductus arteriosus is kept open by prostaglandins. For temporary maintenance of patency in the infant, the PGE_1 analog alprostadil is used. Closure of the ductus in the infant can often be accomplished by intravenous indomethacin, which ↓ PG synthesis by inhibiting COX. Epoprostenol is a prostacyclin analog used in primary pulmonary hypertension.

12. **Answer: B.** If the patient had been able to mention tinnitus, this would be a classic case of aspirin poisoning. At high salicylate blood levels, the combination of effects leading to respiratory depression (respiratory acidosis) and metabolic acidosis results in the observed pH and electrolyte changes, the anion gap (a marker for acidosis), and hyperthermia.

13. **Answer: E.** Back to basic principles. Zero-order elimination means that plasma levels of a drug decrease linearly with time. This occurs with ASA at toxic doses, with phenytoin at high therapeutic doses, and with ethanol at all doses. Enzymes that metabolize ASA are saturated at high plasma levels ~ constant rate of metabolism = zero-order kinetics. Remember that application of the Henderson-Hasselbalch principle can be important in drug overdose situations. In the case of aspirin, a weak acid, urinary alkalinization favors ionization of the drug ~↓, tubular reabsorption ~ ↑ renal elimination.

14. **Answer:** A. Etanercept binds to tumor necrosis factor (TNF), resulting in the inactivation of this cytokine, which plays a major role in a number of inflammatory disorders, including Crohn disease and rheumatoid arthritis. In the synovium, TNF recruits inflammatory cells and leads to neoangiogenesis and joint destruction. Infliximab, a monoclonal antibody, also inactivates TNF.

15. Answer: D. Ocular side effects of glucocorticoids include the development of cataracts and glaucoma through increases in increased intraocular pressure (lOP). All of the other effects listed are "opposites;' so anticipate possible hyperglycemia, hypertension, decreased wound healing, and CNS excitatory effects that have been interpreted as psychosis.

16. Answer: A. PGE_z and PGF_{za} both increase in primary dysmenorrhea, and the therapeutic effects of NSAIDs appear to be due to inhibition of the synthesis of these prostaglandins. Both ibuprofen and naproxen are nonselective COX inhibitors that can inhibit the synthesis of prostacyclin (PGl_z). NSAIDs do not inhibit phospholipase Az, and they do not decrease leukotrienes.

17. Answer: A. In chronic gout, the strategy is to decrease uric acid formation from purines by inhibiting xanthine oxidase with allopurinol or increasing urate elimination with uricosurics such as probenecid or sulfinpyrazone. The latter drugs cause formation of urate crystals in "high excreters" of uric acid, and there is potential cross-allergenicity between them and antibacterial sulfonamides, which are structurally related. Colchicine and NSAIDs are less effective and cause more side effects when used. in chronic gout. Although ASA is uricosuric at antiintlammatory doses, its toxicity makes the drug a poor choice.

18. Answer: B. Several drugs, including ketoconazole and tluoroquinolones, require an acidic environment in the gastrointestinal tract for effective absorption into the systemic circulation. Drugs used in treatment of gastrointestinal ulcers commonly increase gastric pH, leading to the J.. absorption of such drugs and, consequently, a J.. in their effects.

19. Answer: C. Cromolyn is a mast-cell stabilizer used in asthma (especially antigen-induced) and in food allergies. Inhibition of degranulation with decreased release of histamine and eicosanoids contributes to its antiintlammatory effectiveness in asthma, where it is used for prophylaxis. Methylxanthines, such as theophylline, exert bronchodilating effects via their inhibition of phosphodiesterases and their antagonism of adenosine receptors. Steroids used in asthma J.. bronchial hyperactivity by several mechanisms, including inhibition of interleukin synthesis. COX 2 inhibitors have no established role in asthma management.

20. Answer: C. Dinoprostone is a PGE_z agonist that stimulates contractions in the gravid uterus similar to the contractions of term labor. Ergonovine causes more profound smooth muscle contraction (both uterine and vascular) and is used for control of postpartum hemorrhage. Alprostadil is a PGE_1 agonist that causes vasodilation and is used in erectile dysfunction. Uterine contraction is largely under SANS control; a ~z agonist (e.g., terbutaline) will cause relaxation, and such drugs are used in preterm labor. CNS depressants also tend to relax uterine smooth muscle and prolong delivery.

21. Answer: C. Allopurinol is a uricosuric drug used in chronic gout that prevents formation of uric acid from purines by acting as a suicide substrate of xanthine oxidase. The drug is commonly used in patients undergoing treatment of cancer to slow down formation of uric acid derived from purines released by the cytotoxic action of drugs or radiation. The metabolism of 6-mercaptopurine (6-MP), a substrate for xanthine oxidase, is also inhibited by allopurinol, necessitating a major dose reduction to avoid its toxic effects.

22. Answer: B. Docusate is a stool-softening laxative that facilitates mixing of oil and water via its surfactant properties. Drugs that have muscarinic blocking effects, such as scopolamine and the antihistamines diphenhydramine and promethazine, tend to cause constipation by decreasing gastrointestinal motility. Loperamide is an opioid derivative, with no analgesic activity, used in the treatment of diarrheal states.

23. Answer: C. Acetylcysteine is the antidote to acetaminophen in overdose and should be administered within 12 hours for maximum effectiveness. It enhances the elimination of the reactive metabolite N-acetyl~benzoquinoneimine, which is responsible for liver damage. In overdose of acetaminophen, the metabolite accumulates because there is limited availability of reduced glutathione (GSH). The precise mechanism of action of acetylcysteine is unclear, but it either i the availability of GSH, which would normally inactivate the reactive metabolite, or it interacts with and inactivates the metabolite.

24. Answer. E. Ethanol has mixed effects on liver metabolism of drugs. Acutely, it can act as an enzyme inhibitor, but chronic use may lead to enzyme induction. Acetaminophen is metabolized mainly via conjugation reactions, but a minor pathway involving P-450 (probably the CYP2E1 isoform) results in formation of small amounts of the reactive metabolite, which is (normally) rapidly inactivated by GSH. The chronic ingestion of more than average amounts of ethanol induces the formation of the P-450 isozyme that converts acetaminophen to its reactive metabolite. Thus, more than normal amounts of N-acetyl-benzoquinoneimine would be formed in an overdose situation, resulting in enhanced hepatotoxicity.

SECTION VII

Drugs Used in Blood Disorders

Anticoagulants

1

Blood coagulates by transformation of soluble fibrinogen into insoluble fibrin. Circulating proteins interact in a "cascade;' where clotting factors undergo limited proteolysis to become active serine proteases. Anticoagulants are drugs that decrease the formation of fibrin clots. Oral anticoagulants (e.g., warfarin) inhibit the hepatic synthesis of clotting factors II, VII, IX, and X. Heparin inhibits the activity of several activated clotting factors (especially factors IIa and Xa) via its activation of antithrombin III. The endogenous anticoagulants, protein C and protein S, cause proteolysis of factors Va and VIIIa.

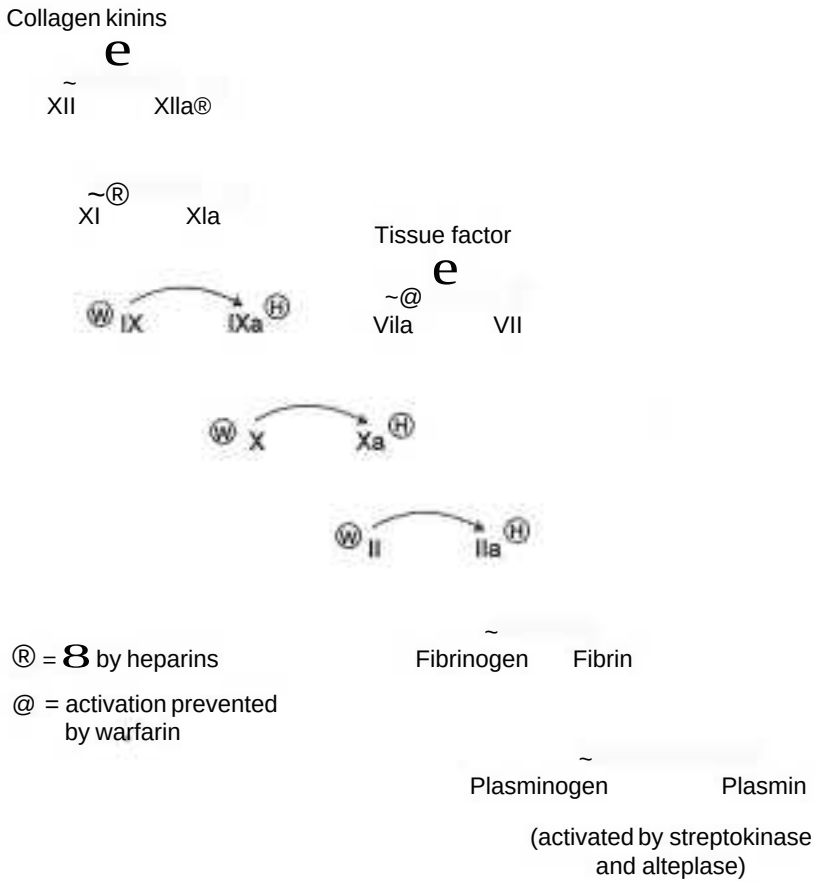


Figure VII-1-1. Actions of Blood Drugs

COMPARATIVE PROPERTIES OF HEPARIN AND WARFARIN

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins)

Feature	Heparln(s)	Warfarin (Coumarins)
Chemical nature	Large polysaccharide, water-soluble	Small molecule, lipid-soluble derivatives of vitamin K
Kinetics	Given parenterally (IV, SC), hepatic and reticuloendothelial elimination, half-life = 2 h, no placental access	Given orally, 98% protein bound, PO, liver metabolism, half-life = 30+ h, placental access
Mechanism	Heparin catalyzes the binding of antithrombin III (a serine protease inhibitor) to factors IIa, IXa, Xa, XIa, and XIIa, resulting in their rapid inactivation	↓ Hepatic synthesis of vitamin K-dependent factors II, VII, IX, X-coumarins prevent y-carboxylation by inhibiting vitamin K epoxide reductase; no effect on factors already present. *In vivo* effects only
Monitoring	Partial thromboplastin time (PTT)	Prothrombin time (PT); INR
Antagonist	Protamine sulfate-chemical antagonism, fast onset	Vitamin K- ↑ cofactor synthesis, slow onset; fresh frozen plasma (fast)
Uses	Rapid anticoagulation (intensive) for thromboses, emboli, unstable angina, disseminated intravascular coagulation (DIC), open-heart surgery, etc.	Longer-term anticoagulation (controlled) for thromboses, emboli, post-Ml, heart valve damage, atrial arrhythmias, etc.
Toxicity	Bleeding, osteoporosis, heparin-induced thrombocytopenia (HIT), hypersensitivity	Bleeding, skin necrosis (if low protein C), drug interactions, teratogenic (bone dysmorphogenesis)

Note

- Argatroban is a direct thrombin inhibitor.
- It does not require ATIII.
- It does not interact with heparin-induced antibodies.
- It can be used in HIT.

Heparins

- Heparin is a mixture of sulfated polysaccharides with molecular weights of 15-20,000 daltons.
- Low-molecular-weight (LMW) heparins (e.g., enoxaparin) have potential advantage of longer half-lives, less thrombocytopenia, and possibly enhanced activity against factor Xa.
- Danaparoid, a heparin of different structure, may be safer in hypersensitivity to heparin.

Warfarin

- Drug interactions:
  - Acidic molecule: oral absorption ↓ by cholestyramine
  - Extensive (but weak) plasma protein binding: displacement by other drugs may increase free fraction → ↑ anticoagulant effects (e.g., ASA, sulfonamides, phenytoins)

- Slow hepatic metabolism via P450:
  - Inducers (barbiturates, carbamezepine, rifampin) ↓ activity
  - Inhibitors (cimetidine, macrolides, azole antifungals) ↑ activity
- Protein C deficiency:

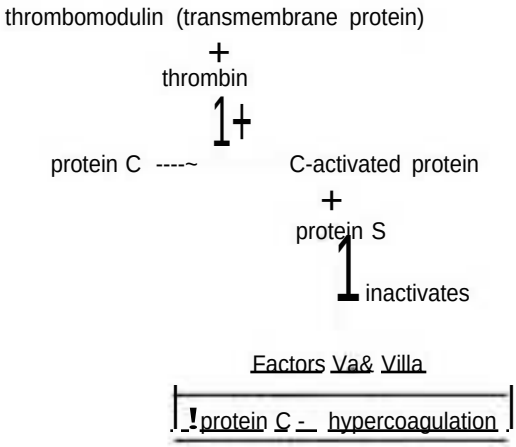


Figure VII-1-2. Activation and Role of Protein C

Table VII-I-2. Coagulation Factor Half-Lives

Factor	IIa	VIla	IXa	Xa	C
Half-life (h)	60	8	24	40	14

- Transient protein C deficiency can be induced when initiating treatment with warfarin because factors VII and protein C have the shortest half-lives of the coagulation factors (Table VII-1-2).
- Consequently, the extrinsic pathway and protein C system are inactivated, whereas the intrinsic system remains active for a few days. Hypercoagulability occurs (Figure VII-1-2), which may result in dermal vascular thrombosis and skin necrosis.

Bivalirudin

- Thrombin-specific anticoagulant
- Used with aspirin in unstable angina when undergoing percutaneous transluminal coronary angioplasty (PTCA)

Chapter Summary

Table VII-I-I summarizes the properties of heparin and warfarin (a coumarin).

Low-molecular-weight heparin derivatives (e.g., enoxaparin) and danaparoid, a heparan with heparin-like properties, have potential advantages over heparin itself.

The drug interactions of warfarin are given.

The activation and role of protein C in the clotting cascade are illustrated in Figure VII-I- 2. Transient protein C deficiency can be induced by treatment with warfarin, which promotes hypercoagulation through the action of the intrinsic pathway.

Thrombolytics

2

- Also called fibrinolytics, these agents lyse thrombi by catalyzing the formation of the endogenous fibrinolytic plasmin (a serine protease) from its precursor, plasminogen.
- Thrombolytics include tissue plasminogen activator (tPA, recombinant) and streptokinase (bacterial). They are used intravenously for short-term emergency management of coronary thromboses in myocardial infarction (MI), deep venous thrombosis, pulmonary embolism, and ischemic stroke (tPA).
- Drugs:
  - Streptokinase
    - Acts on both bound and free plasminogen (not clot specific), depleting circulating fibrinogen and factors V and VIII
    - Is antigenic (foreign protein derived from l3-hemolytic streptococci); may cause a problem if recent past use or infection-strep antibodies may t activity
  - Alteplase (tPA)
    - Clot specific, acting mainly on fibrin-bound plasminogen, the natural activator, so no allergy problems
- Clinical features:
  - Overriding factor in effectiveness is early administration, e.g., >60% decrease in mortality post-MI if used within 3 hours
  - ASA, beta blockers, and nitrates further t mortality, and adenosine t infarct size
  - Complications include bleeding, possible intracerebral hemorrhage
  - Streptokinase may cause hypersensitivity reactions and hypotension
  - Antifibrinolysins (aminocaproic and tranexamic acids)-possible antidotes in excessive bleeding

Chapter Summary

Thrombolytics (also referred to as fibrinolytics) are of clinical value in the early treatment of fibrin-dot-induced ischemia (e.g., >60% decrease in post-MI mortality if used within 3 hours).

Antiplatelet Drugs

3

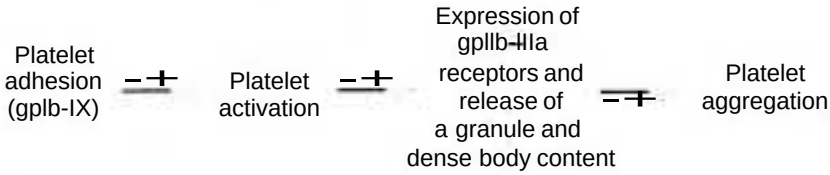


Figure VII-3-1. Platelet Activation

Thrombus (clot) formation involves:

- Platelet adhesion to site of vascular injury
- Activation of platelets by factors that include TxA_2, ADP, collagen, 5HT, and thrombin → ↑ expression of glycoprotein IIb/IIIa receptors
- Aggregation of platelets by a cross-linking reaction due to fibrinogen binding to glycoprotein IIb/IIIa receptors

Drugs:

- Aspirin
  - Irreversibly inhibits COX in platelets → ↓ activation
  - Low doses prevent MI and recurrence; prophylaxis in atrial arrhythmias and TIAs
  - Adverse effects *(see* Section VI, Drugs for Inflammatory and Related Disorders)
- Ticlopidine and clopidogrel
  - Block ADP receptors on platelets → ↓ activation
  - Alternatives to ASA in TIAs, post-MI, and unstable angina
  - Hemorrhage, leukopenia, and thrombocytopenic purpura
- Abciximab, eptifibatide, and tirofiban
  - Antagonists that bind to glycoprotein IIb/IIIa receptors → ↓ aggregation by preventing the cross-linking reaction
  - Used mainly in acute coronary syndromes and postangioplasty

In A Nutshell

Platelet Aggregation

Inaeased by:
ADP, 5HT, T~, thrombin, ~agonists

Decreased by:
PGI_2, rAMP, ftSA, ticlopidine, c1opidogrel, gp lib/Ilia blockers

Chapter Summary

Platelets adhere to sites of vascular injury, where they are activated by various factors to express a glycoprotein to which fibrinogen binds, resulting in platelet aggregation and formation of a platelet plug. Antiplatelet drugs inhibit this process, thus reducing the chances of thrombi formation. The major drugs are aspirin, ticlopidine, c1opidogrel, abciximab, eptifibatide, and tirofiban.

List of Drugs Used in Blood Disorders and Practice Questions

4

Anticoagulants

- Heparin
- Warfarin
- Argatroban
- Bivalirudin

Thrombolytics

- Alteplase (tPA)
- Streptokinase

Antiplatelet

- Aspirin
- Ticlopidine
- Clopidogrel
- Abciximab

PRACTICE QUESTIONS

1. Following a myocardial infarction, a patient is stabilized on warfarin, the dose being adjusted to give a prothrombin time of 22 seconds. Which of the following statements regarding potential drug interactions in this patient is accurate?

   (A) Cholestyramine will increase prothrombin time.
   (B) Cimetidine is likely to decrease prothrombin time.
   (C) Antibacterial sulfonamides may enhance the effects of warfarin.
   (D) Vitamin K would restore prothrombin time to normal within 30 minutes.
   (E) If this patient takes half an aspirin tablet daily, the dose of warfarin will need to be increased.

2. Which of the following compounds is most likely to cause platelet aggregation?

   (A) Clopidogrel
   (B) Cyclic AMP
   (C) Prostacyclin
   (D) Serotonin
   (E) Ticlopidine

3. Which of the following statements about heparin is accurate?

   (A) Increases thrombin levels after 3 to 5 days of treatment
   (B) Increases binding of AIII, a serine protease inhibitor
   (C) Peak effects occur within 5 minutes of injection
   (D) Thrombocytopenia is due to increased formation of PGI_2
   (E) None of the above

4. Which of the following statements regarding warfarin is true?

   (A) It is a prodrug converted to its active metabolite spontaneously in the blood.
   (B) It has low lipophilicity and does not cross the placental barrier.
   (C) It causes a depletion in protein C before it decreases prothrombin.
   (D) It inhibits release of vitamin K-dependent clotting factors from hepatocytes.
   (E) It is inactivated by protamine.

5. Which of the following statements is true regarding the parenteral administration of streptokinase?

   (A) It increases the formation of plasminogen.
   (B) It is less effective than tPA when given after a myocardial infarction.
   (C) It causes a high incidence of thrombocytopenia.
   (D) It may cause bleeding reversible by amino caproic acid.
   (E) It results in clot-specific thrombolysis.'

6. A woman who has a mechanical heart valve and who is taking warfarin informs you that she hopes to get pregnant in the near future. What advice should she receive regarding her antithrombotic medication during the anticipated pregnancy?

   (A) Warfarin should be continued until the third trimester.
   (B) Warfarin should be replaced with aspirin at analgesic doses.
   (C) All medications that affect the blood should be discontinued.
   (D) Warfarin should be replaced with heparin.
   (E) Warfarin should be discontinued, and supplementary vitamin K should be taken throughout the pregnancy.

ANSWERS

1. **Answer:** C. Warfarin binds extensively (98%) but weakly to plasma proteins and can be displaced by other drugs (e.g., ASA, chloral hydrate, phenytoin, sulfinpyrazone, and sulfonamides), resulting in an increase in its anticoagulant effects. Bile acid sequestrants bind acidic drugs such as warfarin, preventing their gastrointestinal absorption (t prothrombin time [PT]), and cimetidine, which inhibits the metabolism of warfarin, causing an increase in PI. Vitamin K restores levels of prothrombin and several other coagulation factors, but the action is slow (24 to 48 hours). Due to antiplatelet effects, even low doses of ASA may enhance bleeding in patients on warfarin.

2. **Answer:D.** Platelet aggregation is stimulated by many compounds, including ADP, thromboxane A_2, fibrin, and serotonin. Prostacyclin (PGI_2) from endothelial cells and cAMP are naturally occurring compounds that inhibit platelet aggregation. Clopidogrel and ticlopidine are antagonists of ADP that are used both in acute coronary syndromes and as alternatives to ASA for prophylaxis post-Ml and for transient ischemic attacks (TIAs).

3. **Answer:B.** Heparin forms a 1:1 complex with antithrombin III and enhances its activity from 100-fold to LOOO-foid.The peak effect of heparin is not reached for several hours, and continued use over several days has no effect on thrombin levels. Prostacyclin (PGI_2) is a platelet inhibitor, and its levels are not affected by heparin.

4. Answer: C. Warfarin inhibits the hepatic synthesis of factors II (prothrombin), VII, IX, and X. Its onset of anticoagulation activity is slow, and its impact on individual coagulation factors depends on their half-lives. Factor VII and protein C have much shorter half-lives than prothrombin, and so the extrinsic pathway and protein C system are the first to be affected by warfarin. The intrinsic pathway continues to function for 2 to 3 days, causing a state of hypercoagulability and possible vascular thrombosis.

5. **Answer: D.** Streptokinase is thrombolytic (or "fibrinolytic") because it activates plasminogen, resulting in the increased formation of plasmin. Its efficacy is equivalent to that of tPA, but streptokinase is not clot specific. All thrombolytics can cause bleeding, which may be counteracted to some extent by administration of antifibrinolysins, such as aminocaproic acid.

6. **Answer: D.** Discontinuing warfarin is appropriate during pregnancy because it is a known teratogen that causes bone dysmorphogenesis. The patient will need continued protection against thrombus formation, and heparin (or a related low molecular weight compound) is usually advised, despite the fact that the drug will require parenteral administration and can cause thrombocytopenia.

SECTION VIII

Endocrine Pharmacology

Drugs Used in Diabetes

1

INSUUNS

Diabetes Mellitus

- Type 1 (IDDM):
  - Early onset
  - Loss of pancreatic B cells → absolute dependence on insulin (diet + insulin ± oral agents)
  - Ketoacidosis-prone
- Type 2 (NIDDM)
  - Usually adult onset
  - ↓ response to insulin → (diet → oral hypoglycemics ± insulin)
  - Not ketoacidosis-prone

Insulin Forms

Table VIII-1-1. Kinetics (in Hours) of Insulin Forms with Subcutaneous Injection

Form	Onset	Peak Effect	Duration
Lispro"	0.3-0.5	1-2	3-4
Regular"	0.5-1	2-4	5-7
Lente	2-4	8-12	18-24
Ultralente	3-4	8-16	24-36

'Only forms that that can be used intravenously; peak action in 2 to 4 min.

- Glargine:
  - Insulin analog with no onset or peak ("peakless;' i.e., broad plasma concentration plateau)
  - Ultralong duration of action
  - Used to supply a constant background level

In A Nutshell

Insulin Release

Increased by:

Glucose
Sulfonylureas
M-agonists
~2-agonists

Decreased by:

~-agonists

Clinical Correlate

Diabetic Ketoacidosis

- Symptoms: polyuria, polydipsia, nausea, fatigue, dehydration, Kussmaul breathing, "fruity" breath
- Treatment: regular insulin IV, fluid and electrolyte replacement

ORAL HYPOGLYCEMICS: SULFONYLUREAS

Note

Hypoglycemic Reactions

- Symptoms: lip/tongue tingling, lethargy, confusion, sweats, tremors, tachycardia, coma, seizures
- Treatment: oral glucose, IV-dextrose if unconscious, or glucagon (1M or inhalation)

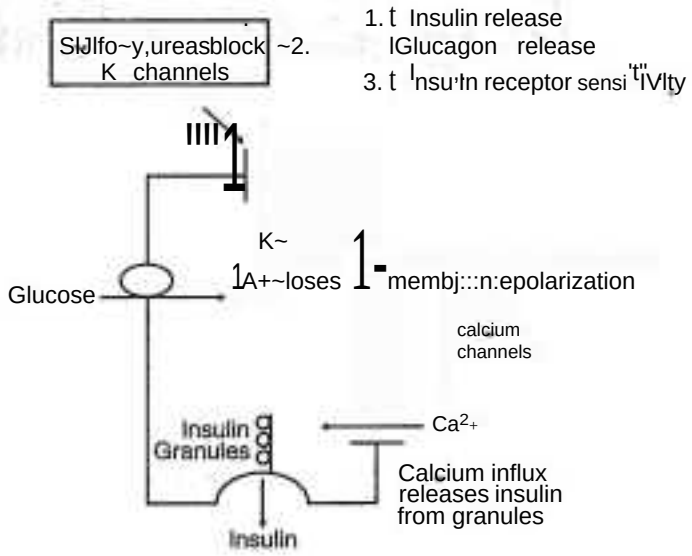


Figure VIII-1-1. Mode of Action of Sulfonylureas

- Mechanisms:
  - Normally, K+ efflux in pancreatic β cells maintains hyperpolarization of membranes, and insulin is released only when depolarization occurs.
  - Glucose acts as an insulinogen by increasing intracellular ATP → closure of K+ channels → membrane depolarization → ↑ Ca^{2+} influx → insulin release.
  - The acute action of sulfonylureas is to block K+ channels → depolarization → insulin release.
- Effects of increased insulin:
  - ↓ glucagon release from pancreatic α cells
  - Continued use of sulfonylureas ↓ tissue responses to insulin (especially muscle and liver) via changes in receptor function
- Drugs:
  - First generation:
    - Acetohexamide (active metabolite, ↑ dose in renal dysfunction)
    - Tolbutamide (appropriate in renal dysfunction)
    - Chlorpropamide (long-acting, SIADH/disulfiram reactions)
  - Second generation:
    - Glipizide (↑ dose in hepatic dysfunction)
    - Glyburide (active metabolite, ↑ dose in renal dysfunction)
- Side effects:
  - Hypoglycemia
  - Weight gain
  - Hypersensitivity (possible cross-allergy with sulfonamides)
  - Drug interactions mainly with first-generation drugs → ↑ hypoglycemia with cimetidine, insulin, salicylates, sulfonamides

METFORMIN

- "Euglycemic," ↓ postprandial glucose levels, but does not cause hypoglycemia or weight gain
- Mechanisms: may involve ↑ tissue sensitivity to insulin and/or ↓ hepatic gluconeogenesis (Figure VIII-1-2)
- Use: monotherapy or combinations (synergistic with sulfonylureas)
- Side effects: possible lactic acidosis; gastrointestinal distress is common

ACARBOSE

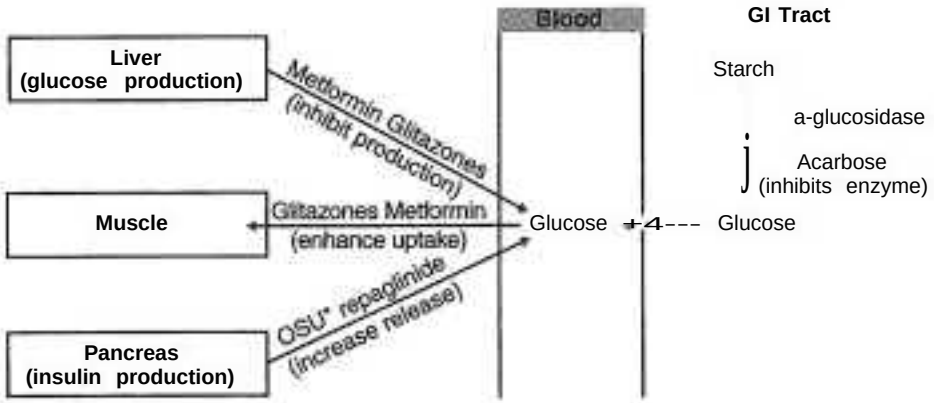
- No hypoglycemia
- Mechanisms: inhibits a-glucosidase in brush borders of small intestine → formation of absorbable carbohydrate → postprandial glucose → demand for insulin (Figure VIII-1-2).
- Side effects: gastrointestinal discomfort, flatulence, and diarrhea-recent concern over potential hepatotoxicity

THIAIOUDINEDIONES: PIOGUTAlONE AND ROSIGlITAIONE

- Mechanisms: bind to nuclear peroxisome proliferator-activating receptors (PPARs) involved in transcription of insulin-responsive genes → sensitization of tissues to insulin, plus ↓ hepatic gluconeogenesis and triglycerides and ↑ insulin receptor numbers (Figure VIII-1-2).
- Side effects: less hypoglycemia than sulfonylureas, but weight gain and edema reported

GLUCAGON-LIKE PEPTIDE-l (GLP-l) ANALOG: XENATIDE

- Mechanism: GLP-1 is an incretin released from the small intestine. It augments glucose-dependent insulin secretion. Xenatide is a long-acting GLP-1 receptor full agonist used in combination with other agents in type 2 diabetes.
- Side effects: nausea, hypoglycemia when used with oral sulfonureas



* osu ::: oral sulfonylureas

Figure VIII-1-2. Modes of Action of Drugs Used to Treat Diabetes

Note

Repaglinide

- Mechanisms: stimulates insulin release from pancreatic beta cells
- Use: adjunctive use in type 2 diabetes-administer just before meals due to short half-life

Chapter Summary

Type 1 (100M) and type 2 (NIOOM) diabetes mellitus are defined at the beginning of the chapter.

The times of activity onset, peak activity, and duration of activity for lispro, regular, lente, and ultralente insulins are summarized in Table VIII-H.

The oral antidiabetic drugs are the sulfonylureas, metformin, acarbose, thiazolidinediones, and repaglinide.

By blocking K+ channels in the pancreatic ~ cells, the sulfonylureas stimulate insulin release. The extra insulin in turn inhibits glucagon release from the a cells and increases peripheral tissue sensitivity to insulin (Figure VIII-l-l). The first- and second-generation drugs are listed. The adverse effects include weight gain and potential hypoglycemia.

Metformin enhances tissue sensitivity to insulin and inhibits liver gluconeogenesis. The potential side effect is lactic acidosis.

Acarbose inhibits intestinal a-glucosidase, thereby slowing glucose absorption and decreasing insulin demand. The side effect is gastrointestinal distress.

The thiazolidinediones (glitazones) act via peroxisome proliferation activating receptors that control insulin-responsive genes. They are less hypoglycemic than the sulfonylureas, but they still induce weight gain and edema and have potential liver toxicity.

Repaglinide, like the sulfonylureas, stimulates ~-cell secretion of insulin. Figure VIII-1-2 summarizes the modes of action of these drugs.

Steroid Hormones

2

ADRENAL STEROIDS

- Nonendocrine uses: For use in inflammatory disorders (and accompanying adverse effects), *see* Section VI, Drugs Used for Inflammatory and Related Disorders.
- Endocrine uses of glucocorticoids (e.g., prednisone, dexamethasone) and the mineralocorticoid (fludrocortisone) include:
  - Addison disease--replacement therapy
  - Adrenal insufficiency states (infection, shock, trauma)--supplementation
  - Premature delivery to prevent respiratory distress syndrome--supplementation
  - Adrenal hyperplasia--feedback inhibition of ACTH
- Adrenal steroid antagonists:
  - Spironolactone
  - Blocks aldosterone and androgen receptors *(see* Section III, Cardiac and Renal Pharmacology)
- Mifepristone:
  - Blocks glucocorticoid and progestin receptors
- Synthesis inhibitors:
  - Metyrapone (blocks 11-hydroxylation)
  - Ketoconazole

ESTROGENS

- Pharmacology: Estradiol is the major natural estrogen. Rationale for synthetics is to ↑ oral bioavailability, ↑ half-life, and ↑ feedback inhibition of FSH and LH.
- Drugs:
  - Conjugated equine estrogens (Premarin)-natural
  - Ethinyl estradiol and mestranol-steroidal
  - Diethylstilbestrol (DES)-nonsteroidal
- Clinical uses:
  - Female hypogonadism
  - Hormone replacement therapy (HRT) in menopause ~↓ bone resorption (↓PTH)
  - Contraception-feedback ↓ of gonadotropins
  - Dysmenorrhea
  - Uterine bleeding
  - Acne
  - Prostate cancer (palliative)

- Side effects:
  - General
    - Nausea
    - Breast tenderness
    - Endometrial hyperplasia
    - ↑ gallbladder disease, cholestasis
    - Migraine
  - ↑ blood coagulation-via ↓ antithrombin III and ↓ factors II, VII, IX, and X (only at high dose)
  - Cancer risk
    - ↑ endometrial cancer (unless progestins are added)
    - ↑ breast cancer-questionable, but caution if other risk factors are present
    - DES given during breast feeding → ↑ vaginal adenocarcinoma cancer in offspring
- Other drugs:
  - Anastrozole
    - Mode of action: aromatase inhibitor →↓ estrogen synthesis
    - Use: estrogen-dependent, postmenopausal breast cancer
  - **Clomiphene** (fertility pill)
    - Mode of action: ↓ feedback inhibition → ↑ FSH and LH → ↑ ovulation → pregnancy
    - Use: fertility drug
    - Adverse effect: ↑ multiple births
- Selective estrogen-receptor modulators (SERMs):
  - **Tamoxifen**
    - Variable actions depending on "target" tissue
    - E-receptor agonist (bone), antagonist (breast), and partial agonist (endometrium)
    - Possible ↓ risk of endometrial cancer
    - Used in estrogen-dependent breast cancer and for prophylaxis in high-risk patients
  - Raloxifene
    - E-receptor agonist (bone), antagonist breast and uterus
    - When used in menopause, there is no ↑ cancer risk
    - Use: prophylaxis of postmenopausal osteoporosis

PROGESTIN

- Pharmacology: Progesterone is the major natural progestin. Rationale for synthetics is ↑ oral bioavailability and ↑ feedback inhibition of gonadotropins, especially luteinizing hormone (LH).
- Drugs:
  - Medroxyprogesterone
  - Norethindrone
  - Desogestrel is a synthetic progestin devoid of androgenic and antiestrogenic activities, common to other derivatives

- Clinical uses:
  - Contraception (oral with estrogens)—depot contraception (medroxyprogesterone 1M every 3 months)
  - Hormone replacement therapy (HRT)-with estrogens to ↓ endometrial cancer
- Side effects:
  - ↓ HDL and ↑ LDL
  - Glucose intolerance
  - Breakthrough bleeding
  - Androgenic (hirsutism and acne)
  - Antiestrogenic (block lipid changes)
- Antagonist: mifepristone-abortifacient (use with prostaglandins [PGs])

ORAL CONTRACEPTIVES

- Pharmacology:
  - Combinations of estrogens (ethinyl estradiol, mestranol) with progestins (norgestrel, norethindrone) in varied dose, with mono-, bi-, and triphasic variants
  - Suppress gonadotropins, especially midcycle LH surge
- Side effects:
  - Estrogens
    - Nausea
    - Bloating
    - Headache
    - Mastalgia
  - Progestins
    - Weight gain
    - Hirsutism
    - Acne
    - Tiredness
    - Depression
    - ↓ HDL and ↑ LDL (high progestins)
- Interactions: ↓ contraceptive effectiveness when used with antimicrobials and enzyme inducers
- Benefits:
  - ↓ risk of endometrial and ovarian cancer
  - ↓ dysmenorrhea
  - ↓ endometriosis
  - ↓ pelvic inflammatory disease (PID)
  - ↓ osteoporosis

ANDROGENS

- Pharmacology: include methyltestosterone and 17-alkyl derivatives with increased anabolic actions, e.g., oxandrolone, nandrolone
- Uses:
  - Male hypogonadism and for anabolic actions -7 i muscle mass, i RBCs, J, nitrogen excretion
  - Illicit use in athletics
- Side effects:
  - Excessive masculinization
  - Premature closure of epiphysis
  - Cholestatic jaundice
  - Aggression
  - Dependence
- Antagonists:
  - Flutamide: androgen receptor blocker-used for androgen-receptor-positive prostate cancer
  - **Leuprolide:** GnRH analog-repository form used for androgen-receptor-positive prostate cancer
  - **Finasteride**
    - oS-Alpha reductase inhibitor, preventing conversion of testosterone dihydrotestosterone (DHT)
    - o DHT is responsible for hair loss and prostate enlargement
    - o Uses: BPH, male pattern baldness
    - o Caution: teratogenicity

Chapter Summary

Adrenal Steroids

The nonendocrine uses in inflammatory disorders were discussed in the previous chapter.

The glucocorticoids are used to treat Addison disease and adrenal insufficiency states, as a supplement in infantile respiratory distress syndrome, and in adrenal hyperplasia.

Estrogens

Synthetic estrogens are used to increase the oral bioavailability and half-life relative to that obtained with estradiol and to induce feedback inhibition of FSH and LH.

The uses and adverse affects of estrogens are listed.

The clinical uses of anastrozole (decreases estrogen synthesis), danazol (decreases ovarian steroid synthesis), clomiphene (decreases feedback inhibition), and the selective estrogen-receptor modulators tamoxifen and raloxifene are considered.

Progestin

Synthetic progestins are used to increase oral bioavailability and half-life relative to progesterone and to induce feedback inhibition of gonadotropins, especially LH.

The progestin-like drugs, their use in contraception and in hormonal replacement therapy, and their adverse effects are considered.

Mifepristone is an antagonist used with PG as an abortifacient.

The pharmacology of oral contraceptives and their adverse effects, drug interactions, and benefits are pointed out.

Androgens

Clinicallyuseful androgen analogs include methyltestosterone and 17-alkylderivatives. Their clinical and illicituses and side effects are presented.

Clinicallyuseful drug antagonists are flutamide (an androgen-receptor blocker used to treat prostate cancer), leuprolide (a GnRH analog used to treat prostate cancer), and finasteride (a 5-a-reductase inhibitor used to treat benign prostatic hyperplasia and male pattern baldness).

Antithyroid Agents

3

Table VIII-3-1. Sites of Action and Effects of Antithyroid Agents

Thyroid Hormone Synthesis and Actions	Effects of Antithyroid Agents
Active accumulation of iodide into gland	Basis for selective cell destruction of ^{131}I
Organification by peroxidase	Inhibited by thioamides
Iodination of tyrosyl residues on thyroglobulin to form MIT and DIT	Inhibited by thioamides
Coupling reactions to form DIT, T_3, and T_4	Inhibited by thioamides and high levels of iodide
Coupling reactions of MIT and DIT to form T_3 and T_4	Inhibited by iodide† and high-dose ipodate
Conversion of T_4 to T_3 via 5' deiodinase in periph	Inhibited by ipodate, propranolol,† propylthiouracil†

Definition of abbreviations: MIT: monoiodotyrosine; DIT: diiodotyrosine; T_3: triiodothyronine; T_4: thyroxine

†Thyroid storm management may include use of any or all of these agents.

- Thioamides: propylthiouracil and methimazole
  - Use: uncomplicated hyperthyroid conditions; slow in onset
  - High-dose propylthiouracil inhibits 5' deiodinase
  - Common maculopapular rash
  - Both drugs cross the placental barrier, but propylthiouracil is safer in pregnancy because it is extensively protein bound
- Iodide
  - Potassium iodide plus iodine (Lugol's solution) possible use in thyrotoxicosis: used preoperatively to decrease gland size, fragility, and vascularity
  - No long-term use because thyroid gland "escapes" from effects after 10 to 14 days

Chapter Summary

The steps in thyroid hormone synthesis and the antithyroid agents' effects upon them are summarized in Table VIII-3-1. The clinical uses and their potential complications are presented in greater detail for the thioamides (propylthiouracil and methimazole) and iodine.

Drugs Related to Hypothalamic and Pituitary Hormones

4

Table VIII-4-1. Drugs Related to Hypothalamic and Pituitary Hormones

Hormone	Pharmacologic Agent	Clinical Uses
GH	Somatrem or somatropin	Pituitary dwarfism, osteoporosis
Somatostatin	Octreotide	Acromegaly, carcinoid and secretory-GI tumors
ACTH	Cosyntropin	Infantile spasms
GnRH	Leuprolide, nafarelin	Endometriosis, prostate carcinoma (repository form)
FSH and LH	Urofollitropin (FSH), placental HCG (LH), menotropins (FSH and LH)	Hypogonadal states
PIH (DA)	Pergolide, bromocriptine	Hyperprolactinemia
Oxytocin	Oxytoxin	Labor induction
Vasopressin	Desmopressin (V2 selective)	▪ Neurogenic (pituitary) diabetes insipidus ▪ Hemophilia A (i factor VIII from liver) ▪ von Willebrand disease (i vW factor from endothelium) ▪ Primary nocturnal enuresis

Definition of abbreviations: ACTH, adrenocorticotropin hormone; DA, dopamine; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PIH, prolactin-inhibiting hormone.

Chapter Summary

The clinical uses of drugs used to treat functions associated with hypothalamic or pituitary hormones are summarized in Table VIII-4-1.

Drugs Used for Bone and Mineral Disorders

5

BISPHOSPHONA1ES

- Mechanisms: stabilize hydroxyapatite bone structure and also induce osteoblasts to secrete inhibitors of osteoclasts ~t bone resorption ~t progression of osteoporosis
- Clinical uses:
  - Established use in Paget disease
  - Efficacy in postmenopausal osteoporosis depends on individual drug, but alendronate is effective and with HRT causes t bone mineral density (BMD).
  - Alendronate is drug of choice for glucocorticoid-induced osteoporosis
- Side effects:
  - Etidronate and pamidronate -7 bone mineralization defects
  - Gastrointestinal distress, including esophageal ulcers (alendronate)

TERIPARATIDE

- Mechanism: recombinant DNA PTH analog
- Clinical use: once daily to stimulate osteoblasts and new bone formation
- Continuous infusion would stimulate osteoclast activity
- Used for less than 2 years; may t risk of osteosarcoma

Chapter Summary

The bisphosphonates decrease bone resorption and slow the progress of osteoporosis. Alendronate is effective for treatment of postmenopausal and steroid-induced osteoporosis. The principal potential side effects are gastrointestinal distress and esophageal ulcers.

Endocrine Drug List and Practice Questions

6

Table VIII-6-1. Endocrine Drug List

Drugs Used in Diabetes
Insulins, glargine
Sulfonylurea&----chlorpropamide, tolbutamide, acetohexamide, glipizide, glyburide
Metformin
Acarbose
Thiazolidinediones--pioglitazone, rosiglitazone

Steroid Hormones
Adrenosteroids
Cortisol
Triamcinolone
Fludrocortisone
Prednisone
Dexamethasone
Estrogens
Ethinyl estradiol
Mestranol
Diethylstilbestrol
Tamoxifen (SERM)
Raloxifene (SERM)
Progestins
Medroxyprogesterone
Norgestrel
Norethindrone
Desogestrel
Mifepristone (antagonist)

Steroid Hormones *(Cont'd)*
Androgens
Methyltestosterone
Oxandrolone
Flutamide (antagonist)
Finasteride (5-a.-reductase inhibitor)

Antithyroid Drugs
Propylthiouracil
Methimazole
KI and I (Lugol's)

Hypothalamic/Pituitary Drugs
Somatropin
Octreotide
Leuprolide
Oxytocin, vasopressin

Drugs Used in Bone and Mineral Disorders!
Alendronate
Teriparatide

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REVIEW QUESTIONS

1. A 60-year-old college professor is diagnosed with benign prostatic hyperplasia (BPH), and his physician is considering drug treatment of the condition. Which one of the following statements about treatment of BPH is accurate?

   (A) Use of finasteride causes a high incidence of retrograde ejaculation.
   (B) Prostate-specific antigen (PSA) must be determined prior to drug treatment.
   (C) Leuprolide is an inhibitor of 5-alpha-reductase.
   (D) Finasteride is a GnRH analog.
   (E) Compared with placebo, alpha-l blockers improve symptoms of BPH and urinary flow rate.

2. Regarding drug management of hyperthyroidism, which one of the following statements is accurate?

   (A) Thyroid "escape" refers to decreased response to antithyroid actions of propranolol.
   (B) High-dose propylthiouracil inhibits the conversion of thyroxine to triiodothyronine.
   (C) Methimazole is used to decrease gland vascularity prior to thyroidectomy.
   (D) Iodide salts inhibit 5'-deiodinase,
   (E) Thioamides are known to be teratogenic and should not be used in pregnancy.

3. What is the drug of choice for management of neurogenic diabetes insipidus?

   (A) Amiloride
   (B) Demeclocycline
   (C) Desmopressin
   (D) Hydrochlorothiazide
   (E) Lithium

4. The release of insulin from the pancreatic B cell would most likely be inhibited by which of the following?

   (A) Clonidine
   (B) Glucose
   (C) Albuterol
   (D) Pilocarpine
   (E) Glipizide

5. Which of the following has been used in the treatment of adrenal malignancies but is more likely to be identified as a progestin-receptor antagonist that acts as an abortifacient?

   (A) Flutamide
   (B) Misoprostol
   (C) Dinoprostone
   (D) Tamoxifen
   (E) Mifepristone

6. In a patient with type 2 diabetes, which of the following is most likely to cause hypoglycemic reactions?

   (A) Acarbose
   (B) Glucagon
   (C) Glyburide
   (D) Metformin
   (E) Rosiglitazone

7. Which one of the following is least likely to increase insulin requirement in a diabetic patient?

   (A) Furosemide
   (B) Hydrochlorothiazide
   (C) Prednisone
   (D) Spironolactone
   (E) Taking the USMLE

8. What is the drug of choice for management of adrenal glucocorticoid-induced osteoporosis?

   (A) Alendronate
   (B) Calcitonin
   (C) Estrogen
   (D) Ketoconazole
   (E) Vitamin D

9. Finasteride, approved for use in male pattern baldness, appears to act as

   (A) an activator of estrogen receptors
   (B) an inhibitor of 5-alpha reductase
   (C) an aromatase inhibitor
   (D) an androgen receptor antagonist
   (E) a feedback inhibitor of FSH

ANSWERS AND EXPLANATIONS

1. Answer: E. Alpha-I blockers such as doxazosin are effective in BPH, especially if the prostate is not greatly enlarged. Hypotension and retrograde ejaculation are possible side effects of such drugs. Finasteride is an inhibitor of 5-alpha-reductase, and leuprolide is a GnRH analog that in repository form decreases circulating gonadotropins, leading to decreased formation of androgens. Prostate-specific antigen (PSA) is nearly always elevated in BPH and is not a prerequisite for drug treatment of the disorder.

2. Answer: B. Thioamides used at conventional doses in Graves disease are slow to act; they inhibit iodination and the coupling reactions in hormone synthesis and do not affect the release of stored thyroxine. At high doses, propylthiouracil may act more rapidly because of its inhibition of 5'-deiodinase, preventing the conversion of T_4 to T_3. Thioamides are not teratogenic, and they do not decrease glandular size or vascularity; KI plus iodine (Lugol's solution) is used preoperatively to this end. Use of iodide in hyperthyroidism is only temporary because the thyroid gland "escapes" from its actions within a week or two.

3. Answer: C. Neurogenic diabetes insipidus is treated with desmopressin, a drug that is similar to vasopressin (ADH), yet is a selective activator of V_2 receptors in the kidney. Remember that VI receptors are present in smooth muscle, and their activation leads to vasoconstriction and bronchoconstriction. Nephrogenic diabetes insipidus (decreased response of vasopressin receptors) is treated with thiazides, except in the case of that induced by lithium, when amiloride is preferred (because thiazides increase blood levels of lithium).

4. Answer: A. Back to ANS pharmacology! The release of insulin from the pancreas is stimulated by insulinogens (glucose), sulfonylurea hypoglycemics (glipizide), activators of beta-Z adrenoceptors (e.g., albuterol), and activators of muscarinic receptors (e.g., pilocarpine). The only receptor that, when activated, inhibits insulin release is the alpha-Z receptor, which could be stimulated by clonidine or methyldopa.

5. Answer: E. Mifepristone (RU486) is both a glucocorticoid and progestin receptor antagonist, the latter being responsible for its abortifacient activity. Dinoprostone is also a stimulant of uterine smooth muscle, but is a PGE_2 derivative, not a progestin antagonist. Flutamide is an androgen-receptor antagonist, and tamoxifen is a partial agonist (or mixed agonist-antagonist) at estrogen receptors.

6. Answer: C. The sulfonylurea hypoglycemics release insulin from the pancreas, and newer drugs in the class, such as glyburide, are more likely to cause hypoglycemia than are other oral agents used for diabetes mellitus. Metformin is "euglycernic," lowering elevated glucose levels to the normal range, and acarbose simply prevents postprandial hyperglycemia. Glucagon causes hyperglycemia, an effect that is sometimes employed in management of hypoglycemia.

7. Answer: D. Drugs that decrease extracellular potassium, such as the thiazide and loop diuretics and adrenal glucocorticoids, will lead to an increased requirement for insulin by making it more difficult to release the hormone from the B cells of the pancreas. Spironolactone is K+ sparing, tends to cause hyperkalemia, and does not interfere with the release of insulin. Stress conditions, such as examinations, also increase insulin requirement.

8. Answer: A. Alendronate is currently the drug of choice to prevent osteoporosis in patients who must be maintained on steroids for their antiinflammatory and immunosuppressive effects. The drug also decreases bone resorption during menopause and is sometimes favored in patients who are at risk for neoplasias if treated with sex hormones. Care must be taken with alendronate to avoid esophageal ulceration. Estrogen hormone replacement therapy ± vitamin D also has proven valuable for slowing bone resorption in menopause, and increases in bone mass have been reported for combinations of estrogens with alendronate.

9. Answer: B. Finasteride blocks the formation of dihydrotestosterone by inhibiting 5-alpha reductase and may be useful in both male pattern baldness and benign prostatic hyperplasia. It is quite possible that drugs acting to block androgen receptors, or to cause suppression of FSH, may also be useful in these conditions. Aromatase inhibitors tend to cause increased levels of androgens, with excessive masculinization as a side effect.

SECTION IX

Anticancer Drugs

Anticancer Drugs

1

PRINCIPLES AND DEFINITIONS

log-kill hypothesis

Cytotoxic actions of anticancer drugs follow first-order kinetics: They kill a fixed percentage of tumor cells, not a fixed number ~ one rationale for drug combinations.

Growth fraction

Cytotoxic drugs are more effective against tumors that have a high growth fraction (large percentage actively dividing). Normal cells with high growth fraction (e.g., bone marrow) are also more sensitive to anticancer drugs.

Cell-cycle specificity

- Drugs that act specifically on phases of the cell cycle are called cell-cycle specific (CCS) and are more effective in tumors with high-growth fraction (leukemias, lymphomas).
- Drugs that are cell-cycle nonspecific (many bind to and damage DNA) can be used in tumors with low-growth fraction, as well as tumors with high-growth fraction.

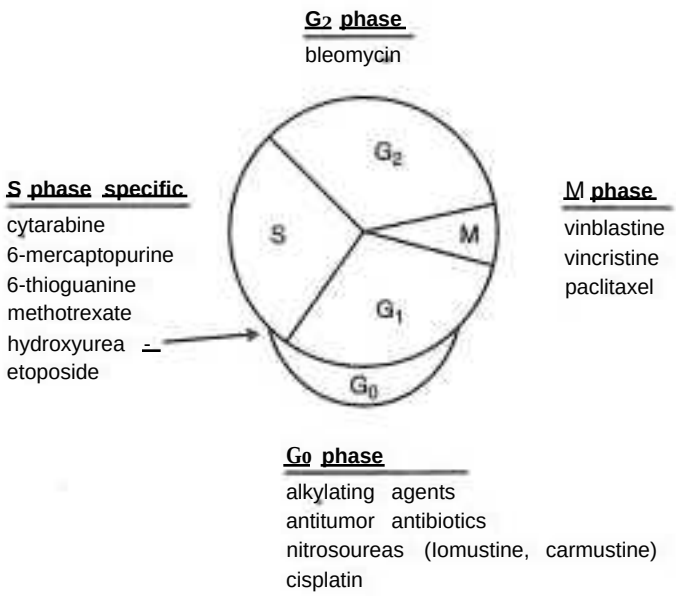

Figure IX-1-1. Cell-Cycle Specificity of Anticancer Drugs

DRUGS

Table IX-I-I. Characteristics of Important Anticancer Drugs

Drug	Mechanism	Uses	Side Effects
Cyclophosphamide	Alkylating agent-attacks guanine N7-dysfunctional DNA	Non-Hodgkin, ovarian, breast cancer, neuroblastoma	BMS, mucositis, hemorrhagic cystitis (mesna, traps acrolein and is protective), hepatotoxicity (high dose)
Cisplatin	Alkylating agent-cross-links DNA strands	Testicular, ovarian, bladder, lung cancer	Nausea, vomiting (use ondansetron); nephrotoxicity (use amifostine); neurotoxicity (deafness)
Procarbazine	Alkylating agent	Hodgkin	BM5, pulmonary toxicity, hemolysis, neurotoxicity, leukemogenic
Doxorubicin	Intercalator, forms free radicals, inhibits topoisomerase	Hodgkin, breast, endometrial, lung, and ovanan cancers	BM5--delayed CHF (dexrazoxane is an iron-chelating agent preventing the formation of free radicals; it is not a free radical "trapper"), alopecia, vesicant, radiation "recall"
Methotrexate (CC5)	Antimetabolite-inhibits DHF reductase (5 phase)	Leukemias, lymphomas, breast cancer; rheumatoid arthritis, psoriasis	BM5, mucositis, crystalluria; leucovorin (folinic acid) rescue
5-Fluorouracil (CCS)	Pyrimidine antimetabolite (5 phase) bioactivated to inhibit thymidylate synthetase	Breast, ovarian, head, and neck cancer-topical for basal cell cancer and keratoses	BMS, GI irritation, alopecia
6-Mercaptopurine (CCS)	Purine antimetabolite (S phase) bioactivated by HGPR transferase	Acute lymphocytic leukemia; immunosuppression	BMS, hepatotoxicity (jaundice, necrosis), GI distress
Bleomycin (CC5)	Complexes with Fe and O_2 ~ DNA strand scission (G_2 phase)	Hodgkin, testicular, head, neck, skin cancer	Pneumonitis, pulmonary fibrosis, mucocutaneous reactions (blisters), alopecia, hypersensitivity
Vincristine Vinblastine (CC5)	Microtubular polymerization-spindle poisons (M phase)	Vinblastine-Hodgkin, testicular cancer, Kaposi Vincristine-Hodgkin, leukemias, Wilms	BMS, GI, alopecia Neurotoxicity

Definition of abbreviations: BMS, bone marrow suppression; CCS, cell-cycle specific; CHF, congestive heart failure; GI, gastrointestinal.

Clinical Correlate

Thymineless Death of Cells

Flucytosine (Fe) and 5-fluorouracil (S-FU) are bioactivated to S-fluorodeoxyuridine (S-FdUMP), which inhibits thymidylate synthetase ~ "thymineless death" of fungal cells (Fe) or neoplastic cells (S-FU).

TOXICITY OF ANTICANCER DRUGS

- Rapidly proliferating cells, such as the bone marrow, gastrointestinal tract mucosa, hair follicles, and gonads are the most sensitive to cytotoxic drugs.
- Most often *bone marrow suppression* (BMS) is dose limiting.
- Anticancer drug dosage is usually carefully titrated to avoid excessive neutropenia (granulocytes <SOO/mm^3) and thrombocytopenia (platelets <20,OOO/mm^3).
- Colony-stimulating factors, erythropoietin, and thrombopoietin can be supportive $\downarrow$ infections and need for antibiotics.

Table IX-1-2. Other Dose-Limiting or Distinctive Toxicities

Toxicity	Drug(s)
Renal	Cisplatin, * methotrexate
Hepatic	6-MP, busulfan, cyclophosphamide
Pulmonary	Bleomycin, * busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine, * cisplatin, paclitaxel
Immunosuppressive	Cyclophosphamide, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase" (pancreatitis)

'Less BMS-"marrow sparing"

RESISTANCE TO ANTICANCER DRUGS

Another rationale for combination drug regimens in cancer is to prevent or delay the emergence of resistance.

Table IX-1-3. Modes of Resistance to Anticancer Drugs

Mechanism	Drugs or Drug Groups
Change in sensitivity (or $\uparrow$ level) or $\downarrow$ binding affinity of target enzymes or receptors	Etoposide, methotrexate, vinca alkaloids, estrogen and androgen receptors
Decreased drug accumulation via $\uparrow$ expression of glycoprotein transporters, or $\downarrow$ permeability	Methotrexate, alkylating agents, dactinomycin
Formation of drug-inactivating enzymes	Purine and pyrimidine antimetabolites
Production of reactive chemicals that "trap" the anticancer drug	Alkylators, bleomycin, cisplatin, doxorubicin
Increased nucleic acid repair mechanisms	Alkylating agents, cisplatin
Reduced activation of prodrugs	Purine and pyrimidine antimetabolites

Chapter Summary

The "log-kill" hypothesis states that cytotoxic anticancer agents kill a certain percentage, not a fixed number, of cells.

Cytotoxic drugs are most effective against rapidly dividing cells.

Drugs that act on proliferating cells are cell-cycle specific and are usually also cycle-phase specific. Figure IX-l-l illustrates the cell cycle and the drugs acting in each cycle phase.

Drugs that act on nonproliferating cells are dose dependent and cell-cycle independent.

Rationales for combination drug usage are that each drug will independently kill a fixed percentage and that one drug will still kill a cancer cell that has developed resistance to a different drug in the cocktail.

Rapidly proliferating normal cells are more sensitive to cytotoxic drugs. Bone marrow suppression often determines the upper limit of tolerable chemotherapy. Table IX-l-l lists mechanisms of action, selected clinical uses, and side effects of major anticancer drugs. Table IX+2 shows the dose-limiting and distinctive toxicities of anticancer drugs.

Table IX-1-3summarizes the modes of resistance developed by cancers toward specific anticancer drugs.

Anticancer Drug Practice Questions

2

REVIEW QUESTIONS

1. A patient undergoing cancer chemotherapy has an increase in urinary frequency with much discomfort. No specific findings are apparent on physical examination. Laboratory results include hematuria and mild leukopenia, but no bacteria or crystalluria. If the symptoms experienced by the patient are drug related, what is the most likely cause?

   (A) Cyclophosphamide
   (B) 5-FU
   (C) Methotrexate
   (D) Prednisone
   (E) Tamoxifen

2. Which of the following is a prodrug that causes "thymineless" death of cells?

   (A) Cytarabine
   (B) Azathioprine
   (C) 5-Fluorouracil
   (D) Methotrexate
   (E) 6-Mercaptopurine

3. After surgery for breast cancer, a patient is to undergo chemotherapy with a regimen that consists of cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin. Which one of the following agents is most likely to be protective against the toxicity of methotrexate?

   (A) Dexrazoxane
   (B) Folinic acid
   (C) Mercaptoethanesulfonate
   (D) Tamoxifen
   (E) Vitamin C

4. Which anticancer drug, acting mainly in the G_2 phase of the cell cycle, can cause blisters on the palms of the hands and soles of the feet and can make it difficult for the patient to breathe?

   (A) Bleomycin
   (B) Busulfan
   (C) Cyclophosphamide
   (D) Doxorubicin
   (E) Procarbazine

5. Resistance to which anticancer drug, used mainly in childhood leukemia, is high in neoplastic cells that have low activities of hypoxanthine guanine phosphoribosyltransferase?

   (A) Doxorubicin
   (B) Vinblastine
   (C) 6-MP
   (D) Cytarabine
   (E) Methotrexate

ANSWERS AND EXPLANATIONS

1. **Answer: A.** These symptoms are those of a mild case of hemorrhagic cystitis. Bladder irritation with hematuria is a fairly common complaint of patients treated with cyclophosphamide. It appears to be due to acrolein, a product formed when cyclophosphamide is bioactivated by liver P450 to form cytotoxic metabolites. Urinary tract problems may also occur with methotrexate from crystalluria due to its low water solubility.

2. **Answer:** C. All of the drugs listed are antimetabolites used in cancer chemotherapy or as immunosuppressants. The 5-fluorouracil is bioactivated to 5-fluorodeoxyuridine monophosphate (5-FdUMP), a substrate for and inhibitor of thymidylate synthase. When used in drug regimens for treatment of cancer, 5-FU causes "thymineless" death of cells.

3. **Answer: B.** Folinic acid (leucovorin) reduces the toxicity of methotrexate because it provides an active form of folate to normal' (nonneoplastic) cells, resulting in "leucovorin rescue." Dexrazoxane is a free-radical trapping agent that is thought to reduce the cardiotoxicity of anthracyclines (e.g., doxorubicin). Mercaptoethanesulfonate (rnesna), which inactivates acrolein, is available for protection against hemorrhagic cystitis in patients treated with cyclophosphamide and related drugs.

4. **Answer: A.** It helps to know which anticancer drugs are cell-cycle specific and which have characteristic toxicities. Bleomycin fits both categories; acting mainly in G_2, it is cell-cycle specific and is distinctive for causing mucocutaneous reactions and pulmonary dysfunction. Busulfan and procarbazine may also cause pulmonary toxicity, but neither drug is cell-cycle specific.

5. **Answer:** C. The purine antimetabolite 6-mercaptopurine is bioactivated in cancer cells by the purine salvage enzyme, hypoxanthine guanine phosphoribosyltransferase (HGPRT). The most common form of resistance to 6-MP is a decrease in activity of this enzyme. Azathioprine, a drug used as an immunosuppressant, is closely related to 6-MP, and also requires bioactivation to exert cytotoxic actions.

SECTION X

Immunopharmacology

Immunopharmacology

1

CYCLOSPORINE

- Mechanism of action:
  - Binds to cyclophilin ~ ↓ calcineurin (cytoplasmic phosphatase) ~ ↓ activation of T-cell transcription factors ~ ↓ IL-2, IL-3, and interferon-γ
  - Tacrolimus, another antibiotic with immunosuppressant actions, does not bind to cyclophilin, but acts similarly to cyclosporine to inhibit calcineurin.
- Uses:
  - DOC organ or tissue transplantation (+/- mycophenolate, +/- steroids, +/- cytotoxic drugs)
  - Tacrolimus used alternatively to cyclosporine in renal and liver transplants
  - Mycophenolate, an inhibitor of de novo synthesis of purines, has adjunctive immunosuppressant actions, permitting dose reductions of cyclosporine to limit toxicity.
- Side effects: peripheral neuropathy, nephrotoxicity, hyperglycemia, hypertension, hyperlipidemia, hirsutism, gingival overgrowth, cholelithiasis

AZATHIOPRINE

Immunosuppressant converted to 6-mercaptopurine-same properties as 6-MP.

ANTI-D IMMUNOGLOBULIN

- Human IgG antibodies to red cell D antigen (rhesus antigen)
- Uses: Administer to Rh-negative mother within 72 hours of Rh-positive delivery to prevent hemolytic disease of newborn in subsequent pregnancy

MONOCLONAL ANTIBODIES

Table X-I-I. Clinical Uses of Monoclonal Antibodies

Mab	Clinical Uses
Abciximab	Antiplatelet-antagonist of Ilb/Illa receptors
Infliximab	Rheumatoid arthritis and Crohn disease-binds TNF
Trastuzumab	Breast cancer-antagonist to ERB-B2
Dacliximab	Kidney transplants-blocks lL-2 receptors
Muromonab	Kidney transplant-blocks allograft rejection
Palivizumab	Respiratory syncytial virus-blocks RSV protein
Rituximab	Non-Hodgkin lymphoma-binds to surface protein

CYTOKINES (RECOMBINANT FORMS)

Table X-I-2. Clinical Uses of Cytokines

Cytokine	Clinical Uses
Aldesleukin (IL-2)	t Lymphocyte differentiation and t NKs-use in renal cell cancer and metastatic melanoma
Interleukin-Ll	t Platelet formation-used in thrombocytopenia
Filgrastim (G-CSF)	t Granulocytes-used for marrow recovery
Sargramostim (GM-CSF)	t Granulocytes and macrophages-used for marrow recovery
Erythropoietin	Anemias, especially associated with renal failure
Thrombopoietin	Thrombocytopenia
Interferon-a	Hepatitis Band C, leukemias, melanoma
Interferon-B	Multiple sclerosis
Interferon-y	Chronic granulomatous disease ~ t TNF

Chapter Summary

The mechanism of action, uses, and toxicities associated with cyclosporine are presented. Azathioprine converts to 6-mercaptopurine, making it a useful immunosuppressant.

Anti-D immunoglobin is given to Rh-negative mothers shortly after parturition to prevent hemolytic disease in future births.

Table X-l-l summarizes the clinical uses of monoclonal antibodies. Table X+2 summarizes the clinical uses of recombinant cytokines.

Immunopharmacology Practice Questions

2

QUESTIONS

1. Which one of the following compounds increases the synthesis of tumor necrosis factor (TNF), leading to activation of phagocytosis in patients with chronic granulomatous disease?

   (A) Aldesleukin
   (B) Cyclosporine
   (C) Interferon-y
   (D) Infliximab
   (E) Prednisone

2. Which one of the following agents is paired correctly with its suggested clinical use and/or mechanism of action?

   (A) Abciximab-active in treatment of hepatitis Band C
   (B) Interferon-a-prevents postangioplasty clotting
   (C) Aldesleukin-blocks IL-2 receptors
   (D) Filgrastim-sequesters TNF
   (E) Trastuzumab-blocks ERB-B2 receptors

ANSWERS

1. Answer: C. Interferon-ylb (recombinant form) is used in chronic granulomatous disease to decrease infection liability because it increases the formation of TNE Infliximab is a monoclonal antibody to TNF used in rheumatoid arthritis, and its use may lead to an increased infection rate. Aldesleukin is a recombinant form of IL-2.

2. Answer: E. Trastuzumab is a monoclonal antibody specific for blocking the ERB-B2 receptors associated with genotypically linked breast cancers. Abciximab binds to the glycoprotein IIb/IIIa receptor and is used postangioplasty; interferon-a is used in hepatitis Band C. Aldesleukin is a recombinant form of IL-2 that activates interleukin receptors, and filgrastim is a granulocyte colony-stimulating factor (G-CSF).

SECTION XI

Toxicology



Toxicology

1

COMMON TOXIC SYNDROMES

Table XI-I-I. Signs, Symptoms, and Interventions or Antidotes for Common Toxic Syndromes

Compound(s)	Signs and Symptoms	Interventions and Antidotes
AChE inhibitors	Miosis, salivation, sweats, GI cramps, diarrhea, muscle twitches -7 seizures, coma, respiration failure	Respiratory support; atropine + pralidoxime (for irreversible AChE inhibitors)
Atropine and muscarinic blockers	i HR, t BP, hyperthermia (hot, dry skin), delirium, hallucinations	Control cardiovascular symptoms and hyperthermia + physostigmine (crosses blood-brain barrier)
Carbon monoxide (> 10% carboxyHb)	Nausea and vomiting, dyspnea with hyperventilation, mydriasis, vertigo; cardiovascular signs prominent, J, BP, syncope, t HR, arrhythmias	Hyperbaric 02 and decontamination (humidified 100% 02 okay in mild overdose)
CNS stimulants	Anxiety/agitation, hyperthermia (warm, sweaty skin), mydriasis, i HR, t BP, psychosis, seizures	Control cardiovascular symptoms, hyperthermia, and seizures-+/- BZs or antipsychotics
Opioid analgesics	Lethargy, sedation, J, HR, J, BP, hypoventilation, miosis, coma, respiration failure	Ventilatory support; naloxone at frequent intervals
Salicylates (ASA)*	Confusion, lethargy, hyperventilation, hyperthermia, dehydration, hypokalemia, acidosis, seizures, coma	Correct acidosis and electrolytes-urinary alkalinization, possible hemodialysis
Sedative-hypnotics and ethanol	Disinhibition (initial), lethargy, ataxia, nystagmus, stupor, coma, hypothermia, respiratory failure	Ventilatory support-flumazenil if BZs implicated
SSRIs	Agitation, confusion, hallucination, muscle rigidity, hyperthermia, t HR, t BP, seizures	Control hyperthermia and seizures-possible use of cyproheptadine, antipsychotics, and BZs
Tricyclic antidepressants	Mydriasis, hyperthermia (hot, dry skin), 3 Cs (convulsions, coma, and cardiotoxicity) -7 arrhythmias	Control seizures and hyperthermia, correct acidosis and possible antiarrhythmics

"More details in antiinflammatory section

HEAVY METAL POISONING

Signs and symptoms distinctive but usually result from inhibition of -SH groups on enzymes and regulatory proteins.

Table XI-I-2. Signs, Symptoms, and Interventions or Antidotes for Heavy Metal Poisoning

Metals and Source	Signs and Symptoms	Interventions and Antidotes
Arsenic (wood preservatives, pesticides, ant poisons)	*Acute:* gastroenteritis, hypotension, metabolic acidosis, garlic breath, "rice water" stools, torsades, seizures *Chronic:* pallor, skin pigmentation (raindrop pattern), alopecia, stocking glove neuropathy, myelosuppression	Activated charcoal, dimercaprol Penicillamine or succiIller
Iron (medicinal for anemias and prenatal supplements)	*Acute* (mainly children): severe GI distress → necrotizing gastroenteritis with hematemesis and bloody diarrhea, dyspnea, shock, coma	Gastric aspiration + carbonate lavage, deferoxamine IV
Lead (tap water, leaded paint chips, herbal remedies, gas sniffing, glazed kitchenware, etc.)	*Acute:* nausea and vomiting, GI distress and pain, malaise, tremor, tinnitus, paresthesias, encephalopathy (red or black feces) *Chronic:* multisystem effects-anemia (↑ heme synthesis), neuropathy (wrist drop), nephropathy (proteinuria, failure), hepatitis, mental retardation (from pica), ↓ fertility and ↑ stillbirths	Decontamination-gastric lavage + dimercaprol (severe) or EDTA or succimer (penicillamine if unable to use dimercaprol orsuccimer) Children: succimer PO
Mercury (elemental in instruments); salts used in amalgams, batteries, dyes, electroplating, fireworks, photography	*Acute:* vapor inhalation-chest pain, dyspnea, pneumonitis *Acute:* inorganic salt ingestion-hemorrhagic gastroenteritis, acute tubular necrosis, shock *Chronic:* organic Hg-CNS effects, ataxia, paresthesias, auditory and visual loss, loosening of teeth	Succimer PO or dimercaprol (1M) Activated charcoal for oral ingestion, then support with succimer PO or dimercaprol *(not* IV) → causes redistribution of Hg to the CNS → neurotoxicity

ANTIDOTES

Table XI-1-3. Summary of Antidotes

Acetylcysteine	Acetaminophen
Atropine + pralidoxime (for irreversible AChE inhibitors)	AChE inhibitors-physostigmine, neostigmine, and pyridostigmine; organophosphates, including insecticides, such as malathion and parathion
Deferoxamine	Iron and iron salts
Digoxin immune F(ab)	Digoxin
Dimercaprol (BAL)	Arsenic, gold, mercury, lead; oral succimer for milder lead and mercury toxicity
EDTA	Backup in lead poisoning, then for rarer toxicities (Cd, Cr, Co, Mn,Zn)
Esmolol	Theophylline, beta agonists
Ethanol, fomepizole	Methanol or ethylene glycol
Flumazenil	Benzodiazepines, zolpidem, zaleplon
Naloxone	Opioid analgesics
Oxygen	Carbon monoxide
Penicillamine	Copper (e.g., Wilson disease), iron,lead.rnercury
Physostigmine	Anticholinergics: atropine, antihistamine, antiparkinsonian-*not* tricyclics
Protamine	Heparins
Vitamin K	Warfarin and coumarin anticoagulants
Activated charcoal	Nonspecific: all oral poisonings except Fe, CN, Li, solvents, mineral acids, or corrosives

NATURAL MEDICINALS

"Natural" medicinals. are available without prescription and are considered to be nutritional supplements rather than drugs. Herbal (botanic) products are marketed without FDA review of safety and efficacy, and there are no requirements governing the purity or the. chemical identities of constituents. Evidence supporting the clinical effectiveness of herbal products is commonly incomplete.

Table XI-1-4. Characteristics of Selected Herbals

Name	Medicinal Use(s)	Possible Mechanism(s)	Side Effects
Echinacea	t Cold symptoms	r ILs and TNF	GI distress, dizziness, headache
Garlic	Hyperlipidemias, cancer (evidence is weak)	Inhibits HMG-CoA reductase and ACE	Allergies, hypotension, antiplatelet actions; use caution when used with anticoagulants
Gingko	Intermittent claudication; Alzheimer disease (evidence is weak)	Antioxidant, free radical scavenger, i NO	Anxiety, GI distress, insomnia, antiplatelet actions; use caution when used with anticoagulants
Ginseng	Possible i in mental and physical performance (evidence is weak)	Unknown	Insomnia, nervousness, hypertension, mastalgia, vaginal bleeding
Saw palmetto	Symptomatic treatment of BPH	5'-reductase inhibitor and androgen receptor antagonist	GI pain, decreased libido, headache, hypertension
St.Iohn's wort	Depressive disorder (variable evidence for clinical efficacy)	May enhance brain 5HT functions	Major drug interactions: serotonin syndrome with SSRIs; induces P450, leading to t effects of multiple drugs

Table XI-1-5. Purified Nutritional Supplements

Name	Pharmacology	Side Effects
Dehydroepiandrosterone (DHEA)	Androgen precursor advocated for treatment of AIDS (↓ CD4 in females), Alzheimer disease and "aging," diabetes, hypercholesterolemia, and SLE (↓ in symptoms and "flare-ups" in females)	*Females:* androgenization and concern regarding CV disease and breast cancer *Males:* feminization in young and concern in elderly regarding BPH and cancer
Melatonin	Serotonin derivative used for "jet-lag" and sleep disorders. Purported activity as a contraceptive and in the treatment of cancer, depression, and HIV	Drowsiness, sedation, headache. Contraindicated in pregnancy, in woman trying to conceive (↓ LH), and in nursing mothers (↓ prolactin)

Chapter Summary

Table XI-l-l lists the common toxic syndromes with their signs and symptoms and potential modes of intervention and/or antidotes.

Table XI-1-2lists the common heavy metal poisons with their most common sources, signs, and symptoms and potential modes of intervention and/or antidotes.

Table XI-1-3lists antidotes and the type of poisoning against which they act.

Table XI-1-4lists the characteristics of selected herbals, and Table XI-1-5lists the relevant purified nutritional supplements.

Toxicology Practice Questions

2

QUESTIONS

1. Symptoms of iron poisoning in a 3-year-old child may include severe gastrointestinal distress with hematemesis, a shock-like state with marked dehydration and progressive hemorrhagic gastritis. Regarding the management of iron toxicity, which one of the following statements is accurate?

   (A) Gastric lavage should not be attempted because of possible aspiration of stomach contents.

   (B) The patient is likely to have a reduced anion gap.

   (C) Urinary alkalization increases elimination of iron.

   (D) Deferoxamine should be administered as soon as possible.

   (E) Activated charcoal is highly effective in iron poisoning.

2. Which one of the following symptoms is most likely to be associated with lead poisoning?

   (A) Loose teeth

   (B) Breath that smells like garlic

   (C) Gingivitis

   (D) Rice-water stools

   (E) Wrist drop

ANSWERS

1. Answer: D. Deferoxamine chelates iron and is the antidote in iron poisoning. Gastric lavage should be attempted with care regarding aspiration, but changes in urine pH have no effect on the elimination of iron. Laboratory results will reveal an increased anion gap indicative of acidosis. The systemic absorption of many drugs taken orally can be reduced by activated charcoal; unfortunately, iron is not one of them.

2. Answer: E. The profile of lead toxicity includes decreased heme synthesis, anemia, nephropathy, and peripheral neuropathy, the last leading to foot or wrist drop. Garlic breath and watery stools are associated with arsenic poisoning. Chronic gingivitis and loose teeth are features of mercury poisoning.

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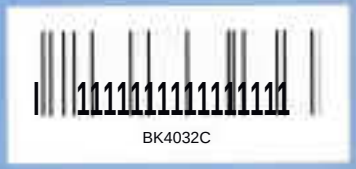

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