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USMLE* Step 1

Lecture Notes

Pharmacology

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SECTION I

General Principles

Pharmacokinetics

1

PERMEATION

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.

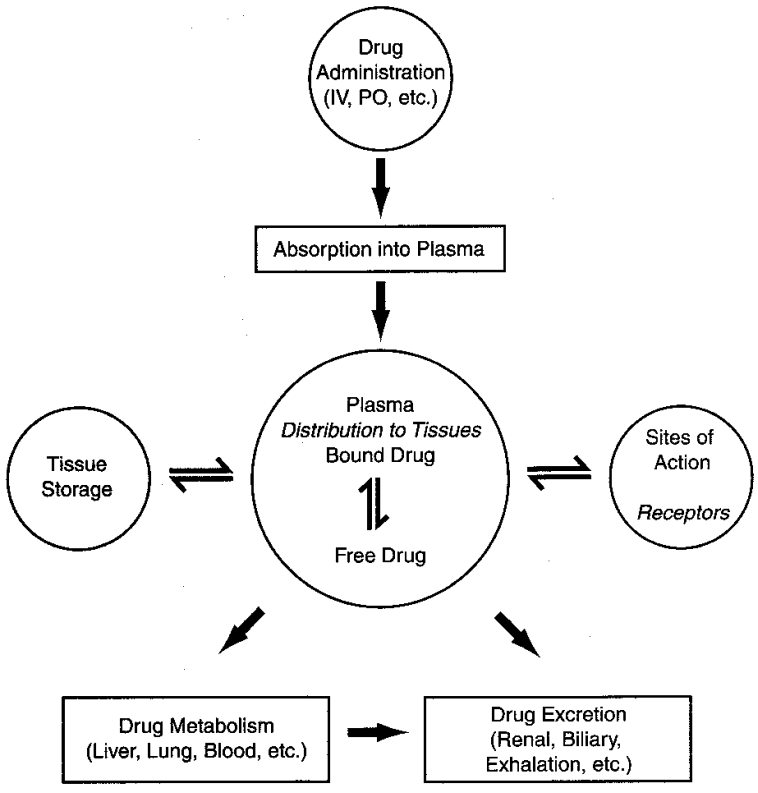


Figure I-1-1. Drug Biodisposition

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 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, the better the vascularity, the better the absorption of the drug is.

In A Nutshell

For Weak Acids and Weak Bases

Ionized = Water soluble

Nonionized = Lipid soluble

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 their 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.

	Acidic media: pH < pKa		Basic media: pH > pKa
Weak Acid	**R.COOH** (crosses membranes)	$\rightleftharpoons$	**$R.COO^- + H^+$** (better cleared)
Weak Base	**$R.NH_3^+$** (better cleared)	$\rightleftharpoons$	**$R.NH_2 + H^+$** (crosses membranes)

The percentage of ionization is determined by the Henderson-Hasselbalch equation.

$$\text{For weak acids: } pH - pKa = \log \frac{[\text{ionized}]}{[\text{nonionized}]}$$

$$\text{For weak bases: } pH - pKa = \log \frac{[\text{nonionized}]}{[\text{ionized}]}$$

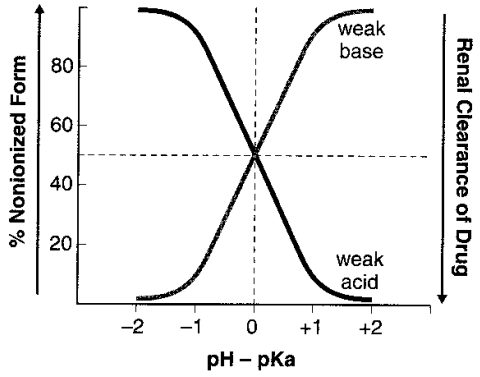


Figure I-1-2. Degree of Ionization and Clearance Versus pH Deviation from pKa

Table I-1-1. Percentage Nonionized as a Function of pH

pH – pKa	–2	–1	0	+1	+2
Weak acid: % nonionized	99	90	50	10	1
Weak base: % nonionized	1	10	50	90	99

Example: Morphine is a weak base (pKa 8.0). What percentage will be in the ionized form in the urine at a pH of 6.0?

$$pH - pKa = -2$$

From Table I-1-1, 1% of morphine is in the nonionized form; thus, 99% is ionized.

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 acids → increases renal elimination.

Clinical Correlate

To Change Urinary pH

- Acidify: NH_4Cl, vitamin C, cranberry juice
- Alkalinize: $NaHCO_3$, acetazolamide
- See Aspirin Overdose and Management in Section VI.

Modes of Drug Transport Across a Membrane

Table I-1-2. 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

Bridge to Physiology

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

ABSORPTION

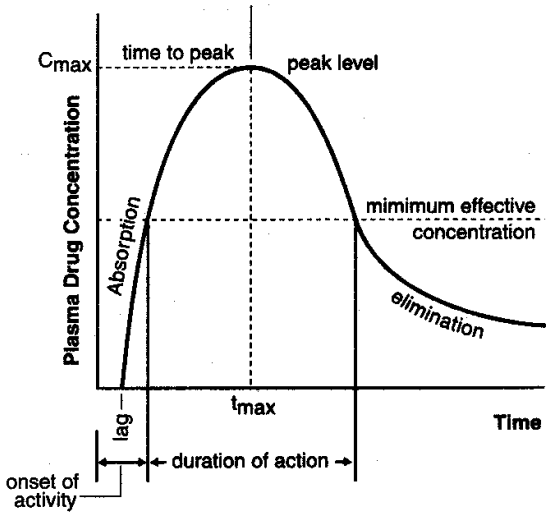
Concerns the processes of entry of a drug into the systemic circulation from the site of its administration.

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.

With extravascular administration (e.g., per os [PO; oral], intramuscular [IM], subcutaneous [SC], inhalation), less than 100% of a dose may reach the systemic circulation because of variations in bioavailability.

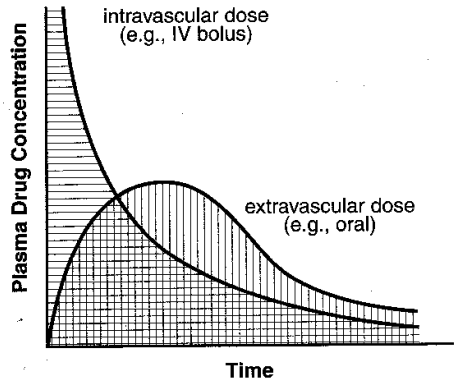
Plasma Level Curves



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

Figure I-1-3. 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.

$$f = \frac{AUC_{PO}}{AUC_{IV}}$$

Figure I-1-4. Area Under the Curve for an IV Bolus and Extravascular Doses

Figure Legend

AUC: area under the curve

po: oral

iv: intravenous bolus

AUC_{IV}: 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 and the same rate of absorption. When this occurs, the plasma levels of the two products will be superimposable, if they are given at same dose, by the same mode.

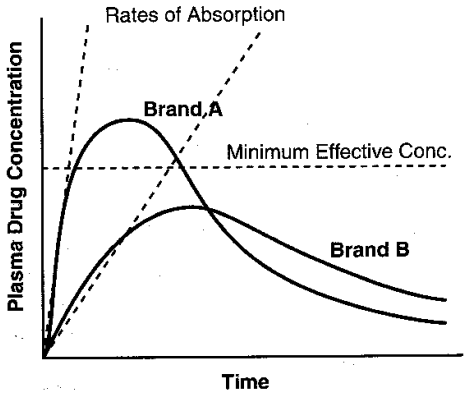


Figure I-1-5. Effect of Rate of Absorption on Plasma Concentration

Figure Legend

Figure I-1-5 illustrates an example of bioinequivalence. The two formulations differ in rate of absorption. Brand B is more slowly absorbed than is brand A.

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.

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.

DISTRIBUTION

The processes of distribution of a drug from the systemic circulation to organs and tissue involve its permeation through membrane barriers and are dependent on its solubility (recall that only nonionized drugs cross biomembranes), the rate of blood flow to the tissues, and the binding of drug molecules to plasma proteins.

Plasma Protein Binding

Many drugs bind to plasma proteins, including albumin, with an equilibrium between bound and free molecules (recall that only unbound drugs cross biomembranes).

$$\text{Drug} + \text{Protein} \rightleftharpoons \text{Drug-Protein Complex}$$

Competition between drugs for plasma protein binding sites may increase the "free fraction," possibly enhancing the effects of the drug displaced.

Special Barriers to Distribution

- Placental: most small molecular weight drugs cross the placental barrier, although fetal blood levels are usually lower than maternal
- Blood–brain: permeable only to lipid-soluble drugs or those of very low molecular weight

Apparent Volume of Distribution (V_d)

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

$$V_d = \frac{\text{Dose}}{C^0} \quad \text{where } C^0 = [\text{plasma}] \text{ at zero time}$$

Bridge to Physiology

Approximate V_d Values (weight 70 kg)

plasma volume (3 L), blood volume (5 L),

extracellular fluid (ECF 12–14 L),

total body water (TBW 40–42 L)

Points to remember:

- The higher the V_d, the lower the plasma concentration and vice versa.
- V_d is low when a high percentage of a drug is bound to plasma proteins.
- This relationship can be used for calculating V_d by using the *dose* only if one knows or can calculate C^0.
- Tissue binding and accumulation of drugs with high V_d values raise the possibility of displacement by other agents → changes in pharmacologic activity, i.e., quinidine or verapamil with digoxin.

Redistribution

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

In the case of CNS drugs, the duration of action of an initial dose may depend more on the redistribution rate than on the half-life. With repeated doses, fat and other tissue depots become saturated, resulting in longer durations of action than the first dose.

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 such cases, biotransformation rate can be a primary factor determining the duration of drug action.

In other cases, biotransformation of an active compound may lead to the formation of metabolites that also have pharmacologic actions.

A few compounds (pro-drugs) have no activity until they undergo metabolic activation.

Biotransformation Classification

Phase I: modification of the drug molecule via oxidation, reduction, and hydrolytic reactions.

Phase II: conjugation with endogenous compounds via the activity of transferases—a prerequisite is the presence of a reactive group (–OH, $-NH_2$) on the molecule.

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.

Reactions include hydroxylations and dealkylations.

Multiple CYP families differing by amino acid (AA) composition, by substrate specificity, and by sensitivity to inhibitors and to inducing agents.

Clinical Correlate

Grapefruit Juice

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

Table I-1-3. Cytochrome P450 Isozymes

CYP450	Substrate Example	Inducers	Inhibitors	Genetic Polymorphisms
1A2	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

Active Metabolites

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

Hydrolysis

Phase I reactions involving addition of a water molecule with subsequent bond breakage.

Include pseudocholinesterases responsible for metabolism of the skeletal muscle relaxant, succinylcholine. Genetically determined defects in plasma esterases may result in prolonged actions of succinylcholine in some persons.

Another hydrolysis reaction involves amidases.

Nonmicrosomal Oxidations

Include monoamine oxidases that metabolize both endogenous amines (e.g., dopamine, serotonin) and exogenous compounds (e.g., tyramine).

Alcohols are metabolized by alcohol dehydrogenase (ADH) to aldehydes, which are then substrates for aldehyde dehydrogenase, which can be inhibited by disulfiram. The enhanced sensitivity of some persons to acetaldehyde formed from low doses of ethanol can result from genotypic variations in aldehyde dehydrogenase activity. Ethanol is also metabolized by CYP2E1 once ADH is saturated.

Conjugation

Phase II reactions via transferases that usually inactivate drugs but occasionally activate (for example, morphine and minoxidil). May follow a phase I hydroxylation but also occur directly.

Types of Conjugation

Glucuronidation: inducible; conjugates may undergo enterohepatic cycling; reduced activity in neonate.

Acetylation: genotypic variations (fast and slow). Drug-induced systemic lupus erythematosus (SLE) by *slow acetylators* with hydralazine > procainamide > isoniazid (INH).

Sulfation: minoxidil, 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 ($t_{1/2}$).

Zero-Order Elimination Rate

Rate of elimination is independent of plasma concentration (or amount in the body).

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:

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

Drugs with zero-order elimination have no fixed half-life ($t_{1/2}$ is a variable). Graphically, zero-order elimination follows a straight-line decay versus time.

Drugs with zero-order elimination include ethanol (except low blood levels), phenytoin (high therapeutic doses), and salicylates (toxic doses).

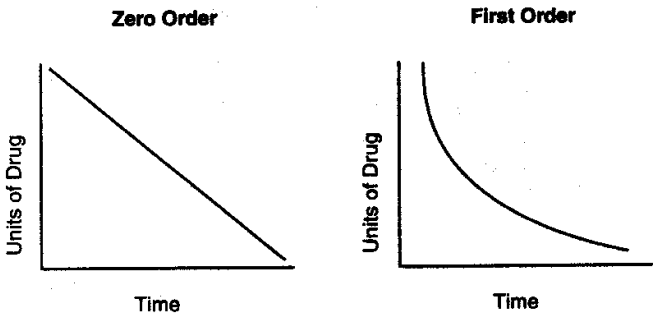


Figure I-1-6. Plots of Zero- and First-Order Drug Elimination versus Time

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}.

First-Order Elimination Rate

Rate of elimination is directly proportional to plasma level (or the amount present)—the higher the amount, the more rapid the elimination.

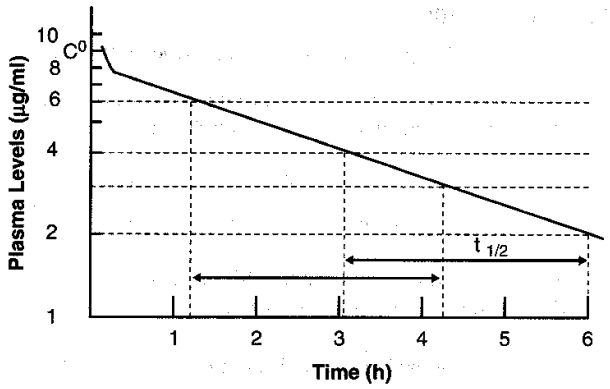
A constant fraction of the drug is eliminated per unit time ($t_{1/2}$ is a constant). Graphically, first-order elimination follows an exponential decay versus time.

For example, if 80 mg of a drug is administered and its elimination half-life = 4 h, the time course of its elimination is:

	4 h		4 h		4 h		4 h	
80 mg	→	40 mg	→	20 mg	→	10 mg	→	5 mg

Most drugs follow first-order elimination rates.

Graphic Analysis



C^0 = plasma concentration at zero time

Figure I-1-7. Plasma Decay Curve—First-Order Elimination

The figure 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 (C^0) can be estimated from the graphic relationship between plasma concentrations and time. C^0 is estimated by extrapolation of the linear plasma decay curve to intercept with the vertical axis.

Useful relationships: $\text{Dose} = V_d \times C^0$

$t_{1/2} = 0.7/k$, where k = first order rate constant of elimination

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

Clearance is defined as the volume of blood cleared of the drug in unit time. It represents the relationship between the rate of drug elimination and its plasma level. For drugs with first-order elimination, clearance is constant because rate of elimination is directly proportional to plasma level.

Total body clearance (Cl) may involve several processes, depending on different routes of drug elimination.

$Cl = Cl_R + Cl_{NR}$ where Cl_R = renal clearance

and Cl_{NR} = nonrenal clearance

With no active secretion or reabsorption, the renal clearance is the same as glomerular filtration rate (Cl_R = GFR); if the drug is protein bound, then Cl_R = GFR × free fraction.

PHARMACOKINETICS CALCULATIONS

The following six relationships are important for calculations:

Single Dose Equations

(1) Volume of distribution (V_d)

$V_d = D/C^0$

(2) Half-life ($t_{1/2}$)

$t_{1/2} = 0.7/k$

(3) Clearance (Cl)

$Cl = k \times V_d$

Multiple Doses or Infusion Rate Equations

(4) Infusion rate (k_0)

$k_0 = Cl \times C^{ss}$

(5) Loading dose (LD)

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

(6) Maintenance dose (MD)

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

Bridge to Renal Physiology

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

Note

C^0 = conc. at time zero

Cl = clearance

C^{ss} = steady state conc.

D = dose

k = elimination constant

k_0 = infusion rate

LD = loading dose

MD = maintenance dose

τ = dosing interval

V_d = volume of distribution

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 I-1-8 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** (τ). With such intermittent dosing, plasma levels oscillate through peaks and troughs, with averages shown in the diagram by the dashed line.

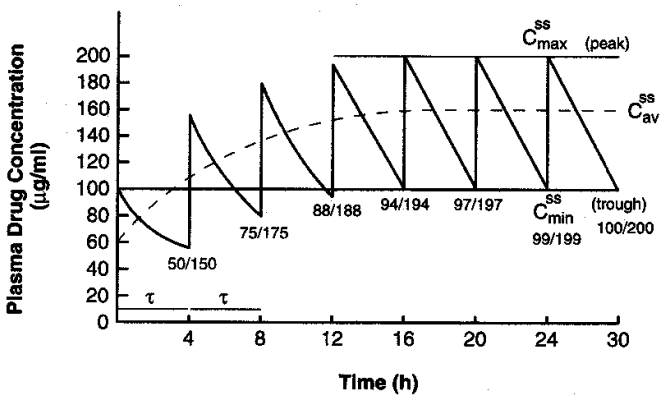


Figure I-1-8. Oscillations in Plasma Levels Following IV Bolus Administration at Intervals Equal to Drug Half-Life

Classic Clues

Time and Steady State

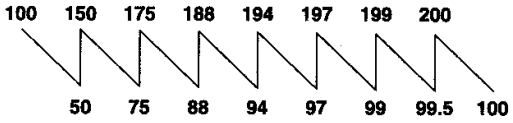
50% = 1 × half-life

90% = 3.3 × half-life

95% = 4–5 × half-life

"100"% = >7 × half-life

In other words, plasma levels zigzag up and down, because at the end of each half-life the plasma level has decreased to 50% of its level immediately following the last dose:



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 $t_{1/2}$.

Rate of Infusion

The graph in Figure I-1-9 shows the increases in plasma levels of the same drug infused at five different rates. Irrespective of the rate of infusion, it takes the same amount of time to reach steady state.

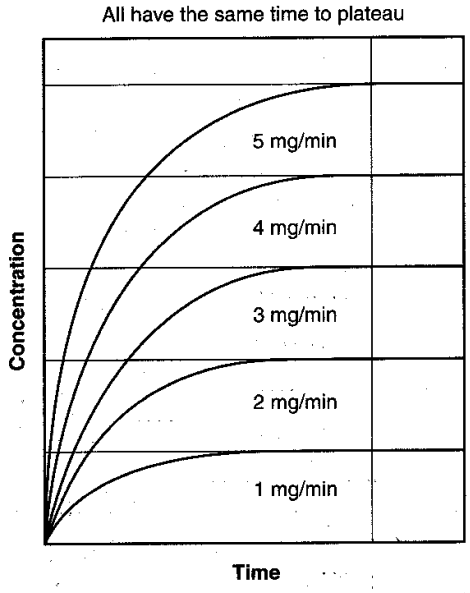


Figure I-1-9. Effect of Rate of Infusion on Plasma Level

Rate of infusion 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. **Linear kinetics** refers to this direct relationship between infusion rate and steady-state plasma level. 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.

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.

Note

Remember that dose and concentration are directly proportional.

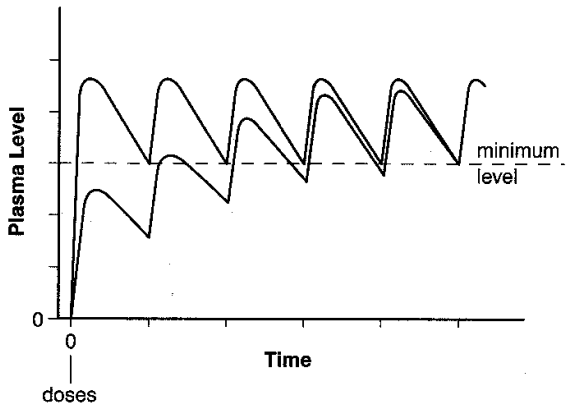


Figure I-1-10. Effect of a Loading Dose on the Time Required to Achieve the Minimal Effective Plasma Concentration

Such loading doses are often one time only and (as shown in Figure I-1-10) 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, then the loading dose is twice the amount of the dose used for maintenance. For any other interval of dosing, equation (5) is used.

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 I-1-2 illustrates the principles associated with ionization, and Table I-1-2 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. Salient aspects of these principles and how they lead to bioavailability and relate to bioequivalence are illustrated in Figures I-1-3, -4, and -5.

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.

(Continued)

Chapter Summary (*continued*)

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 V_d 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 II metabolism occurs via conjugation.

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 II reactions involve conjugation, sometimes after a phase I hydroxylation. The conjugation may be a glucuronidation, an acetylation, a sulfation, or an 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. Figure I-1-6 compares zero- and first-order elimination, and Figure I-1-7 demonstrates how the $t_{1/2}$ and the theoretical zero time plasma concentration (C^0) can be graphically determined. Two important relationships are dose = $V_d \times C^0$ and $t_{1/2} = 0.7/k$ (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 $Cl = k \times V_d$.

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

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 I-1-8, -9, and -10).

Pharmacodynamics 2

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

Plots of dose (or log dose) versus response for drugs (**agonists**) that activate receptors can reveal the following characteristics of such drugs:

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.

Parallel and Nonparallel D-R Curves

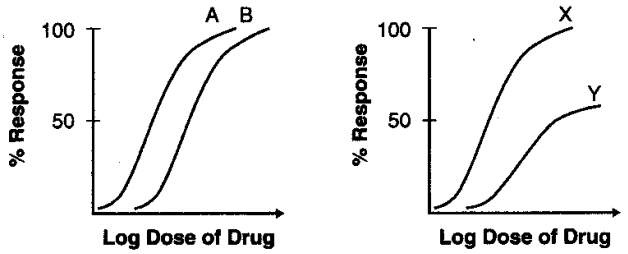


Figure I-2-1. Comparison of D-R Curves for Two Drugs Acting on the Same (left panel) and on Different (right panel) Receptors

It may be seen from the log dose-response curves in Figure I-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.

Bridge to Biochemistry

Definitions

Affinity: how well a drug and a receptor recognize each other. Notice the analogy to the Km 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.

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 I-2-2, drug B is a full agonist, and drugs A and C are partial agonists.

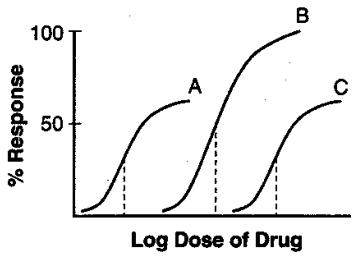


Figure I-2-2. Efficacy and Potency of Full and Partial Agonists

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 I-2-3, the lower curve represents effects of a partial agonist when used alone—its *ceiling effect* = 50% of maximal.

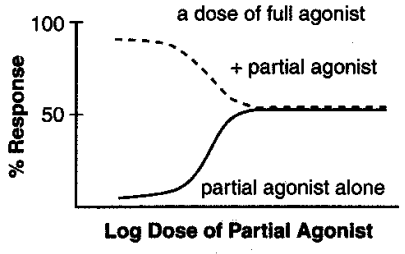


Figure I-2-3. Duality of Partial Agonists

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 by agonists.

Antagonists displace D-R curves for agonists to the right.

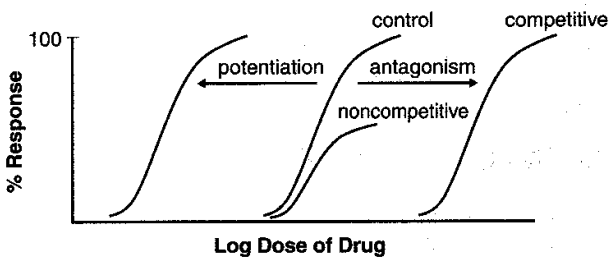


Figure I-2-4. D-R Curves of Antagonists and Potentiators

Competitive antagonists cause a parallel shift to the right and can be reversed completely by increasing the dose of the agonist drug. In effect, such antagonists appear to decrease the potency of the agonist drug.

Most receptor antagonists used in medicine are competitive. Examples include atropine block of acetylcholine (ACh) at M receptors and propranolol block of norepinephrine (NE) at beta receptors.

Noncompetitive antagonists cause a nonparallel shift to the right and can be reversed only partially by increasing the dose of the agonist drug. Such antagonists appear to decrease both the potency and the efficacy of agonists. One example is phenoxybenzamine, which irreversibly blocks the effects of NE at alpha receptors by formation of a covalent bond.

Pharmacologic Antagonism (Same Receptor)

An agonist and antagonist compete for a single receptor type, i.e., a β-agonist with a β-blocker.

Physiologic Antagonism (Different Receptors)

Occurs when an agonist response mediated through activation of one receptor is antagonized by an opposing agonist action at a different receptor; e.g., acetylcholine (ACh) bradycardia induced through M receptor activation may be antagonized by NE tachycardia induced via beta receptor activation.

Chemical Antagonism

Occurs when a drug effect is antagonized by formation of a complex between the effector drug and another compound; e.g., protamine binds to heparin to reverse its actions.

Bridge to Biochemistry

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}).

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

Potentiation

Potentiation of agonist action leads to displacement of D-R curves to the left. Examples include the effect of benzodiazepines to enhance the activity of gamma-aminobutyric acid (GABA) and the effect of amphetamine to enhance the activity of NE.

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—ED50.

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.

$$TI = \frac{TD50}{ED50} \text{ or } \frac{LD50}{ED50}$$

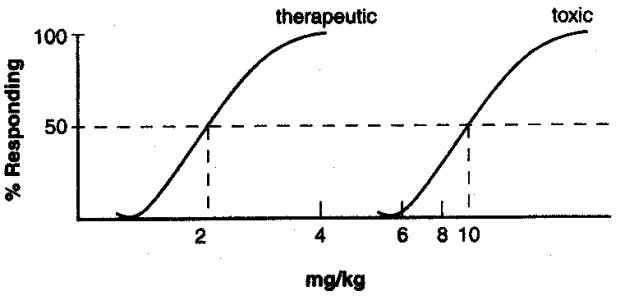


Figure I-2-5. Quantal D-R Curves of Therapeutic and Toxic Effects of a Drug

As shown in Figure I-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, TI = 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 mechanism are known.

Intracellular Receptors

These include receptors for steroids. Binding of hormones or drugs to such receptors releases regulatory proteins that permit dimerization of the hormone-receptor complex. Such complexes interact with response elements on nuclear DNA to modify 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 one 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.

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_1), glucagon, histamine (H_2), prostacyclin, and some serotonin subtypes.

In A Nutshell

Key ANS Receptors

M_1, M_3, α_1: G_q activation of phospholipase C

M_2, α_2: G_i inhibition of adenylyl cyclase

β_1, β_2, D_1: G_s activation of adenylyl cyclase

G_i Proteins

Binding of agonists to receptors linked to G_i proteins decreases cAMP production. Such receptors include adrenoreceptors (alpha$_2$), ACh (M_2), dopamine (D_2 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_2). The IP_3 induces release of Ca^{2+} 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_1 and M_3), norepinephrine (alpha$_1$), angiotensin II, and several serotonin subtypes.

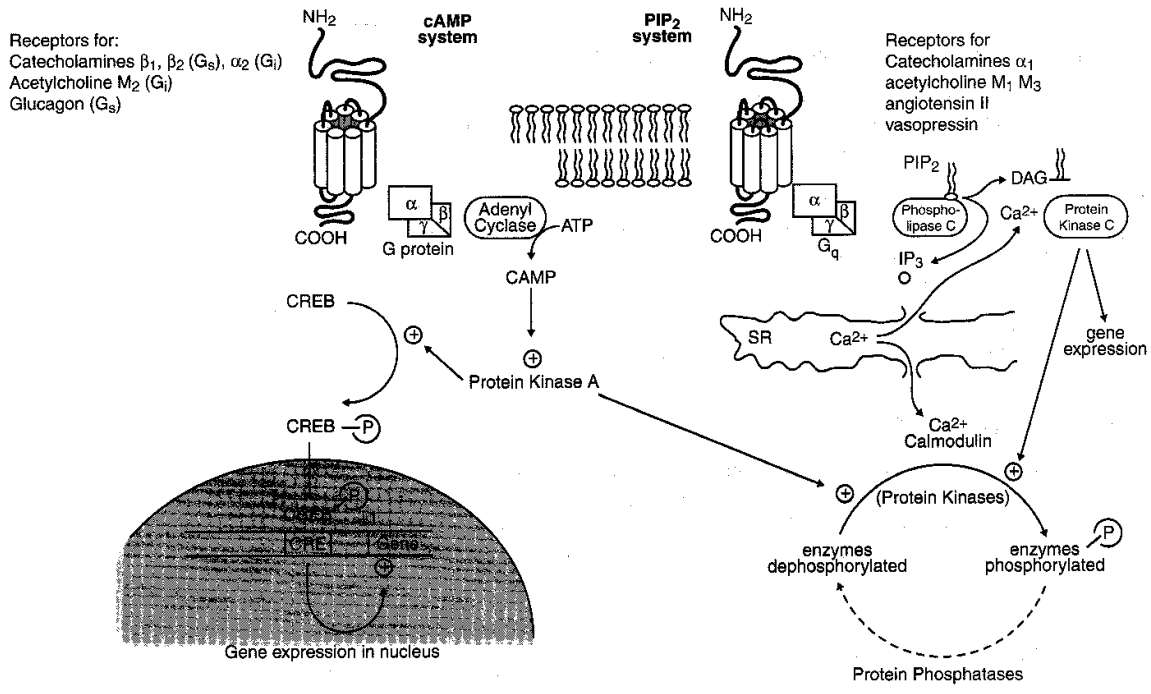


Figure I-2-6. Receptors Using Cyclic-AMP and IP3, DAG, Ca^{2+} as Second Messengers

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), which can be released from endothelial cells by vasodilators (e.g., H_1 and M_3 agonists), activates guanylyl cyclase, thus increasing cGMP in smooth muscle.

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.

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.

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

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.

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 (from A through 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 I-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	+ 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 (a substance directly interacts with and inactivates an agonist).

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 (ED_{50}) or the median toxic dose (TD_{50}). 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.

GENERAL PRINCIPLES

Review Questions

1. The pKa of acetylsalicylic acid is 3.5. What percentage of the drug is in an absorbable form in the stomach at a pH of 1.5?

   A. 0.1%
   B. 1%
   C. 10%
   D. 90%
   E. 99%

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

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

3. 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

4. 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

5. A patient who experiences migraines has accidentally overdosed with methysergide, a weak base of pKa = 6.5. If urinary pH in this patient is 5.5, which of the following statements regarding elimination of methysergide from the body is accurate?

   A. Increase in urinary pH will increase excretion rate.
   B. Urinary excretion is already maximal, and changes in pH will have no effect.
   C. Attempts should be made to acidify the urine to at least 4 units below drug pKa.
   D. At a urinary pH of 5.5, methysergide is 99% ionized.
   E. None of the above

6. 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

7. A subject in whom the renal clearance of inulin is 120 mL/min is given a drug, the clearance of which is found to be 18 mL/min. 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

8. 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

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

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

10. 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

11. The data presented in the figure below show that

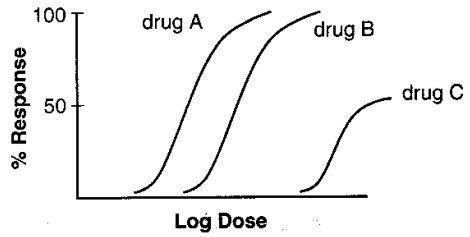


Figure I-2-7

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

12. A 500-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 1-g dose be effective?

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

13. 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 h, 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

14. 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

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

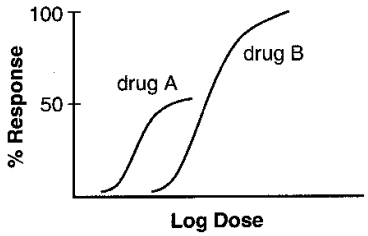


Figure I-2-8

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

16. In a patient weighing 70 kg, acetaminophen has a V_d = 70 L and Cl = 350 mL/min. The elimination half-life of the drug is approximately

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

17. Pharmacokinetic characteristics of propranolol include V_d = 300 L/70 kg, Cl = 700 mL/min, oral bioavailability f = 0.25. What is the dose needed to achieve a plasma level equivalent to a steady-state level of 20 μg/L?

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

18. 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. 1 h
B. 2 h
C. 3 h
D. 6 h
E. 9 h

19. At 12 h after IV administration of a bolus dose, the plasma level of a drug is 3 mg/L. 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. 480 mg
    E. 600 mg

20. An IV infusion of a drug is started at 400 mg/h. If Cl = 50 L/h, what is the anticipated plasma level at steady state?

    A. 2 mg/L
    B. 4 mg/L
    C. 8 mg/L
    D. 16 mg/L
    E. 32 mg/L

Answers

1. **Answer: E.** Aspirin (pKa = 3.5) is absorbed quite readily from the stomach. At a stomach pH of 1.5 (pH – pKa = –2), 99% of aspirin molecules are in the unionized form. Remember, unionized molecular forms of drugs are capable of permeation through biomembranes—ionized forms are "trapped".

2. **Answer: A.** The key word is *absorption.* By definition, IV injection does not involve absorption processes because 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.

3. **Answer: C.** Drugs with extensive plasma protein binding usually have low V_d values (recall V_d = dose/C^0) 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).

4. **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.

5. **Answer: E.** Weak bases are more readily excreted in the urine when pH < pKa, so urinary acidification can often be of value in overdose situations (choice A is wrong). With just one unit of pH difference from pKa, excretion is not maximal for methysergide, in that 10% of the drug molecules would be in nonionized form capable of tubular reabsorption (choices B and D are wrong). Acidification of the urine to a pH of 2.5 (4 pH units < pKa) is not compatible with life (choice C is wrong).

6. **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 × 2 × 2) or 160/8 = 20 mg.

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

8. **Answer: A.** This is a "loading dose" question. Remember LD = $V_d \times C^0$. In this case, V_d = 42 L, which approximates total body water in a patient weighing 70 kg.

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

9. **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.

10. **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.

11. **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.

12. **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.

13. **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 mg/L, but just before it would be close to half of that level.

14. **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.

15. **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.

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

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

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

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

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

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

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

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

19. **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 (C^0) = 3 × 2 × 2 mg/L = 12 mg/L.

$$\text{Dose injected} = V_d \times C^0$$

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

$$= 120 \text{ mg}$$

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

$$k_0 = Cl \times C^{ss}$$

$$\text{rearrange: } C^{ss} = k_0/Cl$$

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

SECTION II

Autonomic Pharmacology

The Autonomic Nervous System (ANS)

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 CNS 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:

N_N—Nicotinic receptors are located on cell bodies in ganglia of both PANS and SANS and in the adrenal medulla.

N_M—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.

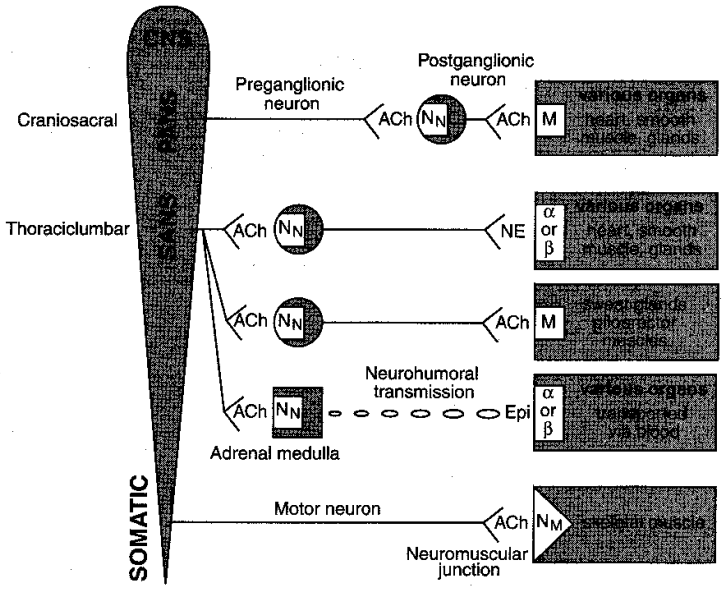


Figure II-1-1. Anatomy of the Autonomic Nervous System

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.

Bridge to Physiology

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

BLOOD PRESSURE CONTROL MECHANISMS

Autonomic Feedback Loop

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.

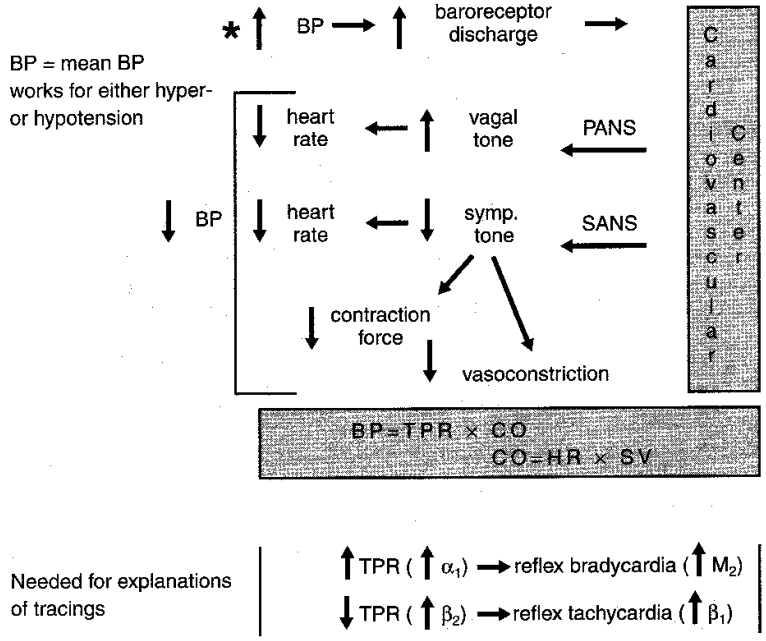


Figure II-1-2. Automatic Feedback Loop

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

Baroreceptor reflexes can be blocked at the ganglionic synapse with N_N receptor antagonists. Alternatively, a reflex bradycardia can be blocked with muscarinic antagonists; a reflex tachycardia can be blocked with β_1 antagonists.

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.

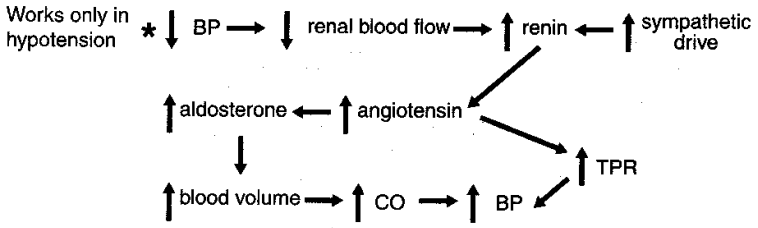
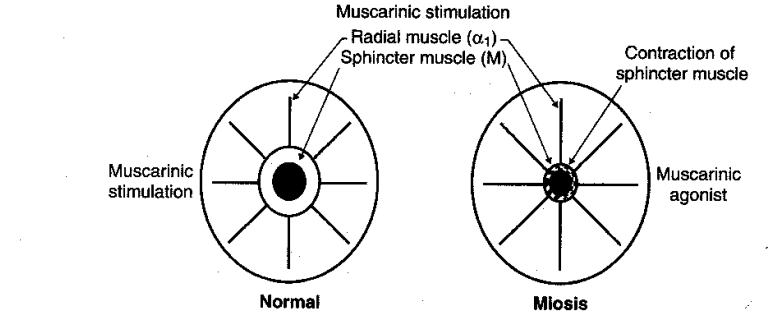
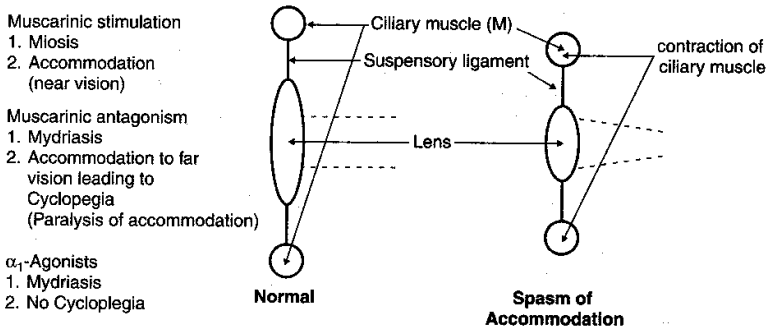


Figure II-1-3. Hormonal Feedback Loop





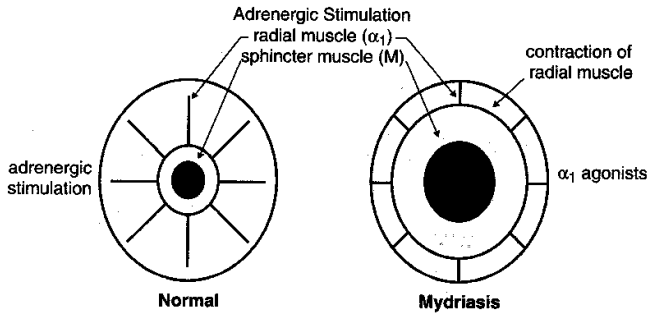


Figure II-1-4. Effects of ANS Drugs on the Eye

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 (N_N), endplate nicotinic (N_M), muscarinic (M_{1-3}), and adrenergic receptor of four major subtypes (α_1,α_2, β_1, β_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 (SV). The autonomic (neural) system helps regulate the BP through feedback control involving the baroreceptors, the cardiovascular centers in the brain stem, 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

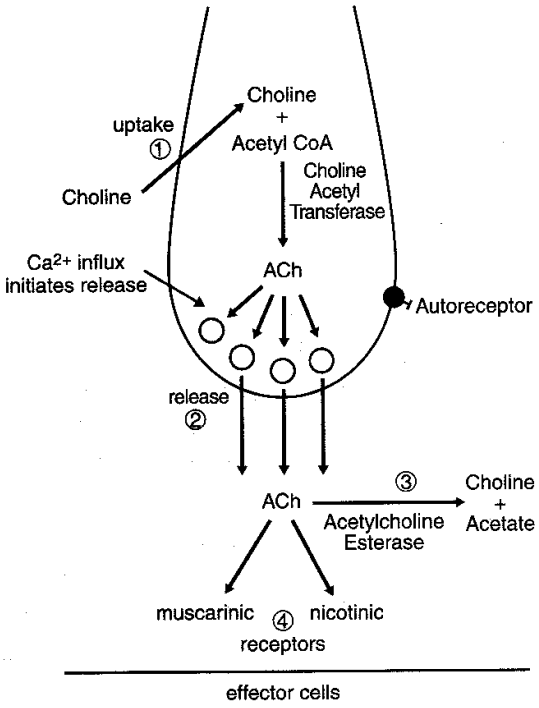


Figure II-2-1. Cholinergic Neuroeffector Junction

Choline is accumulated in cholinergic presynaptic nerve endings via an active transport mechanism linked to a Na^+ pump.

Choline uptake is inhibited by hemicholinium (① in Figure II-2-1). 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 (② in Figure II-2-1) interacts with synaptobrevin and other proteins to prevent ACh release.

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 (③ in Figure II-2-1) include edrophonium, physostigmine, and neostigmine. Irreversible AChE inhibitors include echothiophate, malathion, and parathion.

Postjunctional receptors (N and M) (④ in Figure II-2-1) activated by ACh are major targets for both activating drugs (direct-acting cholinomimetics) and cholinoceptor blocking agents.

Cholinomimetics

Nicotinic: nicotine

Muscarinic: bethanechol, methacholine, pilocarpine

Cholinoceptor Blockers

Nicotinic (N_N): hexamethonium, mecamylamine

Nicotinic (N_M): tubocurarine, atracurium, succinylcholine

Muscarinic: atropine, benztropine, glycopyrrolate, scopolamine

In A Nutshell

M receptor activation →↓ CV function

↑ secretions and ↑ smooth muscle contraction

All M receptor activators are nonspecific.

Table II-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	↓ Heart rate (HR)—negative chronotropy
	AV node	M_2	↓ 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	↑ Motility—cramps
	Glands	M_1	Secretion
	Intestine	M_3	Contraction—diarrhea, involuntary defecation
Bladder		M_3	Contraction (detrusor), relaxation (trigone/sphincter), voiding, urinary incontinence
Sphincter		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	N_N	Secretion of epinephrine and NE
Autonomic ganglia	N_N	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_3	G_q coupled	↑ phospholipase C →↑ IP_3, DAG, Ca^{2+}
M_2	G_i coupled	↓ adenylyl cyclase →↓ cAMP
N_N and N_M	No 2nd messengers	activation (opening) of Na/K channels

MUSCARINIC RECEPTOR ACTIVATORS (PARASYMPATHOMIMETICS)

Muscarinic Agonists

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

Drug	Activity	AChE Hydrolysis	Clinical Uses
ACh	M and N	+++	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 GI tract is dominated by the PANS, so ganglionic stimulation causes increased GI 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 II-2-5. Properties of Indirect-Acting Cholinomimetics

Drug	Characteristics	Clinical Uses
Edrophonium	Short-acting	Dx—myasthenia; used to differentiate myasthenia from cholinergic crisis
Physostigmine	Tertiary amine (enters CNS), intermediate-acting	Rx—glaucoma; antidote in atropine OD
Neostigmine, pyridostigmine	Quarternary amines (no CNS entry), intermediate-acting	Rx—ileus, urinary retention, myasthenia, reversal of nondepolarizing NM blockers
Donepezil, tacrine	Lipid-soluble (CNS entry)	Rx—Alzheimer disease
Organoposphates	Lipid-soluble, long-acting 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) have wide use in agriculture as insecticides. Malathion and parathion are pro-drugs rapidly bioactivated by insect P450 to form AChE inhibitors, which covalently bond to serine hydroxyl groups at the esteratic site of the enzyme. Such bioactivation occurs only slowly by human P450; nonetheless, these insecticides may cause human toxicity with symptoms of cholinergic excess via activation of both M and N receptors.

Classic Clue

AChE inhibitor poisoning: Dumbbelss

Diarrhea

Urination

Miosis

Bradycardia

Bronchoconstriction

Excitation (Muscle and CNS)

Lacrimation

Salivation

Sweating

Acute Toxicity

Acute toxicity includes pupillary constriction, stimulation of GI tract (cramps, nausea, vomiting, and diarrhea [NVD]) and urinary tract (incontinence, urination), bronchoconstriction (wheezing, dyspnea), increased glandular secretions (sweating, salivation, lacrimation), bradycardia and hypotension, skeletal muscle fasciculations and then paralysis (e.g., respiratory muscles), and CNS effects (behavioral excitation, depression of cardiovascular [CV] and respiratory centers).

Management

M blockers such as atropine (enters CNS), plus pralidoxime (2-PAM), may regenerate AChE, particularly at the skeletal neuromuscular junction (NMJ). Because time-dependent "aging" of the phosphorylated enzyme may decrease the effectiveness of the regenerator, 2-PAM should be used ASAP.

Chronic Toxicity

Chronic toxicity of AChE inhibitors: peripheral nerve demyelination with both muscle weakness and sensory loss

MUSCARINIC RECEPTOR ANTAGONISTS (PARASYMPATHOLYTICS)

Atropine, the Prototype

Atropine is the prototype of the class. As a tertiary amine, it enters CNS, where it acts as an M receptor antagonist.

Other M blockers differ mainly in their pharmacokinetic properties, which can influence their clinical uses.

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

In A Nutshell

Atropine makes you:
"dry as a bone, red as a beet, hot as a pistol, blind as a bat, and mad as a hatter."

Toxicity

Overdose of M blockers: Poisoning most commonly follows excessive ingestion of over-the-counter (OTC) antihistamines and cold medications, or attempts to induce hallucinations. Note that M-blocking side effects (and possible toxicity) occur with both tricyclic antidepressants and phenothiazines. Management is largely symptomatic, although physostigmine can be useful and may counter both peripheral and central effects.

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 OD, antidiarrheal, ophthalmology (but long action)
Tropicamide	Ophthalmology (topical)
Ipratropium	Asthma and COPD (inhalational)—no CNS entry, no change in mucus viscosity
Scopolamine	Antimotion sickness, causes sedation and short-term memory block
Glycopyrrolate	Antispasmodic, antisecretory, antiulcer—no CNS entry
Benztropine, trihexyphenidyl	Lipid-soluble (CNS entry) used in parkinsonism and drug-induced extrapyramidal dysfunction

NICOTINIC RECEPTOR ANTAGONISTS

Ganglion Blocking Agents

Bridge to Physiology

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.

Effects

Ganglion blocking agents are competitive antagonists at N_N receptors on cell bodies in autonomic ganglia.

Effects are predictable, knowing ANS innervation to effectors and relative **dominance** in terms of PANS and SANS. Net effect of a ganglion blocker is to reduce the predominant tone.

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

Effector	System	Effect of Ganglion Blockade
Arterioles	SANS	Vasodilation, hypotension
Veins	SANS	Dilation, ↓ CO, ↓ venous return
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

Drugs

Hexamethonium—prototype with no clinical use.

Mecamylamine—used in severe hypertension, for controlled hypotension in surgery, for smoking cessation, and for Tourette syndrome.

Physiologic Effects

Ganglion blockers prevent ANS reflexes, including changes in heart rate elicited by increases or decreases in mean blood pressure. This characteristic can be of value in questions of drug identification because it helps to determine if a drug action (e.g., on heart rate) is direct or due to an autonomic reflex response. For the USMLE, this is the main relevance of ganglionic blockers.

Example: Hexamethonium will block the reflex bradycardia that occurs when phenylephrine (an alpha-adrenoceptor agonist) causes vasoconstriction, but it will not block a bradycardia that results from the direct activation by ACh of M receptors in the heart.

SKELETAL NMJ BLOCKERS

See CNS section.

Nondepolarizing

These act as competitive antagonists at N_M receptors at muscle end plate. Drugs include tubocurarine, atracurium, and pancuronium.

Depolarizing

These act as agonists at N_M receptors. They induce initial fasciculation, then paralysis, through desensitization of nicotinic acetylcholine receptors (N_N). Succinylcholine is a drug in this class.

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 (cholinoceptor) blockers. Specific blocking agents acting on ganglionic nicotinic (N_N) 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, glycopyrrolate, 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 II-2-1 summarizes the type of M receptor involved and the specific end-organ responses to M-receptor activators.

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

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

(Continued)

Chapter Summary (*continued*)

Long-acting AChE inhibitors are commonly used as insecticides. Whereas 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 (2-PAM), which helps reactivate AChE.

Atropine is the prototype of the muscarinic receptor antagonist (parasympatholytic) drugs. In simple terms, increasing doses of atropine progressively make you "dry as a bone, red as a beet, hot as a pistol, blind as a bat and mad as a hatter." 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 II-2-6.

The N_N antagonists act as ganglionic blockers. They will therefore affect both the SANS and PANS tracts.

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

Skeletal neuromuscular junction effectors act as competitive inhibitors of the N_M muscle end-plate receptor or as depolarizing agonists. Tubocurarine, atracurium, and pancuronium are competitive antagonists, whereas succinylcholine is a depolarizing agent. Both the antagonists and agonists are used clinically to relax muscle.

Adrenergic Pharmacology

3

CATECHOLAMINE SYNTHESIS, ACTION, AND DEGRADATION

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

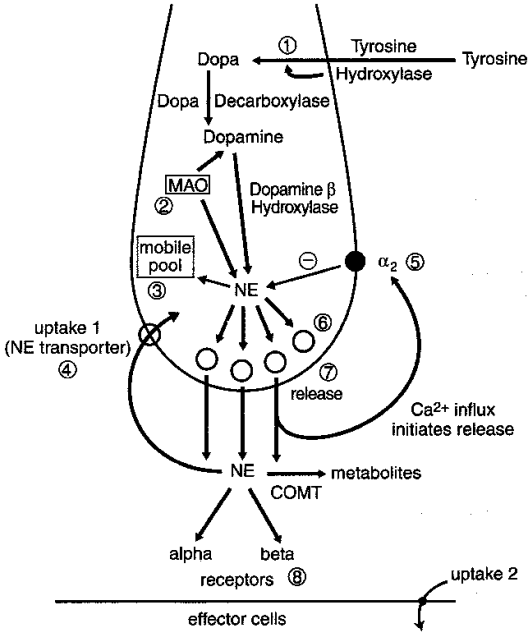


Figure II-3-1. Adrenergic Neuroeffector Junction

Tyrosine is actively transported into nerve endings and is converted to dihydroxyphenylalanine (DOPA) via tyrosine hydroxylase (1). This step is rate limiting in the synthesis of NE. DOPA is converted to dopamine (DA) via L-aromatic amino acid decarboxylase (DOPA decarboxylase). DA in turn is metabolized to NE via DA beta hydroxylase and is taken up and stored in granules (6). Inactivation of NE via monoamine oxidase (MAO) (2) may regulate prejunctional levels of transmitter in the mobile pool (3) but not the NE stored in granules.

Presynaptic membrane depolarization opens voltage-dependent Ca^{2+} channels. Influx of this ion causes fusion of the synaptic granular membranes, with the presynaptic membrane leading to NE exocytosis into the neuroeffector junction (7). NE then activates postjunctional receptors (8), leading to tissue-specific responses depending on the adrenoceptor subtype activated.

Figure Legend

① Methyl-p-tyrosine

② MAO inhibitors

③ Releasers

④ Reuptake blockers

⑤ α_2 agonists and antagonists

⑥ Reserpine

⑦ Guanethidine

⑧ Agonists and blockers of α_1, β_1 receptors

Note

β_2 are targets of agonists and blockers but are mostly not innervated.

Termination of NE actions is mainly due to removal from the neuroeffector junction back into the sympathetic nerve ending via a NE transporter system (uptake 1) (4). At some sympathetic nerve endings, the NE released may activate prejunctional alpha adrenoceptors (5) involved in feedback regulation, which results in decreased release of the neurotransmitter. Diffusion away from the neuroeffector junction may also contribute to termination of actions. NE accumulated into target cells (e.g., via uptake 2) is rapidly inactivated by catechol-O-methyltransferase (COMT).

DRUG "TARGETS"

Numbers correspond to Figure II-3-1.

1. Tyrosine Hydroxylase

Tyrosine hydroxylase can be inhibited by methyl-*p*-tyrosine and is subject to feedback inhibition by high levels of NE in the mobile pool.

In A Nutshell

Forms of MAO

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

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

2. MAO

Inhibitors of MAO (e.g., phenelzine, tranylcypromine) may increase prejunctional levels of NE. Note that MAO type A, the enzyme form that metabolizes NE, also metabolizes tyramine and serotonin (5HT).

3. The Mobile Pool

Many indirect-acting sympathomimetics (e.g., amphetamine, ephedrine, tyramine) can displace NE from the mobile pool.

4. Uptake

Some indirect-acting sympathomimetics (e.g., cocaine, tricyclics) inhibit uptake into the nerve cell, increasing the postjunctional actions of NE.

5. Prejunctional Alpha Receptors

Activators of prejunctional alpha receptors (e.g., clonidine, alpha methyldopa) cause inhibition of NE release from synaptic vesicles.

6. Granular Uptake of NE

Blockers of granular uptake of NE (e.g., reserpine) decrease prejunctional levels available for release.

7. NE Release From Granules

Blockers of NE release from granules (e.g., guanethidine) decrease postjunctional actions of NE.

8. Postjunctional Receptors

Postjunctional receptors can be activated by many direct-acting sympathomimetics. These receptors are also "targets" for many antagonist drugs.

Table II-3-1. Adrenoceptor 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 ↑ GFR, RBF and Na^+ excretion

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.

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

α_1	G_q coupled	↑ phospholipase C → ↑ IP_3, DAG, Ca^{2+}
α_2	G_i coupled	↓ Adenylyl cyclase → ↓ cAMP
β_1 β_2 D_1	G_s coupled	↑ Adenylyl cyclase → ↑ cAMP

DIRECT-ACTING ADRENOCEPTOR AGONISTS

α_1 Agonists

Given systemically, they increase mean blood pressure (BP) via vasoconstriction, with minimal effects on pulse pressure (PP). The increase in BP elicits a reflex bradycardia. Cardiac output (CO) may be decreased but can be offset by an increase in venous return, which may increase stroke volume (SV).

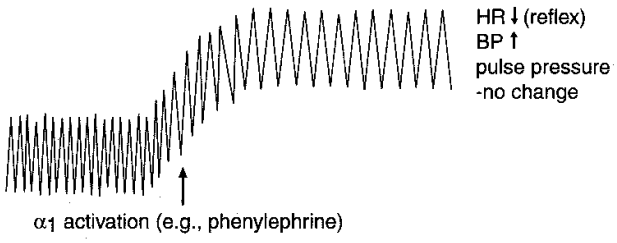


Figure II-3-2. Effect of Alpha Activators on Heart Rate and Blood Pressure

Drugs

Phenylephrine (α_1): decongestant—mydriasis without cycloplegia.

Methoxamine (α_1): use in paroxysmal atrial tachycardia—elicits vagal reflex.

α_2 Agonists

Stimulate prejunctional receptors in the CNS to decrease vasomotor outflow and decrease mean BP. Primary use is in mild-to-moderate HTN.

Drugs

Clonidine: initial increase in BP (some α_1 activity) followed by decrease—abrupt discontinuation causes rebound HTN.

α-Methyldopa: a pro-drug forming α-methyl NE.

β Agonists

β_1: ↑ HR, SV, and CO.

β_2: ↓ TPR.

Agents that activate both β_1 and β_2 receptors cause a decrease in peripheral vascular resistance (TPR), a decrease in mean BP, and an increase in HR. Diastolic pressure falls more than systolic pressure, so pulse pressure (PP) increases.

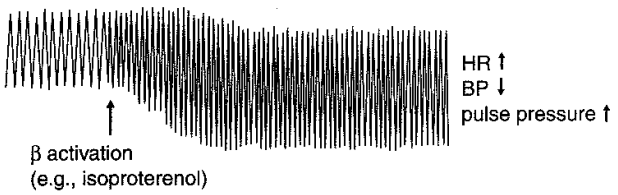


Figure II-3-3. Effect of Beta Activators on Heart Rate and Blood Pressure.

Drugs

Isoproterenol ($\beta_1 = \beta_2$): Rx uses include bronchospasm, heart block, and bradyarrhythmias. May cause flushing, angina, and arrhythmias.

Dobutamine ($\beta_1 > \beta_2$): ↑ HR, SV, and CO (positive inotropy and chronotropy).

No change in TPR, GFR, or renal blood flow (RBF). Rx use in acute congestive heart failure (CHF)—tachyphylaxis occurs.

Selective β_2 Agonists
Salmeterol, albuterol, metaproterenol, and terbutaline—use in asthma.

Ritodrine—use in premature labor.

Norepinephrine

(α_1 α_2 β_1)

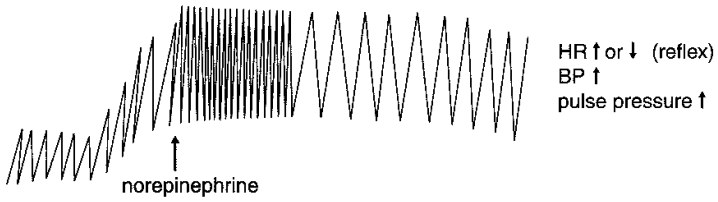


Figure II-3-4. Effect of Norepinephrine on Heart Rate and Blood Pressure

Norepinephrine (NE) has little effect on β_2 receptors. It increases TPR and both diastolic and systolic BP. Positive inotropic action of NE causes a small to moderate increase in pulse pressure (PP). Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of NE (reflex bradycardia may ensue), but the positive inotropic effects are maintained.

Epinephrine

(α_1 α_2 β_1 β_2)

Epinephrine increases HR, systolic BP, and PP. Its effects on diastolic blood pressure depend on dose. At moderate to high doses, alpha activation predominates, leading to increases in TPR, diastolic pressure, and mean BP. At low doses, beta activation predominates, resulting in a decrease in TPR and diastolic pressure, although mean BP may not decrease significantly.

Clinical Correlate

Epinephrine Reversal

Describes the effect of using an alpha blocker after eliciting a hypertensive response with a high dose of epinephrine. When the α_1 activating effects of epinephrine are blocked, the patient goes from hypertension to hypotension because of unrestricted β_2 activation.

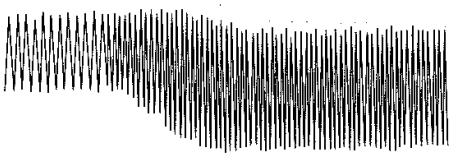


Figure II-3-5a. Effect of Low-dose Epinephrine on Heart Rate and Blood Pressure

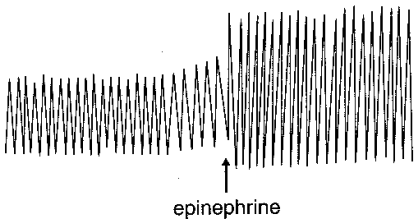


Figure II-3-5b. Effect of Medium-Dose Epinephrine on Heart Rate and Blood Pressure

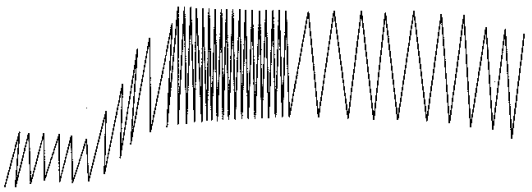


Figure II-3-5c. Effect of High-dose Epinephrine Is Similar to Norepinephrine

Other actions—lungs (bronchodilation), liver (glycogenolysis stimulated—↑ serum glucose), pancreas (↓ insulin release because α_2 predominates), muscle (glycogenolysis), fat (↑ mobilization and use of fat).

Clinical uses—anaphylaxis, cardiac arrest, adjunct to local anesthetics, glaucoma.

INDIRECT-ACTING ADRENOCEPTOR AGONISTS

Drugs

Tyramine: Present in certain foods and beverages—rapidly metabolized by MAO type A in GI tract and liver. At high levels displaces NE from the mobile pool, thus increasing pressor response—potential problem when MAO inhibitors are present, leading to hypertensive crisis. No CNS entry.

Amphetamine: Releases NE from mobile pool in nerve ending, causing increased NE activity—peripheral effects are those of sympathetic stimulation with reflex bradycardia. CNS actions include release of both NE and DA. Clinical uses include attention deficit hyperactivity disorder (ADHD), short-term weight loss, and narcolepsy (see CNS section).

Ephedrine: Releases NE from sympathetic neurons and can cause amphetamine-like CNS effects. Clinical use: decongestant (note similar use of pseudoephedrine).

Cocaine: Blocks reuptake of NE into sympathetic nerve endings, causing vasoconstriction. CNS effects are via block of reuptake of NE, DA and 5HT. Cocaine also blocks voltage-dependent Na^+ channels and is used as a local anesthetic.

Dopamine: DA is probably not a "natural" transmitter in periphery but can be released from some sympathetic fibers. When infused, it has dose-dependent actions on DA and adrenoceptors. Low dose increases renal/mesenteric blood flow via D_1 activation → ↑ RBF and GFR. Medium dose ↑ CO (positive inotropy) via β_1 activation. Useful in management of shock states. Very high dose causes vasoconstriction—↑ systolic and diastolic BP via α_1 activation.

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.

α ADRENOCEPTOR ANTAGONISTS

Because α_1 receptor activation causes vasoconstriction, alpha adrenoceptor antagonists will decrease TPR and mean BP, which will result in compensatory responses, including reflex tachycardia and salt and water retention.

Nonselective alpha blockers also block prejunctional α_2 receptors, preventing feedback inhibition of the release of NE from sympathetic nerves, resulting in increased vasomotor outflow.

Drugs

Phentolamine: nonselective, competitive, and short-acting—increases gastric acid secretion. Clinical use in pheochromocytoma and for local vasoconstrictor overdose.

Phenoxybenzamine: nonselective, irreversible—short-term use in pheochromocytoma.

Prazosin: prototype α_1 selective blocker (others include doxazosin, terazosin, amsulosin). Less reflex tachycardia (because NE feedback mechanism is intact), but postural hypotension occurs (first-dose syncope). Clinical uses include mild-to-moderate HTN and benign prostatic hyperplasia (BPH).

Yohimbine: antagonist at α_2 prejunctional receptors in CNS, increasing sympathetic outflow. Clinical uses include postural hypotension and impotence.

Mirtazapine: antagonist at α_2 prejunctional receptors in CNS; used in treatment of depression.

In A Nutshell

Receptor Antagonists

Competitive: effects depend on dose and elimination half-life.

Noncompetitive: effects depend on dose and time needed for synthesis of new receptors (if irreversible).

β ADRENOCEPTOR ANTAGONISTS

Effects are largely predictable, based on the sympathetic nervous system (SNS) innervation and the adrenoceptor subtypes present on effectors.

Heart: ↓ contractility, HR, CO, oxygen demand, and BP (without orthostatic hypotension).

Possible AV block and heart failure.

Eye: ↓ ciliary epithelial secretions—↓ intraocular pressure—use in glaucoma.

Lungs: bronchospasm in asthmatics.

Metabolism: delay recovery from hypoglycemia (↓ glycogenolysis).

Drugs

Propranolol is the prototype of the class and is a nonselective beta blocker. Its chronic use is associated with effects on blood lipids (↑ LDL and/or triglycerides [TGs]).

Clinical Correlate

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

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

Characteristics of other drugs include:

- Cardioselectivity (β_1 selective blockers)—less effect on vasculature, bronchioles, uterus, and metabolism—safer in asthma, diabetes, and peripheral vascular disease.
- Intrinsic sympathomimetic activity (ISA)—less bradycardia and minimal change in plasma lipids. These are partial agonists.
- Pharmacokinetic properties, e.g., no CNS entry of atenolol and nadolol; long half-life of carvedilol and nadolol.
- Combined alpha- and beta-blocking activity, e.g., carvedilol, labetalol.

Table II-3-3. Clinical Uses and/or Characteristics of Some Beta Blockers

Drugs	β_1-Selective	ISA	Sedation	Blood Lipids	Clinical Uses
Acebutolol	+	++	+	–	Angina, HTN
Atenolol	+	–	–	↑↑	Angina, HTN
Esmolol	+	–	+	–	Antiarrhythmic (IV)—half-life 10 min
Metoprolol	+	–	+	↑↑	Angina, HTN, post-MI, antiarrhythmic
Pindolol	–	++	+	–	Angina, HTN
Propranolol	–	–	+++	↑↑	Angina, HTN, post-MI, migraine, tremor, performance anxiety, thyrotoxicosis
Timolol	–	–	++	↑↑	HTN, migraine, glaucoma

Labetalol and carvedilol: α and β blockers (see drugs in heart failure); Sotalol: K^+ channel blocker and β blocker (see antiarrhythmics)

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, pre-junctional α-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 uptake to feedback inhibition. Tyrosine conversion to dopamine can be inhibited by methyl-p-tyrosine, a tyrosine hydroxylase inhibitor.

MAO inhibitors, such as phenelzine and tranylcypromine, 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 clonidine or alpha methyldopa, which are activators of the prejunctional α_2-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 II-3-1 summarizes the distribution and physiological effects associated with the activation of alpha 1 and 2, beta 1 and 2, and D_1 receptors. Table II-3-2 summarizes 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 β_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 α_1-selective blockers (e.g., prazosin) cause less reflex tachycardia because they do not block autoreceptors and 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 II-3-3). Drugs that block both alpha and beta adrenoceptors are identified.

Autonomic Drugs: The Eye and Cardiovascular System

4

AUTONOMIC DRUGS AND THE EYE

Table II-4-1. ANS Innervation of the Eye

Target	PANS Activity	SANS Activity
Iris sphincter (circular) muscle	M_3 receptors—contraction → miosis	—
Iris radial muscle	—	α_1 receptors—contraction →mydriasis (no cycloplegia)
Ciliary muscle	M_3 receptor—contraction → accommodation for near vision	—

Glaucoma

Open-Angle Glaucoma

A chronic condition with increased intraocular pressure (IOP) due to decreased reabsorption of aqueous humor, leading to progressive (painless) visual loss and, if left untreated, blindness. IOP 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-4-2).

Angle-Closure Glaucoma

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

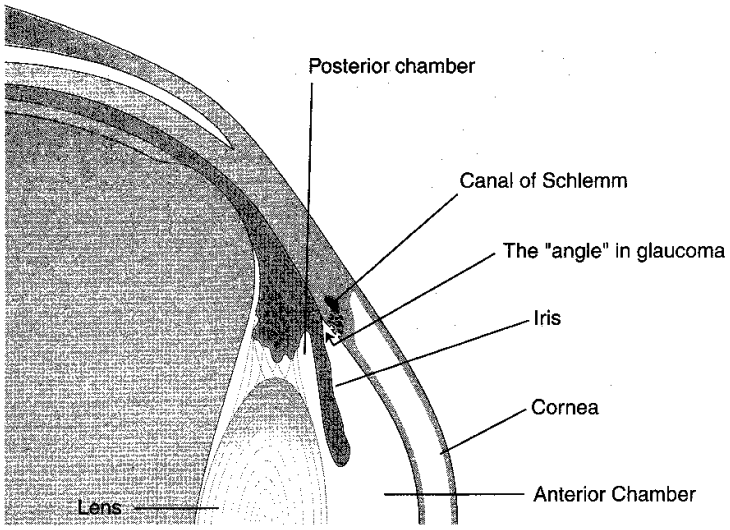


Figure II-4-1. Anatomy of the Eye Showing Irido-Corneal Angle Where Aqueous Humor Is Recirculated

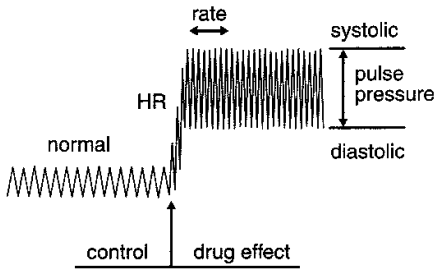
Treatment

Table II-4-2. Mechanism of Action of Drugs Used to Treat Glaucoma

Drug	Drug Class	Mechanism of Action
Carbachol, 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 → ↑ outflow
Apraclonidine epinephrine	Sympathomimetic	α_2 agonist effects (prejunctional) cause ↓ NE release → ↓ aqueous humor formation; E causes ↑ outflow
Betaxolol, timolol	Beta blockers	Block actions of NE at ciliary epithelium ↓ aqueous humor formation
Acetazolamide,* dorzolamide	Carbonic anhydrase inhibitor	↓ HCO_3^- availability leads to ↓ aqueous humor formation
Latanoprost	$PGF_{2\alpha}$ analog	↑ Outflow through the uveoscleral meshwork

*Only drug used orally; all others are topical.

AUTONOMIC DRUGS AND THE CARDIOVASCULAR SYSTEM



↑diastolic	↑TPR (↑α_1)
↓diastolic	↓TPR (↑β_2, ↓α_1, Direct acting Vasodilators and Cholinominetics)
↑heart rate	↑β_1 (May be a reflex)
↓heart rate	↑Cholinergic (May be a reflex)
↑pulse pressure	↑β_1(↑Inotropic activity)

Figure II-4-2. ANS Receptor Activation and Blood Pressure

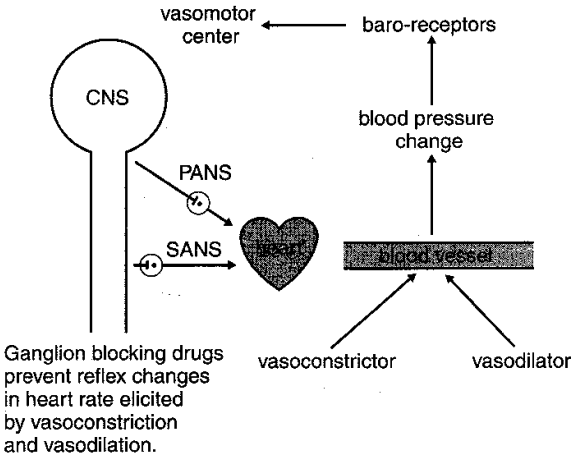
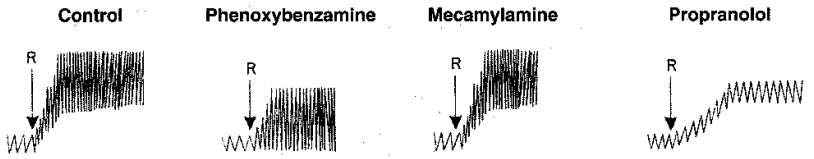
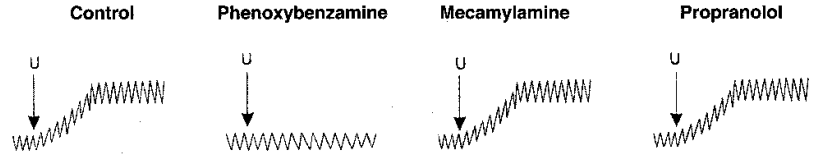


Figure II-4-3. Algorithm: Reflex Control of Heart Rate



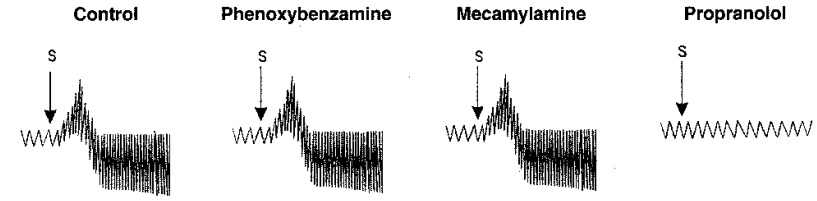
R is A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. terbutaline

Figure II-4-4



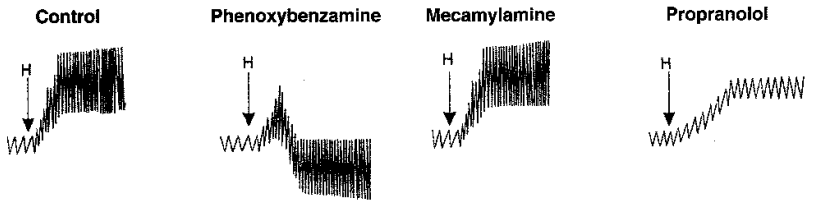
U is A. epinephrine
B. norepinephrine
C. phenylephrine
D. isoproterenol
E. tyramine

Figure II-4-5



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

Figure II-4-6



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

Figure II-4-7

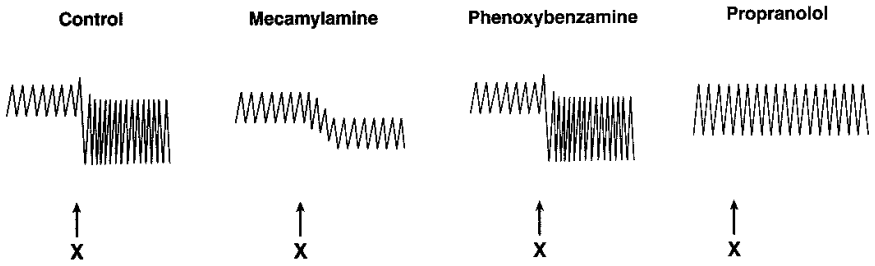
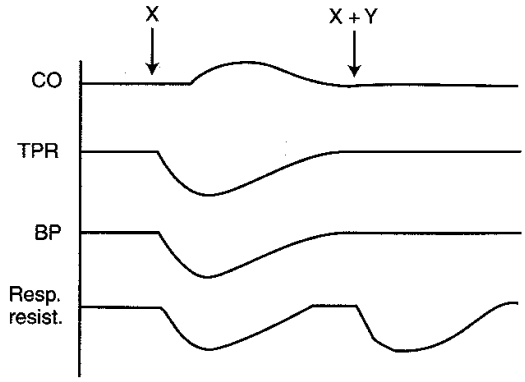


Figure II-4-8

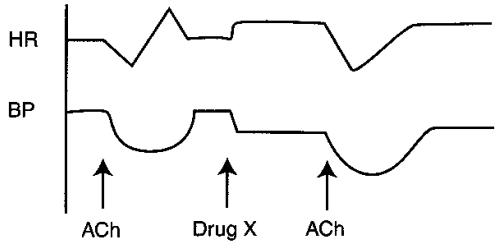
Drug X is most like:
A. Epinephrine
B. Isoproterenol
C. Norepinephrine
D. Phenylephrine
E. Terbutaline



X and Y are, respectively:

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

Figure II-4-9.

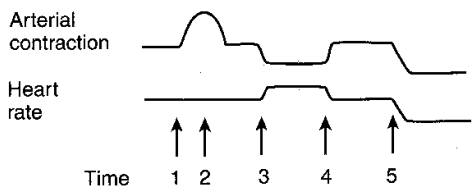


What is drug X?

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

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

Figure II-4-10.

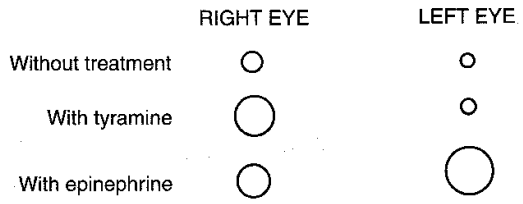


Given the following information:
- Contractile force is measured in an isolated arterial preparation, and heart rate is measured in an isolated heart preparation.
- One drug is added at each specified time.
- No washout between drugs

A. bethanechol
B. epinephrine
C. phenoxybenzamine
D. pindolol
E. methoxamine

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

Figure II-4-11.



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 II-4-12.

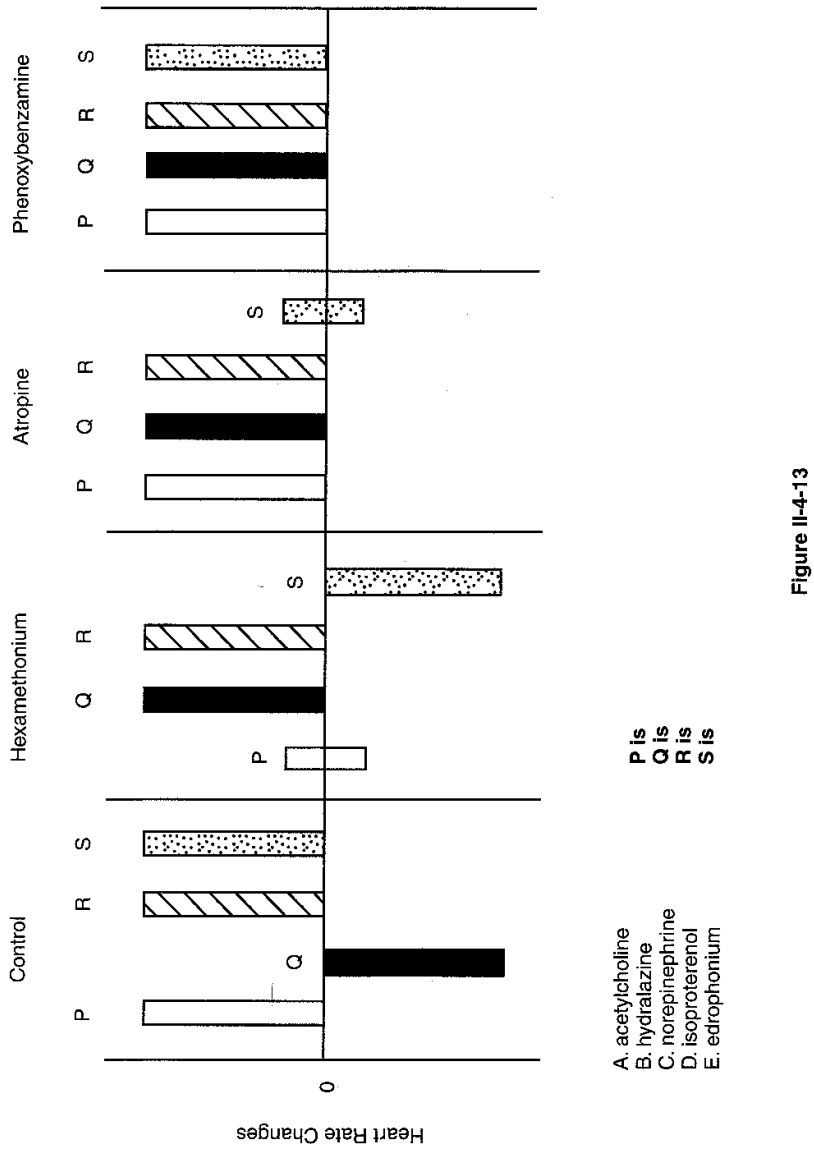


Figure II-4-13

Chapter Summary

The drugs used to treat open-angle glaucoma and their modes of action are summarized in Table II-4-2.

The effects of autonomic drugs affecting the cardiovascular system are summarized visually in Figures II-4-2 through II-4-13.

Autonomic Drug Summary

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, glycopyrrolate, scopolamine

Ganglionic blockers: hexamethonium, mecamylamine

NMJ blockers:

Nondepolarizing: atracurium, pancuronium, tubocurarine
Depolarizing: succinylcholine

Adrenergic Receptor Activators

α_1 agonists: phenylephrine, methoxamine

α_2 agonists: clonidine, α-methyldopa

3 agonists: isoproterenol, ($\beta_1 = \beta_2$), dobutamine ($\beta_1 > \beta_2$)

3_2 agonists: albuterol, metaproterenol, ritodrine, terbutaline

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

α_1 antagonists: doxazosin, prazosin, terazosin

α_2 antagonists: yohimbine, mirtazapine

Mixed α antagonists: phenoxybenzamine, phentolamine

3_1 (cardioselective) antagonists: acebutolol, atenolol, esmolol, metoprolol

3_1 β_2 (nonselective): pindolol, propranolol, timolol

α_1 and β 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. doxazosin
   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	110 mm Hg
Diastolic BP	85 mm Hg	55 mm Hg
Heart rate	60/min	120/min

    The most probable receptor affinities of drug X are

    A. α_1, α_2
    B. $\alpha_1, \alpha_2, \beta_1$
    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 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 IOP, 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	↑	↓	↓
Atropine	↑	–	↑
Prazosin	↑	–	↑
Propranolol	–	↓	↓
Mecamylamine	↑	–	↑

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 muscaria*, 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 α_2 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 β_2 receptor activation. This can result in a decrease in PVR and mean BP, which elicits a reflex tachycardia. Methoxamine and phenylephrine are α-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 like isoproterenol. PVR and mean BP are decreased because of activation of β_2 receptors in the vasculature. Systolic BP decreases less than diastolic BP because of activation of β_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 autoreceptors 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 α_1 receptors in the vasculature. Epinephrine (high dose), norepinephrine, and tyramine all exert pressor effects via activation of α_1 receptors. However, only epinephrine is active on β_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 (phentolamine) cause 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 (C is the correct answer). 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 α_1 and β_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 β_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 (β_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 IOP 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 β_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 β_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 β_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 α_1 receptors in blood vessels (it has no effects

on β_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 β_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 II-4-4 through II-4-13: Drug Identification from Effects on Heart Rate and Blood Pressure.

Figure II-4-4: 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 B, 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 II-4-5: 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 II-4-6: The effects of Drug S are changed by treatment with the beta-blocker, but not by the alpha blocker (**choices A, C,** and **D** are ruled out). Terbutaline is β_2 selective and would not increase heart rate directly. Drug S is isoproterenol.

Figure II-4-7: 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 B, D,** and **E** are ruled out). "Reversal" of a pressor effect can only occur if the drug has β_2 activity (**choice C** is ruled out). Drug H is epinephrine.

Figure II-4-8: Mecamylamine blocked reflexed tachycardia induced by Drug X, which dropped blood pressure by vasodilation. Propranolol prevented all responses. Drug X is a β_2 agonist (terbutaline).

Figure II-4-9: 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 β_2 response).

Figure II-4-10: 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 II-4-11: 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 II-4-12: 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 II-4-13: 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 III

Cardiac and Renal Pharmacology

Fundamental Concepts

1

CARDIAC ACTION POTENTIAL

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

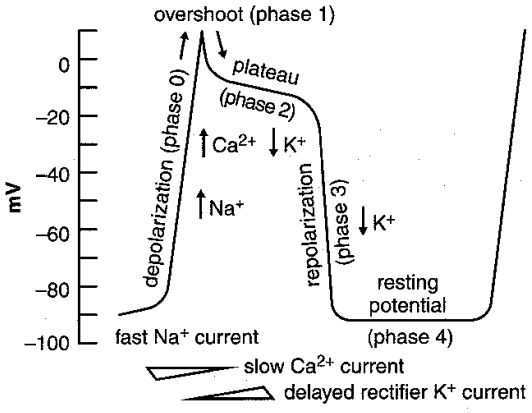


Figure III-1-1. Cardiac Action Potentials in Fast-Response Fibers

Phase 0

Na^+ channels open—sodium enters the cell down its concentration gradient (fast I_{Na}) 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 Cl^- 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 Ca^{2+} ($I_{Ca\text{-}L}$) 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^+-ATPase.

Responsiveness

Capacity of a cell to depolarize, associated with the number of Na^+ channels in a ready state (see Na channel below). 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)

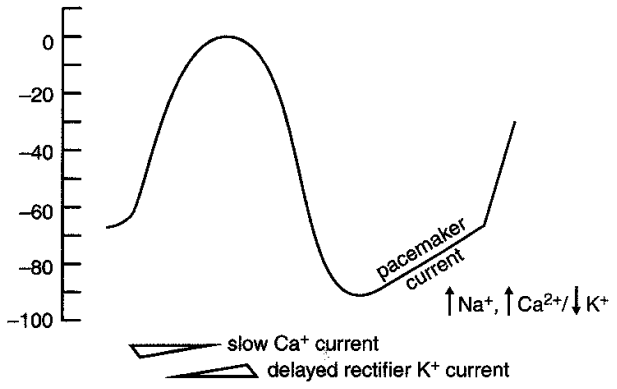


Figure III-1-2. Cardiac Action Potentials in Slow-Response Fibers

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 Ca^{2+} channels ($I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$).

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^+ (I_f) and Ca^{2+} ($I_{Ca\text{-}T}$) currents and outward K^+ currents (I_K).

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 below. Decreases in ERP favor the formation and propagation of premature impulses.

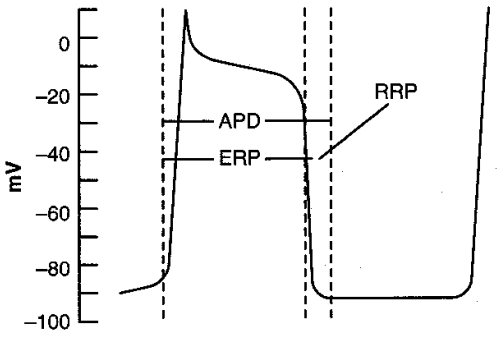


Figure III-1-3. Relationship of ERP to APD

Na^+ CHANNEL

Activation

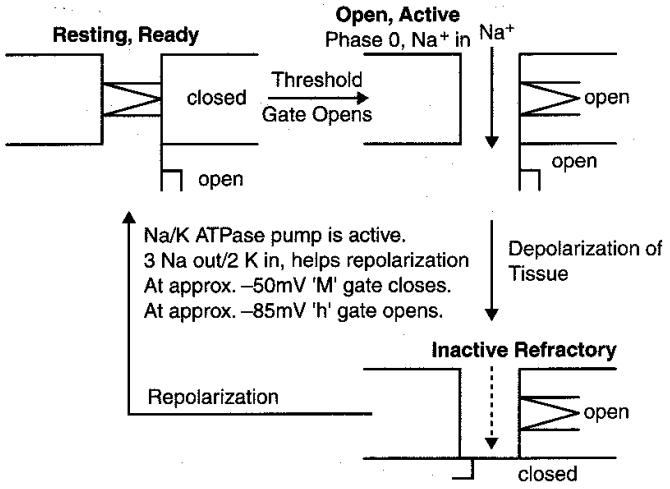


Figure III-1-4. Mechanism of Action of Voltage-Gated Na^+ Channels

This voltage-gated channel, which is responsible for the fast Na current (I_{Na}), 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 β_1 receptors, respectively. Phase 4 slope is increased by an increase in

cAMP resulting from β_1 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 $I_{Ca\text{-}L}$
- shorten AP duration by increase of I_K
- increase HR by increase of I_f, thus increasing slope of phase 4

Decrease in cAMP:

- does the opposite plus produces a K^+ current ($I_{K/ACh}$), 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 III-1-4 depicts 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 1A

Antiarrhythmic: $\downarrow V_{max}$—block fast Na channels ($\downarrow I_{Na}$)

Preferentially in the open or activated state—"state-dependent" blockade.

$\uparrow$ action potential duration (APD) and effective refractory period (ERP)

Also blocks K^+ channel (prolongs repolarization)

Quinidine

In addition to the above, causes M-block, which can $\uparrow$ 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: nausea and vomiting, cinchonism (GI, tinnitus, ocular dysfunction, CNS excitation), hypotension, prolongation of QRS and $\uparrow$ QT interval associated with syncope (torsades).

Drug interactions: hyperkalemia enhances effects and vice versa; displaces digoxin from tissue binding sites, enhancing toxicity; may oppose effects of AChE inhibitors in myasthenia.

Procainamide

Less M block than quinidine and no alpha block, but more cardiodepressant.

Orally effective, often substituting for quinidine. Metabolized via *N*-acetyltransferase (genotypic variation) to *N*-acetyl procainamide (NAPA), an active metabolite, which prolongs APD. With IV use, this is less likely to occur.

Adverse effects: systemic lupus erythematosus (SLE)-like syndrome (30% incidence) more likely with slow acetylators, hematotoxicity (thrombocytopenia, agranulocytosis), CNS effects (dizziness, hallucinations), CV effects (torsades).

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.

Class 1B

Antiarrythmic: ↓ V_{max} (in tachyarrhythmias): block fast Na channels (↓ I_{Na}).

Less state-dependent, 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.

↓ APD—due to block of the slow Na^+ "window" currents, but this increases diastole and extends the time for recovery.

Lidocaine

IV use in arrhythmias post-MI, during open heart surgery, or due to digitalis; drug of choice (DOC) for arrhythmias following attempted cardioversion.

Clearance depends markedly on liver blood flow, and rapid first-pass effects preclude oral use.

Adverse effects: CNS toxicity culminating in seizures in severe OD. Least cardiotoxic of conventional antiarrhythmics.

Mexiletine and Tocainide

Orally active drugs, otherwise similar to lidocaine.

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.

Class 1C

↓↓ V_{max}—block fast Na channels (↓I_{Na}), especially His-Purkinje tissue.

No effect on APD.

No ANS effects.

Flecainide and Encainide

Limited use because of pro-arrhythmogenic effects leading to ↑ sudden death post-MI and when used prophylactically in VT.

CLASS II: BETA BLOCKERS

↓ SA and AV nodal activity.

↓ Slope of phase 4 (diastolic currents) of AP in pacemakers.

Prevent β_1 adrenoceptor activation, which would normally ↑ cAMP.

Propranolol (nonselective) and the cardioselective drugs: acebutolol, metoprolol, and esmolol.

Antiarrhythmic uses: prophylaxis post-MI and in supraventricular tachyarrhythmias (SVTs); esmolol (IV) is used in acute SVTs.

CLASS III: K^+ CHANNEL BLOCKERS

↑ APD and ERP, especially in Purkinje and ventricular tissues.

↓ I_K (delayed rectifier current) slowing phase 3 (repolarization) of AP.

Bretylium

IV use (backup) in life-threatening ventricular arrhythmias.

Releases amines and is pro-arrhythmogenic (torsades).

Amiodarone

Activity mimics all antiarrhythmic drug classes (I, II, III, and IV); blocks Na, Ca, and K channels and beta adrenoceptors.

↑ APD and ERP in all cardiac tissues.

Half-life 30 to 60 days.

Effective in a wide range of atrial and ventricular arrhythmias.

Adverse effects: pulmonary fibrosis, corneal deposits, blue pigmentation ("smurf" skin), photoxicity, thyroid dysfunction, ↑ LDL-C, torsades, hepatic necrosis.

Drug interactions: ↓ clearance of digoxin, phenytoin, quinidine, theophylline, and warfarin.

Sotalol

Two enantiomers, both of which ↑ APD and ERP (↓ I_K delayed rectifier current), and one acts as a β_1 blocker to ↓ HR and AV nodal conduction.

Approved for prophylaxis in life-threatening ventricular arrhythmias.

Adverse effects: lassitude, impotence, depression, torsades, AV block.

CLASS IV: Ca^{2+} CHANNEL BLOCKERS

↓ SA and AV nodal activity.

↓ Slope of phase 4 (diastolic currents) of AP in pacemakers.

Verapamil

Prototype Ca^{2+} channel blocker (see also sections on drugs for angina and HTN).

Cardioselective, but also blocks vascular Ca^{2+} channels → hypotension and possible reflex tachycardia (blunted). Diltiazem is similar.

Prophylaxis in reentrant nodal and atrial tachycardias—not Wolff-Parkinson-White syndrome (WPW). Avoid in VT, as may progress to VF. In digitalis toxicity, can ↓ delayed after-depolarization.

Adverse effects: GI distress, dizziness, flushing, hypotension, AV block, CHF—avoid use concomitantly with beta blockers.

UNCLASSIFIED

Adenosine

↓ SA and AV nodal activity and ↑ AV nodal refractory period.

Activates A-receptors → causes G_i-coupled decrease in cAMP.

→ ↑ K efflux, causing membrane hyperpolarization.

DOC for PSVTs and AV nodal arrhythmias; used IV, half-life less than 30 seconds.

Possible flushing, sedation, and dyspnea; antagonized by theophylline.

Magnesium

Possible use as antiarrhythmic agent in torsades. Note that most of the antiarrhythmic drugs that block K channels associated with the delayed rectifier current have been implicated in torsades de pointes arrhythmias.

Other drugs associated with prolongation of the QT interval include thioridazine and tricyclic antidepressants.

Magnesium interferes with Na^+/K^+ ATPase, Na^+, K^+, and Ca^{2+} channels.

Clinical Correlate

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 fast Na^+ 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, but it has more cardiodepressant activity. The uses and contraindications 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.

Class IC drugs block fast Na^+ channels, especially of His-Purkinje cells, and have no effect on the APD and no ANS effects. The limited uses for flecainide and encainide are given.

Class II antiarrhythmic drugs are beta-blockers that decrease SA and AV nodal activity, decrease the phase 4 slope, and prevent β_1 adrenocepter activation, thereby circumventing the normal increase in cAMP. Propranolol is nonselective; acebutolol, metoprolol, 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. Bretylium, 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 Ia and III antiarrhythmics) associated with torsades include thioridazine and tricyclic antidepressants.

Antihypertensive Drugs

3

RATIONALE FOR USE

The rationale underlying the treatment of chronic HTN concerns its association with atherosclerosis and the increased risk of stroke, heart failure, renal diseases, peripheral vascular disease, and coronary artery disease. Except in severe HTN, there is no rush to start drug Rx prior to "lifestyle" changes because the goals are long term. Factors in hypertension include decreases in vagal tone, increases in sympathetic tone, increased renin-angiotensin activity, and water retention.

Strategies

Strategies underlying drug Rx include reduction in blood volume, reduction in sympathetic tone, reduction in vagal tone, and relaxation of vascular smooth muscle. Note that depending on the anti-HTN drug used, homeostatic mechanisms may lead to compensatory responses of salt and water retention and/or reflex tachycardia.

Table III-3-1. Classes of Drugs Used Categorized by Blood Pressure Determinant Affected

BP Determinant	Factor in HTN	Antihypertensive Drugs
CO—heart rate	↓ Vagal tone	Beta blockers, some Ca channel antagonists (CCBs)
CO—contractile force	↑ Sympathetic tone	Beta blockers
Peripheral resistance	↑ Sympathetic tone	Sympathoplegics, CCBs, direct-acting vasodilators, diuretics
Body fluid volume	Edema, ↑ renin and AII	Diuretics, ACE inhibitors, AII antagonists

Clinical Correlate

Antihypertensive Drug Efficacy

Although many different drug classes are used in the management of hypertension, only three classes of agents are known to prolong survival: beta blockers, thiazide diuretics, and ACE inhibitors.

SYMPATHOPLEGICS

Drugs Acting in the CNS

Methyldopa

Pro-drug converted to α-methyl-NE, which activates presynaptic α_2 adrenoceptors in the medulla to ↓ vasomotor outflow, mainly lowers TPR. Used in mild-to-moderate HTN. Decreases left ventricular (LV) hypertrophy.

Adverse effects: sedation, dizziness, decreased libido, edema, positive Coombs' (hemolysis).

Safe in renal dysfunction and in pregnancy.

Clonidine

Also activates presynaptic α_2 adrenoceptors in the medulla $\rightarrow\downarrow$ vasomotor outflow.

Used in mild-to-moderate HTN (patch causes fewer side effects) and also in dependency states such as opioids or nicotine.

Adverse effects: dry mouth, sedation/insomnia, edema, bradycardia. Severe rebound HTN on abrupt withdrawal.

Neither drug causes much postural hypotension, but water retention may warrant concomitant diuretic use.

Adrenergic Neuron Blockers

Reserpine

Causes destruction of storage granules in peripheral and central nerve endings; $\rightarrow\downarrow$ NE in sympathetic neurons $\rightarrow\downarrow$ CO and TPR. In CNS, $\downarrow$ NE, DA, and 5HT.

Adverse effects: mild orthostatic hypotension, fluid retention, sedation, depression (often severe), $\uparrow$ GI secretions.

Guanethidine

Binds to storage granules to inhibit NE release. Accumulated into nerve endings by uptake 1—actions decreased by TCAs.

Adverse effects: diarrhea, fluid retention (need diuretics), orthostatic hypotension, sexual dysfunction.

Alpha Blockers

$\downarrow$ arteriolar resistance and $\uparrow\uparrow$ venous capacitance; initial reflex $\uparrow$ HR, but ultimately vasodilation with $\downarrow$ TPR persists—no change in RBF.

Prazosin

Doxazosin and terazosin are α_1 selective blockers (less reflex tachycardia than nonselective blockers, but it still occurs).

Also used in BPH: the lack of sphincter tone allows a better voiding of the bladder, resulting in a decreased frequency of urination, particularly at night.

Unlike finasteride, α-blockers do not change prostate size much.

Adverse effects: "first-dose" syncope, orthostatic hypotension, urinary incontinence (especially in women).

No adverse effects on plasma lipids—may even be beneficial.

Beta Blockers

$\downarrow$ BP—long-term mechanism unclear, probably $\downarrow$ CO, but $\downarrow$ TPR in some patients.

Bridge to Physiology

Vasodilators may have specificity

Arteriolar: diazoxide, hydralazine, minoxidil

Venular: nitrates

Both arteriolar and venular: "the rest"

Orthostatic (postural) hypotension results from venular dilation (not arteriolar) and mainly results from alpha-1 blockade or decreased sympathetic tone.

Propranolol

Prototype drug, but many other beta blockers are used in HTN (see ANS section, Chapter 3, for specifics on cardioselective drugs and those with intrinsic sympathomimetic activity [ISA]). All appear to be equally effective with respect to HTN.

European American patients respond better than African American; young better than old.

Adverse effects: CV depression, fatigue, sexual dysfunction, and with chronic use → ↑ low-density lipoprotein cholesterol (LDL-C) and TGs (not ISA drugs). Nonselective drugs may cause problems in asthmatics and diabetics and in PVD. Watch for rebound HTN on abrupt withdrawal (less with ISAs).

DIRECT-ACTING VASODILATORS

Hydralazine

↓ TPR via arteriolar dilation—mechanism likely to involve the NO/EDRF pathway (see schematics in section on drugs used in angina).

↓ Resistance in coronary, renal, and cerebral beds; less in skin and muscle vessels.

Used in moderate-to-severe HTN—orally active, metabolized by *N*-acetyltransferase with genotypic variation.

Adverse effects: headache, flushing, sweating, fluid retention (use diuretic), reflex tachycardia (use beta blocker), SLE-like syndrome in slow acetylators.

Nitroprusside

↓ TPR via dilation of both arterioles and venules. Mechanism involves stimulation of guanylyl cyclase → ↑ cGMP via release of NO (see schematics in section on drugs used in angina).

Given by IV infusion in hypertensive emergencies (DOC); forms thiocyanate and cyanide ions, which can cause toxicity (cyanosis, muscle spasms, toxic psychosis) with infusion >12 hr. Can ↑ renin secretion.

Rebound HTN may occur after even a short infusion.

Minoxidil

Pro-drug that on sulfation opens K^+ channels, causing membrane hyperpolarization → arteriolar vasodilation. Potent renal vasodilator ↑ renin.

Used in moderate-to-severe HTN—orally active.

Adverse effects: headache, flushing, sweating, fluid retention (use a diuretic), reflex tachycardia (use a beta blocker), possible pulmonary HTN due to volume shifts, hypertrichosis (clinical use, topically).

Diazoxide

Arteriolar vasodilation via K^+ channel opening. Reflex tachycardia → ↑ CO, ↑ renin secretion.

Used IV for hypertensive emergencies.

Adverse effects: fluid retention (use diuretic, but not a thiazide), tachycardia (use a beta blocker), hyperglycemia via ↓ insulin release.

Clinical use—insulinoma; also relaxes uterine smooth muscle.

CALCIUM CHANNEL ANTAGONISTS (CCBs)

Block L-type Ca^{2+} channels in both cardiac and vascular tissues.

→ ↓ Intracellular Ca^{2+} → ↓ contractility (see schematics in section on drugs used in angina).

Vasodilation especially in arterioles and coronary vessels, plus natriuretic renal effects.

African American patients and elderly patients respond well.

Drugs

Verapamil and diltiazem > effects on heart than dihydropyridines (e.g., nifedipine)—possible AV block at high doses.

Nifedipine may cause reflex tachycardia—possible arrhythmias/MI from rapid-onset forms.

Nimodipine is used for subarachnoid hemorrhage—prevents vasospasm.

Adverse effects: constipation, headache, gingival overgrowths (dihydropyridines in general), proteinuria (dihydropyridines in general), inhibition of P-glycoprotein drug transporter (only verapamil).

No effects on plasma lipids.

ACE INHIBITORS AND AT-1 RECEPTOR ANTAGONISTS

ACE inhibitors (ACEIs) (e.g., captopril) inhibit kininase II (angiotensin-converting enzyme), blocking the formation of angiotensin II and preventing its activation of AT-1 receptors in the adrenal cortex → ↓ aldosterone and its effect on vasculature, thereby ↓ vasoconstriction. ACEIs also inhibit the metabolism of bradykinin (BK), which causes NO/EDRF-mediated vasodilation → ↓ TPR.

AT-1 receptor antagonists (e.g., losartan) block the effects of angiotensin II but do not affect BK levels or enhance its effects.

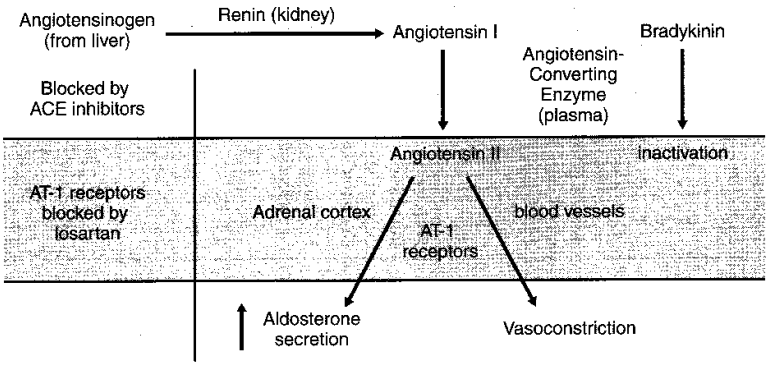


Figure III-3-1. The Angiotensin System

Both types of agent are commonly used in mild-to-moderate HTN. They also slow the development and the progression of nephropathy in diabetes by decreasing glomerular efferent resistance.

Adverse effects: hypotension, hypovolemia, dry cough (30% incidence with ACEIs, much less with AT-1 antagonists), hyperkalemia, acute renal failure (especially in renal artery stenosis), angioedema.

No effects on plasma lipids.

Teratogenicity → fetal hypotension, renal failure, skull and renal malformations.

DIURETICS

The pharmacology of diuretics is described later in a separate section. Both thiazide and loop diuretics are commonly used in the management of HTN. For the initial drug management of mild-to-moderate hypertension, the Joint National Committee (JNC) report VI recommends either a beta blocker or a thiazide diuretic as the drugs of first choice.

INDICATIONS FOR USE OF ANTIHYPERTENSIVE DRUGS IN COMORBID CONDITIONS

Table III-3-2. Use of Antihypertensive Drugs in Comorbid Conditions

Indication	Suitable Drug(s)
Angina	Beta blockers, CCBs
Diabetes	ACEIs, AT-1 antagonists
Heart failure	ACEIs, AT-1 antagonists
Post-MI	Beta blockers
BPH	Alpha blockers
Dyslipidemias	Alpha blockers, CCBs

Classic Clues

"Family Names" of Antihypertensives

Beta blockers: "–olols," except for labetalol and carvedilol

ACEIs: "–prils"

AII antagonists: "–sartans"

Vascular-selective CCBs: "–dipines"

Table III-3-3. Summary of the Types and Properties of Antihypertensive Drugs

Property	$Alpha_2$ Agonists	$Alpha_1$ Blockers	Beta Blockers	Diuretics	ACE Inhibitors and AT-1 Antagonists	Calcium Channel Antagonists (CCBs)	Adrenergic Neuron Blockers	Direct-Acting Vasodilators
Hemodynamics	↓ TPR	↓ TPR	↓ CO	↓ blood volume ↓ TPR	↓ TPR ↓ TPR	↓ TPR	↓ CO ↓ TPR	↓ TPR
Adverse effects	Dry mouth, sedation, sexual dysfunction, rebound HTN, positive Coombs' (methyldopa)	1st-dose syncope, postural hypotension, incontinence	Bronchospasm, fatigue, sexual dysfunction, ↑ plasma lipids, glucose intolerance, rebound HTN	Alkalosis, hypokalemia, hyperuricemia, glucose intolerance, ↑ plasma lipids	Cough, acute renal failure, proteinuria hyperkalemia, angioedema, neutropenia	Flushing, pedal edema, constipation, decreased AV conduction (verapamil, nifedipine)	Reserpine: sedation, depression. Guanethidine: diarrhea, orthostatic fluid retention.	Headache, flushing, sweating, ↑ HR. Hydralazine: SLE. Nitroprusside: toxicity. Minoxidil: hypertrichosis diazoxide; insulin
Cautions	Autoimmune disease (methyldopa)	Orthostatic hypotension	Allergy, bradyarrhythmias, coronary spasm, PVD	Diabetes mellitus, digitalis toxicity, gout, hyperlipidemias	Renal insufficiency, autoimmune diseases, drug interactions with diuretics, digoxin, Li		Guanethidine: asthma, GI ulcers, renal dysfunction	Potent vasodilators → major compensatory fluid retention and cardiac stimulation
Contraindications	Orthostatic hypotension, liver disease	Orthostatic hypotension	Asthma, heart block	Volume depletion	Pregnancy	Orthostatic hypotension	Pheochromocytoma. Reserpine: depression. Guanethidine: CHF.	
Advantages	No change in plasma lipids. Safe in pregnancy. Chonidine used in dependency states.	↓ VLDL and LDL, no change in cardiac parameters. Used in BPH and for pheochromocytoma (phenoxybenzamine).	Prolong survival. Used in angina, arrhythmias, post-MI, migrane pheochromocytoma, tremors. Safe in pregnancy.	Prolong survival, enhance effects of other anti-HTN drugs. Safe in pregnancy.	No CNS effects, no change in plasma lipids, protection in diabetic nephropathy. Used in CHF, PVD, diabetic nephropathy, edematous states.	No CNS effects. No change in plasma lipids. Used in angina, PVD, migraine, preterm labor, stroke (nimodipine), and arrhythmias (verapamil)	No changes in plasma lipids	Used for mod–severe HTN, hypertensive emergencies and in acute heart failure. Diazoxide: insulinoma

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.

Table III-3-1 lists the blood pressure (BP) determinants and the HTN factors being affected and the class of drugs used to treat each effect.

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 antagonists enhance vasodilation by blocking L-type Ca^{2+} channels in cardiac and vascular tissues. They are particularly effective for elderly and African American patients. Drugs considered are verapamil, diltiazem, nifedipine, and nimodipine.

Drugs that act via the renin-angiotensin system are the angiotensin conversion enzyme (ACE) inhibitors (e.g., captopril) and the angiotensin-II (AT-1) blockers (e.g., losartan). Figure III-3-1 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 III-3-2 summarizes the use of antihypertensives in comorbid conditions.

Table III-3-3 is a summary of the types and properties of the antihypertensive drugs.

Drugs for Heart Failure

4

RATIONALE FOR USE

Heart failure is due to defects in cardiac contractility (the "vigor" of heart muscle), leading to inadequate cardiac output. Signs and symptoms include decreased exercise tolerance and muscle fatigue, coupled with the results of compensatory responses (neural and humoral) evoked by decreases in mean BP. Increased SANS activity leads to tachycardia, increased arteriolar tone (↑ afterload, ↓ output, ↓ renal perfusion), and increased venous tone (↑ preload, ↑ fiber stretch). Activation of the renin-angiotensin system results in edema, dyspnea, and pulmonary congestion. Intrinsic compensation results in myocardial hypertrophy. These effects are summarized in Figure III-4-1.

Compensation in heart failure is offset by specific drugs that can:

- ↓ preload—diuretics, ACEIs, AT-1 receptor antagonists, and vasodilators.
- ↓ afterload—ACEIs, AT-1 antagonists, and vasodilators.
- ↑ contractility—digitalis, beta agonists, and bipyridines.

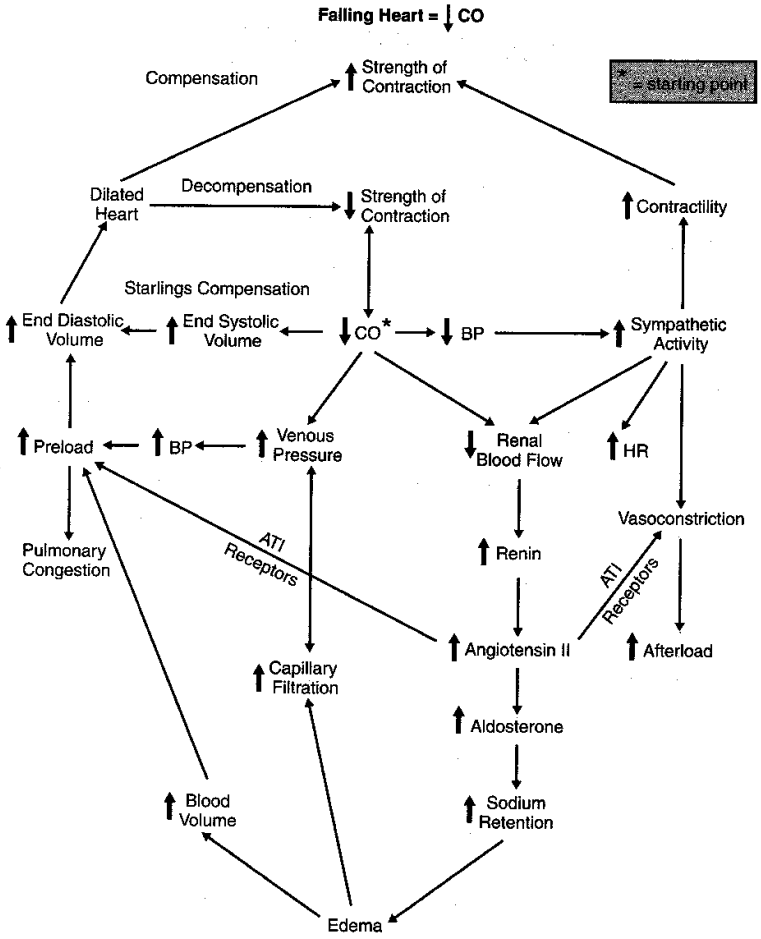


Figure III-4-1. The Failing Heart

ACE INHIBITORS AND AT-1 ANTAGONISTS

ACEIs block formation of AII and inhibit bradykinin metabolism →↓ aldosterone →↓ fluid retention →↑ vasodilation →↓ preload and afterload.

In addition to improving symptoms and exercise tolerance, they slow progression of heart failure and prolong survival. In addition, ACEIs have prophylactic value post-MI because they oppose "remodeling" that can lead to heart failure.

ACEIs are now the primary drugs used for management of heart failure. AT-1 antagonists appear to have similar efficacy. For characteristics, see the section on antihypertensive drugs.

CARDIAC GLYCOSIDES

Cardiac glycosides exert positive inotropic actions on the heart. Their initial action is to inhibit cardiac membrane Na^+/K^+-ATPase $\rightarrow\downarrow$ Na^+/Ca^{2+} exchange $\rightarrow\uparrow$ Ca^{2+} in sarcoplasmic reticulum $\rightarrow\uparrow$ Ca^{2+} release and binding to troponin $\rightarrow$ tropomyosin moves $\rightarrow\uparrow$ actin and myosin interaction $\rightarrow\uparrow$ contractile force.

Binding of digitalis to the "pump" is inhibited by K^+, so hyperkalemia decreases the effects and hypokalemia may increase the effects and cause toxicity. These relationships are summarized in Figure III-4-2.

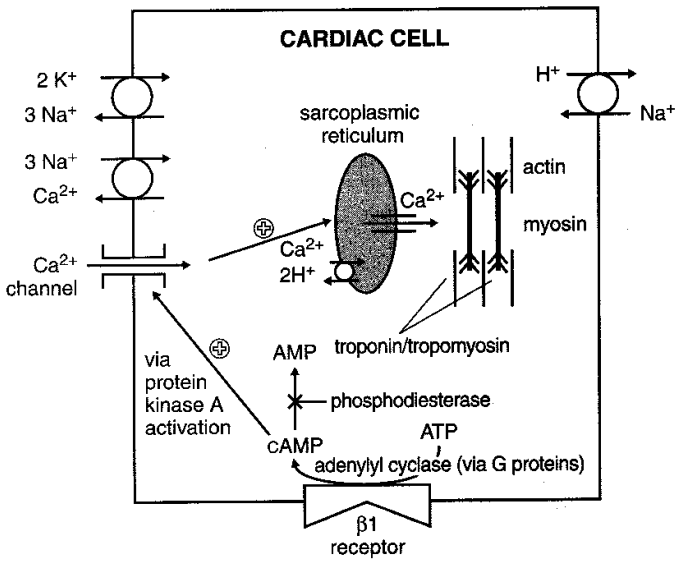


Figure III-4-2. Effects Resulting From Inhibition of Cardiac Membrane Na^+/K^+ATPase

The increase in contractility improves cardiac output, reversing the compensatory tachycardia and the increases in BP and TPR that occur in heart failure. Renal perfusion and diuresis are also improved, providing additional beneficial effects in heart failure. However, cardiac glycosides do not improve survival; thus, ACEIs are now considered drugs of first choice in most situations.

Cardiac glycosides exert electrophysiologic effects on the heart (via PANS) that include central vagal stimulation, facilitation of muscarinic activity, and sensitization of baroreceptors. These effects occur at conventional doses and in the absence of heart failure lead to a decrease in CO without effects on BP and TPR.

Cardiac Effects of Digitalis

Table III-4-1. Summary of the Cardiac Effects of Digitalis

Mode of Action	Atria	AV Node	Ventricles and Purkinje
Direct inhibition of Na/K–ATPase →↑ intracellular sodium	↓ APD and ERP, ↑ Abnormal automaticity (possible arrhythmias)	↓ Conduction velocity, reinforced by cholinomimetic action	↓ APD and ERP, less significant than atrial actions
Indirect: cholinomimetic actions, vagal stimulation, baroreceptor sensitization	↓ SA nodal rate	↑ ERP, ↓ Conduction velocity (possible AV block)	No significant action
Sympathomimetic (β_1-like): positive chronotropy, dromotropy, and inotropy	↑ SA rate ↑ Conduction velocity	↓ RP (possible AV nodal tachycardia)	↑ Conduction velocity, ↑ Phase 4 slope, ↑ Abnormal automaticity

Clinical Uses

Digoxin is the most widely used cardiac glycoside.

Table III-4-2. Properties of Digoxin

	Digoxin
Half-life (h)	20–40
Clearance (mL/min)	130 (renal)
Protein binding (%)	25
V_d (L/kg)	6

In addition to use in heart failure, the vagomimetic properties of digoxin may be used prophylactically in supraventricular tachyarrhythmias (SVTs), including atrial fibrillation, and for slowing the increase in AV conduction caused by quinidine.

Toxicity

Early signs include anorexia and nausea with ECG changes (↓ QT interval, T-wave inversion, PVBs, bigeminy). Later CNS effects include disorientation, visual effects (halos), and hallucinations. Signs of more severe cardiac toxicity include SVTs, AV nodal tachycardias or AV block, and ventricular tachycardias or VF.

Management includes adjustment of electrolytes, use of antiarrhythmics (lidocaine, phenytoin), use of digitalis Fab antibodies (Digibind), and pacemakers. Cardioversion is usually reserved for VF.

Toxicity is increased by ↓ K, ↓ Mg, ↑ Ca (note effects of diuretics on electrolytes) and by quinidine, NSAIDs, amiodarone, verapamil, sympathomimetics, and some antibiotics (e.g., erythromycin). Avoid digitalis in Wolff-Parkinson-White arrhythmias.

OTHER DRUGS USED IN HEART FAILURE

Bipyridines

Inamrinone and milrinone are used occasionally short term. They inhibit PDE →↑ cAMP, exerting positive inotropy and causing vasodilation. Amrinone causes thrombocytopenia; milrinone decreases survival in heart failure!

Sympathomimetics

Dobutamine and dopamine have been used in acute failure; tachyphylaxis occurs to positive inotropic actions.

Diuretics

By increasing renal elimination of Na and fluid, thiazide and loop diuretics help relieve symptoms of heart failure. They are commonly used in chronic failure and for rapid reduction of congestion and edema in acute failure. Most diuretics do not slow the progression of heart failure. However, spironolactone reduces the mortality rate when used in conjunction with ACEIs.

Beta Blockers and CCAs

Cardiodepressant drugs, including beta blockers and cardioactive CCAs like verapamil, have usually been avoided in management of heart failure. Recently, survival benefits in heart failure have been demonstrated for specific drugs, including metoprolol.

Carvedilol has both alpha- and beta-blocking action and slows the remodeling that accompanies sympathetic stimulation.

Amlodipine is a vascular selective CCA.

Nesiritide: recombinant human B-type natriuretic peptide (rh BNP) used intravenously. The old name was ANF. ANF receptors have guanylate cyclase activity, and nesiritide stimulation of the receptor ↑ concentrations of cGMP, relaxing smooth muscles of veins and arteries. Nesiritide is used in decompensated CHF patients who have dyspnea at rest or with minimal activity.

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 III-4-1.

Drugs used to combat heart failure include those that decrease preload (e.g., diuretics, ACE inhibitors, AT-1 receptor antagonists, and vasodilators), those that decrease afterload (e.g., ACE inhibitors, AT-1 receptor antagonists, and vasodilators), and those that increase cardiac contractibility (e.g., digitalis, beta agonists, and bipyridines).

Digoxin is the most commonly employed cardiac glycoside. Digoxin enhances cardiac contraction by inducing a series of responses initiated by inhibiting the Na^+/K^+ ATPase. Figure III-4-2 shows how inhibition of cardiac membrane Na^+/K^+ ATPase leads to increased contractility.

Although cardiac glycosides ameliorate symptoms, they do not increase survival. That is why the ACE inhibitors are the primary choice for treating heart failure.

Table III-4-1 summarizes the cardiac effects of digitalis.

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

Bipyridines, sympathomimetics, diuretics, beta blockers, and calcium channel blockers 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; unstable angina (crescendo) presents as an acute coronary syndrome with platelet aggregation.

Drug Strategies in Classic and Vasospastic Angina

Drug strategies in classic and vasospastic angina involve:

↑ oxygen delivery by ↓ vasospasm (nitrates and CCBs).

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

NITRATES

The mechanism of action of nitrates involves activation of the nitric oxide (NO) pathway. The formation of NO in endothelial cells can be triggered by ACh, bradykinin, histamine, and serotonin. NO activates guanylyl cyclase to form cGMP, which effects a relaxation of vascular smooth muscle. Vasodilation occurs because cGMP promotes the dephosphorylation of myosin light-chain phosphate, preventing its interaction with actin. These mechanisms are summarized in Figure III-5-1.

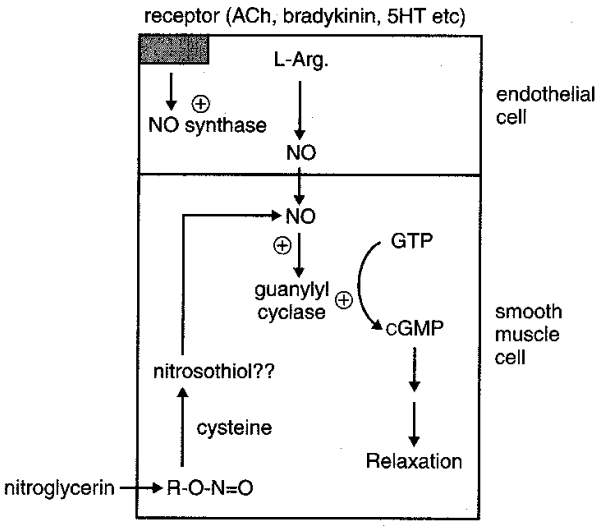


Figure III-5-1. Nitrates and the Nitric Oxide Pathway

Nitrates form NO, causing marked dilation of large veins →↓ preload →↓ cardiac work →↓ cardiac oxygen requirement. Nitrates also improve collateral blood flow, decrease coronary vasospasm, and inhibit platelet aggregation. At high doses, nitrates cause arteriolar dilation →↓ afterload →↓ cardiac oxygen requirement.

Nitrates decrease infarct size and post-MI mortality.

Nitroglycerin

Nitroglycerin is available in oral, sublingual, transdermal, and IV forms.

Isosorbide

Mono-or dinitrate; oral, some extended-release.

Adverse Effects of Nitrates

Flushing, headache, orthostatic hypotension (syncope).

Reflex tachycardia and fluid retention (possibly counterproductive).

Tachyphylaxis—require "rest periods" of >12 h.

Contraindications: sildenafil → ↑ sudden death.

Methemoglobinemia (more likely with nitrites, e.g., amyl nitrite).

Clinical Correlate

Cyanide Poisoning

Sodium nitrite or amyl nitrite can be used in cyanide poisoning. They promote formation of methemoglobin, which binds CN^- 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^-).

CALCIUM CHANNEL ANTAGONISTS (CCBs)

Rationale for Use

As shown in Figure III-5-2, smooth muscle contraction is triggered by the influx of Ca^{2+} through voltage-regulated membrane channels. Ca^{2+} combines with calmodulin, and the complex activates myosin LC kinase, the active form of which (MLCK*) phosphorylates myosin light chains, enabling the interaction between myosin and actin.

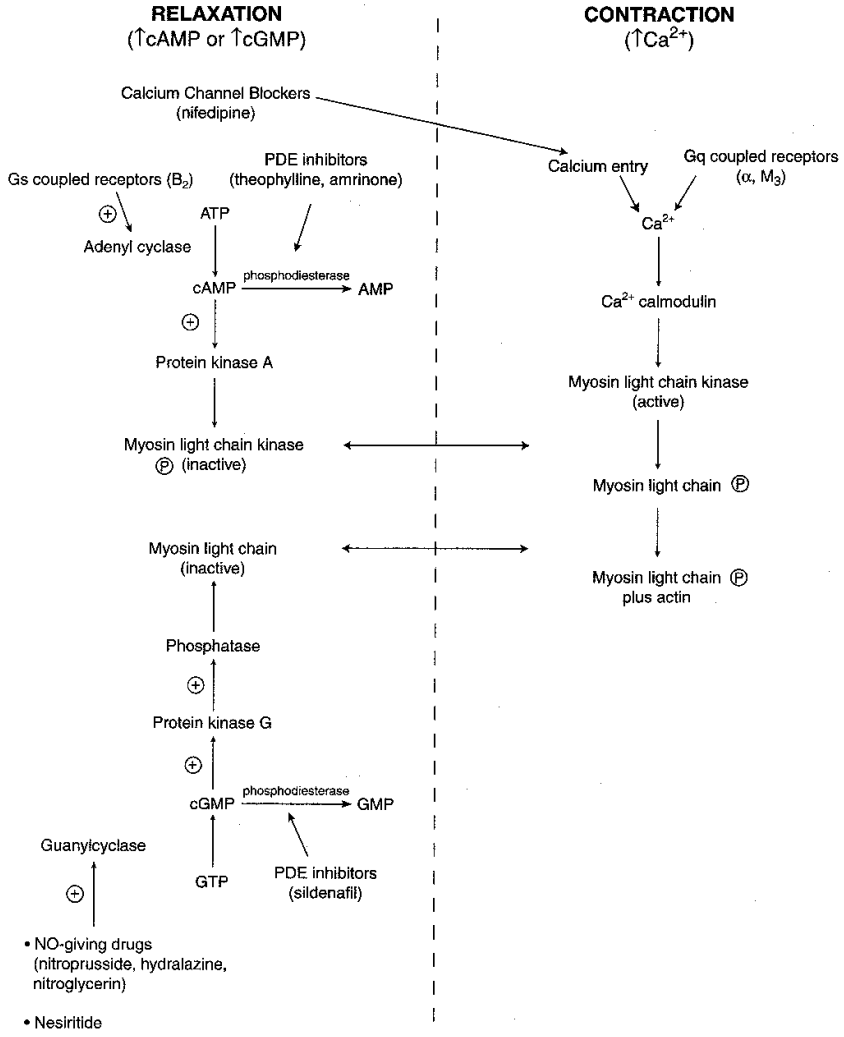


Figure III-5-2. Mechanisms of Smooth Muscle Contraction

Clinical Correlate

Sildenafil (Viagra)

Phosphodiesterase 5 (PDE5) is found in blood vessels supplying the corpora cavernosa. Sildenafil inhibits PDE 5 → ↑ 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.

CCBs block the vascular L-type Ca^{2+} channels $\rightarrow\downarrow$ contractility $\rightarrow$ vasodilation.

Arterioles are most sensitive ($\rightarrow\downarrow$ afterload $\rightarrow\downarrow$ cardiac work); orthostatic hypotension is minimal. CCBs also decrease vasospasm. The role of the vascular L-type Ca^{2+} channels in smooth muscle contraction is summarized in Figure III-5-2.

Drugs

Dihydropyridines (e.g., Nifedipine)

Are largely vascular selective. Caution with use of rapid-onset forms in emergency treatment of angina or HTN.

Verapamil and Diltiazem

Also block Ca^{2+} channels in the heart $\rightarrow\downarrow$ CO.

Bepridil

A CCB approved for angina because it dilates coronary vessels. It also blocks Na^{+} and K^{+} channels and has been implicated in torsades.

Other CCB Characteristics

See section on antihypertensive drugs.

BETA BLOCKERS

Have no direct actions on vascular smooth muscle in angina. They act directly on the heart $\rightarrow\downarrow$ HR, force of contraction, and CO $\rightarrow\downarrow$ oxygen requirement.

Effective prophylactically in angina of effort (not vasospastic) and offset reflex tachycardia caused by nitrates.

Most beta blockers have been used (for other characteristics see sections on autonomic drugs and antihypertensive drugs).

- Carvedilol: an alpha and beta blocker that has been shown equivalent to isosorbide.

DRUG STRATEGIES IN UNSTABLE ANGINA

Combinations of nitrates with beta blockers used initially with supplemental oxygen. To prevent thrombosis (and MI): heparin, warfarin, and antiplatelets (ASA, ticlopidine).

Consider glycoprotein IIb/IIIa receptor inhibitors in acute coronary syndromes, including unstable angina: abciximab, eptifibatide, tirofiban.

Chapter Summary

Angina is the principle 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 III-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 III-5-2. The CCBs considered are the dihydropyridines (e.g., nifedipine), verapamil, diltiazem, and bepridil.

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

More complex strategies are used to treat unstable angina.

Diuretics 6

CLINICAL USES

Diuretics have a wide range of clinical uses, including HTN, heart failure, edematous states, renal dysfunction, hypercalcemias, nephrolithiasis, glaucoma, and mountain sickness. Although they are classed as diuretics, recognize that both loops and thiazides cause significant vasodilation, an action that contributes to their clinical effectiveness, especially in HTN and heart failure.

IMPORTANT PRINCIPLES

Approximate Percentage of Sodium Reabsorption in Renal Tubular Segments

Proximal convoluted tubule (PCT >60%).

Thick ascending limb of the loop of Henle (TAL <25%).

Distal convoluted tubule (DCT <10%).

The collecting tubules and ducts (CT <4%).

Hypokalemia and Alkalosis

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

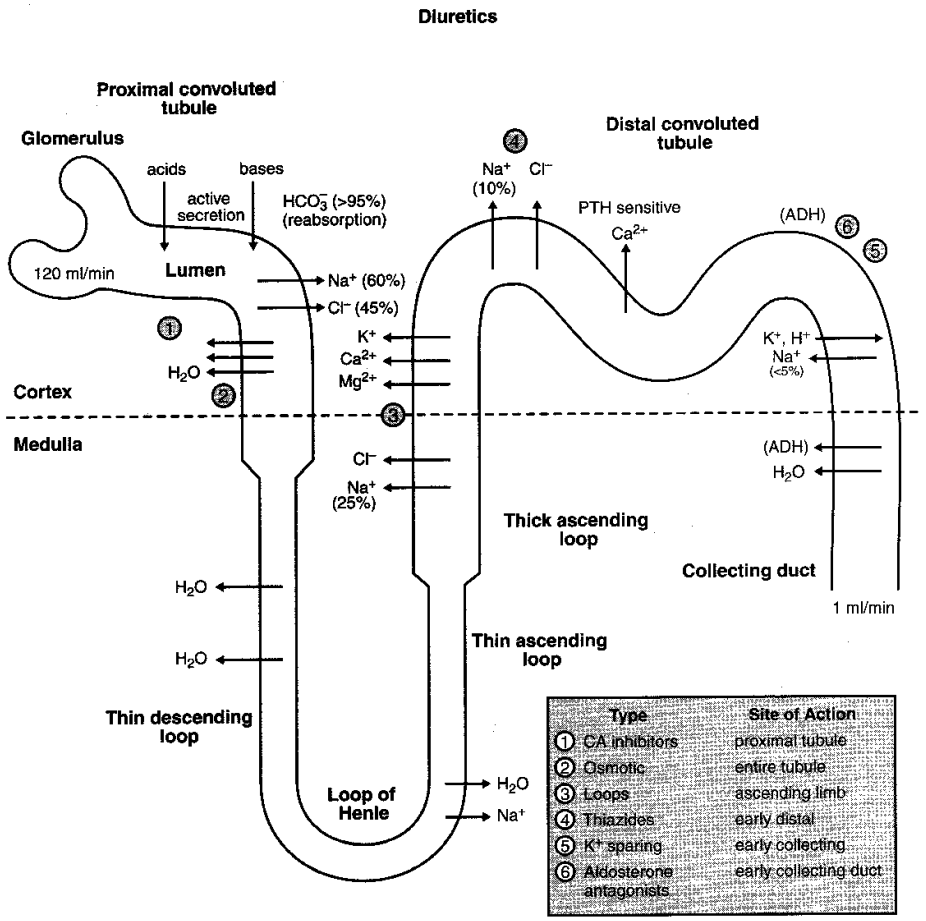


Figure III-6-1. Actions of Diuretics at the Various Renal Tubular Segments

OSMOTIC DIURETICS

Mannitol (IV only) inhibits water reabsorption in the proximal convoluted tubule (PCT) (main site), the thin descending limb of the loop of Henle, and the collecting ducts. It increases urine volume, preventing anuria in hemolysis and rhabdomyolysis, and facilitates elimination of toxic drugs (e.g., cisplatin). Similar osmotic actions in the ECF of other tissues →↓ intraocular and intracerebral pressure.

Adverse effects: nausea and vomiting, chills, electrolyte imbalance, hypovolemia, chest pain.

CARBONIC ANHYDRASE INHIBITORS

Actions

Acetazolamide and dorzolamide inhibit CA on both the luminal membrane and in the PCT cell. Inhibition of CO_2 formation in the lumen decreases its intracellular availability. This, together with inhibition of formation of carbonic acid (CA is reversible), decreases intracellular bicarbonate and H^+ levels.

Na^+ reabsorption across the luminal membrane is decreased because of ↓ availability of protons needed for the Na^+/H^+ antiporter.

Filtered bicarbonate and Na^+ ions continue down the tubule, leading to bicarbonaturia (with resulting acidosis) and presenting a major Na^+ load downstream.

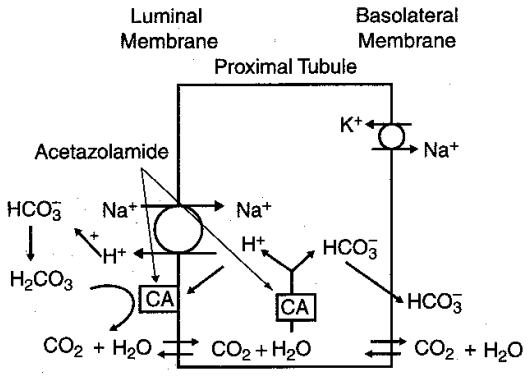


Figure III-6-2. Actions of Carbonic Anhydrase Inhibitors

Clinical Uses

Glaucoma (decreases formation of aqueous humor ↓ IOP), acute mountain sickness (→↓ pulmonary and cerebral edema), metabolic alkalosis (e.g., thiazide-induced), elimination of acidic drugs (e.g., ASA, uric acid).

Adverse Effects

Acidosis, bicarbonaturia, hypokalemia, hyperchloremia, paresthesias, and renal stones (hypercalciuria, phosphaturia).

LOOP DIURETICS

Actions

Ethacrynic acid and furosemide are weak acids that are both filtered and secreted, so they achieve high levels in the tubular lumen. Loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransporter on the luminal membrane of the thick ascending loop (TAL).

Normally, Na^+ reabsorbed via the $Na^+/K^+/2Cl^-$ transporter is transported back into the blood by a Na^+/K^+-ATPase exchange mechanism and by a Na^+/Cl^- cotransporter, the excess Cl^- returning to the blood via passive diffusion. High intracellular K^+ results in its back-diffusion across the luminal membrane, providing a positive potential (electrogenic) that drives reabsorption of both Ca^{2+} and Mg^{2+}.

Inhibition of the $Na^+/K^+/2Cl^-$ cotransporter decreases intracellular K^+ levels $\rightarrow\downarrow$ back-diffusion of K^+ $\rightarrow\downarrow$ positive potential $\rightarrow\downarrow$ reabsorption of Ca^{2+} and Mg^{2+}. Thus, loop diuretics increase urinary levels of Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-.

The delivery of an increased Na^+ load downstream enhances loss of K^+ ions and protons at the level of the collecting tubules.

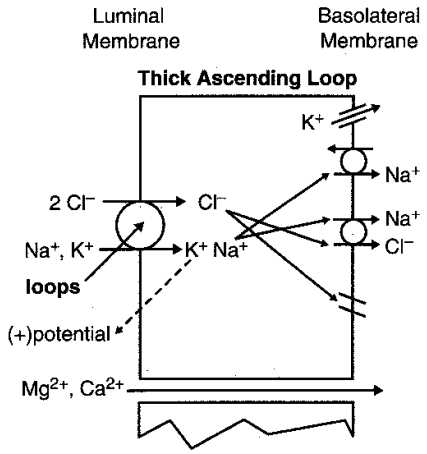


Figure III-6-3. Actions of Loop Diuretics on the Thick Ascending Loop (TAL)

Clinical Uses

Acute pulmonary edema, acute renal failure, anion overdose, heart failure, hypercalcemic states, hypertension, and refractory edemas.

Adverse Effects

Allergies, alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hyperuricemia, hypovolemia, ototoxicity (ethacrynate > furosemide) enhanced by aminoglycosides. Loop diuretics may decrease lithium clearance.

THIAZIDES

Actions

Hydrochlorothiazide, indapamide, and metolazone (and many others) are organic acids that are both filtered and secreted and that inhibit the Na^+/Cl^- cotransporter on the luminal membrane of the distal convoluted tubule (DCT).

1. Normally Na^+ brought in by the Na^+/Cl^- cotransporter is exchanged for K^+ via the pump on the basolateral membrane, K^+ returning to the blood by back-diffusion. Cl ions return to the blood via diffusion through special channels. Ca^{2+} diffuses across the luminal membrane through channels regulated by PTH and is returned to the blood by a Ca^{2+}/Na^+ antiporter.

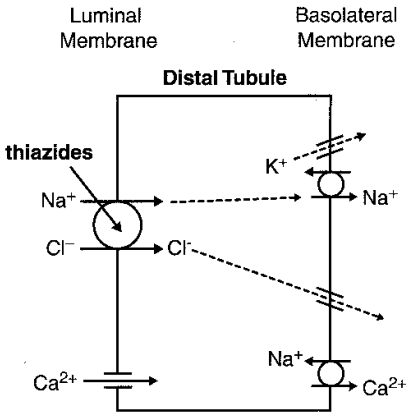


Figure III-6-4. Actions of Thiazides on the Distal Convoluted Tubule

2. Inhibition of the Na^+/Cl^- cotransporter increases the luminal concentrations of these ions. Hypokalemia and alkalosis occur consequent to the Na^+ load downstream. Increased activity of the Ca^{2+}/Na^+ antiporter (regulated by PTH) leads to increased reabsorption of Ca^{2+} → possible hypercalcemia.
3. The delivery of an increased Na^+ load downstream enhances loss of K^+ ions and protons at the level of the collecting tubules.

Thus, thiazides increase urinary levels of Na^+, K^+, and Cl^- ions but decrease levels of Ca^{2+}.

Clinical Uses

Thiazides are widely used in HTN and heart failure with proven long-term efficacy. Their actions are improved by Na^+ restriction. Their activity is reduced at low GFR. Also used in edematous states (+/– loops), including pulmonary edema, nephrolithiasis, and diabetes insipidus (ADH resistance), including that due to lithium.

Adverse Effects

Allergies, alkalosis, hypokalemia, hypercalcemia, hyperuricemia, hypovolemia, hyperglycemia, hyperlipidemia (↑ LDL-C and TGs, not indapamide), and sexual dysfunction.

K SPARING AGENTS

Actions

Spironolactone, amiloride, and triamterene act at the level of the collecting tubules and ducts. These are weak diuretics because most of the filtered Na^+ is reabsorbed before reaching the CT. The CT determines final urinary Na^+ concentration and is a major site of secretion of K^+ ions and protons.

1. Normally, aldosterone exerts its mineralocorticoid actions via interaction with its receptors $\rightarrow\uparrow$ formation of Na^+ channels on the luminal membrane of the principal cell and $\rightarrow\uparrow$ activity of Na^+/K^+ and H^+ exchangers. Na^+ diffuses through its channels, increasing intracellular positive charge, which leads to extrusion of K^+ into the lumen. By mechanisms that are unclear, Na^+ entry into cells of the CT leads to an increase in the energy-dependent extrusion of protons across the luminal membranes of intercalated cells.
2. Spironolactone (aldosterone receptor antagonist) and amiloride and triamterene (Na^+ channel blockers) prevent the above effects, leading to minor effects on Na^+ reabsorption but major effects on the retention of K^+ ions and protons. Thus, they cause small increases in urinary Na^+ and marked decreases in urinary K^+, resulting in hyperkalemia and acidosis.

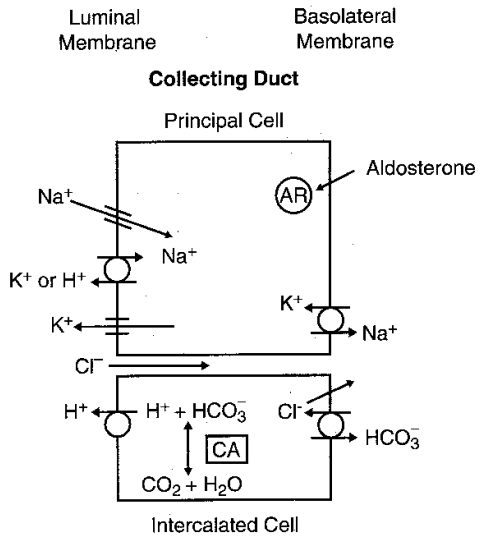


Figure III-6-5. Actions of Potassium-Sparing Agents on Collecting Tubules

Clinical Use

Spironolactone

In hyperaldosteronic states, as an adjunctive with other diuretics in HTN and in heart failure (improves survival when used with ACEIs). It also has antiandrogenic uses (e.g., female hirsutism).

Na Channel Blockers

As an adjunctive with other diuretics in HTN and heart failure to decrease K^+ loss, and in lithium-induced diabetes insipidus (amiloride).

Adverse Effects

Acidosis, hyperkalemia, azotemia, gynecomastia and libido changes (spironolactone), nephrolithiasis (triamterene).

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 Chemistry and pH
Acetazolamide	Inhibition of carbonic anhydrase in PCT	↑ Na^+ ↑ K^+ ↑ Ca^{2+} ↑↑ HCO_3^- ↑ PO_4^{2-}	Hypokalemia, acidosis (↓ pH), hyperchloremia
Ethacrynic acid, furosemide, torsemide	Inhibition of $Na^+/K^+/2Cl^-$ cotransporter in TAL	↑↑ Na^+ ↑ K^+ ↑ Ca^{2+} ↑ Mg^{2+} ↑ Cl^- ↓ HCO_3^-	Hypokalemia, alkalosis (↑ pH), hypomagnesemia
Hydrochlorothiazide, indapamide, metolazone	Inhibition of Na^+/Cl^- cotransporter in DCT	↑ Na^+ ↑ K^+ ↑ Cl^- ↓ Ca^{2+}	Hypokalemia, alkalosis (↑ pH), hypercalcemia
Amiloride, triamterene, spironolactone	Block Na^+ channels, block aldosterone receptors in CT	↑ Na^+ (small) ↓ K^+	Hyperkalemia, acidosis (↓ pH)

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 III-6-1 illustrates 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 III-6-2. The clinical uses and adverse affects are listed.

Loop diuretics (e.g., ethacrynic acid and furosemide) inhibit the $Na^+/K^+/2Cl^-$ cotransporter on the luminal membrane of the thick ascending loop. The mechanisms causing their diuretic actions (Figure III-6-3) and their clinical uses and adverse effects are discussed.

The thiazides (e.g., hydrochlorothiazide, indapamide, and metolazone) inhibit the Na^+/Cl^- cotransporter on the luminal membrane of the distal convoluted tubule. The mechanisms leading to their diuretic actions (Figure III-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 III-6-5) and their clinical uses and adverse effects are discussed.

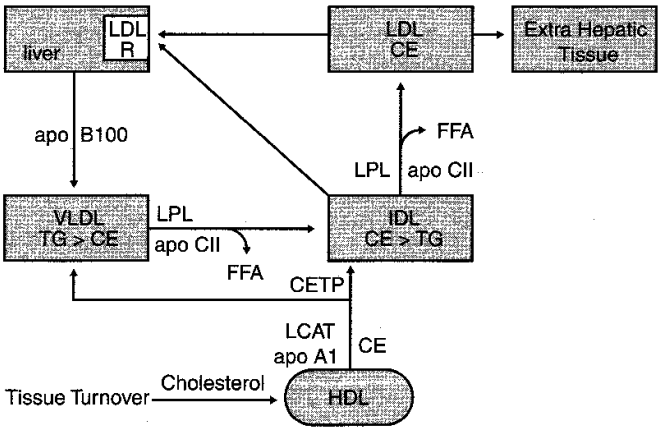
Table III-6-1 summarizes the mechanisms of action, the urinary electrolyte patterns, and the resultant blood chemistries associated with administration of the various classes of diuretics.

Antihyperlipidemics

7

RATIONALE FOR USE

Increased risk of atherosclerosis and CHD is associated with plasma lipid changes, including ↑ LDL, ↑ VLDL, ↑ TG, and ↓ HDL. The goal of management of hyperlipidemias is the restoration of plasma lipid profiles toward a more "normal" state by dietary modification and/or the use of drugs. Although drug treatment can prevent formation and promote regression of atherosclerotic lesions (and decrease mortality in CHD), once initiated, it must be continued indefinitely.



CE = cholesterol esters
TG = triglycerides
LPL = lipoprotein lipase
FFA = free fatty acids
apo CII = cofactor for LPL
apo A1 = cofactor for LCAT
LCAT = lecithin cholesterol acetyl transferase
CETP = cholesterol ester transport protein

Figure III-7-1. The Endogenous Cholesterol Pathway

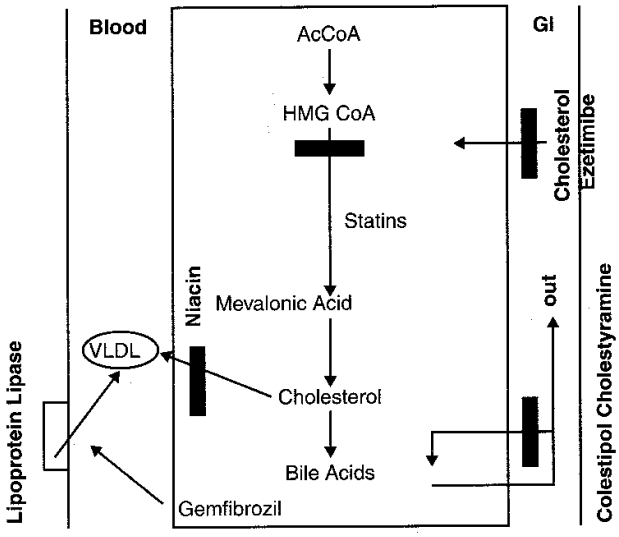


Figure III-7-2. Site of Action of Statins, Niacin, and Gemfibrozi on the Sythesis of Lipids

BILE ACID SEQUESTRANTS

Cholestyramine and colestipol are resins that complex bile salts, preventing their reabsorption from the GI tract →↓ feedback inhibition of 7 alpha hydroxylase →↑ synthesis of new bile salts →↓ liver cholesterol →↑ LDL receptors →↓ plasma LDL.

Not used in hypertriglyceridemias because they ↑ VLDL and TGs.

Adverse Effects

Bloating, constipation, ↓ absorption of digoxin, thiazides, tetracyclines, warfarin, and vitamin K.

HMG-CoA REDUCTASE INHIBITORS

Lovastatin and the other "statins" inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis. This induces the following:

→↓ liver cholesterol →↑ LDL receptors →↓ plasma LDL and ↓ hepatic synthesis of VLDL and apo B. Statins cause small increases in HDL and ↓ TGs (atorvastatin).

They also increase NO and decrease mRNA for endothelin-1 (potent vasoconstrictor).

Adverse Effects

Diarrhea, myalgia/myopathy (watch CK), rhabdomyolysis (↑ with gemfibrozil and nicotinic acid), ↑ LFTs, possible enhanced toxicity with P450 inhibitors.

SLE-like syndrome has been reported.

NICOTINIC ACID

Inhibits VLDL synthesis and apoprotein synthesis in hepatocytes and ↑ HDL →↓ plasma VLDL, LDL, and TGs. Activates lipoprotein lipases.

Also ↑ tPA and ↓ serum fibrinogen.

Adverse Effects

Flushing and pruritus (use aspirin [ASA]), rashes, hyperuricemia, hyperglycemia, hepatotoxicity, GI ulcer exacerbation.

GEMFIBROZIL

Activates lipoprotein lipases, which promotes catabolism of VLDL and IDL →↓ plasma VLDL, TGs, and LDL and causes small increases in HDL.

Adverse Effects

GI distress, rash, gallstones, hypokalemia, myositis; potentiates warfarin and sulfonylurea hypoglycemics.

EZETIMIBE

Prevents intestinal absorption of cholesterol; often used with a statin for additive effect on ↓LDL.

Adverse Effects

GI distress.

Chapter Summary

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

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 LDL levels. Their adverse effects are also listed.

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 HDL, and atorvastatin lowers triglycerides (TGs). They also increase NO levels and lower the levels of endothelin-1 mRNA. The adverse effects are listed.

Figure III-7-1 illustrates the endogenous cholesterol pathways.

Nicotinic acid inhibits the hepatic synthesis of VLDL and apoprotein. It also increases HDL levels and decreases plasma VLDL, LDL, and TG levels. The adverse effects are listed.

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

Ezetimibe prevents cholesterol absorption.

Figure III-7-2 summarizes the effects of statins, niacin, and gemfibrozil on the synthesis of lipids.

Table III-7-1 lists the major cardiovascular and renal drugs by their clinical use.

Section III Summary

Table III-7-1. The Major Cardiovascular and Renal Drugs

Antiarrhythmics	Antihypertensives	Antianginals
1A quinidine, procainamide	α_2 agonists: clonidine, methyldopa	Nitrates: nitroglycerin, isosorbide
1B lidocaine, phenytoin	Neuron blockers: reserpine, guanethidine	CCBs: verapamil, nifedipine, bepridel
1C flecainide	α blockers: prazosin, doxazosin, etc.	β blockers: propranolol, etc.
II propranolol, acebutolol (ISA) esmolol	β blockers: propranolol, metoprolol, acebutolol, labetalol, etc.	
III bretylium, amiodarone	ACEIs: captopril, etc., and AT-1 antagonists: losartan, etc.	
IV verapamil, diltiazem	Vasodilators: hydralazine, nitroprusside, diazoxide, minoxidil	
Adenosine	CCBs: verapamil, nifedipine, etc.	
Diuretics	**Drugs for Heart Failure**	**Antihyperlipidemics**
CA inhibitors: acetazolamide	Digoxin	Resins: cholestyramine, colestipol
Loops: ethacrynic acid, furosemide, torsemide	Bipyridines: inamrinone, amrinone, milrinone, β agonists: dobutamine, dopamine	Statins: lovastatin atorvastatin, etc. Fibrates: gemfibrozil
Thiazides—hydrochlorothiazide, indapamide, metolazone	CCB: amlodipine α β blocker: carvedilol	Other: nicotinic acid, ezetimibe
K sparing: amiloride, triamterene, spironolactone	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 of Na 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. bretylium
   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-MI

8. Calcium channel antagonists

   A. ↑ intracellular cAMP
   B. ↓ myocardial contractility
   C. ↑ reactivation of Na^+ channels
   D. ↓ intracellular K^+
   E. ↑ 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 L/h. The elimination half-life of lidocaine in this patient approximates

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

11. Which of the following drugs is proven to have clinical value in the management of subarachnoid hemorrhage?

    A. Captopril
    B. Dopamine
    C. Guanethidine
    D. Nifedipine
    E. Nimodipine

12. 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^+/Cl^- cotransporter

13. 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

14. A new diuretic is being studied in human volunteers. Compared with placebo, the new drug increases urine volume, decreases urinary Ca^{2+}, increases body 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

15. 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. Encainide
    C. Lidocaine
    D. Phenytoin
    E. Verapamil

16. 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 HDL
    E. no change in total cholesterol in the plasma

17. A 54-year-old male patient with hypertension has been treated with a thiazide and clonidine for several years, with repeated BP measurements close to 140/90 and no significant side effects, except a decreased sexual interest. In your office, he complains of palpitations, and now his pulse is 100/min with BP of 165/118 both sitting and standing. He has not gained weight but admits to mild anxiety over his marital relationship. The most likely cause of his current problem is

    A. a dietary change to include foods containing tyramine
    B. discontinuance of clonidine
    C. excessive use of alcoholic beverages
    D. salt and water retention
    E. tachyphylaxis

18. 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

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

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

20. 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

21. Following an acute myocardial infarction, a patient develops signs of pulmonary edema requiring drug management. What effect would amrinone, 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

22. 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 140/95)
    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)

23. 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

24. 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.

25. A patient with a supraventricular tachycardia has an atrial rate of 280/min with a ventricular rate of 140/min via a 2:1 AV nodal transmission. After treatment with a drug, the atrial rate slowed to 180/min, but the ventricular rate increased to 180/min! 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. Bretylium is an IV agent reserved for ventricular arrhythmias. 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 β_1-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-MI 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 L-type 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^+/K^+-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:

$$t_{1/2} = \frac{0.7 \times V_d}{Cl} = \frac{0.7 \times 80}{28} = \frac{56}{28} = 2\ h$$

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: E.** Only one drug currently has FDA approval in the management of subarachnoid hemorrhage. Nimodipine appears to have some degree of selectivity for cerebral vascular beds in terms of its vasodilating effects, preventing post-hemorrhagic vasospasm. Other CCBs have yet to be proven equally effective. The vasodilating actions of DA are restricted to mesenteric and renal vascular beds.

12. **Answer: D.** Cardiac glycosides increase contractility by inhibiting the Na^+/K^+-ATPase pump, causing an increase in intracellular Na. This, in turn, increases intracellular Ca by slowing down Na^+/Ca^{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.

13. **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.

14. **Answer: A.** The effects described are typical of thiazide diuretics, which inhibit the Na^+/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.

15. **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. Encainide is a class IC drug, lidocaine and phenytoin are class IB, and verapamil is class IV, none of which inhibits the delayed rectifier K^+ current responsible for membrane repolarization during the cardiac action potential.

16. **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.

17. **Answer: B.** Tyramine present in certain food and beverages can displace NE from sympathetic nerve endings, causing CV stimulation, but only if its metabolism is inhibited by MAO inhibitors. Patients suffering from HTN commonly discontinue medications (without physician consultation) based on perceived undesirable side effects, such as sexual dysfunction. In the case of clonidine, rebound hypertension and tachycardia, especially with abrupt discontinuance, can be problematic. Discontinuance of thiazide is likely to result in fluid retention with weight gain and unlikely to cause tachycardia and marked increase in BP. Ethanol is an effective vasodilator and tends to decrease BP. Tachyphylaxis refers to the development of a decreased response to drug treatment over a time span of minutes to hours, not years.

18. **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.

19. **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 AII 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.

20. **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.

21. **Answer: E.** In heart failure following a myocardial infarct, amrinone, digoxin, and dopamine (at high dose) can improve cardiac function (and relieve pulmonary congestion) by exerting a positive inotropic effect; they each increase cardiac contractility. Amrinone, and at lower doses 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.

22. **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.

23. **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.

24. **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!

25. **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

CNS Pharmacology

1

ION CHANNELS AND CNS NEUROTRANSMITTERS

Neuronal excitability depends on the flux of ions through specific channels in neuronal membranes:

↑ Na^+ influx or ↓ K^+ efflux → excitation via membrane depolarization.

↑ Cl^- influx or ↑ K^+ efflux → inhibition via membrane hyperpolarization.

Ion channels in the brain are of two major types.

Voltage-Gated

Regulated by changes in membrane potential—include axonal Na^+ channels involved in propagation of action potentials and Ca^{2+} channels located presynaptically that play a critical role in the release of neurotransmitters from synaptic vesicles.

Transmitter-Gated

Regulated by neurotransmitter interactions with specific receptors. Such receptors may be directly linked to ion channels or change ion channel function via second-messenger effector systems.

MOLECULAR TARGETS FOR CNS DRUGS

In Figures IV-1-1 and IV-1-2, three types of neuronal ion channels are illustrated, and examples are given of drugs that appear to modify their functions either directly or indirectly. Axonal Na channels can be blocked by anesthetics and by some anticonvulsants, resulting in decreases in neuronal excitability, actions in accord with the CNS depressant actions of such drugs. However, most drugs that modify ion channels that are transmitter-gated exert variable effects on neuronal excitability, depending on the specific neurotransmitter involved and the subtype of receptor through which it regulates ion channel function.

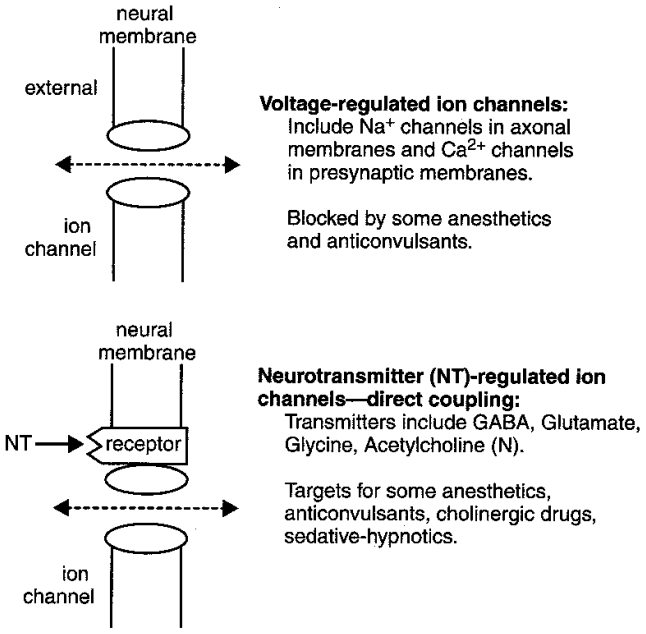
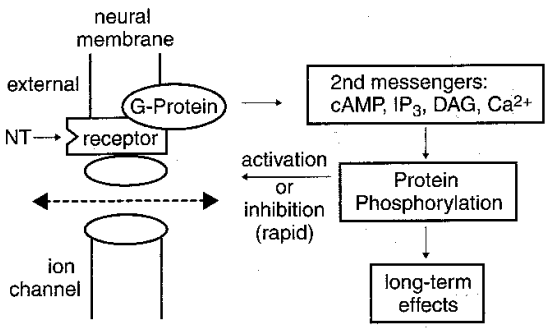


Figure IV-1-1. Voltage-Regulated and Neurotransmitter-Regulated Ion Channels

MOLECULAR TARGETS FOR CNS DRUGS



Neurotransmitter (NT)-regulated ion channels–G-Protein coupling:
Transmitters include most amines (ACh, DA, NE, 5HT) and peptides (endorphins).

Targets for many drugs including analgesics, antidepressants, antipsychotics, and anxiolytics.

Figure IV-1-2. Neurotransmitter-Regulated Ion Channels Coupled to a G-Protein

CNS TRANSMITTERS AND RECEPTORS

Glutamic acid: Excitatory via ↑ influx of cations (direct coupling and G-protein linked); the NMDA receptor is a potential target for ketamine and PCP.

GABA: Inhibitory via ↑ Cl^- influx or ↑ K^+ efflux (direct coupling); activities ↑ by anticonvulsants, sedatives, hypnotics, and some muscle relaxants.

ACh: M_1 excitatory (↓ K^+ efflux, via DAG), M_2 inhibitory (↑ K^+ efflux via cAMP), and N excitatory (Na^+ influx—direct coupling); activities modified by nicotine, AChE inhibitors in Alzheimer's, and M blockers in Parkinson's.

Dopamine: Inhibitory, multiple subtypes (5+)—G-protein linked to cAMP; activities ↑ by CNS stimulants and anti-Parkinson drugs, ↓ by antipsychotics.

Norepinephrine: Excitatory or inhibitory, depending on subtype (second messenger coupling); activities modified by CNS stimulants, antidepressants, and some anxiolytics.

Serotonin (5HT): Excitatory or inhibitory, depending on receptor subtype (multiple) with second messenger coupling (except $5HT_3$ subtype coupled directly to ion channel); activities modified by CNS stimulants, antidepressants, some anxiolytics.

Opioid peptides: Inhibitory, several subtypes, second messenger coupling; activities modified by opioid analgesics.

Bridge to Physiology

A further discussion of ion channels and neurotransmitter is present in Physiology Notes Section II, Chapter 1.

SEDATIVE-HYPNOTIC (S-H) DRUGS

Drug group includes benzodiazepines (BZs), barbiturates, and alcohols.

Sedatives (anxiolytic agents) should reduce anxiety with as little effect on motor or mental functions as possible. However, most of the drugs used for anxiety states cause dose-dependent depression of the CNS that extends to sleep-inducing effects (hypnosis) and possible anesthesia.

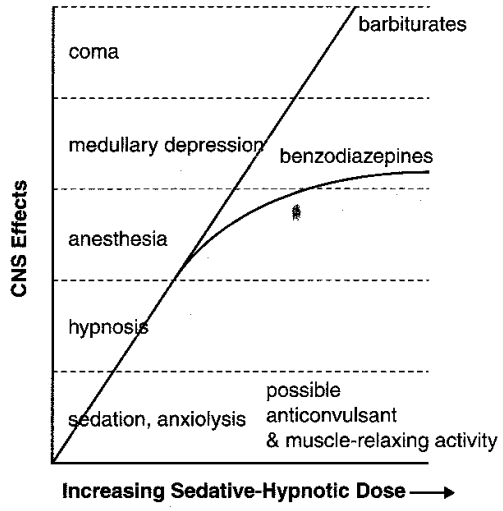
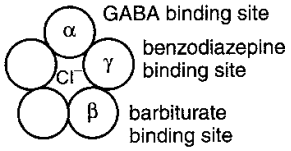


Figure IV-1-3. CNS Effects Associated with Increasing Doses of Sedative-Hypnotic (S-H) Drugs

In overdose, depression of respiratory and vasomotor centers in the medulla occurs with most drugs in this class, although the dose–response relationship is flatter for the benzodiazepines than for older drugs such as alcohol and barbiturates.

Other CNS actions of clinical value include anticonvulsant and muscle-relaxing effects.

MECHANISM OF ACTION:



5 subunit types: α, β, γ, ρ, δ

Figure IV-1-4. The $GABA_A$ Receptor and S-H Drug

Mechanisms of Action

Most S-H drugs facilitate the actions of GABA, a major inhibitory transmitter in the CNS. $GABA_A$ receptor activation leads to increased Cl^- ion influx; $GABA_B$ receptor activation causes increased efflux of K^+. Both mechanisms result in membrane hyperpolarization.

The pentameric structure of the $GABA_A$ receptor has binding sites for benzodiazepines (BZ receptors) and for other drugs, including barbiturates and ethanol.

Benzodiazepines potentiate GABA by increasing the frequency of Cl^- ion channel opening. This action is blocked by flumazenil, a BZ receptor antagonist.

Barbiturates increase the duration of Cl^- ion channel opening. (At high doses, they also open Cl^- ion channels and block Na^+ channels.) Flumazenil does not block the effects of barbiturates.

BZ receptors are heterogeneous. BZ_1 receptors mediate hypnotic actions; zolpidem, although not a benzodiazepine, preferentially binds to this receptor. The BZ_2 receptor may play a role in memory, sensory-motor, and cognitive functions.

Benzodiazepines

Uses and Effects

Most commonly used drugs for treatment of anxiety states and sleep disorders. Dose-dependent CNS depression occurs (sedation, disinhibition, nystagmus, ataxia, respiratory depression at very high doses), additive with other CNS depressants, including ethanol. Flumazenil IV reverses effects (use in ER and OR). Possible anterograde amnesia at conventional doses.

Metabolites

Liver metabolism to form active metabolites (see Table IV-1-1 and sidebar), but no induction of drug metabolism—variable half-life.

Tolerance and Dependency

Chronic use leads to tolerance (cross with other S-H drugs), possibly via down-regulation of BZ receptors. Psychological and physical dependence occurs, but abuse liability and withdrawal signs are less intense than with ethanol or barbiturates. Rebound REM sleep, insomnia, and anxiety are common on discontinuance.

Clinical Correlate

Flumazenil

This BZ receptor antagonist has characteristics similar to the opioid receptor antagonist naloxone. Both drugs are given IV; both drugs have half-lives shorter than their respective receptor-agonist drugs and may have to be administered repetitively; both drugs are used extensively in anesthesia to facilitate recovery from the CNS depressant actions of receptor-activating drugs.

Classic Clues

"Out The Liver"

Three benzodiazepines undergo **extrahepatic** metabolism and do not form active metabolites: **O**xazepam, **T**emazepam, **L**orazepam.

Table IV-1-1. The Uses and Characteristics of Various Benzodiazepines

Drug	Indications	Specific Characteristics
Alprazolam	Anxiety, panic, phobias	Most commonly used anxiolytic
Diazepam	Anxiety, preop sedation, muscle relaxation, withdrawal states	Longest-acting BZ, forms three active metabolites
Lorazepam	Anxiety, preop sedation, status epilepticus (IV)	No active metabolites
Midazolam	Preop sedation, anesthesia IV	Shortest-acting BZ
Temazepam	Sleep disorders	Slow oral absorption
Triazolam	Sleep disorders	Short-acting, possible early A.M. waking

Barbiturates

Uses

Include phenobarbital (long acting, used for seizures) and thiopental (short acting, used as IV anesthetic). Dose-dependent CNS depression, with nystagmus and ataxia progressing to respiratory depression, coma, and possible mortality—no specific antidote in OD. Additive CNS depression with other drugs.

Metabolites

Hepatic metabolism (some to active metabolites). Induction of cytochrome P450s is characteristic and may lead to drug interactions. Because of ↑ heme synthesis, they are contraindicated in porphyrias.

Tolerance and Dependence

Tolerance and dependence occur with chronic use. Withdrawal symptoms may be severe, especially with short-acting barbiturates: anxiety, agitation, hyperreflexia, seizures, and postseizure depression of vital functions. Management involves treatment with long-acting BZs (e.g., diazepam) and dose tapering.

Other Sedative and Hypnotics

Zolpidem and Zaleplon

Zolpidem and a newer agent, zaleplon, are nonbenzodiazepines used in sleep disorders. They activate BZ_1 receptors (reversed by flumazenil) and are more selective hypnotics because they are not effective in chronic anxiety, for seizure disorders, or for muscle relaxation. Possibly less tolerance and lower abuse liability and dependence than BZs.

Buspirone

Totally different anxiolytic from BZs. No effects on GABA systems, possible partial agonist at $5HT1_A$ receptors. Nonsedating, no additive CNS depression with other drugs.

Indicated for generalized anxiety states (GAD) but takes 1 to 2 weeks to exert anxiolytic effects.

Buspirone does not cause dependence and does not reduce symptoms of withdrawal from S-H drugs.

Other Drugs

Sedation and sleep promotion can be achieved with drugs that are not classed as sedatives or hypnotics, including antihistamines (e.g., hydroxyzine) and opioid analgesics. Tricyclic antidepressants (TCAs) have been used in anxiety characterized by panic and/or phobias, and more recently the selective serotonin reuptake inhibitors (SSRIs) have been used. Propranolol has efficacy in performance anxiety and social phobias.

ALCOHOLS

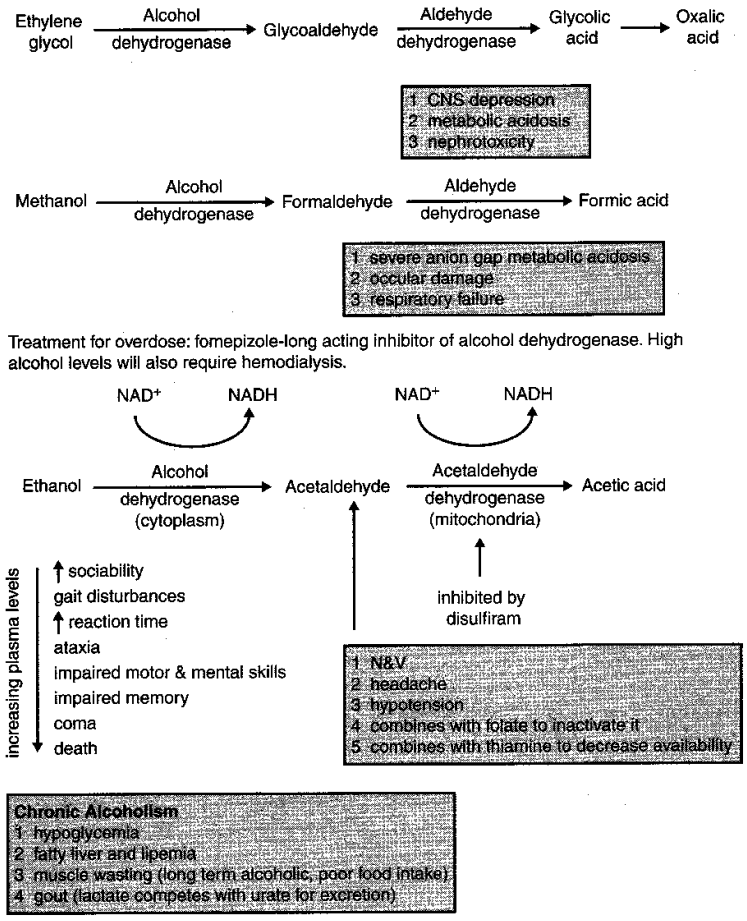


Figure IV-1-5. Metabolism and Pharmacologic Actions of the Alcohols

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

Disulfiram-like effect causing drugs:

- Metronidazole
- Cefamandole
- Cefoperazone
- Cefotetan
- Chlorpropamide

ANTICONVULSANTS

Mechanisms of Action

Seizures result from episodic electrical discharges in cerebral neurons associated with pro longed depolarization, during which sustained, high-frequency, repetitive firing (SHFRF occurs, followed by prolonged hyperpolarization. The goal of drug management is restoratio of normal patterns of electrical activity. The mechanisms by which this may be achieve include:

- ↑ inhibitory tone by facilitation of GABA-mediated hyperpolarization—barbiturates, benzodiazepines
- ↓ axonal conduction by preventing Na^+ influx through fast Na channels—carbamazepine, phenytoin; also, at high doses, barbiturates and valproic acid
- ↓ presynaptic Ca^{2+} influx through type-T channels in thalamic neurons—ethosuximide and valproic acid
- ↓ excitatory effects of glutamic acid—lamotrigine, topiramate (blocks AMPA receptors); felbamate (blocks NMDA receptors)

Table IV-1-2. Seizure States and Drugs of Choice

Seizure Type	Drug(s) of Choice	Backup Drugs
Partial—simple or complex	Valproic acid, phenytoin, carbamazepine	Phenobarbital in pregnancy; most newer drugs are also effective
General—tonic -clonic	Valproic acid, phenytoin, carbamazepine	Phenobarbital in pregnancy; some newer drugs are also effective
General—absence	Ethosuximide, valproic acid, clonazepam	Lamotrigine
General—myoclonic	Valproic acid	Clonazepam, felbamate (adjunct)
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*	Phenobarbital (long term)

*Fosphenytoin IV more water soluble.

Primary Anticonvulsant Drugs

Phenytoin

Blocks axonal Na^+ ion channels in their inactivated state (state or "rate"-dependent blockade) and results in decreased SHFRF. Also used as antiarrhythmic and backup in bipolar disorder.

Variable oral absorption and first-pass metabolism—plasma level monitoring. Competition for plasma protein binding and induction of P450 lead to drug interactions.

Adverse effects: sedation, ataxia, diplopia, acne, gingival overgrowth, hirsutism, osteomalacia, hematotoxicity (granulocytopenia, megaloblastic anemia).

Teratogenic—fetal hydantoin syndrome (cleft palate and lip).

Carbamazepine

Mechanism like phenytoin. Currently DOC for trigeminal neuralgia and backup in bipolar disorder.

Induces P450, including its own metabolism.

Adverse effects: sedation, ataxia, diplopia (seizures in OD), osteomalacia, hematotoxicity (granulocytopenia, megaloblastic anemia, aplastic anemia), water retention (↑ ADH), and exfoliative dermatitis.

Teratogenic—craniofacial abnormalities and spina bifida.

Ethosuximide

Blocks T-type Ca^{2+} ion currents in thalamic neurons. Absence seizures are sole use.

Adverse effects: GI distress, fatigue, lethargy. Although rare, extrapyramidal dysfunction, exfoliative dermatitis, and hematotoxicity may occur.

Valproic Acid

Multiple actions including block of T-type Ca^{2+} channels, inhibition of GABA transaminase, and block of axonal Na channels. In addition to seizure states, it is a backup in bipolar disorders and used in migraine treatment.

Inhibits P450—possible drug interactions, including carbamazepine and phenytoin.

Adverse effects: GI distress, hepatotoxicity due to formation of toxic metabolite, pancreatitis, alopecia, tremor, photosensitivity.

Teratogenic—spina bifida.

Barbiturates and Benzodiazepines

- Phenobarbital has selective antiseizure activity at low doses and has a long half-life suitable for maintenance treatment in seizure disorders (for characteristics of barbiturates, see sedative-hypnotics). Clonazepam is usually a backup drug in absence and myoclonic seizures; it causes marked sedation at anticonvulsant doses. IV lorazepam and diazepam are both used in status epilepticus.

General Features of Anticonvulsant Drug Use

- Additive CNS depression commonly occurs with other drugs, including antihistamines, ethanol, sedative-hypnotics, and opioids.
- Avoid abrupt withdrawal, which may precipitate seizures.
- Decreased efficacy of oral contraceptives via induction of drug-metabolizing enzymes.

Table IV-1-3. Newer Anticonvulsant Drugs

Drug	Possible Mechanism(s)	Indications	Toxic Potential
Felbamate	Blocks Na^+ and Ca^{2+} channels; blocks glutamate receptors	Partial seizures, Lennox-Gastaut syndrome, myoclonic (adjunct)	Aplastic anemia, acute liver failure
Lamotrigine	Blocks Na^+ channels and glutamate receptors	Absence and partial seizures	Sedation, ataxia, diplopia, Stevens-Johnson syndrome
Topiramate	Blocks glutamate (AMPA) receptors; ↑ GABA effects	Partial seizures	Sedation, ataxia, weight loss, word-finding difficulty, renal stones
Gabapentin	↑ GABA effects	Partial seizures, bipolar disorder, migraine, neuropathic pain	Sedation, ataxia, cognitive change
Tiagabine	Blocks GABA transporter	Partial seizures	Sedation, dizziness, "flu-like" symptoms
Vigabatrin	Inhibits GABA transaminase	Partial seizures	Depression, psychosis, visual dysfunction

ANESTHETICS

Inhaled Anesthetics

Current anesthesia protocols usually include several agents in combinations that vary according to the depth of anesthesia required for specific procedures. Inhalational anesthetics, which include nitrous oxide and six halogenated hydrocarbons, have varying potency in proportion to their lipid solubilities. MAC value, a measure of anesthetic potency, is defined as the minimal alveolar anesthetic concentration (% of inspired air) at which 50% of patients do not respond to a surgical stimulus. MAC values are additive, lower in elderly patients, and lower in the presence of opioid analgesics and sedative hypnotics.

The mechanism of action of inhaled anesthetics may involve their interaction with neuronal membrane lipids, leading to inhibition of ion flux.

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

Anesthetic	MAC Value	Blood–Gas Ratio	CV Effects	Specific Characteristics
Nitrous oxide	>100%	0.5	Minimal	Lowest potency, but often used in combinations—rapid onset and recovery
Desflurane	7.2%	0.4	Vasodilation—↑ HR	Most rapid onset, but airway irritation and coughing—rapid recovery
Sevoflurane	2.5%	0.7	↓ HR	Rapid onset and recovery
Enflurane	1.7%	1.9	↓ HR	Tonic/clonic muscle spasms
Isoflurane	1.3%	1.4	Vasodilation—↑ HR	Bronchiolar secretions and spasms
Halothane	0.8%	2.3	↓ HR directly, but sensitizes heart to catecholamines	Hepatitis, malignant hyperthermia, cardiac arrhythmias

Rates of Onset and Recovery

The rates of onset and recovery from inhaled anesthetics depend on their individual blood–gas partition coefficient, a measure of blood solubility. The more soluble the anesthetic in the blood, the longer it takes to achieve a partial pressure that will permit movement from the blood into the CNS or other body tissues; thus, anesthetics with high blood–gas solubility ratios are slow in onset. When anesthesia is discontinued, once again agents with high blood solubility take longer to achieve a partial pressure that permits movement from the blood into the alveoli, and thus their recovery rates are slower. This principle underlies the introduction of several newer agents (desflurane and sevoflurane) that each have low blood–gas solubility ratios, affording both rapid onset of anesthesia and rapid recovery.

Actions

Inhaled anesthetics lower response to increased P_{CO_2}, increase cerebral vascular flow (increased intracranial pressure), and relax uterine smooth muscle. They may be used at lower inhaled concentrations in protocols that include intravenous anesthetics and opioids, or local anesthetics.

Note that the euphoric and behavioral disinhibitory effects of inhaled nitrous oxide ("laughing gas") are often abused, sometimes leading to overdose toxicity.

Intravenous Anesthetics

Thiopental

Highly lipid-soluble, rapid-onset, and short-acting barbiturate used mainly for induction. Depresses respiratory and cardiac function but does not increase cerebral blood flow. Rapid recovery associated with redistribution from CNS to peripheral tissues, but liver metabolism required for elimination.

Midazolam

IV benzodiazepine used for preoperative sedation and commonly in anesthesia protocols (e.g., conscious sedation) affording anterograde amnesia. Depresses respiratory function but reversed by the BZ receptor antagonist flumazenil.

Propofol

Very rapid onset and recovery, plus antiemetic effects, used for both induction and maintenance; especially useful in outpatient surgery.

Fentanyl

One of several related opioid analgesics used in anesthesia. Potent analgesic, with shorter durations of action than most opioids; oral and patch formulations are also used. Chest wall rigidity with IV use.

Neurolept anesthesia = combination of fentanyl, droperidol, and nitrous oxide.

Ketamine

Rapid-onset and short-duration agent that causes "dissociative anesthesia" with amnesia, catatonia, and analgesia. Only anesthetic that causes CV stimulation! Emergence reactions (vivid dreams, hallucinations) partly offset by benzodiazepines.

Local Anesthetics

Mode of Action

Local anesthetics provide regional anesthesia via infiltration near nerve bundles or by epidural or subarachnoid injection. Used as sole anesthetics and also in combination regimens with inhaled and intravenous agents.

Weak bases that can exist in both ionized (protonated) and nonionized (nonprotonated) forms.

Esters (procaine, cocaine, benzocaine) are metabolized by plasma and tissue esterase.

Amides (lidocaine, bupivacaine, mepivacaine) are metabolized by liver amidases.

Local anesthetic molecules bind to the *inactivated* Na^+ channel in axonal membranes, decreasing the change from inactivated to resting state and thus blocking its reactivation. The ionized forms of the local anesthetic molecule ($R.NH_3^+$) bind to a specific component of the Na^+ ion channel that is located on the inner side of the membrane. To gain access to its "target," the local anesthetic molecule must first cross the lipid bilayer, and it does so in its nonionized form ($R.NH_2$). Increases in extracellular acidity favor ionization of local anesthetics and can decrease their intracellular access, possibly decreasing activity.

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).

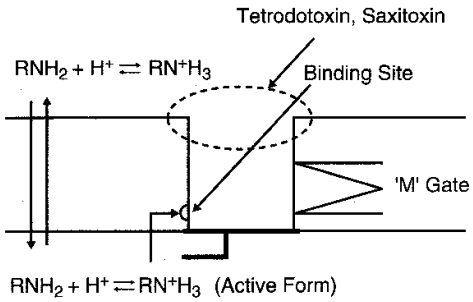


Figure IV-1-6. Mode of Action of Local Anesthetics

Nerve Fiber Sensitivity

Nerve fibers most sensitive to blockade are of smaller diameter and have high firing rates (note state-dependent actions similar to effects on Na^+ channels in cardiac tissue). The order of sensitivity is:

type B and C > type A delta > type A beta and gamma > type A alpha

Absorption

Coadministration of alpha adrenoceptor agonists (e.g., epinephrine) will decrease local anesthetic (LA) absorption into the systemic circulation, prolonging effects and possibly decreasing toxicity. Cocaine is distinctive because it causes vasoconstriction via its blockade of NE reuptake at sympathetic nerve endings.

Adverse Effects

Neurotoxicity
Dizziness, nystagmus, sensory impairment, seizures.

Cardiovascular
↓ CV parameters, except cocaine (↑ HR and BP).

Allergies
Esters via PABA formation.

Sodium Channel Toxins

Tetrodotoxin and Saxitoxin

Tetrodotoxin (puffer fish) and saxitoxin (dinoflagellates in "red tide") bind externally to the "ready state" of Na^+ channels in both cardiac and nerve cell membranes. Block of Na^+ influx prevents conduction.

Ciguatoxin and Batrachotoxin

Ciguatoxin (exotic fish, Moray eel) and batrachotoxin (South American frogs) bind in the Na^+ channel, keeping it open to cause a persistent depolarization and channel inactivation.

SKELETAL MUSCLE RELAXANTS

Used mainly in anesthesia protocols or in the ICU to afford muscle relaxation and/or immobility. Occasionally used to treat tetanus. These muscle relaxants interact with nicotinic receptors at the skeletal muscle end plate. Nicotinic receptors are comprised of five subunits, two of which (alpha) bind ACh, a requirement for opening of the Na^+ channel. Most drugs in this class bind competitively to one of the alpha subunits to prevent depolarization (receptor antagonists); one drug (succinylcholine) binds noncompetitively and opens the Na^+ channel, causing excessive depolarization and desensitization.

Nicotinic Receptor Antagonists

Actions

Nondepolarizing (competitive) and can be reversed by AChE inhibitors (e.g., neostigmine, pyridostigmine), which increase ACh at the end plate. They decrease the frequency of Na^+ channel opening but do not affect conductance or duration.

Cause a progressive paralysis starting with muscles of the eye and face and progressing via the limbs to respiratory muscles—no effects on cardiac or smooth muscle, no effects on consciousness.

Specific Drugs

d-Tubocurarine
Blocks ANS ganglia and releases histamine →↓ BP, may cause bronchial secretion and bronchospasm. Implicated in malignant hyperthermia.

Pancuronium
More rapid onset and recovery, ↑ BP (vagolytic and sympathomimetic).

Atracurium
Also more rapid recovery and safer in hepatic or renal dysfunction because spontaneously inactivated → forms laudanosine, which enters CNS → seizures.

Mivacurium
Very short duration (metabolized by plasma pseudocholinesterase; see succinylcholine below), histamine release.

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.

Nicotinic Receptor Agonist (Succinylcholine)

Actions

Depolarizing (noncompetitive) acting in two phases:

Phase I block (depolarizing)—following a brief fasciculation, a flaccid paralysis ensues, which is augmented (not reversed) by AChE inhibitors.

Phase II block (desensitizing)—with continued infusion of succinylcholine, the endplate repolarizes, but the membrane is desensitized and remains unresponsive to ACh for some time before recovery.

Succinylcholine usually has a short duration of effect because it is rapidly inactivated by pseudocholinesterases, but in genotypic variants with low enzyme activity → prolonged effects.

May cause hyperkalemia and is implicated in malignant hyperthermia.

Spasmolytics

Skeletal muscle can also be relaxed by drugs that act in the CNS, the spinal cord, or even in the muscle itself. These spasmolytics reduce excessive muscle tone or spasm in acute muscle injury and CNS dysfunction (e.g., cerebral palsy, MS, stroke), in most cases without loss of muscle strength.

Drugs That Reduce the Tonic Output of Primary Spinal Motoneurons

Benzodiazepines
Benzodiazepines facilitate GABA actions at $GABA_A$ receptors.

Baclofen
Baclofen facilitates GABA actions by acting as a direct agonist at $GABA_B$ receptors in the spinal cord. The drug is as effective as diazepam in muscle spasticity but causes much less sedation.

Drugs That Block Ca^{2+} Release From the Sarcoplasmic Reticulum

Dantrolene
Dantrolene acts directly on skeletal muscle to decrease contractility—important in states that include extreme muscle rigidity such as malignant hyperthermia associated with inhaled anesthetics and skeletal muscle relaxants.

OPIOID ANALGESICS

Mechanisms of Action

These drugs act in part via receptors for endogenous opiopeptides such as the enkephalins, dynorphins, and β-endorphins. Opioid receptors are of multiple subtypes, all G-protein linked, the most important of which are the μ (mu), δ (delta), and κ (kappa). Effects of specific opioid drugs depend on the receptor subtype with which they interact as full agonists, partial agonists, or antagonists. Some drugs (mixed agonist-antagonists) may activate one receptor subtype and act as antagonists at another subtype. Activation of presynaptic opioid receptors causes inhibition of Ca^{2+} influx through voltage-regulated ion channels $\rightarrow\downarrow$ neurotransmitter release; activation of postsynaptic opioid receptors results in $\uparrow K^+$ efflux $\rightarrow$ membrane hyperpolarization $\rightarrow$ inhibition.

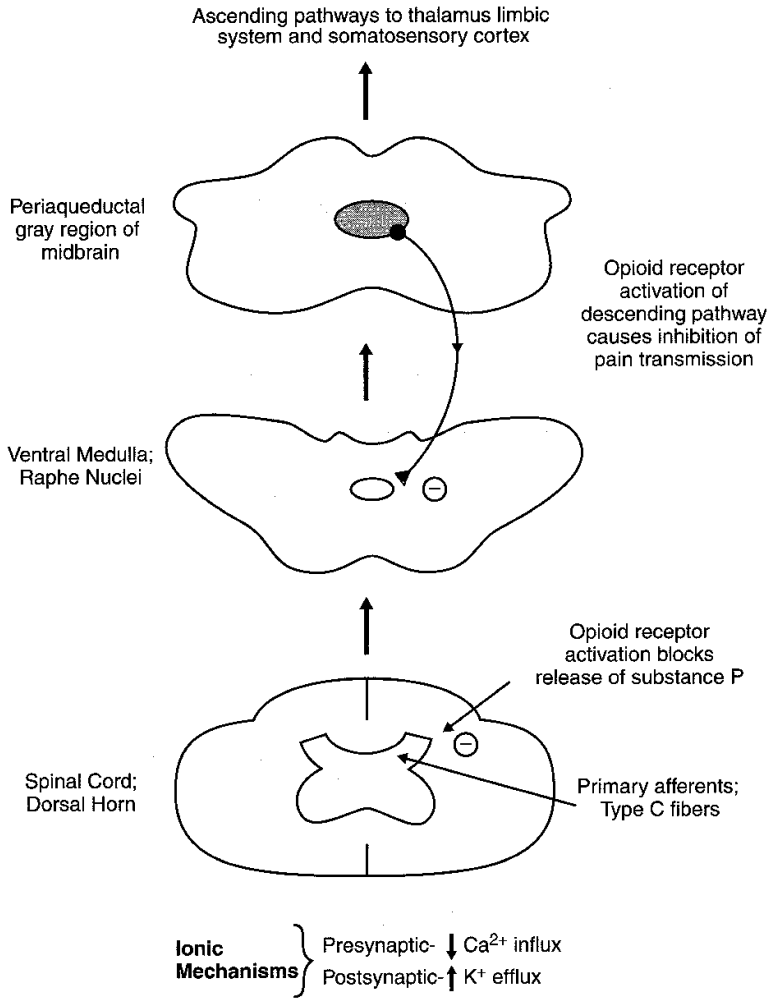


Figure IV-1-7. Opioids and Pain Pathways

Analgesia opioids (and presumably endogenous opiopeptides) act on receptors in the periaqueductal gray region of the midbrain → activation of descending pathways to the Raphe nuclei →↓ transmission in pain pathways. Such supraspinal analgesia appears to result largely (but not exclusively) from activation of the μ receptor subtype.

Opioid receptors are also located presynaptically on primary afferents (type C and A_δ fibers) in the dorsal horn of the spinal cord. Activation of these receptors →↓ release of substance P, a peptide neurotransmitter that causes excitatory actions in pain pathways. Opioid receptors involved in spinal analgesia are of both μ and κ subtypes.

Opioid Analgesic Pharmacology

Variations exist between individual drugs in terms of the following actions, which are based on morphine as the prototype drug of the class.

Analgesia

Increase pain tolerance and ↓ perception and reaction to pain. Variable efficacy—morphine is a full agonist providing maximum pain relief. Persistent, dull, aching pain responds better than intermittent.

Sedation

Drowsiness, possible euphoria, short-term memory loss.

Respiratory Depression

Decreased response to ↑ pCO_2 (even at Rx dose) via depression of neurons in brainstem respiratory center—major problem in overdose.

Cardiovascular

Minimal effects on heart—cerebral vasodilation →↑ intracerebral pressure (avoid in head trauma). Morphine (but not other drugs) releases histamine →↓ BP.

GI Tract

Decreased peristalsis → constipation (or clinical use in diarrheal states, e.g., loperamide and diphenoxylate).

Smooth Muscle

Increased tone of biliary, bladder, and ureter with possible spasms (except meperidine, which blocks M receptors); ↓ tone of vasculature (hypotension via histamine) and uterus (slow delivery).

Pupils

Miosis via ↑ cholinergic activity (except meperidine).

Cough Suppression

Antitussive action—independent of analgesia (e.g., dextromethorphan) and at subanalgesic doses with codeine.

Nausea and Emesis

Stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema.

Kinetics

Morphine undergoes first-pass metabolism in the liver (low oral bioavailability). One of its metabolites, morphine-6-glucuronide, is highly active, contributing greatly to analgesia and causing possible toxicity in renal dysfunction.

Other opioid analgesics undergo liver metabolism; they may differ from morphine kinetically in terms of oral effectiveness and elimination half-life.

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)

Adverse Effects of Opioid Analgesics

Acute Toxicity

Extensions of the pharmacodynamic actions—severity greatest with full agonists like morphine. Characteristic triad: pinpoint pupils, respiratory depression, and comatose state.

Management

Maintain patent airway and assist ventilation (avoid oxygen →↓ breathing) and IV naloxone (short duration may necessitate repeat dosing).

Tolerance

Occurs with continued use and is functional (pharmacodynamic), with changes in cellular adaptive responses but not receptor numbers. Tolerance can be marked for the CNS actions including analgesia, euphoria, and respiratory depression, but it occurs minimally in terms of miosis and the effects on GI motility. Cross-tolerance occurs between individual opioid analgesics.

Dependence

Both psychological and physical components, the latter made evident by the withdrawal or abstinence syndrome, which may include anxiety, lacrimation and rhinorrhea, sweating, yawning, goosebumps ("cold turkey"), hot or cold flashes, muscle cramps and spasms ("kicking the habit"), GI distress (cramps and diarrhea), and "pain" originating in the CNS.

The intensity of symptoms depends both on the drug and on its mode of administration, the dosage that the individual has been using, and the time from abrupt discontinuance. Full agonist opioids used IV, which include heroin, cause the most severe withdrawal symptoms. Management involves administration of oral methadone*, buprenorphine, or clonidine, with gradual dose tapering.

*Methadone maintenance programs: provision of daily oral doses to registered clients at methadone clinics.

Bridge to Behavioral Science

Types of Tolerance

Pharmacodynamic: change in receptors and/or coupling mechanisms.

Pharmacokinetic: changes in elimination rate (e.g., enzyme induction).

Cross-tolerance: ↓ response to one drug due to exposure to another drug.

Table IV-1-5. Properties of the Various Opioid Analgesics

Drug	Receptor Actions	Analgesia	Respiratory Depression	Abuse Liability	Other Characteristics
Morphine	μ agonist—strong (full)	+++	+++	+++	Prototype of the class, marked sedation, poor oral bioavailability, histamine release
Methadone	μ agonist—strong (full)	+++	+++	+++	Oral activity and long duration, useful in maintenance
Meperidine	μ agonist–strong (full)	+++	+++	+++	M blocker (no miosis or smooth muscle contraction), forms normeperidine → possible seizures
Buprenorphine	μ agonist—partial	++(+)	++	++	Long action (binds tightly to receptor), possible use in maintenance
Codeine	μ agonist—weak (partial)	+	+	+	Cough suppressant, weak analgesia but additive with acetaminophen or ASA
Propoxyphene	μ agonist—very weak	+	+	+	Analgesia weaker than codeine, but toxic in OD—difficult withdrawal
Nalbuphine	κ agonist and weak μ antagonist	++(+)	++	++	Analgesia good, less abuse liability than most strong opioids. In OD naloxone may be less effective.
Pentazocine	κ agonist and weak μ antagonist	+	++	+	Analgesia only fair, may impede effects of μ agonists if administered prior
Naloxone	μ antagonist—strong	–	–	–	ER and OR use (IV) to reverse CNS depressant effects of agonists. Naltrexone (PO) ↓ "craving" in alcoholism.

Clinical Correlate

Abuse Liability

Prescription regulations for most CNS drugs are based on their abuse liability. The potent opioid analgesics (e.g., morphine, methadone, meperidine, fentanyl) are judged to have the highest potential for abuse, along with CNS stimulants (e.g., amphetamine, cocaine) and short-acting barbiturates (e.g., secobarbital). No refills or telephone prescriptions are permissible.

DOPAMINE AND CNS NEUROTRANSMISSION

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 the regulation of affect, reinforcement, psychomotor functions, and sensory perception.

Drugs that ↑ DA functions →↑ psychomotor activity and reinforcement and, at high doses, may cause psychoses.

DA antagonists →↓ psychomotor function.

Tubero-Infundibular

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 amenorrhea-galactorrhea.

Chemoreceptor Trigger Zone

Activation of DA receptors →↑ emesis.

DA agonists (e.g., apomorphine) are emetic, and DA antagonists are antiemetic.

Table IV-1-6. States of Dopamine/Acetylcholine Imbalance

Pathology	Nigrostriatal	Mesolimbic and Mesocortical	Tubero-Infundibular
↑ DA/ACh	Hyperkinetic states: Huntington chorea, Tourette syndrome, tardive dyskinesia	Euphoria, paranoia, psychoses, schizophrenia	Hypoprolactinemia
↓ DA/ACh	Hypokinetic states: Parkinson disease, acute EPS, dystonias		Hyperprolactinemia

Dopamine Receptor Subtypes

Table IV-1-7. Characteristics of the Dopamine Receptor Subtypes

Subtype	Characteristics
D_{1A}	Formerly D_1, ↑ cAMP, micromolar DA sensitivity—similar to peripheral DA receptors
D_{1B}	Formerly D_5, ↑ cAMP
D_{2A}	Formerly D_2, ↓ cAMP, nanomolar sensitive to DA—major type in striatum; block of these receptors is associated with Parkinsonian effects of older antipsychotic drugs
D_{2B}	Formerly D_3, ↓ cAMP
D_{2C}	Formerly D_4, ↓ cAMP, antagonized by clozapine

DRUGS FOR PARKINSONISM (PD)

Signs and symptoms of PD include resting tremor, bradykinesia, muscle rigidity, postural instability, and flat facies. Pathologic basis is degeneration of nigrostriatal DA tracts so that neurochemical balance in striatum shifts toward ↓ DA/↑ACh.

Pharmacologic strategy in treatment involves attempts to restore normal balance by ↑ DA activity and/or ↓ ACh activity at M receptors in the striatum. Drugs may improve symptomatology but do not alter the course of PD.

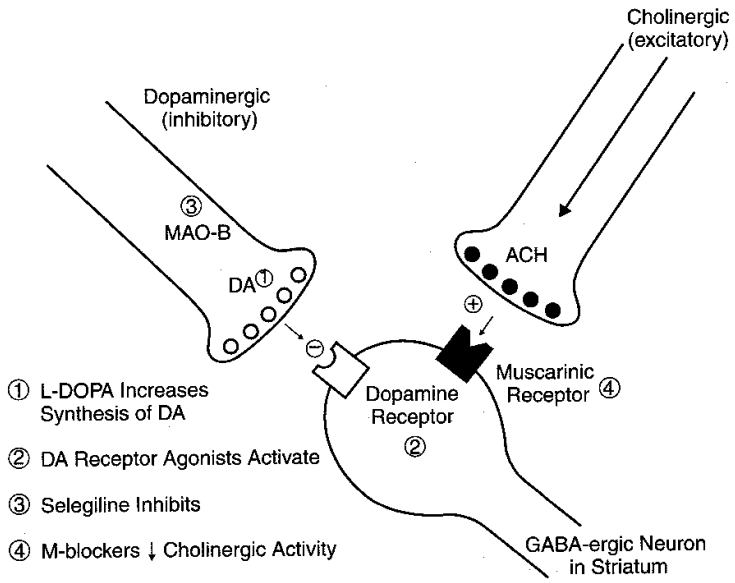


Figure IV-1-8. CNS Targets for Antiparkinsonian Drugs

Drugs Increasing DA Function

Levodopa

Precursor, converted to DA by aromatic amino acid decarboxylase (AAAD, dopa-decarboxylase)—usually given with carbidopa, which inhibits peripheral AAAD and increases CNS availability of L-dopa (carbidopa does not cross the blood–brain barrier [BBB]).

Still a primary drug in PD, but activity declines over 5 to 10 years, possibly due to slow but progressive neuronal oxidative damage.

Adverse effects: dyskinesias, hypotension, "on-off "effects, hallucinations, and psychoses.

Tolcapone and Entacapone

When AAAD is inhibited, more L-dopa is converted by COMT to 3-0-methyldopa, a partial agonist at DA receptors that can also compete with L-dopa for uptake into the CNS. These drugs inhibit peripheral COMT, enhancing the CNS uptake of L-dopa and possibly reducing its on-off effects. Tolcapone is hepatotoxic.

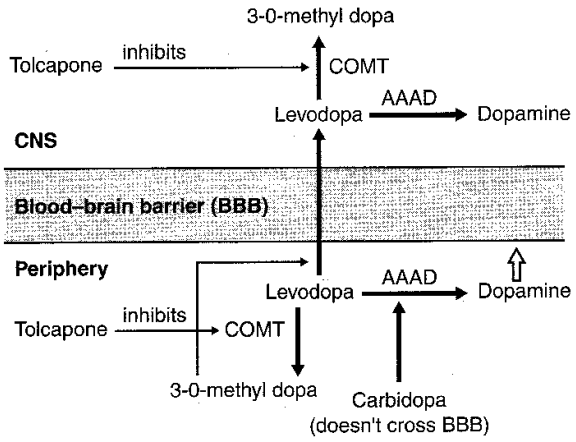


Figure IV-1-9. Inhibitors of Levodopa Metabolism

DA Receptor Agonists

Bromocriptine

Bromocriptine is the prototype but causes marked dyskinesias and CNS dysfunctions, including hallucinations, confusion, and psychosis. Formerly used as adjunct or alternative to levodopa, bromocriptine has been largely replaced by the non-ergots **pramipexole** and **ropinirole**, which are less toxic. However, they may cause sedation, including abrupt sleep onset.

Selegiline

Selegiline is a selective MAO type B inhibitor, increasing DA levels in CNS.

Used in initial PD as sole drug and/adjunctive with L-dopa.

CNS stimulation via metabolism to amphetamine; does not cause tyramine interactions.

Drugs Decreasing ACh Function

Drugs

Include benztropine and trihexyphenidyl, which are M receptor blockers more lipid-soluble than atropine and with greater CNS access.

Actions

Reduce tremor and rigidity in PD but have little effect on bradykinesia.

Reduce EPS dysfunction (pseudo-Parkinsonism, dystonias) caused by DA receptor antagonists. Diphenhydramine IM is especially useful in acute dystonias.

Exacerbate tardive dyskinesias (see antipsychotic drug section).

Cause typical atropine-like adverse effects.

Amantadine

Mild and temporary anti-PD actions, possibly via M receptor block. Causes atropine-like side effects and livedo reticularis (edema and skin mottling).

ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

Schizophrenia

Schizophrenia is a dysfunction characterized by positive symptoms that include thought disorders, delusions, hallucinations, and bizarre behavior and by negative symptoms that include amotivation, social withdrawal, flat affect, and poverty of speech.

The "dopamine hypothesis of schizophrenia" posits that such symptoms arise because of a functional excess of dopaminergic activity in the CNS. The notion is based on the facts that drugs that activate DA receptors may cause psychotic symptoms and those that block DA receptors often have antipsychotic actions. However, drugs used for schizophrenia do not remedy all symptoms; they are not "curative," and some newer agents appear to be effective in many patients, even though they do NOT act as antagonists at brain DA receptors but may modify serotonin functions.

Pharmacology

Antipsychotic Drugs

Drugs from several chemical families, most of which are capable of blocking D_{2A} receptors (formerly D_2). To varying degrees, they also block muscarinic receptors (typical atropine-like effects) and alpha receptors (postural hypotension, sexual dysfunction) and are sedating.

- Phenothiazines: chlorpromazine, thioridazine, fluphenazine
- Butyrophenone: haloperidol
- Newer drugs: clozapine, risperidone, olanzapine

Clinical Correlate

Antipsychotic Drug Potency

Low potency drugs, (e.g., chlorpromazine, thioridazine), requiring daily doses in the 100s of mg range, cause more autonomic dysfunction than other drugs. High potency drugs (e.g., fluphenazine, haloperidol), with daily doses in the range of 10 to 50 mg, cause less autonomic dysfunction but more extrapyramidal side effects.

DA Receptor Antagonism

DA receptor block is most intense with haloperidol, pimozide, and high-potency phenothiazines. Can result in reversible pseudo-Parkinsonism (bradykinesia, rigidity, tremor), akathisia, and acute dystonic reactions.

Management: Dose reduction, or change to a different drug, or addition of an M blocker. Acute dystonias may respond to botulinum toxin.

Extrapyramidal (EP) dysfunction is least likely to occur with clozapine and olanzapine, which do not block D_{2A} receptors but are strong antagonists at $5HT_2$ receptors.

Drugs causing EP dysfunction also block DA receptors in the pituitary $\rightarrow\uparrow$ prolactin and may cause endocrine dysfunction, including gynecomastia and amenorrhea-galactorrhea.

Summary of Antipsychotic Drug Pharmacology

Table IV-1-8. Characteristic Properties of Antipsychotic Drugs

Drug Group Examples	EPS*	M Block	Alpha Block	Sedation	Other Characteristics
Chlorpromazine	++	++	+++	+++	Prototype phenothiazine (low potency), ocular dysfunction
Thioridazine	+	+++	+++	+++	Low potency, phenothiazine, retinal deposits, cardiotoxicity (torsades—"quinidine-like")
Fluphenazine	+++	+	+	+	High potency, phenothiazine
Haloperidol	+++	+	+	+	High potency, butyrophenone, long-acting depot forms available
Clozapine	+/–	++	+++	+	Blocks D_{2c} and $5HT_2$ receptors, no EP dysfunction or TDs, agranulocytosis—requirement for weekly blood test, weight gain
Olanzapine	+/–	+	++	+	Blocks $5HT_2$ receptors, improves negative symptoms
Risperidone	+	+/–	++	++	Blocks $5HT_2$ receptors, improves negative symptoms, possible TDs
Aripiprazole	+	+/–	+/–	+/–	Partial agonist of D_2 receptor; blocks $5HT_2$ receptors

*Extrapyramidal symptoms.

Toxicity

Overdose presents as a magnification of the pharmacodynamic actions shown in Table IV-1-8 and includes M block, alpha block, and sedation, plus a decrease in seizure threshold.

Tardive Dyskinesia

Choreoathetoid-like muscle movements are associated with long-term use of DA blockers, especially haloperidol and high-potency phenothiazines. They are not readily reversible, and M blockers appear to make them worse. Have not been reported for clozapine or olanzapine.

Neuroleptic Malignant Syndrome

Life-threatening condition that includes extreme muscle rigidity, hyperthermia, CV instability, and altered level of consciousness, presumed due to enhanced sensitivity of DA receptors to blocking agents. Treatment involves bromocriptine (DA agonist) and dantrolene, plus symptomatic management.

Clinical Uses of Antipsychotics

Schizophrenia

Symptoms may take several weeks to respond to drug treatment. Newer drugs (very costly) may improve negative 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.

Schizoaffective States
Drug-induced psychosis, delusions, and psychoses of Alzheimer disease.

Bipolar Disorder
Initial management.

Tourette Syndrome
Pimozide now DOC.

Preoperative Sedation
Promethazine has minimal antipsychotic activity. Clinical uses are based on its potent H_1-blocking and sedative actions.

Drug or Radiation Emesis
Prochlorperazine.

Neurolept Anesthesia
Droperidol + fentanyl + nitrous oxide.

ANTIDEPRESSANTS

Major depressive disorders have been postulated to arise from a functional deficiency in brain NE and/or 5HT (amine hypothesis of depression). This notion is largely based on the acute actions of antidepressant drugs (which may ↑ NE and/or 5HT actions) and the fact that reserpine (which depletes brain amines) causes depression. However, no antidepressant takes effect rapidly, and some drugs do not appear to have significant effects on brain amines.

MAO Inhibitors (MAOIs)

Include phenelzine and tranylcypromine, which inhibit both MAO type A (which metabolizes NE, 5HT, and tyramine) and type B (which metabolizes DA).

Possible use in atypical depressions, but infrequent use because of side effects (orthostatic hypotension, weight gain) and drug interactions that include:

- Hypertensive crises with tyramine, NE uptake blockers, alpha agonists, and L-dopa
- Hyperthermia, HTN, seizures with meperidine or dextromethorphan
- Serotonin syndrome (see below) with selective serotonin reuptake inhibitors

Tricyclic Antidepressants (TCAs)

Include amitriptyline, imipramine, and clomipramine, which block the reuptake of both NE and 5HT →↑ adrenergic and serotonergic neurotransmission.

Exert four actions similar to phenothiazines: M block, alpha block, sedation, and decrease seizure threshold, plus greater cardiotoxicity ("quinidine-like"), a major mortality factor in OD. Triad ("3 Cs"): coma, convulsions, and cardiotoxicity. Autonomic side effects, additive sedation with other CNS depressants, and weight gain commonly occur with TCAs.

Uses include major depressions, phobic and panic anxiety states, neuropathic pain, enuresis, and obsessive-compulsive disorder (OCD) (clomipramine now backup). Withdrawal syndrome follows discontinuance in depression—nausea, headache, vertigo, malaise, nightmares.

Drug interactions: hyperthermia, seizures, coma, and death with MAOIs; serotonin syndrome with selective serotonin reuptake inhibitors; prevent anti-HTN effect of guanethidine and CNS-acting α_2 agonists.

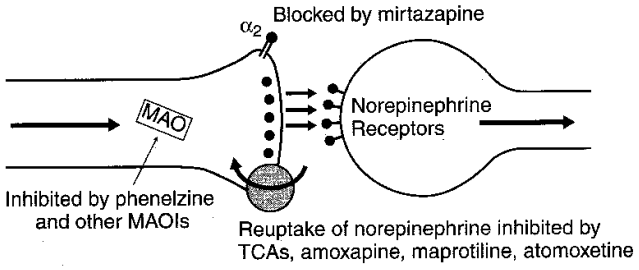


Figure IV-1-10. Antidepressants and Noradrenergic Transmission

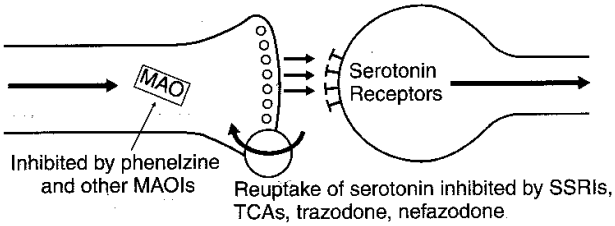


Figure IV-1-11. Antidepressants and Serotonergic Transmission

Selective Serotonin Reuptake Inhibitors (SSRIs)

Include fluoxetine, paroxetine, and sertraline, which selectively block the reuptake of 5HT $\rightarrow\uparrow$ serotonergic neurotransmission. Fluoxetine forms a long-acting metabolite, norfluoxetine, that contributes to its effects.

Adverse effects: anxiety, agitation (may need sedative), bruxism, sexual dysfunction (anorgasmia), and seizures (OD). Weight loss, but regained after 12 months Rx.

Clinical uses include major depressions, anxiety states (panic, phobias, social), premenstrual dysphoric disorder, bulimia, OCD, and alcoholism. Withdrawal syndrome following discontinuance in depression: nausea, headache, vertigo, malaise.

Drug interactions: serotonin syndrome includes diaphoresis, rigidity, myoclonus, hyperthermia, ANS instability, and seizures. Has been reported for SSRIs when used with MAOIs, TCAs, meperidine, and dextromethorphan.

Heterocyclic Antidepressants

Mechanisms of action vary: Amoxapine and maprotiline block NE reuptake; nefazodone (weak) and trazodone block 5HT reuptake, but both drugs also act as antagonists at certain

Note

Atomoxetine is a selective NE reuptake blocker used in attention deficit hyperactivity disorder.

5HT receptor subtypes. Mirtazapine blocks presynaptic α_2 receptors, preventing feedback inhibition of transmitter release. Bupropion has minimal effects on NE or 5HT systems but may affect DA neurotransmission.

Other characteristics: bupropion (smoking cessation); nefazodone (P450 inhibitor); trazodone (priapism).

Table IV-1-9. Characteristic Properties of Antidepressant Drugs

Drug	↓ NE Reuptake	↓ 5HT Reuptake	M Block	Alpha Block	Sedation
Amitriptyline (TCA)	++	++++	+++	++	+++
Imipramine (TCA)	++	+++	++	+++	++
Clomipramine (TCA)	++	++++	+++	++	++
Fluoxetine (SSRI)	+	++++	+/0	+	+/0
Paroxetine (SSRI)	+	++++	0	0	+/0
Sertraline (SSRI)	+	++++	+/0	0	+/ 0
Bupropion*	+/0	+/0	+/0	+/0	+
Nefazodone	+/0	+	++	+	+
Trazodone	0	++	+/0	+	+++

*Bupropion is atypical as an antidepressant: it appears to block DA reuptake.

BIPOLAR DISORDER (BD)

Lithium

Mood stabilizer that remains DOC for bipolar disorder but also usually needs antidepressants to improve depressive phases of the dysfunction. Slow onset (2 weeks) and sedative drugs may be needed initially for manic phase. Lithium has a narrow therapeutic window—eliminated by kidney similarly to Na; low Na (or chronic diuretic treatment) enhances toxicity.

Mechanism

Mechanism involves inhibition of the dephosphorylation of both IP_2 to IP_1, and IP_1 to IP, necessary steps in the recycling of inositol $\rightarrow\downarrow$ PIP_2. This second messenger system is involved in receptor interactions involving ACh, NE, and 5HT. Lithium may also cause ↓ cAMP $\rightarrow\downarrow$ in its function as a second messenger (renal V_2 receptors are coupled to cAMP; see below).

Adverse Effects

Include tremor, ataxia, choreoathetosis, acne, edema, visual dysfunction, seizures, goiter, and hypothyroidism via inhibition of 5′ deiodinase; nephrogenic diabetes insipidus via uncoupling of vasopressin V_2 receptors. Treat with amiloride since it is a side effect and lithium needs to be cleared. A thiazide would treat the *disease* nephrogenic diabetes insipidus but may cause an increased reabsorption of lithium. Therefore, thiazides are not the best choice. Neonatal toxicity following lithium use in pregnancy includes lethargy, cyanosis, and possible hepatomegaly. Cardiac anomalies have been reported, but teratogenicity of lithium remains to be confirmed.

Backup Drugs

Valproic acid, carbamazepine, and in pregnancy clonazepam or gabapentin.

DRUGS OF ABUSE

Table IV-1-10. Properties of Drugs of Abuse

CNS Stimulant	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 symptoms	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
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)

(*Continued*)

Table IV-1-10. Properties of Drugs of Abuse (*continued*)

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
	Propoxyphene—strong "psychological dependence"

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
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

CNS DRUG LIST

Table IV-1-11

Sedative-Hypnotics	Anticonvulsants
Barbiturates: phenobarbital, secobarbital Benzodiazepines: alprazolam, diazepam, lorazepam, triazolam Others: buspirone, zolpidem BZ receptor antagonist: flumazenil	Carbamazepine, ethosuximide, valproic acid, phenytoin, clonazepam, diazepam, lorazepam, gabapentin, lamotrigine, felbamate, topiramate, tiagabin, vigabatrin
Anesthetics (IV)	**Anesthetics (inhaled)**
Fentanyl, ketamine, midazolam, propofol, thiopental	Enflurane, desflurane, halothane, isoflurane, nitrous oxide, sevoflurane
Local Anesthetics	**Skeletal Muscle Relaxants**
Lidocaine, bupivacaine, mepivacaine, procaine, cocaine	Depolarizing: succinylcholine Nondepolarizing: D-tubocurarine, atracurium, pancuronium
Opioid Analgesics	**Antipsychotics**
Full agonists: morphine, meperidine, methadone, fentanyl, and heroin Partial agonists: buprenorphine, codeine, propoxyphene Mixed agonist-antagonists: nalbuphine, pentazocine Antagonists: naloxone, naltrexone	Phenothiazines: chlorpromazine, fluphenazine, thioridazine Others: haloperidol, clozapine, risperidone, olanzapine, aripiprazole
Antiparkinsonian Drugs	**Antidepressants**
DA agonists: levodopa, bromocriptine, ropinirole, pramipexole, selegiline AAAD inhibitor: carbidopa M–blockers: benztropine, trihexiphenidyl COMT inhibitor: tolcapone	MAOIs: phenelzine, tranylcypromine TCAs: amitriptyline, imipramine, clomipramine SSRIs: fluoxetine, paroxetine, sertraline Others: bupropion, mirtazapine, nefazodone, trazodone, atomoxetine

Chapter Summary

Basic Principles

Voltage-gated ion channels (Figure IV-1-1) are blocked by some anesthetics and anticonvulsants.

Transmitter-gated ion channels are targets for some anesthetics, cholinergic drugs, anticonvulsants, and sedative-hypnotics and are normally regulated by the neurotransmitters GABA, glutamate, glycine, or acetylcholine (ACh) (Figures IV-1-2, IV-1-3).

The action of drugs on voltage- and transmitter-regulated channels is summarized in Figure IV-1-1, and the action of drugs on the neurotransmitter-regulated ion channels coupled to a G-protein is summarized in Figure IV-1-2.

The type of response normally elicited by glutamate, GABA, ACh, dopamine, norepinephrine, serotonin (5HT), and the opioid peptides and the modulations induced by drugs affecting the receptors relevant to each of these transmitters is succinctly presented.

Sedative-Hypnotic Drugs

Sedative-hypnotic (S-H) 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-1-3 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-1-4). The binding of these drugs at these sites leads to increased Cl^- 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_1 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-1-1 summarizes the uses and characteristics of various benzodiazepines.

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.

Sedation and sleep-promoting effects can be achieved with drugs that are not classified as S-H drugs. These include antihistamines, opioids, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Propranolol has been used to treat performance anxiety and social phobias.

Figure IV-1-5 illustrates the metabolism and pharmacologic actions of alcohols.

(*Continued*)

Chapter Summary (*continued*)

Anticonvulsants

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-1-2 summarizes the drugs of choice and the back-up drugs 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.

Table IV-1-3 summarizes the mechanisms, indications for use, and potential toxic effects of some newer anticonvulsants. Those listed are felbamate, gabapentin, lamotrigine, tiagabine, topiramate, and vigabatrin.

Anesthetics

The mechanisms of action of inhaled anesthetics probably involve interaction with neuronal membrane lipids, and they have varying potency (MAC values) in proportion to their lipid solubilities.

Table IV-1-4 summarizes the properties of nitrous oxide and six halogenated anesthetics.

The more soluble in blood the longer it takes for an anesthetic to become effective and the slower the recovery rate.

Inhaled anesthetics lower the response to Pco_2, increase intracranial blood pressure, and relax uterine smooth muscle. They may be used at lower levels in protocols using intravenous anesthetics, opioids, or local anesthetics.

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.

(*Continued*)

Chapter Summary (*continued*)

Sodium-Channel Toxins

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

Skeletal Muscle Relaxants

The skeletal muscle relaxants provide muscle relaxation and/or immobility via N-receptor interactions. Most, including d-tubocurarine, pancuronium, atracurium, and mivacurium, are competitive and nondepolarizing and can be reversed by AChE inhibitors. Succinylcholine is a depolarizing, noncompetitive 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.

Opioid Analgesics

Opioid analgesics act in part by binding to the receptors for the endogenous opio-peptides. These are G-protein–linked, multi-subunit 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 (Figure IV-1-7), types of effects, kinetics, and contraindications are discussed. Table IV-1-5 summarizes the receptor actions, strength of analgesic effect, depth of respiratory depression, abuse liability, and other relevant characteristics of nine opioid analgesics.

Dopamine and CNS Neurotransmission

DA in the nigrostriatal tract helps regulate kinesis by inhibiting GABAergic 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.

Table IV-1-6 summarizes the effects of DA/ACh imbalance in the nigrostriatal, mesolimbic-mesocortical, and tubero-infundibular areas.

Table IV-1-7 summarizes the characteristics of the five DA receptor subtypes.

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-1-8 illustrates the CNS sites targeted in antiParkinsonism therapy.

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

(*Continued*)

Chapter Summary (*continued*)

Antipsychotic Drugs (Neuroleptics)

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 older antipsychotic drugs (e.g., chlorpromazine, thioridazine, fluphenazine, and haloperidol) act primarily as DA antagonists, blocking D_{2A} 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 the neuroleptic malignant syndrome.

Newer drugs (e.g., clozapine, risperidone, and olanzapine) act as antagonists at $5HT_2$ receptors and seem to have fewer adverse effects. Aripiprazole is a D_2 partial agonist.

Table IV-1-8 summarizes the characteristics of the antipsychotic drugs.

Antipsychotics are used to treat schizophrenia, schizoaffective states, Tourette syndrome, preoperative sedation, drug- or radiation-induced emesis, and neuroleptic anesthesia and are used for the initial management of bipolar affective disorder.

Antidepressants

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 inhibitor tricyclic, selective serotonin reuptake inhibitor, and heterocyclic antidepressants are discussed.

Figures IV-1-10 and IV-1-11 illustrate the actions of the antidepressant drugs at synaptic junctions utilizing serotonin and norepinephrine receptors.

Table IV-1-9 summarizes the characteristic properties of major antidepressant drugs.

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 back-up drugs used for treatment of bipolar disorder are considered.

Drugs of Abuse

Table IV-1-10 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 DRUGS

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. α (NE)
   C. D_{2A} (DA)
   D. μ (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. 100 mg
   B. 500 mg
   C. 1 g
   D. 2 g
   E. 5 g

6. Which one of the following is characteristic of phenytoin?

   A. Inhibition of hepatic cytochromes 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. Slows the rising phase of the action potential

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 μ receptor agonist.

8. The data shown in the table concern the effects of drugs on transmitter function in the CNS. 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	Block of ACh M Receptors
A.	++++	0	0
B.	++	++	0
C.	0	0	++++
D.	0	+++++	0
E.	+	+	0

9. Anesthesia protocols for day surgery (outpatient) may include sevoflurane because recovery from this agent is more rapid than that for older inhaled anesthetics. Rapid recovery from anesthesia with sevoflurane is associated with its

   A. redistribution from brain to skeletal muscle
   B. low MAC value
   C. rapid metabolism by liver enzymes
   D. low blood–gas partition coefficient
   E. reversal of anesthesia by naloxone

10. 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

11. 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.

12. Which one of the following do morphine and D-tubocurarine have in common?

    A. Increased bladder tone
    B. ANS ganglion blockade
    C. Malignant hyperthermia
    D. Histamine release
    E. Uterine muscle relaxation

13. 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.

14. 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.

15. A weakly basic local anesthetic has a pKa = 8.0. If it is injected into a region of sepsis (pH = 5.8), what percentage of the drug will be in the form capable of crossing neural membranes?

    A. <0.1%
    B. <1.0% but >0.1%
    C. >90% but <99%
    D. >99%
    E. >99.9%

16. 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

17. The ability of several drugs to inhibit the reuptake of CNS amine neurotransmitters is shown in the table (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	5HT Reuptake	GABA Reuptake
A.	↓↓	0	0	↓↓
B.	0	↓↓↓↓	↓	0
C.	0	0	↓↓↓↓	0
D.	0	0	↓	↓↓↓↓
E.	↓↓↓↓	↓↓	0	0

18. 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

19. 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. butabarbital

20. A patient has been diagnosed has having "long QT syndrome." Which one of the following drugs used in the management of CNS dysfunction is most likely to cause problems in this patient?

    A. Diazepam
    B. Ethosuximide
    C. Fluoxetine
    D. Propoxyphene
    E. Thioridazine

21. 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

22. 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 effect is likely to occur in both of these individuals?

    A. Excessive salivation
    B. Pupillary constriction
    C. Orthostatic hypotension
    D. ↑ Seizure threshold
    E. Weight loss

23. A 30-year-old male patient is brought to the ER with the following symptoms attributed to a drug overdose: ↑ 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

24. 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. Procaine/blocks Ca channels (type T) in thalamic neurons
    E. Lithium/inhibits recycling of inositol

25. 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 CNS 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 cytochromes 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 flumazenil, not naloxone.

3. **Answer: E.** Benzodiazepines interact with components of the GABA receptor–chloride 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 C^0 and is certainly no higher. With such an assumption, the dose ingested is given by:

$$\begin{aligned}\text{Dose} &= C^0 \times V_d \div f = 50 \text{ mg/L} \times 40 \text{ L} \div 1 \\ &= 2000 \text{ mg} \\ &= 2 \text{ g}\end{aligned}$$

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. Its mechanism of action, both as anticonvulsant and antiarrhythmic, involves interaction with Na ion channels to slow membrane depolarization during the rising phase of the action potential.

7. **Answer: B.** Nalbuphine (like pentazocine) is an agonist at κ (kappa) opioid receptors and an antagonist at μ opioid receptors. Mixed agonist-antagonists can displace μ receptor agonists like 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: D.** Saturation of the blood with inhaled anesthetics is more rapid if they have a low blood–gas partition coefficient. This results in the more rapid achievement of a partial pressure of the dissolved anesthetic molecules commensurate with their movement out of the blood into the alveolar spaces of the lung, where they are eliminated. Note that the same physicochemical characteristic is responsible for the rapid onset of the anesthetic action of sevoflurane. Although redistribution of anesthetics between tissues occurs, it is not responsible for rapid recovery. MAC values are a measure of anesthetic potency. With the exception of halothane (and methoxyflurane), inhaled anesthetics are not metabolized to a significant extent. Naloxone is an opioid receptor antagonist.

10. **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.

11. **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, and the drug also appears to cause acne. 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.

12. **Answer: D.** The pharmacologic action common to both morphine and D-tubocurarine is the release of histamine from mast cells, causing vasodilation. Morphine increases, but D-tubocurarine (via ganglion blockade) decreases, bladder tone. When used in combination with inhalational anesthetics (e.g., halothane), D-tubocurarine has been implicated in malignant hyperthermia. Morphine relaxes the uterus, but D-tubocurarine has no effects on smooth muscle neurotransmission.

13. **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.

14. **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.

15. **Answer: B.** Back to Basic Principles and the Henderson-Hasselbalch relationship. From the table, pH – pKa = –2.2. For a weak base, a value of –2 represents 1% nonionized, so in the present case the percentage of the local anesthetic in the nonionized form is <1%. Local anesthetics usually have reduced activity when injected into tissue that is septic because only a small fraction of the molecules are in the form capable of crossing biomembranes. Remember that this is not the form that interacts with the Na ion channel—that's the ionized form of the local anesthetic.

16. **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 insomnia, 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.

17. **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.

18. **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.

19. **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 butabarbital is a barbiturate that may cause dependence.

20. **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.

21. **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.

22. **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).

23. **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 flunitrazepam (a benzodiazepine that has been used in "date rape") are all CNS depressants.

24. **Answer: E.** Lithium inhibits the dephosphorylation of IP_2 (needed for the recycling of inositol), leading to depletion of membrane PIP_2. Consequently, the activation of receptors by neurotransmitters such as ACh, NE, and 5HT fails to release the second messengers IP_3 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.

25. **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

Antibacterial Agents

1

PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

Antibacterial Activity

Antimicrobial drugs can either kill infecting organisms (**bactericidal**) or slow their growth (**bacteriostatic**), depending on many factors, including the specific drug and dosage, the particular microorganism, and the tissue location of the infection. For clinical effectiveness, a bacteriostatic drug depends greatly on active host defense mechanisms; bactericidal drugs are preferred, for example, in severely immunocompromised patients.

In some situations, more than one antimicrobial agent may be used, possibly leading to additive (1 + 1 = 2) or synergistic (1 + 1 = >2) effects. Examples of synergy include penicillins + aminoglycosides in treatment of infections due to enterococci or *Pseudomonas aeruginosa*. In a few cases, antimicrobial drug combinations may result in antagonistic (1 + 1 = <2) effects: penicillins + tetracyclines in pneumococcal meningitis.

Mechanisms of Action

Selective toxicity is the ability of an antimicrobial agent to act on an infecting organism without toxic effects on host cells. The extent of selective toxicity depends on its mechanisms of action, of which there are five basic categories, as shown in Table V-1-1.

Table V-1-1. Mechanism of Action of Antimicrobial Agents

Mechanism of Action	Antimicrobial Agents
Inhibition of bacterial cell-wall synthesis	Penicillins, cephalosporins, imipenem/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
Disruption of cell membrane function	Azole and polyene antifungal agents

Microbial Resistance

Microbial resistance to drugs can emerge via the gradual selecting out of innately resistant mutant strains from a microbial population or, more commonly, via R-factor plasmid-mediated transmission between bacteria. The primary mechanisms of microbial resistance are shown in Table V-1-2.

Table V-1-2. 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
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: PENICILLINS

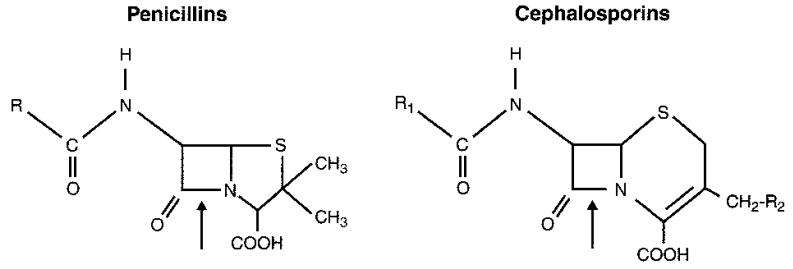


Figure V-1-1. Beta Lactam Antibiotics

Mechanisms of Action

Penicillins are bactericidal inhibitors of cell wall synthesis.

The bacterial cell wall is a 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.

Binding to PBPs also results in activation of autolytic enzymes.

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

Beta-Lactamase–Susceptible and Narrow Spectrum

Penicillin G—streptococci, pneumococci (↑ resistance), meningococci, *Treponema pallidum*

Penicillin V—streptococci and oral pathogens

Beta-Lactamase–Resistant and Very Narrow Spectrum

Nafcillin, methicillin, oxacillin—known or suspected staphylococci (not MRSA)

Beta-Lactamase–Susceptible and Wider Spectrum

Ampicillin (oral, IV) and amoxicillin (oral)—gram-positive cocci (not staph), *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes* (ampicillin). Activity enhanced if used in combination with inhibitors of penicillinase (clavulanic acid, sulbactam). Amoxicillin is a backup drug in Lyme disease and is also used in some regimens to eradicate *Helicobacter pylori* in GI ulcers.

Ticarcillin, piperacillin, azlocillin— ↑ activity versus gram-negative rods, including *Pseudomonas aeruginosa*; activity enhanced in combination with penicillinase inhibitors.

Note synergy with aminoglycosides versus enterococci and pseudomonal species.

Biodisposition

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 is excreted by the kidney. Benzathine penicillin G—repository form (half-life of 2 weeks).

Adverse 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 occurs with methicillin.

Assume complete cross-allergenicity between individual penicillins.

Other

GI distress (NVD), especially ampicillin; Jarisch-Herxheimer reaction in Rx of syphilis; maculopapular rash (common with ampicillin); interstitial nephritis (methicillin).

Bridge to Biochemistry

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.

Bridge to Immunology

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

INHIBITORS OF CELL-WALL SYNTHESIS: CEPHALOSPORINS

Mechanisms of Action and Resistance

Identical to penicillins in terms of mechanism of action (bind to PBPs); are bactericidal and require the intact beta-lactam ring structure for activity. Substituents at R1 group → spectrum variations, substituents at R2 group → kinetic variations (see Beta Lactam Antibiotics figure).

Resistance occurs mainly via production of beta-lactamases, but changed PBPs and changes in porin structure may also be involved.

Subgroups and Antimicrobial Activity

First Generation

Activity includes gram-positive cocci (not MRSA), *E. coli*, *Klebsiella pneumoniae*, and some *Proteus* species. Common use in surgical prophylaxis. None enter CNS. Includes cefazolin, cephalexin, cephradine.

Second Generation

↑ Gram-negative coverage, including some anaerobes. Most do not enter CNS. Includes cefotetan (*Bacteroides fragilis*) and cefaclor (*H. influenzae, Moraxella catarrhalis*).

Third Generation

Wider spectrum that includes gram-positive and gram-negative cocci, plus many gram-negative rods.

- Most enter CNS (not cefoperazone). Important in empiric management of meningitis and sepsis.
- Includes ceftriaxone (IM) and cefixime (PO) used in single dose for gonorrhea, cefotaxime (active versus most bacteria causing meningitis), and ceftizoxime (*B. fragilis*).

Classic Clues

Organisms NOT covered by cephalosporins are "LAME":

*L*isteria monocytogenes

*A*typicals (e.g., *Chlamydia, Mycoplasma*)

*M*RSA

*E*nterococci

Fourth Generation

Even wider spectrum, resistant to most beta-lactamases—cefepime (IV).

Biodisposition

Renal clearance similar to penicillins, with active tubular secretion blocked by probenecid. Dose modification in renal dysfunction, except cefoperazone and ceftriaxone, which are largely eliminated in the bile.

Adverse Effects

Hypersensitivity reactions (2% incidence): 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-hypersensitivity 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).

Cefotetan, cefoperazone and cefamandole cause hypoprothrombinemia and also disulfiram-like interactions with ethanol.

IV injections → phlebitis; IM → pain.

OTHER INHIBITORS OF CELL WALL SYNTHESIS

Imipenem and Meropenem

Mode of Action

Imipenem and meropenem are carbapenems that are bactericidal and bind to PBPs with the same mechanism of action as penicillins and cephalosporins. However, they are resistant to beta-lactamases. Wide spectrum that includes gram-positive cocci, gram-negative rods (e.g., *Enterobacter*, *Pseudomonas* sp.), and anaerobes. Important in-hospital agents for empiric use in severe life-threatening infections.

Use and Elimination

Both drugs are used IV only. Imipenem is given with cilastatin, which inhibits its rapid metabolism by renal dihydropeptidases; both drugs undergo renal elimination— ↓ dose in renal dysfunction.

Adverse Effects

GI distress, drug fever (partial cross-allergenicity with penicillins), CNS effects, including seizures with imipenem in OD or renal dysfunction.

Aztreonam

Mode of Action

Monobactam inhibitor of transpeptidation—resistant to beta-lactamases.

Use

IV drug mainly active versus gram-negative rods. No cross-allergenicity with penicillins or cephalosporins.

Vancomycin

Mode of Action

Bactericidal drug that acts at an early stage in cell-wall synthesis, binding at the D-ala-D-ala pentapeptide to sterically hinder the transglycosylation reactions involved in elongation of peptidoglycan chains.

Activity is restricted to gram-positive cocci including MRSA (DOC) and enterococci and the anaerobe *Clostridium difficile* (backup drug). Vancomycin (+/– rifampin) is also active against pneumococci resistant to the penicillins.

Resistance

Resistance is uncommon, but vancomycin-resistant staphylococcal (VRSA) and enterococcal (VRE) strains are slowly emerging. Enterococcal resistance involves a change in the pentapeptide "target," such that the terminal D-ala is replaced by D-lactate.

Use and Excretion

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) and has a long half-life.

Adverse Effects

Ototoxicity (usually permanent), hypotension, and diffuse hyperemia ("red-man syndrome"); if given too rapidly IV, may enhance other nephrotoxic drugs, hypersensitivity reactions.

INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS: MECHANISMS

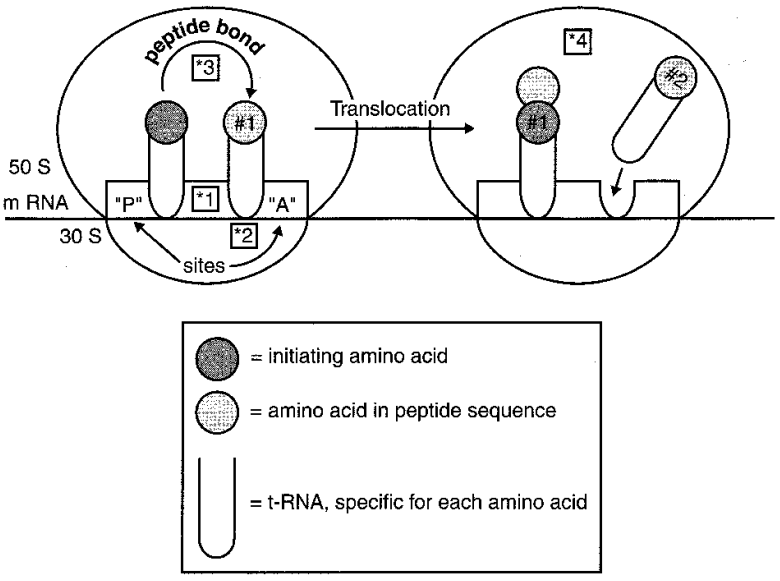


Figure V-1-2. Bacterial Protein Synthesis

Table V-1-3. 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—incorporation of wrong AA (-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, see Principles of Antimicrobial Chemotherapy at the beginning of this chapter.

INHIBITORS OF PROTEIN SYNTHESIS: MACROLIDES

Activity and Clinical Uses

Erythromycin

Erythromycin is used for infections caused by gram-positive cocci (not MRSA), atypical organisms (*Chlamydia*, *Mycoplasma*, and *Ureaplasma* species), *Legionella pneumophila*, and *Campylobacter jejuni*.

Azithromycin

Azithromycin has a similar spectrum but is more active, especially versus organisms associated with sinusitis or otitis media (*H. influenzae*, *M. catarrhalis*), *Chlamydia* (co-DOC, including co-infections with gonorrhea), and *Mycobacterium avium-intracellulare*.

Clarithromycin

Clarithromycin has > activity versus *M. avium* complex (MAC) and *H. pylori*.

Biodisposition

Erythromycin

Erythromycin (estolate is best absorbed oral form)—wide distribution into tissue and is eliminated mainly via biliary excretion.

Bridge to Microbiology

Community-Acquired Pneumonia

With no comorbidity, the most common organisms associated with a community-acquired pneumonia are *M. pneumonia*, *C. pneumoniae*, and viruses. In smokers, the pneumococcus becomes 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.

Azithromycin

Azithromycin accumulates at high levels in tissues and blood cells and is excreted by the kidney with a long half-life (>4 days).

Adverse Effects

Erythromycin

Erythromycin causes GI distress (via stimulation of motolin receptors), inhibits P450 drug metabolism (potential drug interactions), and may cause auditory dysfunction at high IV doses. The estolate form is associated with cholestasis and is not recommended in pregnant or the elderly patients.

Azithromycin

Azithromycin is safe in pregnancy and does not inhibit drug metabolism.

Clarithromycin

Clarithromycin causes less GI distress than erythromycin, but it also inhibits P450 and causes reversible deafness at high doses. Animal studies have shown teratogenic effects.

Clinical Correlate

Don't Use in Pregnancy

Aminoglycosides, erythromycin estolate, clarithromycin, fluoroquinolones, sulfonamides, tetracyclines

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. Its concentration in bone has clinical value in osteomyelitis due to gram-positive cocci. First known drug to cause pseudomembranous colitis.

INHIBITORS OF PROTEIN SYNTHESIS: AMINOGLYCOSIDES

Activity and Clinical Uses

Aminoglycosides are bactericidal, accumulated intracellularly in microorganisms via an O_2-dependent uptake; thus, anaerobes are innately resistant.

Bridge to Microbiology

Once-Daily Dosing of Aminoglycosides

Antibacterial effects depend mainly on peak drug level (rather than time) and continue with blood levels < MIC—a post-antibiotic effect (PAE).

Toxicity depends both on blood level and the time that such levels are > than a specific threshold (i.e., total dose).

Useful spectrum includes gram-negative rods; **gentamicin**, **tobramycin**, and **amikacin** are 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).

Streptomycin

Streptomycin is used in tuberculosis and is the DOC for bubonic plague and tularemia.

Neomycin

Neomycin, too toxic for systemic use, is used topically.

Biodisposition

Aminoglycosides are polar compounds, not absorbed orally or widely distributed into tissues. Renal elimination is proportional to GFR, and major dose reduction is needed in renal dysfunction.

Aminoglycosides have short half-lives (2–3 h) and conventionally are given parenterally at 6- to 12-h intervals. Once-daily administration is becoming more common because it is clinically effective and causes less toxicity.

Adverse 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 and vestibular dysfunction, which are not readily reversible. Toxicity may be enhanced by loop diuretics.

Neuromuscular blockade—may enhance effects of skeletal muscle relaxants.

Contact dermatitis (neomycin).

INHIBITORS OF PROTEIN SYNTHESIS: TETRACYCLINES

Class, 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*, *Brucella*, and *Vibrio*
- Continued use prophylactically in chronic bronchitis and for acne
- Backup to penicillin G in syphilis

Doxycycline

Doxycycline > activity overall than tetracycline HCl and has particular usefulness in prostatitis because it reaches high levels in prostatic fluid.

Minocycline

Minocycline appears in saliva at high concentrations and is used in the meningococcal carrier state.

Demeclocycline

Demeclocycline is used in syndrome of inappropriate secretion of ADH (SIADH) (blocks ADH receptor function in collecting ducts).

Biodisposition

Oral absorption may be decreased by multivalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}). Good tissue penetration. They undergo enterohepatic cycling but are primarily eliminated via the kidney in proportion to GFR (reduce dose in renal dysfunction).

Doxycycline is more lipid-soluble than other tetracyclines and less dependent on renal elimination; more than 50% of the drug is eliminated in the feces.

Classic Clues

Phototoxicity

Rash, in areas of the body exposed to UV light, may be indicative of drug phototoxicity. Among the antibacterial agents, the tetracyclines and the sulfonamides are notably phototoxic. More recently, the fluoroquinolones have been implicated in phototoxic responses, and because these antibiotics are widely used, the incidence of this type of adverse effect is increasing.

Adverse Effects

- GI distress (NVD), superinfections leading to candidiasis or colitis
- Tooth enamel dysplasia and possible ↓ bone growth in children (avoid)
- Renal dysfunction (Fanconi syndrome) with outdated drugs
- Phototoxicity (demeclocycline, doxycycline)
- Have caused liver dysfunction during pregnancy at very high doses (contraindicated)
- Vestibular dysfunction (minocycline, doxycycline)

OTHER INHIBITORS OF PROTEIN SYNTHESIS

Chloramphenicol

Activity and Clinical Uses

Bacteriostatic with a wide spectrum of activity but currently a backup drug for infections due to *Salmonella typhi*, *B. fragilis*, *Rickettsia*, and possibly in bacterial meningitis.

Orally effective, with good tissue distribution, including CSF. Metabolized by hepatic glucuronidation, and dose reductions are needed in liver dysfunction and in neonates.

Adverse Effects

Dose-dependent bone marrow suppression is common; aplastic anemia is rare (1 in 35,000). "Gray baby" syndrome in neonates (↓ glucuronysyl transferase) and optic neuritis in children. Inhibits metabolism of phenytoin, sulfonylureas, and warfarin.

Quinupristin–Dalfopristin

Activity and Clinical Uses

Quinupristin and dalfopristin are streptogramins that act in concert via several mechanisms. Binding to sites on the 50S ribosomal subunit, they prevent the interaction of aminoacyl-tRNA with the acceptor site and stimulate its dissociation from the ternary complex. They may also decrease the release of completed polypeptide by blocking its extrusion.

They are new drugs that are used parenterally in severe infections caused by vancomycin-resistant staphylococci (VRSA) and enterococci (VRE), as well as other drug-resistant gram-positive cocci.

Adverse Effects

Toxic potential remains to be established. Resistance has been reported via the formation of inactivating enzymes and ↑ efflux mechanisms.

Linezolid

Activity and Clinical Uses

Linezolid is an oxazolidinone that inhibits the formation of the initiation complex in bacterial translation systems by preventing formation of the *N*-formylmethionyl-tRNA-ribosome-mRNA ternary complex.

Linezolid is available in oral and parenteral formulations for treatment of VRSA, VRE, and drug-resistant pneumococci.

Adverse Effects

Headache and GI distress occur; bone-marrow suppression is reported following use >2 weeks.

INHIBITORS OF FOLIC ACID SYNTHESIS AND NUCLEIC ACID METABOLISM

Sulfonamides

Mechanisms

Competes with PABA, causing inhibition of dihyropteroate synthase and formation of nonfunctional folic acid (see Figure V-1-3).

Resistance occurs commonly by several mechanisms, including ↑ formation of PABA, structural changes in the synthase, decreased intracellular accumulation, and utilization of folate from exogenous sources.

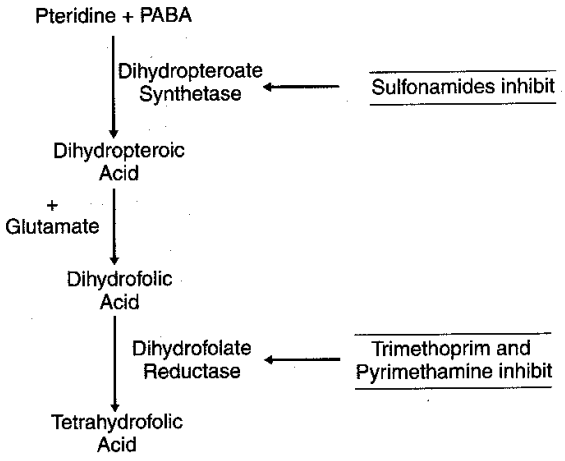


Figure V-1-3. Inhibitors of Folic Acid Synthesis

Activity and Clinical Uses

Have a wide spectrum, but use as individual agents is limited by resistance. Common uses include nocardial infections (DOC), simple UT infections (sulfisoxazole), ulcerative colitis* (sulfasalazine), trachoma (sulfacetamide, topical), burns (Ag sulfadiazine,* topical), and toxoplasmosis (sulfadiazine + pyrimethamine).

Bridge to Biochemistry

Antimetabolites

A substance inhibiting cell growth by competing with, or substituting for, a natural substrate in an enzymatic process. Sulfonamides and trimethoprim are antimetabolites, as are many antiviral agents and drugs used in cancer chemotherapy.

*Sulfas are not the active moieties.

Biodisposition

Effective orally and eliminated via hepatic metabolism (acetylation) and renally as unchanged drug. Less water-soluble metabolites may cause crystalluria. Bind to plasma proteins →↑ drug interactions including ↑ effects of methotrexate, phenytoin, and warfarin.

Adverse Effects

Hypersensitivity, mostly rashes, which can be severe (Stevens-Johnson syndrome). Assume complete cross-allergenicity between sulfonamides and possibly with sulfonylurea hypoglycemics.

GI distress (NVD), phototoxicity, and hemolysis in GPDH deficiency. Avoid in third trimester because they cross placental barrier and may displace bilirubin from plasma proteins in neonates → kernicterus.

Trimethoprim (TMP) and TMP-Sulfamethoxazole (SMX)

Mechanisms

Trimethoprim is an analog of folic acid that inhibits dihydrofolate reductase (see Figure V-1-3). Resistance, which occurs readily if the drug is used as a single agent, is via mutations in the gene that codes for the reductase. When used with sulfamethoxazole (TMP-SMX, cotrimoxazole), there is synergism and decreased emergence of resistance resulting from the sequential blockade of folic acid synthesis; the combination is usually bactericidal.

Clinical Uses

TMP-SMX has a wide spectrum and many clinical uses: possible co-DOC in complicated UT infections and in respiratory, ear, and sinus infections associated with *H. influenzae* or *M. catarrhalis*; backup drug for *L. monocytogenes*, *Proteus mirabilis*, *S. typhi*, MRSA, and vibrios.

DOC for prophylaxis and treatment of *Pneumocystis carinii* pneumonia.

Pyrimethamine inhibits dihydrofolate reductase in *Toxoplasma gondii* and is used with sulfadiazine in prophylaxis and treatment of toxoplasmosis (Figure V-1-3).

Adverse Effects

Sulfonamide-related effects are described above, although crystalluria and drug interactions are not common with TMP-SMX.

Trimethoprim (and pyrimethamine) may cause anemia, leukopenia, and thrombocytopenia, most commonly in debilitated or immunosuppressed patients. Hematotoxicity, drug fever, rashes, and severe GI distress are problematic in patients with AIDS.

Fluoroquinolones

Mechanisms

The fluoroquinolones are bactericidal analogs of nalidixic acid that interfere with bacterial DNA synthesis. They inhibit topoisomerase II (DNA gyrase), blocking the relaxation of supercoiled DNA, required for replication, and topoisomerase IV, responsible for separation of replicated DNA during cell division.

Resistance is increasing and may occur via ↑ drug efflux or via changed sensitivity of the target enzymes—topoisomerase IV in the case of gram-positive cocci (e.g., staphylococci), topoisomerase II in the case of *E. coli*, and increased efflux in the case of *P. aeruginosa*.

Activity and Clinical Uses

Wide spectrum that includes gram-positive and gram-negative cocci, many gram-negative rods (*E. coli*, *S. typhi*, *Shigella*, *Serratia marcescens*, etc.), some anaerobes (*C. jejuni*), and mycobacteria (e.g., multi-drug-resistant *M. tuberculosis*).

Active when administered orally (inhibited by antacids) and have a wide tissue distribution, including bone.

Drugs

- Drug group includes norfloxacin (UT only), ciprofloxacin, and multiple other fluoroquinolones (FQs).
- FQs may have enhanced activity against resistant pneumococci (sparfloxacin) and *Chlamydia* (ofloxacin).
- Ciprofloxacin has been used widely in respiratory, GI, UT, urogenital, and other soft tissue infections. Ciprofloxacin and ofloxacin are alternative drugs for gonorrhea (single doses).

Biodisposition

Eliminated mainly by the kidney via filtration and active tubular secretion (inhibited by probenecid)—reduce dose in renal dysfunction.

Adverse Effects

GI distress (NVD), rash, phototoxicity (especially sparfloxacin). CNS effects usually mild (insomnia, dizziness, and headache), but seizures occur in OD and in susceptible patients.

Contraindicated in pregnancy and children, based on animal studies showing effects on collagen metabolism and cartilage development; tendonitis (and tendon rupture) has occurred in adults.

Drug-specific toxicity: ↑ Q-T interval (sparfloxacin), hepatotoxicity (trovafloxacin).

Note

The activity of fluoroquinolones includes *Bacillus anthracis*. Anthrax may also be treated with penicillins or tetracyclines.

Metronidazole

Mechanism of Action

Mechanism of antibacterial action is unclear, but it appears to necessitate reductive metabolism of the drug—bactericidal.

Clinical Uses

Antiprotozoal

Metronidazole is DOC for most infections caused by *Entamoeba histolytica*, *Giardia* species, and *Trichomonas vaginalis*.

Antibacterial

DOC for most anaerobic infections including those caused by *B. fragilis*, *C. difficile*, and *G. vaginalis*. Used in regimens for *H. pylori*–associated GI ulcers.

Clinical Correlate

Antibiotics for *H. pylori* GI Ulcers

Amoxicillin, clarithromycin, tetracycline, and metronidazole have been used in various regimens for *H. Pylori*–associated GI ulcers, together with H_2 blockers, proton pump inhibitors, and antacids; e.g., "BMT" regimen: bismuth, metronidazole, and tetracycline.

Adverse Effects

Metallic taste, brown-black urine, glossitis, stomatitis, urethral burning, dysuria, neurotoxicity (vertigo, peripheral neuropathy). Disulfiram-like interactions with ethanol.

ANTITUBERCULAR DRUGS

General Principle

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.

Mechanisms of Action, Resistance, and Adverse Effects

Table V-1-4. Summary of the Actions, Resistance, and Adverse Effects of the Antitubercular Drugs

Drug	Mechanisms of Action and Resistance	Adverse Effects
Isoniazid (INH)	Inhibits mycolic acid synthesis; 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), hemolysis in G6PD deficiency, SLE in slow acetylators (rare)
Rifampin	Inhibits DNA-dependent RNA polymerase. Resistance via change in enzyme.	Proteinuria, hepatitis, "flu-like" syndrome, induction of P450, thrombocytopenia, red-orange metabolites
Ethambutol	Inhibits synthesis of arabinogalactan (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	Polyarthralgia, myalgia, hepatitis, rash, hyperuricemia, phototoxicity, ↑ porphyrin synthesis
Streptomycin	Protein synthesis inhibition	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.

Mycobacterium Avium-Intracellulare (MAC)

- Prophylaxis: azithromycin (1 × week) or clarithromycin (daily)
- Treatment: clarithromycin + ethambutol ± rifabutin

Chapter Summary

Basic Principles

Antibacterial drugs can be either bactericidal or bacteriostatic. 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 toxicity for the host. Table V-1-1 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 inhibitors of bacterial cell-wall synthesis are the beta lactam antibiotics (the penicillins and cephalosporins) (Figure V-1-1), the carbapenems, vancomycin, and aztreonam.

The mechanisms of action of penicillins, the bacterial modes of resistance to penicillins, the penicillin subgroups, their biodisposition, and adverse affects are provided. The subgroups discussed are the penicillins that are β-lactamase susceptible with a narrow spectrum of activity, β-lactamase–resistant penicillins having a very narrow spectrum of activity, and β-lactamase–susceptible penicillins with 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 β-lactam ring structure for activity. 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 β-lactam ring. Their clinical uses, routes of elimination, and adverse affects are considered.

Vancomycin inhibits 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 adverse effects are considered.

Aztreonam is a monobactam inhibitor of early cell-wall synthesis. It is used primarily as an IV drug against Gram-negative rods.

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.

(Continued)

Chapter Summary (*continued*)

The macrolides (e.g., erythromycin, clarithromycin, and azithromycin) are translocation inhibitors. Their spectrums of activity, clinical uses, biodisposition, and adverse effects are considered. Clindamycin is not a macrolide but shares many of their properties.

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.

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 adverse effects are discussed.

Chloramphenicol inhibits the activity of peptidyltransferase and is currently used primarily as a backup drug. Its activity, clinical use, and adverse effects are considered.

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 adverse effects are discussed.

Linezolid inhibits initiation by blocking formation of the N-formyl-methionyl-tRNA-ribosome-mRNA ternary complex. The clinical uses and adverse effects of this new drug are mentioned.

Antibiotics that Inhibit Folic Acid Synthesis and Nucleic Acid Metabolism

The sulfonamides compete with para-aminobenzoic acid (PABA) as shown in Figure V-1-3. The methods bacteria use to develop resistance to the sulfonamides, their activity and clinical uses, biodisposition, and adverse effects are considered.

Trimethoprim (TMP), a folate analog and inhibitor of dihydrofolate reductase (Figure 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 adverse 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 adverse effects are reported.

The exact mode of metronidazole action is unknown. Its use as an antiprotozoal and antibacterial drug is discussed, as are its adverse 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 aminoglycoside, fluoroquinolones, capreomycin, and cycloserine.

Table V-1-4 summarizes the actions, resistance, and adverse 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

Amp B has a wide fungicidal spectrum and remains the DOC (or co-DOC) for severe infections caused by *Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma*, *Mucor*, and *Sporothrix*. Amp B is synergistic with flucytosine in candidiasis and cryptococcoses.

Nystatin (too toxic for systemic use) is used topically for localized infections (e.g., candidiasis).

Biodisposition

Amp B is given by slow IV infusion—poor penetration into the CNS (intrathecal possible). Clearance is slow (half-life >2 weeks), via both metabolism and renal elimination.

Adverse Effects

Infusion-Related

Fever, chills, muscle rigor, hypotension (histamine release) occur during IV infusion (a test dose is advisable) and 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 amp B, or by drug combinations (e.g., + flucytosine), permitting ↓ in amp B dose.

AZOLES (KETOCONAZOLE, FLUCONAZOLE, ITRACONAZOLE)

Mechanism

Azoles are fungicidal and interfere with the synthesis of ergosterol by inhibiting the P450-dependent 14 alpha-demethylation of its precursor molecule, lanosterol.

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.

Biodisposition

Class: effective orally.

Absorption of ketoconazole is decreased by antacids.

Absorption of itraconazole is increased 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.

Adverse Effects

- Decreased synthesis of steroids, including cortisol and androgens →↓ libido, gynecomastia, menstrual irregularities
- Rash
- Fluid retention →↑ BP
- LFTs and rare hepatotoxicity
- Inhibition of hepatic P450s →↓ metabolism of cyclosporine, phenytoin, warfarin, etc.
- Disulfiram-like reactions with ethanol

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 amp 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.

Adverse effects: headache, thrush, peripheral neuritis, phototoxicity, potentiates ethanol—avoid with history of porphyria.

Terbinafine

Active only against dermatophytes by inhibiting squalene epoxidase →↓ ergosterol.

Possibly superior to griseofulvin in onychomycoses.

Adverse effects: GI distress, rash, headache, ↑ liver function tests (LFTs) → 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) and nystatin are amphoteric compounds that react with the ergosterol and poke holes in the fugal membranes. The activity, clinical uses, biodisposition, and adverse effects of these polyenes are discussed.

The azoles (ketoconazole, fluconazole, clotrimazole, miconazole, and itraconazole) kill fungi by interfering with ergosterol synthesis. The mechanisms of action, clinical uses, biodisposition, and adverse effects are considered.

Flucytosine is activated by fungal cytosine deaminase to form 5-fluoruracil (5-FU). It is sometimes used in combination with amp-B. Insomuch as 5-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

GENERAL PRINCIPLES

Many antiviral drugs are antimetabolites that resemble the structure of naturally occurring purine and pyrimidine bases or their nucleoside forms. Antimetabolites are usually pro-drugs requiring metabolic activation by host-cell or viral enzymes—commonly, such bioactivation involves phosphorylation reactions catalyzed by kinases.

The steps in viral replication and the main sites of action of antiviral drugs are shown in Figure V-3-1.

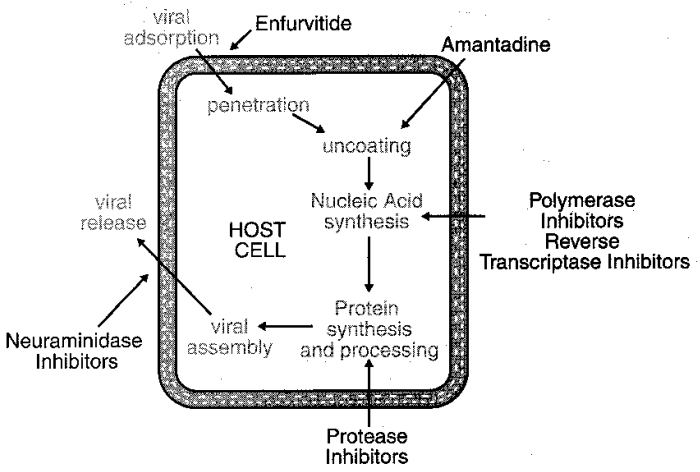


Figure V-3-1. Sites of Antiviral Drug Actions

ANTIHERPETICS

Acyclovir

Mechanisms

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, it acts as a chain terminator because it lacks the ribosyl 3′ hydroxyl group.

Resistance can be due to changes in DNA polymerase or to decreased activity of TK. However, >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. It 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.

Adverse Effects

Minor with oral use, more obvious with IV. Include crystalluria (maintain full hydration) and neurotoxicity (agitation, headache, confusion—seizures in OD). It 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.

Ganciclovir

Mechanisms

Similar mechanism to that of acyclovir. The first phosphorylation step is viral-specific and involves thymidine kinase in HSV and a phosphotransferase (UL97) in CMV. Triphosphate form inhibits viral DNA polymerase but does not cause chain termination.

Resistance mechanisms are similar to acyclovir.

Activity and Clinical Uses

Includes HSV, VZV, and cytomegalovirus (CMV). Mostly used in prophylaxis and treatment of CMV infections, including retinitis, in AIDS and transplant patients—relapses and retinal detachment occur.

Available in oral, IV, and retinal implant forms.

Adverse Effects

Dose-limiting hematotoxicity (leukopenia, thrombocytopenia), mucositis, fever, rash, and crystalluria (maintain hydration). Seizures in OD.

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.

Adverse Effects

Dose-limiting nephrotoxicity with acute tubular necrosis, electrolyte imbalance with hypocalcemia → tremors and seizures. Avoid pentamidine (IV) →↑ nephrotoxicity and hypocalcemia.

REVERSE TRANSCRIPTASE INHIBITORS (RTIs)

General Features

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. Commonly, two NRTIs are used together with a protease inhibitor (PI). During the past 5 or 6 years, such highly active antiretroviral therapy (HAART) has often resulted in ↓ viral RNA, reversal of the decline in CD4 cells, and ↓ opportunistic infections.

Nonnucleoside RTIs that do not require metabolic activation (e.g., delavirdine and nevirapine, efavirenz, which are not myelosuppressants) and a nucleotide reverse-transcriptase inhibitor (adefovir) have been introduced. Resistance emerges rapidly if these drugs are used as individual agents for management of HIV infection. However, they may provide additive or synergistic activity against HIV if used in combination regimens with NRTIs and/or PIs.

Zidovudine (Azidothymidine, ZDV, AZT)

Mechanisms

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.

Biodisposition

Active orally and metabolized to glucuronide conjugate—modify dose in hepatic or renal dysfunction. ZDV plasma levels are increased by azole antifungals, cimetidine, indomethacin, probenecid, and TMP-SMX—plasma levels of ZDV are decreased by rifampin.

Adverse Effects

Hematotoxicity (neutropenia, anemia, granulocytopenia) is dose-limiting and may require transfusions. Other effects include headache, asthenia, myalgia, myopathy, and peripheral neuropathy. Rare, but potentially fatal, lactic acidosis has been reported for ZDV and other NRTIs.

Other NRTIs

The basic mechanism of their action is identical to that of zidovudine—they each require metabolic activation to nucleotide forms that inhibit reverse transcriptase. Resistance mechanisms are similar but involve specific point mutations in the RT gene, so there is not complete cross-resistance between NRTIs. The drugs differ, however, in their toxicity profiles.

Table V-3-1. Adverse Effects of Nucleoside Reverse-Transcriptase Inhibitors

NRTI	Adverse 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

PROTEASE INHIBITORS (PIs)

Mechanisms

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.

Adverse Effects

Indinavir

Nephrolithiasis (maintain hydration), GI distress, thrombocytopenia, inhibition of P450 (3A4 isoform).

Ritonavir

GI distress, asthenia, paresthesias, and major drug interactions: induces CYP 1A2 and inhibits the major P450 isoforms (3A4 and 2D6) $\rightarrow\uparrow$ effects of dronabinol, erythromycin, ketoconazole, and rifampin.

PIs (General)

Syndrome of disordered lipid and CHO metabolism with central adiposity and insulin resistance.

FUSION INHIBITOR

Enfurvitide

Mechanism: binds gp41 and inhibits fusion of HIV-1 to CD4+ cells.

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 → ↓ transmission by 50% to 60%.

OTHER ANTIVIRALS

Amantadine

Mechanisms

Blocks attachment, penetration, and uncoating of influenza A virus.

Clinical Uses

Prophylaxis mainly, but may ↓ duration of flu symptoms by 1–2 days.

Adverse Effects

CNS effects include nervousness, insomnia, and seizures in OD. Causes atropine-like peripheral effects and livedo reticularis.

Zanamivir and Oseltamivir

Mechanisms

Inhibit neuraminidases of influenza A and B, enzymes that prevent clumping of virions, so that more particles are available for infecting host cells. This inhibition decreases the likelihood that the virus will penetrate uninfected cells.

Clinical Uses

Prophylaxis mainly, but may ↓ duration of flu symptoms by 2–3 days.

Adverse Effects

Both cause nausea and vomiting, and zanamivir (via inhalation) causes nasal and throat irritation.

Ribavirin

Mechanisms

Monophosphorylated form inhibits IMP dehydrogenase; triphosphate inhibits viral RNA polymerase and end-capping of viral RNA.

Clinical Uses

Uses include management of respiratory syncytial virus, influenza A and B, Lassa fever, Hantavirus, and as adjunct to alpha-interferons in hepatitis C.

Adverse Effects

Hematotoxic, upper airway irritation, teratogenic.

Table V-3-2. Mechanisms of Action of Antiviral Drugs

Mechanism of Action	Major Drugs
Block viral penetration/uncoating	Amantadine, rimantadine
Inhibit viral DNA polymerases	Acyclovir , foscarnet, ganciclovir
Inhibit viral RNA polymerases	Foscarnet, ribavirin
Inhibit viral reverse transcriptase	Zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine
Inhibit viral aspartate protease	Indinavir, ritonavir, saquinavir, nelfinavir
Inhibit viral neuraminidase	Zanamivir, oseltamivir

Chapter Summary

General Principles

Antiviral drugs are often antimetabolites that are structural analogs of purine or pyrimidine bases or their nucleoside forms. Many are pro-drugs 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.

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-3-1.

Nonnucleoside inhibitors of reverse transcriptase (NNRTIs) and a nucleotide RTI are also used in combinations for treatment in an HIV-positive patient.

Protease Inhibitors

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 enfurvitide, a fusion inhibitor.

HIV Prophylaxis

The courses of therapy used as HIV prophylaxis in cases of needle stick and for reducing the risk of vertical transmission in pregnancy are provided.

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 adverse effects of these viruses are considered.

Table V-3-2 summarizes the mechanisms of action of the major antiviral drugs.

Antiprotozoal Agents and the Antimicrobial Drug List

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	"Back-packer'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)	

*Metronidazole is DOC for most infections caused by *Entamoeba histolytica*, *Giardia* species, and *T. vaginalis*.
†Pyrimethamine inhibits dihydrofolate reductase in *Toxoplasma gondii* (see Figure V-1-3).

ANTIMALARIAL DRUGS

Clinical Uses

Chloroquine-Sensitive Regions

Prophylaxis: Chloroquine +/– primaquine.

Back-up drugs: hydroxychloroquine, primaquine, pyrimethamine-sulfadoxine (self-Rx).

Table V-4-2. Treatment of Chloroquine-Sensitive Malaria

Falciparum	Chloroquine
P. malariae	Chloroquine
P. vivax	Chloroquine + primaquine
P. ovale	Chloroquine + primaquine

Chloroquine-Resistant Regions

- Prophylaxis: mefloquine; back-up drugs: doxycycline, atoraquone-proquanil
- Treatment: quinine +/– either doxycycline or clindamycin or pyrimethamine

Table V-4-3. Adverse Effects of Antimalarial Drugs

Drug	Adverse Effects/Contraindications & Cautions
Chloroquine	GI distress, pruritis, headache, dizziness, hemolysis, ocular dysfunction. Avoid in psoriasis. Hydroxychloroquine is similar.
Mefloquine	NVD, dizziness, syncope, extrasystoles, CNS effects (rare). Avoid in seizure/psychiatric disorders and in cardiac conduction defects.
Primaquine	GI distress, headache, dizziness, neutropenia, hemolysis. Avoid in pregnancy, G6PD deficiency, or autoimmune disorders.
Quinine	GI distress, cinchonism, CNS effects, hemolysis, hematotoxicity. Avoid in pregnancy.

DRUGS FOR HELMINTHIC INFECTIONS

Most Intestinal Nematodes (Worms)

- Mebendazole (↓ glucose uptake and ↓ microtubular structure), or pyrantel pamoate (NM agonist → spastic paralysis)

Most Cestodes (Tapeworms) and Trematodes (Flukes)

- Praziquantel (↑ Ca^{2+} influx, ↑ vacuolization)

Table V-4-4. Antimicrobial Drug List

Penicillins	Cephalosporins	Other Cell Wall Inhibitors	
Penicillin G	Cephalothin (1st)	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		
Fluoroquinolones	**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) Enfurvitide	

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. Pyrimethamine with sulfadoxine or mefloquine is used for prophylaxis. The drugs used in chloroquine-resistant areas are listed separately.

The drugs used to treat helminthic infections are listed, and their mechanisms of action are noted.

Table V-4-4 lists all the major antimicrobial drugs.

ANTIMICROBIAL AGENTS

Review Questions

1. Which one of the following is a mechanism underlying the resistance of strains of *S. pneumoniae* to the widely used antibiotic, ciprofloxacin?

   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 one 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. You need to treat this infection, but you prefer 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. High-level resistance of *Mycobacterium tuberculosis* to isoniazid (INH) involves

   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 female patient 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 you also know that the antibiotic may cause hypoprothrombinemia, you can identify it as

   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, followed by

   A. amphotericin B
   B. ketoconazole
   C. flucytosine
   D. itraconazole
   E. terfenadine

7. The most likely drug to be effective in diseases caused by cestodes and trematodes is

   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. Cefixime
   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

   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. Once-daily dosing regimens with gentamicin are 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-6-phosphate dehydrogenase, it would not be advisable to prescribe

    A. ciprofloxacin
    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 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 "back-packer'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

    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. mutation in the gene that encodes DNA polymerase
    C. 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 TMP-SMX, develops breast hypertrophy, central adiposity, hyperlipidemia, insulin resistance, and nephrolithiasis. If these changes are related to his drug treatment, the most likely cause is

    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. Azidothymidine
    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 UT infection
    B. Amphetamine for weight loss
    C. Nystatin for a yeast infection
    D. Triazolam as a "sleeping pill"
    E. Two glasses of red wine

23. In a patient who has an established hypersensitivity to metronidazole, the most appropriate drug to use for the management of pseudomembranous colitis is

    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

    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 dosage reduction unless creatinine clearance <10 mL/min. 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 a 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 that 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 IV doses of amphotericin B may be life saving. Intravenous amphotericin B causes infusion-related hypotension (via histamine release), fever, 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, 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 cephalosporins cefixime and ceftriaxone (IM) are effective in single doses and are 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 one 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 7–8% 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, TMP-SMX.

13. **Answer: B.** Ceftriaxone (IM) 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 GI infections with diarrhea ("back-packer'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 giardial 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 CSF, 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 hypertriglyceridemia, 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 artifical membrane "pores" (azole antifungals inhibit ergosterol synthesis); tetracyclines prevent binding of aminoacyl-tRNA (chloramphenicol inhibits peptidyltransferase); 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, azithromycin is 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. Though 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, and alternative antibiotics are available. However, penicillin G remains the drug of choice in syphilis, usually given IM 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

Drugs for Inflammatory and Related Disorders

1

HISTAMINE AND ANTIHISTAMINES

Histamine

Histamine is an autacoid present at high levels in lungs, skin, and the GI tract and 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 →↑ GI ulcers

↑ SA nodal rate, positive inotropism, and automaticity

H_1 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.

Clinical Uses

- Allergic reactions: hay fever, rhinitis, urticaria
- Motion sickness, vertigo
- N and V of pregnancy
- Preoperative sedation
- OTC: sleep aids and cold medications

Adverse Effects

Extensions of M block and sedation (additive with other CNS depressants), GI distress, allergic reactions.

Table VI-1-1. Properties of Major Antihistamines

Drug	M block	Sedation	Antimotion	Other Characteristics
Diphenhydramine	+++	+++	+++	Widely used OTC drug
Promethazine	+++	+++	++	Some alpha block and local anesthetic action
Chlorpheniramine	++	+0	++	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

DRUGS USED IN GI DYSFUNCTION

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. H_2 blockers. Also partially antagonize HCl secretion caused by vagal stimulation or by gastrin (see Figure VI-1-1).

No effects on gastric emptying time.

Clinical Uses

Acid peptic disease (overall less effective than proton pump inhibitors), gastroesophageal reflux dystrophy (GERD), Zollinger-Ellison syndrome.

Adverse Effects

GI 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.

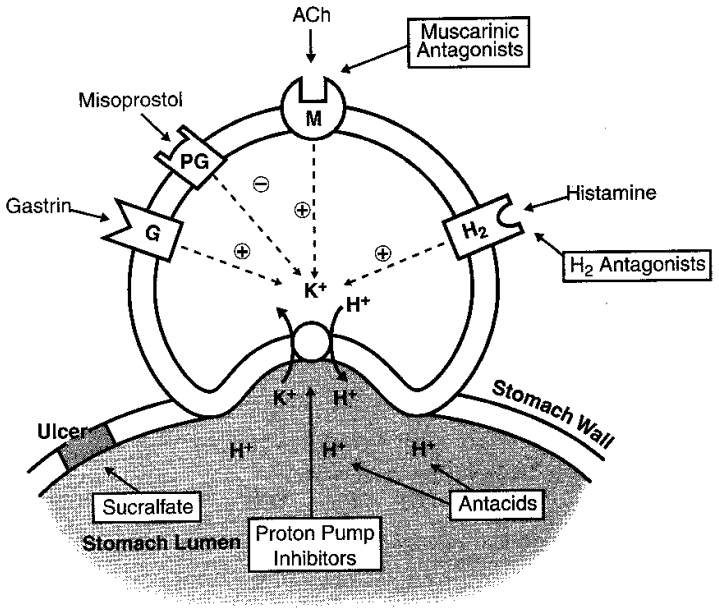


Figure VI-1-1. Drug Actions in Acid Peptic Disease

Other Drugs Used in GI Dysfunction

Proton Pump Inhibitors

Mechanisms of Action

Omeprazole and related "-prazoles" are irreversible, direct inhibitors of the proton pump (K^+/H^+ antiporter) in the gastric parietal cell (see Figure VI-1-1).

Clinical Uses

They are more effective than H_2 blockers in peptic ulcer disease (PUD) and are also effective in GERD and Zollinger-Ellison syndrome.

Adverse Effects

May cause mild CNS and GI effects and ↓ bioavailability of drugs that require acidity for oral absorption (e.g., fluoroquinolones, ketoconazole). Inhibit P450 →↓ elimination of diazepam, phenytoin, and warfarin.

Misoprostol

Mechanisms of Action

PGE_1 analog, which is cytoprotective →↑ mucus and bicarbonate secretion.

Clinical Uses

Selective use in NSAID-induced GI ulcers.

Sucralfate

Mechanisms of Action
Polymerizes on GI luminal surface to form a protective gel-like coating of ulcer beds (see Figure VI-1-1).

Clinical Uses
↑ Healing and ↓ ulcer recurrence. Sucralfate requires acid pH—antacids may interfere. Bismuth subsalicylate is also protective.

Antacids

Mechanisms of Action
Ca, Mg, and Al hydroxides that neutralize protons in the gut lumen (see Figure VI-1-1).

Adverse Effects
May ↓ oral absorption of azoles, fluoroquinolones, and tetracyclines (see Table VI-1-2).

Clinical Correlate

Antacids and Drug Absorption

- ↓ Oral absorption of weak bases (e.g., quinidine)
- ↓ Oral absorption of weak acids (e.g., warfarin)
- ↓ Oral absorption of tetracyclines (via chelation)

Table VI-1-2. The Adverse Effects of Various Antacids

Antacid	Alkalosis	Acid Rebound	Diarrhea	Constipation	Other Toxicity
$Al(OH)_3$	–	–	–	++	Hypophosphatemia, osteodystrophy, dementia
$CaCO_3$	+	++	–	++	Hypercalcemia
$Mg(OH)_2$	–	++	++	–	Hypermagnesemia → loss of deep tendon reflexes, respiratory paralysis
$NaHCO_3$	++	++	–	–	"Gas"

Laxatives

$MgSO_4$:	water-retaining →↑ intraluminal pressure
Bisacodyl:	direct intestinal wall stimulant
Methylcellulose:	collects water and swells →↑ bulk
Docusate:	detergent → stool softener
Mineral oil:	lubricant
Lactulose:	hyperosmotic (also indicated for systemic encephalopathy)

Emetic Pathways and Drug Actions

Figure VI-1-2 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, 5HT, histamine, and endogenous opiopeptides.

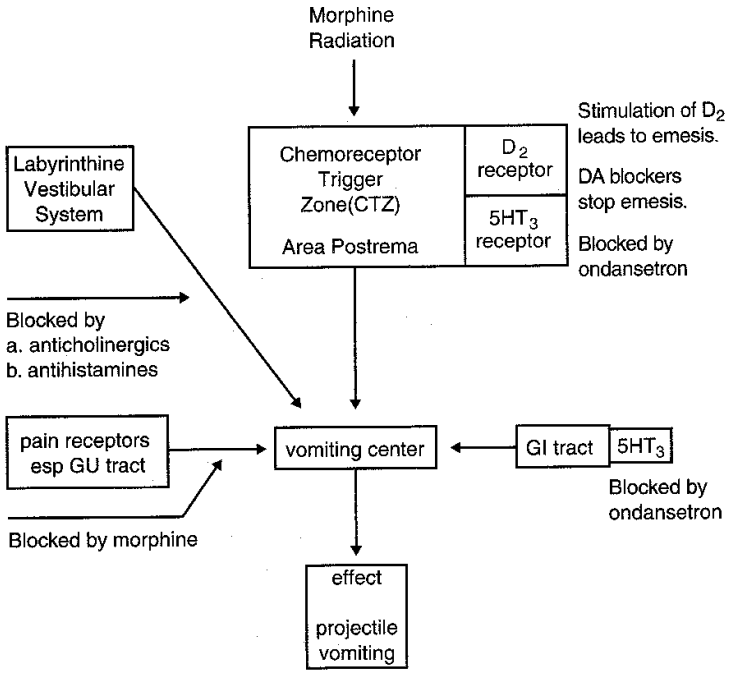


Figure VI-1-2. The Emetic Pathways and Drug Actions

Drugs for nausea and vomiting include:

- $5HT_3$ (a serotonin receptor—see the following section) antagonists: ondansetron,* granisetron
- DA antagonists: prochlorperazine, metoclopramide* (also prokinetic in GERD)
- H_1 antagonists: diphenhydramine, meclizine, promethazine
- Muscarinic antagonists: scopolamine
- Cannabinoids: dronabinol
- NK_1 receptor antagonist: aprepitant (NK_1 is a receptor to substance P)

Clinical Correlate

Opioid analgesics (e.g., morphine) have duality of action: ↓ emesis by activating receptors that decrease pain transmission and ↑ emesis by activating receptors in the CTZ.

DRUGS ACTING ON SEROTONERGIC SYSTEMS

General Features

Serotonin (5-hydroxytryptamine, 5HT) is an autacoid synthesized and stored in GI cells and neurons and in 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.

*Commonly used in cancer chemotherapy.

Drug Actions on 5HT Receptors

$5HT_{1(A-G)}$

Found in the CNS (usually inhibitory) and smooth muscle (excitatory or inhibitory).

Buspirone

Partial agonist at $5HT_{1A}$ receptors → anxiolytic (generalized anxiety disorder [GAD]).

$5HT_{1D}$

Sumatriptan

- Agonist at $5HT_{1D}$ receptors in cerebral vessels →↓ migraine pain
- Adverse effects of "triptans"—possible asthenia, chest or throat pressure or pain

$5HT_2$

Found in CNS (excitatory). In periphery, activation → vasodilation, contraction of GI, bronchial, and uterine smooth muscle, and platelet aggregation.

Olanzapine

Antagonist at $5HT_{2A}$ receptors in CNS →↓ symptoms of psychosis and newer antipsychotics.

Cyproheptadine

$5HT_2$ antagonists used in carcinoid, other GI tumors, and postgastrectomy. Also used for anorexia nervosa. Has marked H_1-blocking action.

$5HT_3$

Found in area postrema, peripheral sensory and enteric nerves. Activation opens ion channels (no second messengers).

Ondansetron and "-setrons"

Antagonists →↓ emesis in chemotherapy and radiation and postoperatively.

$5HT_4$

Found in GI smooth muscle and myenteric nerves.

Tegaserod

Agonist used in inflammatory bowel syndrome when associated with constipation.

Ergot Alkaloids

Ergonovine

- Mechanism of action: uterine smooth muscle contraction
- Clinical use: given (IM) after placental delivery

Ergotamine and Methysergide

Mechanisms of Action

Ergots acts as partial agonists at both alpha adrenoceptors and $5HT_2$ receptors in the vasculature and possibly in the CNS. Vasoconstrictive actions to decrease pulsation in cerebral vessels may be relevant to acute actions of ergotamine during migraine attack.

Clinical Uses
Ergotamine is used in acute attacks; methysergide is prophylactic in migraines.

Adverse Effects
GI distress, prolonged vasoconstriction → ischemia and gangrene, fibroplasia (methysergide), abortion near term.

Drugs for Migraine

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: beta blockers, CCAs, carbamazepine, NSAIDs, gabapentin, methysergide, valproic acid, and tricyclics

Other Drugs Affecting Serotonergic Neurotransmission

Many other drugs affect serotonergic neurotransmission in the CNS, including MAO inhibitors, SSRIs, tricyclic antidepressants, and hallucinogens (LSD, mescaline).

EICOSANOID PHARMACOLOGY

General Features

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.

Leukotrienes (LTs)

Formed (via hydroperoxides) from the action of lipoxygenases on arachidonic acid.

LTB_4

An inflammatory mediator → neutrophil chemoattractant; activates PMNs; ↑ free radical formation → cell damage.

LTA_4, LTC_4, and LTD_4

Cause anaphylaxis and bronchoconstriction (role in asthma).

Drug Effects

See Figure VI-1-3.

Leukotrienes are "targets" for the following.

Glucocorticoids
$\rightarrow\downarrow$ Phospholipase A_2 activity $\rightarrow$ contributes to both anti-inflammatory and immunosuppressive actions.

Zileuton
$\rightarrow$ Inhibits lipoxygenase $\rightarrow\downarrow$ LTs.

Zafirlukast and "-lukasts"
$\rightarrow$ LT receptor antagonists $\rightarrow$ used in treatment of asthma.

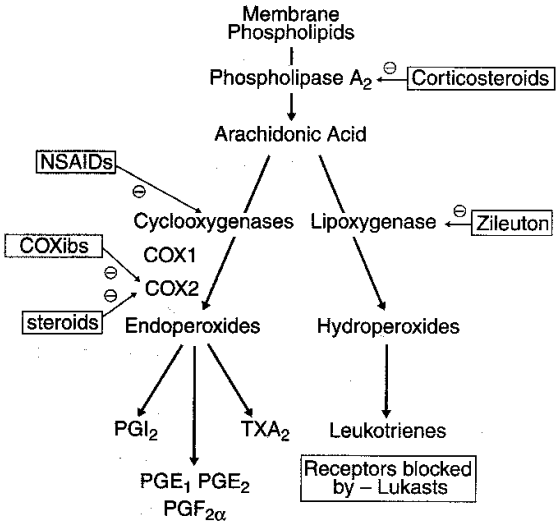


Figure VI-1-3. Drugs Acting on Eicosanoids

Prostaglandins (PGs)

General Features

Formed (via endoperoxides) from the actions of cyclooxygenases (COXs). COX 1 is expressed in most tissues, including platelets, and is thought to protect the gastric mucosa. COX 2 is expressed in the brain and kidney and at sites of inflammation. PGs have multiple physiologic roles, ranging from actions on smooth muscle to involvement in mechanisms of pain and pyroses.

PGE_1

- Protective action on gastric mucosa $\rightarrow$ misoprostol (analog) is used in treatment of NSAID-induced ulcers.
- Maintains patency of ductus arteriosus $\rightarrow$ alprostadil
- Vasodilation $\rightarrow$ alprostadil $\rightarrow$ used in male impotence
- It is contraindicated in pregnancy, unless it is used as an abortifacient.

PGE_2

Uterine smooth muscle contraction → either misoprostol (PGE_1 analog) or dinoprostone can be used for "cervical ripening" and as abortifacient (in conjunction with mifepristone, RU486).

$PGF_{2\alpha}$

Uterine and bronchiolar smooth muscle contraction → dinoprost and carboprost are used as abortifacients with mifepristone.

Decreases intraocular pressure → latanoprost → treatment of glaucoma.

PGE_2 and $PGF_{2\alpha}$

Both increase in primary dysmenorrhea. Therapeutic effects of NSAIDs may be due to inhibition of their synthesis.

PGI_2 (Prostacyclin)

Platelet stabilizer and vasodilator → epoprostenol → used in primary pulmonary HTN.

Thromboxanes (TXAs)

TXA_2

Platelet aggregator (inhibition of synthesis underlies protective role of ASA post-MI) and causes marked bronchoconstriction and vasoconstriction.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

General Features

Most NSAIDs are nonselective inhibitors of cyclooxygenases, acting on both COX 1 and COX 2 isoforms to decrease formation of PGs and thromboxanes. This action is a primary (but not sole) contributor to the pharmacologic actions of NSAIDs. These actions include analgesic, antipyretic, anti-inflammatory, and antiplatelet effects. Acetylsalicylic acid (ASA) is the prototype of the group, which includes more than 20 individual drugs.

Acetylsalicylic Acid (ASA; Aspirin)

Aspirin is the only NSAID that causes irreversible inhibition of COX. It forms a covalent bond via acetylation of a serine hydroxyl group near the active site. Its actions are dose dependent.

Actions of ASA

Antiplatelet Aggregation

Low dose (1 tablet every other day or 1 "baby" aspirin daily) exerts a permanent action on TxA_2 synthesis and is the basis for post-MI prophylaxis.

Analgesia

Moderate doses (2 tablets) inhibit formation of PGs, which sensitize peripheral pain receptors to algesic mediators such as bradykinin and histamine.

Bridge to Physiology and Biochemistry

Platelet Stability and Eicosanoids

Activation of TxA_2 receptors → stimulation of phospholipase C →↑ PIP_2 hydrolysis →↑ IP_3 → mobilization of bound Ca →↑ free Ca → platelet aggregation.

Activation of PGI_2 receptors → stimulation of adenylyl cyclase →↑ cAMP →↑ activity of internal Ca "pumps" →↓ free Ca → platelet stabilization.

Antipyresis
Moderate doses. Pyrogens increase IL-1, which in the hypothalamus →↑ PGE_2 formation →↑ temperature "set-point." ASA lowers it back to normal in hyperthermia (no effect normally and may ↓ temperature in hypothermia).

Antiinflammatory
Moderate to high doses. Inhibits COX 2, an enzyme form that is induced in cells that are involved in inflammatory responses. Also interferes with formation of cell surface selectins and integrins, which promote leukocyte adhesion, a process necessary for their tissue infiltration via endothelial cell junctions.

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 leads to ↑ 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^+).

Adverse Effects

GI 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's Syndrome
→ Encephalopathy.

↑ Bleeding Time (Antiplatelet)
↑ Prothrombin time (high dose).

Chronic Use
Associated with renal dysfunction (↓ PGs) and hypoglycemia. Many drug interactions (ethanol ↑ GI bleeding, ↑ effects of sulfonylurea hypoglycemics, 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. Increased urine volume and its alkalinization facilitate salicylate renal elimination. Note: ASA follows zero-order elimination kinetics at toxic doses.

ASA doses associated with severe toxicity = 150 mg/kg, equivalent to ingestion of 10 g (about 30 adult tablets) in a patient weighing 70 kg. In a small child (weight perhaps 10–12 kg), toxicity can be life threatening with the ingestion of 4–6 tablets!

Other NSAIDs

Types

Reversible inhibitors of COX 1 and COX 2, with analgesic, antipyretic, and anti-inflammatory actions, include ibuprofen, naproxen, indomethacin, ketorolac, and sulindac. When used as anti-inflammatory agents, they are usually no more effective than ASA, but they may be better tolerated. All have antiplatelet actions (reversible) at moderate (not low) doses and cause bleeding tendencies.

Comparisons with ASA

Analgesia
Ketorolac > ibuprofen/naproxen > ASA.

GI Irritation
< ASA, but still occurs (consider misoprostol).

Acid-Base
Minimal, 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 decrease activity of ACE inhibitors, loop diuretics, and beta blockers.

Specific toxicities:

- Indomethacin—thrombocytopenia, agranulocytosis, and > CNS effects
- Sulindac—pancreatitis
- Diclofenac—hepatotoxicity

Selective COX 2 Inhibitors

Celecoxib and rofecoxib at therapeutic doses selectively cause reversible inhibition of COX 2.

Compared with conventional NSAIDs, they are no more effective as anti-inflammatory agents. Many properties are quite similar, including potential for nephrotoxicity and hypersensitivity.

Their primary differences are:

- Less gastrointestinal toxicity
- Less antiplatelet action

However, they increase prothrombin time (PT) when used with warfarin and may possibly exert prothombotic effects via inhibition of endothelial cell function. Celecoxib is cross-allergenic with sulfonamides. Potential cardiotoxicity?

Acetaminophen

Mechanisms

No inhibition of COX in peripheral tissues and lacks significant anti-inflammatory effects. Equivalent analgesic and antipyretic activity to ASA, probably due to inhibition of cyclooxygenases in the CNS.

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's!), and supplementary iron tablets.

Comparisons with ASA

- No antiplatelet action
- Not implicated in Reye syndrome
- No effects on uric acid
- Not bronchospastic
- GI distress is minimal at low to moderate doses

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) that 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 h.

DRUGS FOR RHEUMATOID ARTHRITIS

General Features

NSAIDs are commonly used for initial management of RA, but the doses required generally result in marked adverse effects. COX 2 inhibitors have, to a large extent, replaced older drugs. NSAIDs decrease pain and swelling but have no beneficial effects on the course of the disease or on bone deterioration.

Disease-modifying antirheumatic drugs (DMARDs) are thought to slow disease progression and may be started with NSAIDs at the time of initial diagnosis, especially if symptoms are severe. Hydroxychloroquine is often recommended for mild arthritis and methotrexate (MTX) for moderate to severe RA. Other DMARDs (see Table VI-1-3) are used less frequently, sometimes in combination regimens for refractory cases.

Mechanism of Action and Adverse Effects of DMARDs

Table VI-1-3. Disease-Modifying Antirheumatic Drugs

Drug	Mechanism(s)	Adverse 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-1 receptor antagonist	Infection, injection-site reaction

DRUGS FOR GOUT

Acute Inflammatory Episodes

Colchicine, indomethacin, other NSAIDs (naproxen, sulindac), and intra-articular steroids.

Action of Colchicine

Binds to tubulin →↓ microtubular polymerization, ↓ LTB_4, and ↓ leukocyte and granulocyte migration.

Adverse Effects of Colchicine

Acute—include diarrhea and GI pain.

Longer use → hematuria, alopecia, myelosuppression, gastritis, and peripheral neuropathy.

Chronic Gout

Drug strategy is reduction of the uric acid pool.

Action of Allopurinol

Pro-drug (a suicide substrate) converted by xanthine oxidase, forming alloxanthine, which inhibits the enzyme →↓ purine metabolism →↓ uric acid. Also used in cancer chemotherapy and radiation therapy.

Adverse Effects of Allopurinol

Include GI distress, peripheral neuropathy, rash, vasculitis, and stone formation.

Inhibits 6-mercaptopurine (6-MP) metabolism.

Action of Probenecid and Sulfinpyrazone

Inhibit proximal tubular reabsorption of urate, but ineffective if GFR < 50 mL/min. Also inhibit secretion of many acidic drugs, e.g., cephalosporins, fluoroquinolones.

Adverse Effects of Probenecid and Sulfinpyrazone

Include GI distress, rash, nephrotic syndrome, crystallization if high excretion of uric acid. ASA may ↓ effects.

ANTIINFLAMMATORY STEROIDS

General Features

Synthetic derivatives of cortisol, the major endogenous glucocorticoid, are used extensively in the management of inflammatory disorders and for their immunosuppressive actions. Relative to cortisol, individual steroids may have greater oral bioavailability, longer half-life, less mineralocorticoid activity, improved surface activity, and different potency.

Duration

Cortisol < prednisone < triamcinolone < dexamethasone and betamethasone.

Mechanisms

Cellular Effects

- ↓ Leukocyte migration
- ↑ Lysosomal membrane stability →↓ phagocytosis
- ↓ Capillary permeability

Biochemical Actions

- Inhibit PLA_2 (via lipocortin expression) $\rightarrow\downarrow$ PGs and $\downarrow$ LTs
- $\downarrow$ Expression of COX 2
- $\downarrow$ Platelet activating factor
- $\downarrow$ Interleukins (e.g., IL-2)

Adverse Effects

- Suppression of ACTH: cortical atrophy, malaise, myalgia, arthralgia, and fever—may result in a shock state with abrupt withdrawal
- Iatrogenic cushingoid syndrome: $\rightarrow$ fat deposition, muscle weakness/atrophy, bruising, acne
- Hyperglycemia due to gluconeogenesis: leads to increased insulin demand and other adverse effects
- Osteoporosis: vertebral fractures—aseptic hip necrosis
- $\uparrow$ GI acid and pepsin release: $\rightarrow$ ulcers, GI bleeding
- Electrolyte imbalance: Na/water retention $\rightarrow$ edema and HTN, hypokalemic alkalosis, hypocalcemia
- $\downarrow$ Skeletal growth in children
- $\downarrow$ Wound healing, $\uparrow$ infections (e.g., thrush)
- $\uparrow$ Glaucoma, $\uparrow$ cataracts (via $\uparrow$ sorbitol)
- $\uparrow$ Mental dysfunction

Clinical Correlate

Minimize Steroidal Toxicity

- Alternate-day therapy; local application (e.g., aerosols)
- Supplement with proteins, K, and anabolic steroids
- Dose-tapering to avoid cortical suppression

DRUGS FOR ASTHMA

General Features

Inflammatory disease associated with bronchial hyperactivity (BHR), bronchospasm, $\uparrow$ mucus secretion, edema, and cellular infiltration. Early asthmatic responses (EAR) lasting from 30 to 60 min are associated with bronchospasm from the actions of released histamine and leukotrienes; late asthmatic responses (LAR) involve infiltration of eosinophils and lymphocytes into airways $\rightarrow$ bronchoconstriction and inflammation with mucus plugging.

Management of asthma includes bronchodilators to provide short-term relief and antiinflammatory agents that reduce bronchial hyperactivity and protect against cellular infiltration.

Beta Adrenoceptor 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-1-4).

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 CV toxicity with overuse.

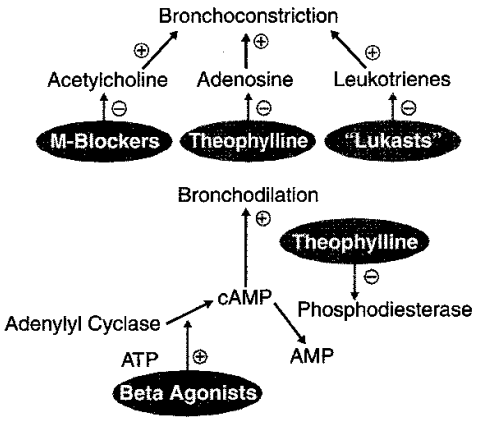


Figure VI-1-4. Drug Actions On Bronchiolar Smooth Muscle

Muscarinic Receptor Blockers

See Figure VI-1-4.

Ipratropium and other M blockers used via inhalation cause bronchodilation in acute asthma, especially in COPD patients, and they may be safer than beta agonists in patients with CV disease.

Drugs of choice in bronchospasm caused by beta blockers. There are minor atropine-like effects.

Theophylline

Bronchodilates via inhibition of phosphodiesterase (PDE) $\rightarrow\uparrow$ cAMP and also by antagonism of adenosine (a bronchoconstrictor) (see Figure VI-1-4).

Mainly adjunctive, regular use may decrease symptoms, but narrow therapeutic window predisposes to toxicity $\rightarrow$ nausea, diarrhea, CV ($\uparrow$ HR, arrhythmias) and CNS excitation.

Many drug interactions—toxicity is increased by erythromycin, cimetidine, and fluoroquinolones.

Aminophylline IV is sometimes used in bronchospasm or status asthmaticus.

Cromolyn and Nedocromil

Prevent degranulation of pulmonary mast cells and decrease release of histamine, PAF, LTC_4 from inflammatory cells. Prophylactic use $\rightarrow\downarrow$ symptoms and bronchial hyperactivity (BHR), especially responses to allergens. Minimal systemic toxicity but may cause throat irritation and cough, relieved by a $beta_2$ agonist.

Adrenal Steroids

Block mediator release and decrease BHR via ↓ PGs, LTs, and inflammatory interleukins (ILs). Surface-active drugs (beclomethasone, flunisolide) are used via inhalation for both acute attacks and for prophylaxis. They may cause oropharyngeal candidiasis and systemic effects with excessive use, including ↓ long bone growth in children. Low dosage may also prevent the desensitization of beta receptors that can occur with overuse of $beta_2$ agonist.

Prednisone (oral) and IV steroids are generally reserved for severe acute attacks.

Antileukotrienes

Zafirlukast (and other "-lukasts") are antagonists at LTD_4 receptors with slow onset of activity (see Figure VI-1-4) used prophylactically for many forms of asthma, including antigen, exercise, or drug induced (e.g., ASA). Adverse effects include diarrhea, headache, and increased infections.

Zileuton is a selective inhibitor of lipoxygenases (LOX), decreasing formation of all LTs. More rapid onset (1–3 h) and is adjunctive to steroids. Adverse effects include asthenia, headache, and ↑ LFTs.

In A Nutshell

Acute Asthma in the ER

Oxygen, beta agonists (aerosolic), steroids (IV)—in that order, ASAP!

SUMMARY: DRUGS FOR INFLAMMATORY DISORDERS

Antihistamines

- H_1 antagonists: diphenhydramine, promethazine, meclizine, hydroxyzine, loratadine
- H_2 antagonists: cimetidine, ranitidine

GI Drugs

- Proton pump inhibitor: omeprazole
- PGE_1 analog: misoprostol
- Polymer: sucralfate

Serotonin Modifiers

- $5HT_{1A}$ partial agonist: buspirone
- $5HT_{1D}$ agonist: sumatriptan
- $5HT_2$ antagonist: cyproheptadine
- $5HT_3$ antagonist: ondansetron
- $5HT_4$ agonist: tegaserod

Antiemetics

- DA antagonist: metoclopramide
- H_1 antagonist: meclizine, promethazine
- Muscarinic antagonist: scopolamine
- Cannabinoid: dronabinol
- $5HT_3$ antagonist: ondansetron
- NK_1 antagonist: aprepitant

NSAIDs

- Aspirin, indomethacin, ibuprofen, naproxen
- COX 2 inhibitors: celecoxib, rofecoxib
- Acetaminophen

Antiinflammatory Steroids

- Prednisone, triamcinolone, dexamethasone

Drugs for Gout

- Acute: colchicine, indomethacin
- Chronic: allopurinol, probenecid

Drugs for RA

(See table in text.)

- NSAIDs
- DMARDs: methotrexate, etanercept, infliximab, anakinra, and others

Drugs for Asthma

- α_2 agonists: albuterol, terbutaline
- M-blocker: ipratropium
- Methylxanthine: theophylline
- Mast cell stabilizer: cromolyn
- Steroids: flunisolide
- LT modifiers: zafirlukast, zileuton

Chapter Summary

Histamine and Antihistamines

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_1 and H_2 types and an H_3 variant.

The sequence of reactions leading to H_1 and H_2 activation is presented.

H_1 antagonists are competitive inhibitors with varying pharmacologic and kinetic properties. All require hepatic metabolism and cross the placental barrier.

The H_1 antagonists are used to treat allergic reactions, motion sickness, vertigo, nausea and vomiting in pregnancy, preoperative sedation, and in over-the-counter sleeping pills.

The adverse effects are excess M block and sedation, GI distress, and allergic reactions.

Table VI-1-1 summarizes the properties of some of the major type 1 antihistamines.

(*Continued*)

Chapter Summary (*continued*)

Drugs Used in GI Dysfunction

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-1-1. The clinical uses and adverse effects are discussed.

Omeprazole and the other "prazole" proton-pump inhibitors are more powerful inhibitors of gastric secretion than the antagonists. Their clinical uses and adverse reactions are considered.

Misoprostol is a cytoprotective prostaglandin E_1 analog.

Sucralfate forms a protective gel, covering GI ulcers. Its clinical use is discussed. Bismuth subsalicylate behaves similarly.

Antacids neutralize preformed protons. Their mechanisms of action and adverse reactions are considered (Table VI-1-2).

The modes of action of various laxatives are recorded.

Figure VI-1-2 illustrates the complex number of factors impinging upon the emetic (vomiting) center. The antiemetic drugs are listed.

Drugs Acting on Serotonergic Systems

Serotonin (5HT) is an autocoid synthesized and stored in GI cells, neurons, and platelets. Monoamine oxidase (MAO) type A degrades it, forming 5-hydroxyindoleacetic acid (5HIAA), a carcinoid marker.

There are seven receptor subtypes, six of which are G-protein coupled. The seventh type, $5HT_3$, is directly coupled to an ion channel.

The locations and normal functions of different types of 5HT 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 α- and D_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.

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 (TX As).

Figure VI-1-3 presents the pathways for the synthesis of PG_{i2}, PGE_1, PGE_2, $PGF_{2\alpha}$, TX A_2, and the leukotrienes from the membrane phospholipids. It also shows the sites of action of the corticosteroids, NSAIDS, COX 2 inhibitors, zileuton and zafirlukast, and other "-lukasts."

The physiologic functions of relevant eicosanoids interacting with specific receptor types and the clinical aspects of the drugs affecting these actions are considered.

(*Continued*)

Chapter Summary (*continued*)

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 adverse 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 and rofecoxib are selective inhibitors of cyclooxygenase 2 (COX 2), providing less GI and antiplatelet activity than 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 for Rheumatoid Arthritis

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-1-3 summarizes the mechanisms of action and the adverse effects of the DMARDS.

Drugs for Gout

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 and sulfinpyrazone decrease the uric acid pool by inhibiting the proximal resorption of urate. Their use and adverse effects are discussed.

Antiinflammatory Steroids

Synthetic derivatives of cortisol are often used to manage inflammatory conditions or to promote immunosuppression. The duration of action of several antiinflammatory steroids, their cellular effects and biochemical actions, as well as the many and severe adverse effects are provided.

Drugs for Asthma

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.

(*Continued*)

Chapter Summary (*continued*)

$Beta_2$ selective agonists are used for the relief of acute bronchoconstriction and as a prophylaxis in exercise-induced asthma. Longer-acting β-adrenoceptor agonists can be used prophylactically to decrease nighttime attacks. The mechanisms responsible for their effects are shown in Figure VI-1-4, which illustrates the action of antiasthmatic drugs.

The roles of muscarinic receptor blockers (theophylline, cromolyn, and nedocromil), adrenal steroids, and antileukotrienes in the treatment of asthma are discussed. Their modes of action are illustrated in Figure VI-1-4.

The various drugs used to treat inflammatory disorders are listed.

ANTIINFLAMMATORY DRUGS

Review 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 ER in convulsions. According to her mother, she had ingested most of a bottle of "sleeping pills," an over-the-counter preparation. The sleeping pills she ingested probably contain

   A. caffeine
   B. chlorpromazine
   C. diphenhydramine
   D. meperidine
   E. temazepam

3. Which one of the following statements about the management of patients with GI ulcers is accurate?

   A. Overall, H_2 receptor blockers are as effective as proton pump inhibitors.
   B. Antimicrobial regimens that eradicate *Helicobacter pylori* are >98% effective in GI 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 anti-inflammatory effects in GI ulcers.

4. Which one of the following statements regarding drug effects on serotonin receptor systems is accurate?

   A. $5HT_2$ receptor blockers counteract bronchoconstriction and diarrhea of carcinoid.
   B. Sumatriptan is an antiemetic because it blocks $5HT_3$ receptors.
   C. MAO type B inhibitors lead to increased levels of serotonin in the CNS.
   D. Ondansetron is used in migraine because it activates $5HT_{1D}$ receptors.
   E. Inhibitors of 5HT 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 that may slow progression of the disease that is to be used with ibuprofen. Unfortunately, side effects develop, including dizziness, tinnitus, blurred vision, and pruritus. Ocular examination reveals corneal deposits and slight retinal pigmentation. The drug more recently prescribed is likely to be

   A. auranofin
   B. etanercept
   C. hydroxychloroquine
   D. methotrexate
   E. thioridazine

6. Your medical student 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. Your best choice would be

   A. betamethasone
   B. cimetidine
   C. hydroxyzine
   D. loratadine
   E. metoclopramide

7. The widely used anticonvulsant phenytoin is often implicated in drug interactions. If phenytoin is used by a patient taking cimetidine for a GI ulcer, which one of the following is likely to occur?

   A. ↓ half-life of phenytoin
   B. ↑ half-life of cimetidine
   C. ↑ clearance of phenytoin
   D. Displacement of cimetidine from plasma proteins
   E. ↑ half-life of phenytoin

8. Which one of the following pairs of "drug-mechanism of action" is accurate?

   A. dexamethasone: ↓ expression of lipoxygenase
   B. leflunomide: inhibition of dihydro-orotic acid dehydrogenase
   C. misoprostol: activates $PGF_{2\alpha}$ receptors
   D. colchicine: ↑ 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 Pa_{O_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 $beta_2$ 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 surgical closure, the drug of choice is

    A. alprostadil
    B. indomethacin
    C. epoprostenol
    D. celecoxib
    E. zileuton

12. Following an overdose of an over-the-counter (OTC) drug, a young college student has marked GI distress and is lethargic and confused, with elevated body temperature. Lab analysis of blood reveals $\uparrow pCO_2$—$\downarrow HCO_3^-$—$\downarrow K^+$ 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. This means that

    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. Rofecoxib
    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. increase 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. $\downarrow PGE_2$ and $PGF_{2\alpha}$
    B. selectively inhibit COX 2
    C. $\downarrow LTB_4$
    D. inhibit PLA_2
    E. $\uparrow PGI_2$

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. The most appropriate drug for treatment of this patient is

    A. allopurinol
    B. acetylsalicylic acid
    C. indomethacin
    D. colchicine
    E. probenecid

18. Chronic use of which agent in migraine prophylaxis has been associated with chest pain and vascular insufficiency due to fibrotic thickening in heart valves and in the major vessels?

    A. Acetaminophen
    B. Ibuprofen
    C. Methysergide
    D. Sumatriptan
    E. Propranolol

19. The plasma levels of ketoconazole are lower than normal following its oral absorption in patients treated with ranitidine. The reason for this is

    A. induction of enzymes that metabolize ketoconazole
    B. ketoconazole requires an acid environment for its oral absorption
    C. ranitidine binds acidic drugs in the GI tract
    D. increased GI transit time because of the prokinetic effects of ranitidine
    E. competition for transport mechanisms in the GI tract

20. Cromolyn is useful in many patients with asthma because it

    A. inhibits cyclooxygenase 2
    B. blocks adenosine receptors in bronchiolar smooth muscle
    C. prevents antigen-induced degranulation of mast cells
    D. inhibits phosphodiesterase
    E. decreases mRNA for IL-2

21. 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

22. 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

    A. cimetidine
    B. sulfinpyrazone
    C. allopurinol
    D. indomethacin
    E. acetylsalicylic acid

23. Constipation is a possible side effect of drugs taken by the oral route, but it is highly unlikely to occur with the use of

    A. diphenhydramine
    B. docusate
    C. promethazine
    D. loperamide
    E. scopolamine

Questions 24 and 25.

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.

24. 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 GI tract
    E. increases hepatic blood flow

25. 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. The most likely explanation for this is

    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 (OTC) sleep aids invariably contain sedating antihistamines like diphenhydramine. Sometimes called sedative-autonomics, 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 is not used as a sleeping aid or available OTC. Caffeine is a CNS stimulant.

3. **Answer: D.** Sucralfate polymerizes in the GI tract, forming a protective gel-like coating of ulcer beds $\rightarrow\uparrow$ healing and $\downarrow$ ulcer recurrence. Overall, proton pump inhibitors such as omeprazole provide more rapid pain relief and faster healing than antihistamines in ulcers caused by acid secretion. Misoprostol activates PGE_1 receptors, not omeprazole. Not all GI 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. Anti-inflammatory steroids cause GI 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 H_1 receptor blocking effects. Sumatriptan is used in migraine (not for emesis) and exerts its effects on cerebral vasculature via activation of $5HT_{1D}$ receptors. Ondansetron is the antiemetic, a blocker of $5HT_3$ 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 be exacerbatory.

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 GI 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 anti-inflammatory effect, but does cause retinal pigmentation.

6. **Answer: D.** The usual choice for pollen-induced allergies would be an H_1 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 anti-inflammatory 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 H_2 antagonist used in GI ulcers.

7. **Answer: E.** Cimetidine is an inhibitor of the hepatic cytochrome P450 isoform that metabolizes phenytoin, consequently decreases its clearance, and thus increases 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 $\rightarrow\downarrow$ formation of UMP $\rightarrow\downarrow$ de novo synthesis of ribonucleotides $\rightarrow$ arrest of lymphocytes in the G1 phase. Glucocorticoids do not decrease expression of lipoxygenase, but by preventing arachidonate formation they decrease activity of the pathway. Misoprostol, used in NSAID-induced GI ulcers, activates receptors; colchicine decreases microtubular polymerization; ketorolac is a potent NSAID but a nonselective inhibitor of cyclooxygenases.

9. **Answer: C.** Inhaled $beta_2$ selective agonists are preferred in most cases of acute asthma. IV 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. Always avoid answers with the word *always*.

10. **Answer: E.** The activation of H_1 receptors in bronchiolar smooth muscle leads to contraction $\rightarrow$ bronchoconstriction, but in vascular smooth muscle relaxation (via release of NO) $\rightarrow$ hypotension. H_1 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 IV indomethacin, which decreases PG synthesis by inhibiting COX. Epoprostenol is a prostacyclin analog used in primary pulmonary HTN.

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 $\rightarrow$ 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 $\rightarrow\downarrow$ tubular reabsorption $\rightarrow\uparrow$ 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 IOP. 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_2 and $PGF_{2\alpha}$ 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 (PGI_2). NSAIDs do not inhibit phospholipase A_2, and they do not decrease leukotrienes.

17. **Answer: A.** In chronic gout, the strategy is to decrease uric acid formation from purines by inhibition of xanthine oxidase with allopurinol or to increase urate elimination with uricosurics like probenecid or sulfinpyrazone. The latter drugs cause formation of urate crystals in "high excretors" 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 antiinflammatory doses, its toxicity makes the drug a poor choice.

18. **Answer: C.** Fibroplasia of heart structures (and the ureter) is associated with the prophylactic use in migraine of methysergide, an ergot derivative. Chest pain can result from the cardiovascular effects brought about by the structural changes in heart valves and major vessels. However, the use of methysergide has also led to pulmonary fibrosis, with early symptoms that include chest pain and tightening. It is important to distinguish these symptoms from those of the "triptan" family of drugs used commonly in the management of migraine, which may also cause feelings of tightness in the chest or throat.

19. **Answer: B.** Several drugs, including ketoconazole and fluoroquinolones, require an acidic environment in the GI tract for effective absorption into the systemic circulation. Drugs used in treatment of GI ulcers commonly increase gastric pH, leading to the decreased absorption of such drugs and consequently a decrease in their effects.

20. **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 anti-inflammatory 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 decrease bronchial hyperactivity by several mechanisms, including inhibition of interleukin synthesis. COX 2 inhibitors have no established role in asthma management.

21. **Answer: C.** Dinoprostone is a PGE_2 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 β_2 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.

22. **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.

23. **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, like scopolamine and the antihistamines diphenhydramine and promethazine, tend to cause constipation by decreasing GI motility. Loperamide is an opioid derivative, with no analgesic activity, used in the treatment of diarrheal states.

24. **Answer: C.** Acetylcysteine is the antidote to acetaminophen in overdose and should be administered within 12 h 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 increases the availability of GSH, which would normally inactivate the reactive metabolite, or itself interacts with and inactivates the metabolite.

25. **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 P450 (probably the CYP2E1 isoform) results in formation of small amounts of the reactive metabolite, which (normally) is rapidly inactivated by GSH. The chronic ingestion of more than average amounts of ethanol induces the formation of the P450 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 and Endocrine Disorders

Blood Pharmacology

1

ANTICOAGULANTS

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.

Comparative Properties of Heparin and Warfarin

Table VII-1-1 summarizes the characteristic properties of heparin and warfarin.

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins)

Feature	Heparin(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 binds to antithrombin III, increasing its serine protease inhibiting activity and resulting in fast inactivation of factors IIa, IXa, Xa, XIa, and XIIa.	↓ Hepatic synthesis of vitamin K–dependent factors II, VII, IX, X—coumarins prevent γ-carboxylation; no effect on factors already present. *In vivo* effects only.
Monitoring	Partial thromboplastin time (PTT)	Prothrombin time (PT); INR

(*Continued*)

Table VII-1-1. Properties of Heparin and Warfarin (Coumarins) (*continued*)

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-MI, 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)

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-life, less thrombocytopenia, and possibly enhanced activity against factor Xa.

Danaparoid, a heparin of different structure, may be safer in hypersensitivity to heparin.

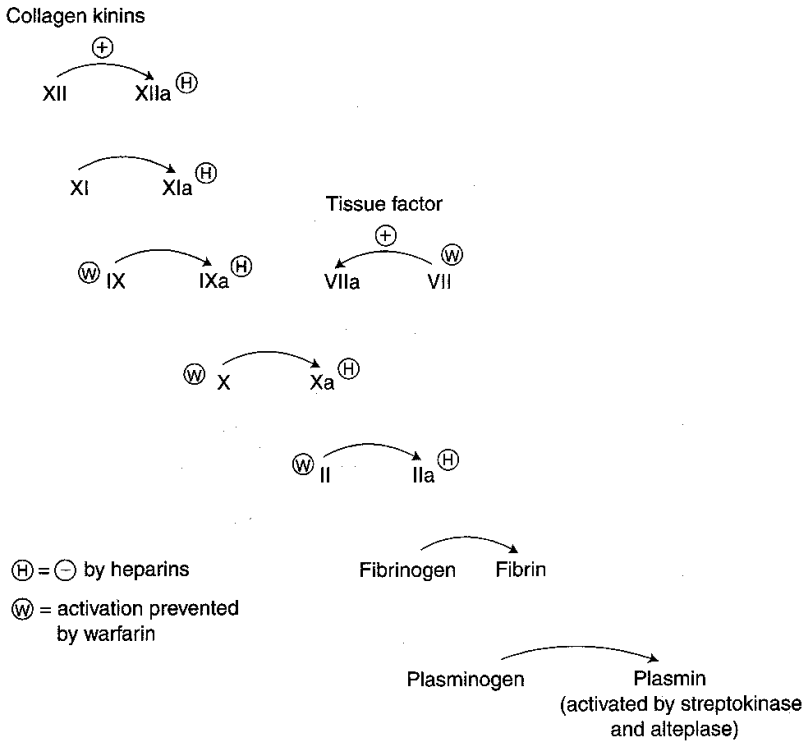


Figure VII-1-1. Actions of Blood Drugs

Warfarin

Drug Interactions

- Acidic molecule: oral absorption ↓ by drugs including bile acid sequestrants.
- Extensive (but weak) plasma protein binding: – displacement by other drugs may increase free fraction →↑ anticoagulant effects.
- Slow hepatic metabolism via P450: inducers or inhibitors of liver enzymes can modify anticoagulant effects.
- Actions increased by ASA, cimetidine, metronidazole, phenytoin, sulfonamides
- Actions decreased by barbiturates, carbamazepine, cholestyramine, rifampin, thiazides, vitamin K

Protein C Deficiency

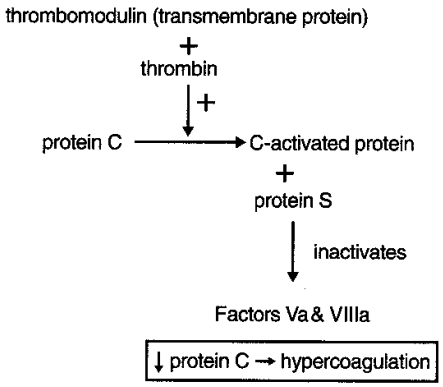


Figure VII-1-2. Activation and Role of Protein C

Table VII-1-2. Coagulation Factor Half-Lives

Factor	IIa	VIIa	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.

THROMBOLYTICS

General Features

Also called fibrinolytics, these agents lyse thrombi by catalyzing the formation of the endogenous fibrinolytic plasmin (a serine protease) from its precursor, plasminogen.

Include tissue plasminogen activator (tPA, recombinant) and streptokinase (bacterial). Used IV for short-term emergency management of coronary thromboses in MI, deep venous thromboses, 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 beta-hemolytic streptococci). This causes a problem if recent past use or infection—strep antibodies may ↓ activity

Alteplase (tPA)

Clot-specific, acting mainly on fibrin-bound plasminogen the natural activator, so no allergy problems.

Clinical Features

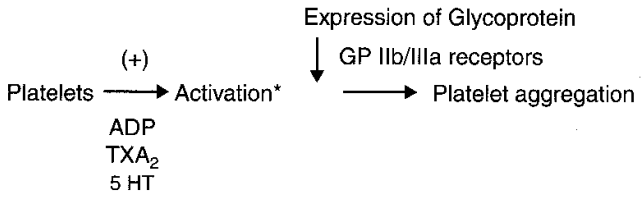
- Over-riding factor in effectiveness is early administration, e.g., >60% decrease in mortality post-MI if used within 3 h.
- ASA further decreases mortality, and adenosine decreases infarct size.
- Complications include bleeding, possible intracerebral hemorrhage.
- Streptokinase may cause hypersensitivity reactions and hypotension.
- Antifibrinolysins (aminocaproic and tranexamic acids) are possible antidotes in excessive bleeding.

ANTIPLATELET DRUGS

Clot Formation

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 $\rightarrow\uparrow$ expression of glycoprotein IIb/IIIa receptors
- Aggregation of platelets by a cross-linking reaction due to fibrinogen binding to glycoprotein IIb/IIIa receptors



* Activation leads to the expression of glycoprotein (GP) IIb/IIIa, the receptor for fibrinogen. This initiates formation of the fibrin plug.

Figure VII-1-3. Platelet Activation

Antiplatelet Drugs

Aspirin

- Irreversibly inhibits COX in platelets →↓ activation
- Low doses prevent MI and recurrence; prophylaxis in atrial arrhythmias and TIAs
- Adverse effects (see anti-inflammatory, Section VI)

In A Nutshell

Platelet Aggregation

Increased by: ADP, 5HT, TxA_2, thrombin, α_2 agonists

Decreased by: PGI_2, cAMP, ASA, dipyridamole, ticlopidine, clopidogrel

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 post-angioplasty

Chapter Summary

Anticoagulants

Table VII-1-1 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-1-2. Transient protein C deficiency can be induced by treatment with warfarin, which promotes hypercoagulation through the action of the intrinsic pathway (Table VII-1-2).

Thrombolytics

Thrombolytics (aka fibrinolytics) are of clinical value in the early treatment of fibrin-clot–induced ischemia (e.g., >60% decrease in post-MI mortality if used within 3 h). The general and clinical features of the primary thrombolytics, streptokinase, and alteplase are discussed.

Antiplatelet Drugs

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. Drugs discussed are aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide, and tirofiban.

Endocrine Pharmacology

2

HYPOTHALAMIC AND PITUITARY HORMONES

Drugs Related to Hypothalamic and Pituitary Hormones

Table VII-2-1. 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 and Vasopressin	Oxytoxin (O) and Desmopressin (D) (V2 selective)	O–labor induction; D–neurogenic (pituitary) diabetes insipidus, hemophilia A (↑ factor VIII from liver), von Willebrand disease (↑ vW factor from endothelium)

**Definitions:* GH = growth hormone, ACTH = adrenocorticotropin hormone, GnRH = gonadotropin-releasing hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, PIH = prolactin-inhibiting hormone, DA = dopamine.

THYROID

Antithyroid Agents

Table VII-2-2. 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
Iodination of tyrosyl residues on thyroglobulin	Inhibited by thioamides
Coupling reactions to form DIT, T_3, and T_4*	Inhibited by thioamides and high levels of iodide
Proteolytic release of T_4 and T_3 from thyroglobulin	Inhibited by iodide† and high-dose ipodate
Conversion of T_4 to T_3 via 5′ deiodinase in peripheral tissues	Inhibited by ipodate,† propranolol,† and at high-dose propylthiouracil†

*Di-, tri-, and tetra-iodotyrosine, respectively.
†Thyroid storm management may include use of any or all of these agents.

Thioamides: Propylthiouracil and Methimazole

- Use in uncomplicated hyperthyroid conditions; slow in onset
- High-dose propylthiouracil inhibits 5′ deiodinase
- Common maculopapular rash
- Less common ↓ prothrombin, hypersensitivity, and immune-based arthralgia, jaundice, lupus, and vasculitis
- Both drugs cross the placental barrier, but PTU is safer in pregnancy because it is extensively protein bound

Iodide

- KI + iodine (Lugol's solution) possible use in thyrotoxicosis: used preoperatively, →↓ gland size, fragility, and vascularity
- No long-term use because thyroid gland "escapes" from effects after 10–14 days

ADRENAL STEROIDS

Nonendocrine Uses

For use in inflammatory disorders (and adverse effects), see Section VI.

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, Diuretics).

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 increase oral bioavailability, to increase half-life, and to increase 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 $\rightarrow\downarrow$ bone resorption ($\downarrow$ PTH)
- Contraception—feedback $\downarrow$ of gonadotropins
- Dysmenorrhea
- Uterine bleeding
- Acne
- Prostate CA (palliative)

Adverse Effects

General

- Nausea
- Breast tenderness
- Endometrial hyperplasia
- ↑ Gall bladder disease, cholestasis
- Migraine

↑ Blood Coagulation

Via ↓ antithrombin III and ↑ factors II, VII, IX, and X (only at high dose).

Cancer Risk

- ↑ Endometrial CA (unless add progestins)
- ↑ Breast CA—questionable, but caution if other risk factors are present
- DES given during breast feeding →↑ vaginal adenocarcinoma CA in offspring

Other Drugs

Anastrozole

- Mode of action: aromatase inhibitor →↓ estrogen synthesis
- Use: breast CA

Danazol

- Mode of action: inhibits ovarian steroid synthesis
- Use: endometriosis and breast fibrocystic disease

Clomiphene (Fertility Pill)

- Mode of action: decreases 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 CA

Raloxifene

- E-receptor agonist (bone), antagonist breast and uterus
- When used in menopause, there is no ↑ CA risk

PROGESTIN

Pharmacology

Progesterone is the major natural progestin. Rationale for synthetics is ↑ oral bioavailability and ↑ feedback inhibition of gonadotropins, especially LH.

Drugs

- Medroxyprogesterone
- Norethindrone, norgestrel (19-nortestosterone derivatives) with some androgenic activity

Clinical Uses

Contraception (Oral with Estrogens)

Depot contraception (medroxyprogesterone IM every 3 months), and implant (norgestrel 5 years).

Hormone Replacement Therapy (HRT)

With estrogens to ↓ endometrial CA.

Adverse Effects

- ↓ HDL and ↑ LDL
- Glucose intolerance
- Breakthrough bleeding
- Androgenic (hirsutism and acne)
- Antiestrogenic (block lipid changes)

Antagonist

Mifepristone—abortifacient (use with PG).

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 mid-cycle LH surge

Pharmacology Adverse 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 CA
- ↓ Dysmenorrhea
- ↓ Endometriosis
- ↓ Pelvic inflammatory disease (PID)
- ↓ Osteoporosis

ANDROGENS

Pharmacology

Include methyltestosterone and 17-alkyl derivatives with increased anabolic actions, e.g., oxandrolone, nandrolone.

Use

- Used in male hypogonadism and for anabolic actions →↑ muscle mass, ↑ RBCs, ↓ nitrogen excretion
- Illicit use in athletics

Adverse Effects

- Excessive masculinization
- Premature closure of epiphysis
- Cholestatic jaundice
- Aggression
- Dependence
- "Roid rage"

Antagonists

Flutamide

Androgen receptor blocker—used for prostate CA.

Leuprolide

GnRH analog—repository form used for prostate CA.

Finasteride

5-alpha reductase inhibitor—used for benign prostatic hypertrophy (BPH), male pattern baldness.

Ketoconazole

Synthesis inhibitor—used in androgen receptor–positive prostate cancer.

INSULINS AND ORAL HYPOGLYCEMICS

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 VII-2-3. Kinetics (h) of Insulin Forms with Subcutaneous (SC) 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 can be used IV—peak action in 2–4 min.

Sulfonylureas

Mechanisms

Normally K^+ efflux in pancreatic β-cells maintains hyperpolarization of membranes, and insulin is only released when depolarization occurs. Glucose acts as an insulinogen by increasing intracellular ATP → membrane depolarization →↑ Ca^{2+} influx → insulin release. The acute action of sulfonylureas is to block K^+ channels → depolarization → insulin release.

In A Nutshell

Insulin Release

Increased by: glucose, sulfonylureas, M-activators, and β_2 agonists

Decreased by: α_2 agonists

Clinical Correlate

Diabetic Ketoacidosis

- Symptoms: polyuria, polydipsia, nausea, fatigue, dehydration, Kussmaul's breathing, "fruity" breath
- Treatment: regular insulin IV, fluid and electrolyte replacement

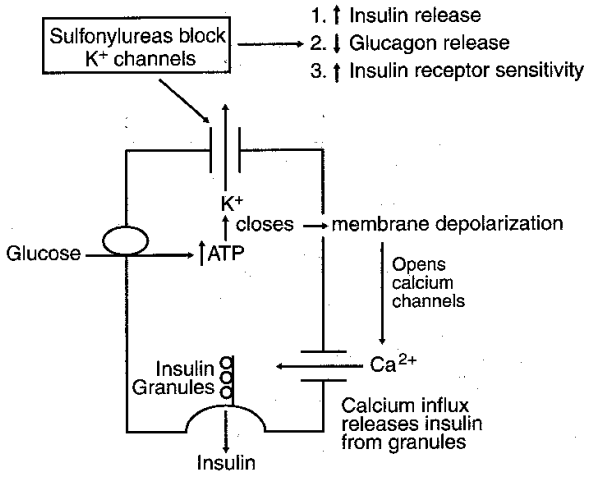


Figure VII-2-1. Mode of Action of Sulfonylureas

Effect of Increased Insulin

- →↓ Glucagon release from pancreatic alpha 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 (OK in renal dysfunction)
- Chlorpropamide (long-acting, SIADH/disulfiram reactions)

Second Generation

- Glipizide (↓ dose in hepatic dysfunction)
- Glyburide (active metabolite, ↓ dose in renal dysfunction)

Adverse Effects

- Hypoglycemia
- Weight gain
- Hypersensitivity (possible cross-allergy with sulfonamides)
- Drug interactions mainly with first-generation drugs

→↑ Hypoglycemia with cimetidine, insulin, salicylates, sulfonamides

Clinical Correlate

Hypoglycemic Reactions

- Symptoms: lip/tongue tingling, lethargy, confusion, sweats, tremors, tachycardia, coma, seizures
- Treatment: oral glucose, IV dextrose if unconscious, or glucagon (IM or inhalation)

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 VII-2-2).

Use

Used in monotherapy or combinations (synergistic with sulfonylureas).

Adverse Effects

Possible lactic acidosis.

Acarbose

No hypoglycemia.

Mechanisms

Inhibits α-glucosidase in brush borders of small intestine →↓ formation of absorbable carbohydrate →↓ postprandial glucose →↓ demand for insulin (Figure VII-2-2).

Adverse Effects

Causes GI discomfort, flatulence, and diarrhea—recent concern over potential hepatotoxicity.

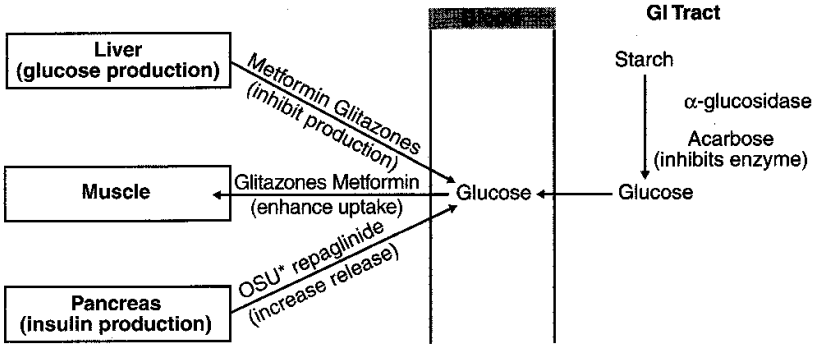


Figure VII-2-2. Modes of Action of Hypoglycemics

Thiazolidinediones (Pioglitazone and Rosiglitazone)

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 VII-2-2).

Clinical Correlate

Glucagon and the Heart

Positive inotropic and chronotropic, not via activation of β_1 receptors, but through glucagon receptors that are G-protein linked to adenylyl cyclase → basis for its use in beta-blocker overdose.

Adverse Effects

Less hypoglycemia than sulfonylureas, but weight gain and edema reported; hepatotoxicity of the prototype drug (troglitazone) led to withdrawal.

Repaglinide

- Mechanisms: stimulates insulin release from pancreatic beta cell
- Use: adjunctive use in type 2 diabetes—use just before meals due to short half-life

DRUGS IN BONE AND MINERAL DISORDERS

Bisphosphonates

Mechanisms

Stabilize hydroxyapatite bone structure and also induce osteoblasts to secrete inhibitors of osteoclasts →↓ bone resorption →↓ 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 ↑ bone mineral density (BMD).
- Alendronate is the DOC for steroid-induced osteoporosis.

Adverse Effects

- Etidronate and pamidronate → bone mineralization defects
- GI distress including esophageal ulcers (alendronate)

Table VII-2-4. Blood and Endocrine Drug List

Anticoagulants	**Thrombolytics**	**Antiplatelets**	
Heparin	Alteplase (tPA)	Aspirin	Clopidogrel
Warfarin	Streptokinase	Ticlopidine	Abciximab
Hypothalamic/Pituitary	**Antithyroid Drugs**	**Adrenosteroids**	
Somatropin	Propylthiouracil	Cortisol	Prednisone
Octreotide	Methimazole	Triamcinolone	Dexamethasone
Leuprolide	KI and I (Lugol's)	Fludrocortisone	
Oxytocin, Vasopressin			
Estrogens	**Progestins**	**Androgens**	
Ethinyl estradiol	Medroxyprogesterone	Methyltestosterone	
Mestranol	Norgestrel	Oxandrolone	
Diethylstilbestrol	Norethindrone	Flutamide (antagonist)	
Tamoxifen (antagonist)	Mifepristone (antagonist)		
Oral Hypoglycemics		**Bone and Mineral Drugs**	
Sulfonylureas – Tolbutamide, Glipizide, Glyburide		Alendronate	
Biguanide – Metformin		Calcitonin	
Acarbose			
"Glitazones" – Pioglitazone			

Chapter Summary

Hypothalamic and Pituitary Hormones

The clinical uses of drugs used to treat functions associated with hypothalamic or pituitary hormones are summarized in Table VII-2-1.

Thyroid

The steps in thyroid hormone synthesis and the antithyroid agents effects upon them are summarized in Table VII-2-2. The clinical uses and their potential complications are presented in greater detail for the thioamides (propylthiouracil and methimazole) and iodine.

Adrenal Steroids

The nonendocrine uses in inflammatory disorders have been 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.

(Continued)

Chapter Summary (*continued*)

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

Clinically useful androgen analogs include methyltestosterone and 17-alkyl derivatives. Their clinical and illicit uses and adverse effects are presented.

Clinically useful drug antagonists are flutamide (an androgen receptor blocker used to treat prostate cancer), leuprolide (a GnRH analog used to treat prostate cancer), finasteride (a 5-α-reductase inhibitor used to treat benign prostatic hyperplasia and male pattern baldness), and ketoconazole (an inhibitor of androgen synthesis used to treat androgen-positive cancers).

Insulin and Oral Hypoglycemics

Type 1 (IDDM) and type 2 (NIDDM) diabetes mellitus are defined.

The times of activity onset, peak activity, and duration of activity for lispro, regular, lente, and ultralente insulins are summarized in Table VII-2-3.

The oral antidiabetic drugs are the sulfonylureas, metformin, acarbose, thiazolidinediones, and repaglinide.

By blocking K^+ channels in the pancreatic β-cells, the sulfonylureas stimulate insulin release. The extra insulin in turn inhibits glucagon release from the α-cells and increases peripheral tissue sensitivity to insulin (Figure VII-2-1). 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 adverse effect is lactic acidosis.

Acarbose inhibits intestinal α-glucosidase, thereby slowing glucose absorption and decreasing insulin demand. The side effect is GI 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.

(*Continued*)

Chapter Summary (*continued*)

Repaglinide, like the sulfonylureas, stimulates β-cell secretion of insulin.

Figure VII-2-2 summarizes the modes of action of these drugs.

Drugs in Bone and Mineral Disorders

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 adverse effects are GI distress and esophageal ulcers.

Table VI-2-4 lists the blood and endocrine drugs.

SECTION VIII

Anticancer Drugs, Immunopharmacology, and Toxicology

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 on cells that are actively proliferating are cell-cycle specific (CCS)—schedule-dependent. In most cases, CCS drugs are also phase specific, as shown in Figure VIII-1-1.

Drugs acting on nonproliferating cells are cell-cycle nonspecific (CCNS)—dose-dependent.

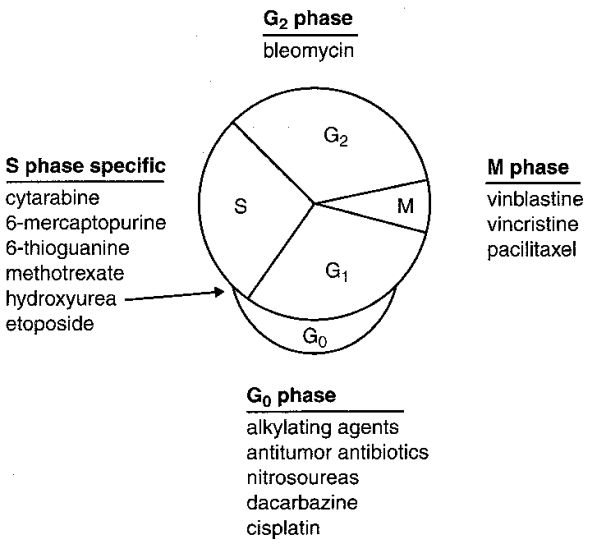


Figure VIII-1-1. Cell-Cycle Specificity of Anticancer Drugs

DRUGS

Table VIII-1-1. Characteristics of "Important" Anticancer Drugs

Drug	Mechanism	Uses	Adverse Effects
Methotrexate (CCS)	Antimetabolite—inhibits DHF reductase (S phase)	Leukemias, lymphomas, breast CA; RA, psoriasis	BMS, mucositis, crystalluria; **leucovorin** (folinic acid) rescue
Cyclophosphamide	Alkylating agent—attacks guanine N7—dysfunctional DNA	Non-Hodgkin's, ovarian, breast CA, 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 CA	Nausea, vomiting (use ondansetron) Nephrotoxicity (use amifostine) Neurotoxicity (deafness)
Doxorubicin	Intercalator, forms free radicals, inhibits topoisomerase	Hodgkin's (ABVD), breast, endometrial, lung, ovarian CA	BMS—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"
6-Mercaptopurine (CCS)	Purine antimetabolite (S phase) bioactivated by HGPR transferase	Acute lymphocytic leukemia; immunosuppression (azathioprine forms 6-MP)	BMS, hepatotoxicity (jaundice, necrosis), GI distress
Vincristine and Vinblastine (CCS)	↓ Microtubular polymerization—spindle poisons (M phase)	Vinblastine—Hodgkin's (ABVD), testicular CA, Kaposi's vincristine—Hodgkin's (MOPP), leukemias, Wilms'	BMS, GI, alopecia Neurotoxicity
Bleomycin (CCS)	Complexes with Fe and O_2 → DNA strand scission (G_2 phase)	Hodgkin's, testicular, head, neck, skin CA	Pneumonitis, pulmonary fibrosis, mucocutaneous reactions (blisters), alopecia, hypersensitivity
Procarbazine	Alkylating agent	Hodgkin's (MOPP)	BMS, pulmonary toxicity, hemolysis, neurotoxicity, leukemogenic
5-Fluorouracil (CCS)	Pyrimidine antimetabolite bioactivated to inhibit thymidylate synthetase	Breast, ovarian, head, and neck CA—topical for basal cell CA and keratoses	BMS, GI irritation, alopecia

Clinical Correlate

Thymineless Death of Cells

Flucytosine (FC) and 5-fluorouracil (5-FU) are bioactivated to 5-fluorodeoxyuridine monophosphate (5-FdUMP), which inhibits thymidylate synthetase → "thymineless death" of fungal cells (FC) or neoplastic cells (5-FU).

TOXICITY OF ANTICANCER DRUGS

Rapidly proliferating cells such as the bone marrow, GI tract mucosa, hair follicles, and gonads are 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 <500/dL) and thrombocytopenia (platelets <20,000/dL); colony stimulating factors, erythropoietin, and thrombopoietin can be supportive →↓ infections and need for antibiotics.

Table VIII-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, cytarabine, dactinomycin, 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 VIII-1-3. Modes of Resistance to Anticancer Drugs

Mechanism	Drugs or Drug Groups
Change in sensitivity (or ↑ level) or ↓ binding affinity of target enzymes or receptors	Etoposide, methotrexate, vinca alkaloids, estrogen and androgen receptors
Decreased drug accumulation via ↑ expression of glycoprotein transporters, or ↓ 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 pro-drugs	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 VIII-1-1 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 VII-1-1 lists mechanisms of action, selected clinical uses, and adverse effects of major anticancer drugs. Table VIII-1-2 shows the dose-limiting and distinctive toxicities of anticancer drugs.

Table VIII-1-3 summarizes the modes of resistance developed by cancers toward specific anticancer drugs.

Immunopharmacology

2

CYCLOSPORINE

Mechanism of Action

Binds to cyclophilin →↓ calcineurin (cytoplasmic phosphatase) →↓ activation of T-cell transcription factors →↓ IL-2, IL-3, and interferon-gamma.

Tacrolimus, another antibiotic with immunosuppressant actions, does not bind to cyclophilin, but acts similarly to cyclosporine to inhibit calcineurin.

Use

DOC organ or tissue transplantation (+/– mycophenolate +/– steroids +/– cytotoxic drugs). Tacrolimus has been 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.

Adverse Effects

Peripheral neuropathy, nephrotoxicity, hyperglycemia, HTN, hyperlipidemia, hirsutism, gingival overgrowth, cholelithiasis.

AZATHIOPRINE

Immunosuppressant converted to 6-mercaptopurine—same properties as 6-MP.

RH_0(D) IMMUNOGLOBULIN

Human IgG antibodies to red cell Rh_0(d) antigens.

Use

- Administer to Rh_0(d)-negative mother within 72 h of Rh-positive delivery to prevent hemolytic disease of newborn in subsequent pregnancy.
- Should also use in miscarriage for same reason.

MONOCLONAL ANTIBODIES (MABs)

Table VIII-2-1. Clinical Uses of Monoclonal Antibodies

Mab	Clinical Uses
Abciximab	Antiplatelet—antagonist of IIb/IIIa receptors
Daclixumab	Kidney transplants—blocks IL-2 receptors
Infliximab	RA and Crohn's—binds TNF
Muromonab	Allograft rejection block in renal transplants
Palivizumab	Respiratory syncytial virus—blocks RSV protein
Rituximab	Non-Hodgkin lymphoma—binds to surface protein
Trastuzumab	Breast CA—antagonist to HER2/neu receptor

CYTOKINES (RECOMBINANT FORMS)

Table VIII-2-2. Clinical Uses of Cytokines

Cytokine	Clinical Uses
Aldesleukin (IL-2)	↑ Lymphocyte differentiation and ↑ NKs—use in renal cell CA and metastatic melanoma
Interleukin-11	↑ Platelet formation—used in thrombocytopenia
Filgrastim (G-CSF)	↑ Granulocytes—used for marrow recovery
Sargramostim (GM-CSF)	↑ Granulocytes and macrophages—used for marrow recovery
Erythropoietin	Anemias, especially associated with renal failure
Thrombopoietin	Thrombocytopenia
Interferon-alpha	Hepatitis B and C, leukemias, melanoma
Interferon-beta	Multiple sclerosis
Interferon-gamma	Chronic granulomatous disease →↑ 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.

Rho(d) immunoglobin is given to Rho(d) negative mothers shortly after parturition to prevent hemolytic disease in future births.

Table VIII-2-1 summarizes the clinical uses of monoclonal antibodies.

Table VIII-2-2 summarizes the clinical uses of recombinant cytokines.

Toxicology 3

Table VIII-3-1. 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 → seizures, coma, respiration failure	Respiratory support; atropine + pralidoxime (for irreversible AChE inhibitors)
Atropine and muscarinic blockers	↑ HR, ↑ BP, hyperthermia (hot, dry skin), delirium, hallucinations	Control CV symptoms and hyperthermia + physostigmine (crosses BBB)
Carbon monoxide (>10% carboxyHb)	N and V, dyspnea with hyperventilation, mydriasis, vertigo; CV signs prominent, ↓ BP, syncope, ↑ HR, arrhythmias	Hyperbaric O_2 and decontamination (humidified 100% O_2 OK in mild OD)
CNS stimulants	Anxiety/agitation, hyperthermia (warm, sweaty skin), mydriasis, ↑ HR, ↑ BP, psychosis, seizures	Control CV symptoms, hyperthermia, and seizures—+/– BDZs or antipsychotics
Opioid analgesics	Lethargy, sedation, ↓ HR, ↓ 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, respiration failure	Ventilatory support—flumazenil if BZs implicated
SSRIs	Agitation, confusion, hallucination, muscle rigidity, hyperthermia, ↑ HR, ↑ 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) → arrhythmias	Control seizures and hyperthermia, correct acidosis + possible antiarrhythmics

*ASA—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 VIII-3-2. 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: GI distress, garlic breath, "rice water" stools, torsades, seizures Chronic: pallor, skin pigmentation, alopecia, stocking glove neuropathy, myelosuppression	Activated charcoal, **dimercaprol** **Penicillamine** or succimer
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: N and V, 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 or succimer) 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—GI distress and bleeding, shock, renal failure Chronic: organic Hg—CNS effects, ataxia, paresthesias, auditory and visual loss	**Succimer** PO or **dimercaprol** (IM). Activated charcoal for oral ingestion, then support with succimer PO or dimercaprol (NOT IV) → causes redistribution of Hg to the CNS → ↑ neurotoxicity

ANTIDOTES

Table VIII-3-3. Summary of Antidotes

Antidote	Type of Poisoning
Acetylcysteine	acetaminophen
Atropine + pralidoxime (for irreversible AChE inhibitors	AChE inhibitors—physostigmine, neostigmine, + pyridostigmine, organophosphates including insecticides such as malathion and parathion
Deferoxamine	Iron and iron salts
Digoxin immune Fab	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	Methanol or ethylene glycol; Fomepizole (ADH inhibitor) now approved for ethylene glycol and methanol poisoning
Flumazenil	Benzodiazepines, zolpidem, zaleplon
Naloxone	Opioid analgesics
Oxygen	Carbon monoxide
Penicillamine	Copper (e.g., Wilson disease), iron, lead, mercury
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 VIII-3-4. Characteristics of Selected Herbals

Name	Medicinal Use(s)	Possible Mechanism(s)	Adverse Effects
Echinacea	↓ Cold symptoms	↑ ILs and TNF	GI distress, dizziness, headache
Ephedra (ma-huang)	Congestion, asthma, hypotension, cold symptoms, weight loss	Contains ephedrine and pseudoephedrine (indirect-acting sympathomimetics)	Anorexia, insomnia, tachycardia, urinary retention, cardiac arrhythmias, hypertension, and psychosis (in high doses)
Feverfew	↓ Migraine frequency and severity	↓ LTs, PGs, and TNF	GI distress, mouth ulcers, antiplatelet actions; use caution when used with anticoagulants
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, ↑ NO	Anxiety, GI distress, insomnia, antiplatelet actions; use caution when used with anticoagulants
Ginseng	Possible ↑ in mental and physical performance (evidence is weak)	Unknown	Insomnia, nervousness, hypertension, mastalgia, vaginal bleeding
Kava	Chronic anxiety states	Facilitates CNS actions of GABA	Ataxia, dystonias, paresthesias, potentiation of CNS depressants, skin reactions and facial swelling; hepatotoxicity
Milk thistle	↑ Liver function in viral hepatitis; antidote to amanita mushroom poisoning	Antioxidant, free radical scavenger, ↑ SOD, ↓ LTs	Loose stools
Saw palmetto	Symptomatic treatment of BPH	5α-reductase inhibitor and androgen receptor antagonist	GI pain, decreased libido, headache, hypertension
St. John'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 ↓ effects of multiple drugs

Table VIII-3-5. Purified Nutritional Supplements

Name	Pharmacology	Adverse 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 VIII-3-1 lists the common toxic syndromes with their signs and symptoms and potential modes of intervention and/or antidotes.

Table VIII-3-2 lists the common heavy metal poisons with their most common sources, signs, and symptoms and potential modes of intervention and/or antidotes.

Table VIII-3-3 lists 16 antidotes with the type of poisoning against which they act.

BLOOD, ENDOCRINE, AND ANTICANCER DRUGS AND TOXICOLOGY

Review Questions

1. Following a myocardial infarct, a patient is stabilized on warfarin, with the dose adjusted to give a prothrombin time of 22 seconds. Which one 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. A 60-year-old college professor is diagnosed as suffering from 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 GHRH analog.
   E. Compared with placebo, alpha$_1$ blockers improve symptoms of BPH and urinary flow rate.

3. 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.

4. Which one of the following compounds increases the synthesis of tumor necrosis factor, leading to activation of phagocytosis in patients with chronic granulomatous disease?

   A. Aldesleukin
   B. Cyclosporine
   C. Interferon-gamma
   D. Infliximab
   E. Prednisone

5. Which one of the following compounds is most likely to cause platelet aggregation?

   A. Clopidogrel
   B. Cyclic AMP
   C. Prostacyclin
   D. Serotonin
   E. Ticlopidine

6. Symptoms of iron poisoning in a 3-year-old child may include severe GI distress with hematemesis, a shocklike 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.

7. Which one of the following statements about heparin is accurate?

   A. Increases thrombin levels after 3–5 days of treatment
   B. Increases binding of A-III, a serine protease inhibitor
   C. Peak effects occur within 5 min of injection
   D. Thrombocytopenia is due to increased formation of PGI_2
   E. None of the above

8. Which one of the following will reverse symptoms of megaloblastic anemia in pernicious anemia but has minimal impact on the neurologic dysfunction?

   A. Folic acid
   B. Iron
   C. Cyanocobalamin
   D. Tranexamic acid
   E. Vitamin K

9. Regarding warfarin, it

   A. is a pro-drug converted to its active metabolite spontaneously in the blood
   B. has low lipophilicity and does not cross the placental barrier
   C. causes a depletion in protein C before it decreases prothrombin
   D. inhibits release of vitamin K–dependent clotting factors from hepatocytes
   E. is inactivated by protamine

10. 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, the most likely cause is

    A. cyclophosphamide
    B. 5-FU
    C. methotrexate
    D. prednisone
    E. tamoxifen

11. The parenteral administration of streptokinase

    A. increases the formation of plasminogen
    B. is less effective following a myocardial infarct than t-pA
    C. causes a high incidence of thrombocytopenia
    D. may cause bleeding reversible by aminocaproic acid
    E. results in clot-specific thrombolysis

12. The drug of choice for management of neurogenic diabetes insipidus is

    A. amiloride
    B. demeclocycline
    C. desmopressin
    D. hydrochlorothiazide
    E. lithium

13. The release of insulin from the pancreatic B cell is most likely to be inhibited by

    A. clonidine
    B. glucose
    C. albuterol
    D. pilocarpine
    E. glipizide

14. A female patient with a mechanical heart valve who is taking warfarin informs you that she hopes to get pregnant in the near future. What advice do you give her regarding her antithrombotic medication during the anticipated pregnancy?

    A. Continue with warfarin until the third trimester.
    B. She should replace warfarin with aspirin at analgesic doses.
    C. Discontinue all medications that affect the blood.
    D. Replace warfarin with heparin.
    E. Discontinue warfarin and use supplementary vitamin K throughout the pregnancy.

15. Which of the following is a pro-drug that causes "thymineless" death of cells?

    A. Cytarabine
    B. Azathioprine
    C. 5-Fluorouracil
    D. Methotrexate
    E. 6-Mercaptopurine

16. This drug 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

17. Which one of the following symptoms is most likely to be associated with lead poisoning?

    A. Loose teeth
    B. Breath smelling like garlic
    C. Gingivitis
    D. Rice water stools
    E. Wrist drop

18. In a type 2 diabetes patient, which one of the following is most likely to cause hypoglycemic reactions?

    A. Acarbose
    B. Glucagon
    C. Glyburide
    D. Metformin
    E. Rosiglitazone

19. For which one of the following agents is the suggested clinical use and/or mechanism of action accurate?

    A. Abciximab—active in treatment of hepatitis B and C
    B. Alfa-interferon—prevents postangioplasty clotting
    C. Aldesleukin—blocks IL-2 receptors
    D. Filgrastim—sequesters TNF
    E. Trastuzumab—blocks HER2/neu receptors

20. Following 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. Mercaptoethansulfonate
    D. Tamoxifen
    E. Vitamin C

21. Which one of the following is LEAST likely to increase insulin requirement in a diabetic patient?

    A. Furosemide
    B. Hydrochorothiazide
    C. Prednisone
    D. Spironolactone
    E. Taking the USMLE

22. The drug of choice for management of adrenal steroid-induced osteoporosis is

    A. alendronate
    B. calcitonin
    C. estrogen
    D. ketoconazole
    E. vitamin D

23. 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

24. Resistance to which anticancer drug, used mainly in childhood leukemia, is high in neoplastic cells that have low activities of hypoxanthine guanine phosphoribosyltransferase?

    A. Dactinomycin
    B. Vinblastine
    C. 6-MP
    D. Cytarabine
    E. Methotrexate

25. Finasteride is approved for use in male pattern baldness, where it 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

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 like warfarin, preventing their GI absorption (↓ prothrombin time, PT), and cimetidine, which inhibits the metabolism of warfarin, causing an increase in PT. Vitamin K restores levels of prothrombin and several other coagulation factors, but the action is slow (24–48 h). Due to antiplatelet effects, even low doses of ASA may enhance bleeding in patients on warfarin.

2. **Answer: E.** Alpha$_1$ 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 GHRH 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.

3. **Answer: B** Thioamides used at conventional doses in Grave 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.

4. **Answer: C.** Interferon-gamma 1b (recombinant form) is used in chronic granulomatous disease to decrease infection liability because it increases the formation of tumor necrosis factor (TNF). 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.

5. **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-MI and for transient ischemic attacks (TIAs).

6. **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.

7. **Answer: B.** Heparin forms a 1:1 complex with antithrombin III and enhances its activity from 100- to 1,000-fold. 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.

8. **Answer: A.** Folic acid can relieve hematologic symptoms in vitamin B_{12} deficiency because it can serve as a cofactor for methionine synthetase in the conversion of homocysteine to methionine. However, it cannot replace vitamin B_{12} (cyanocobalamin) in the reaction that converts malonyl-CoA to succinyl-CoA, so folic acid has no impact on the neurologic dysfunction of pernicious anemia.

9. **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 with possible vascular thrombosis.

10. **Answer: A.** The 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.

11. **Answer: D.** Streptokinase (SK) is thrombolytic (or fibrinolytic) because it activates plasminogen, resulting in the increased formation of plasmin. Its efficacy is equivalent to that of tissue plasminogen activator (t-pA), but SK is not clot-specific. All thrombolytics can cause bleeding, which may be counteracted to some extent by administration of antifibrinolysins, such as aminocaproic acid.

12. **Answer: C.** Neurogenic diabetes insipidus is treated with desmopressin, a drug that is similar to vasopressin (ADH) but a selective activator of V_2 receptors in the kidney. Remember that V_1 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).

13. **Answer: A.** Back to ANS pharmacology! The release of insulin from the pancreas is stimulated by insulinogens (glucose), sulfonylurea hypoglycemics (glipizide), activators of $beta_2$ adrenoceptors (e.g., albuterol), and activators of muscarinic receptors (e.g., pilocarpine). The only receptor that, when activated, inhibits insulin release is the $alpha_2$ receptor, which could be stimulated by clonidine or methyldopa.

14. **Answer: D.** Discontinuance of 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.

15. **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.

16. **Answer: E.** Mifepristone (RU 486) 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.

17. **Answer: E.** The profile of lead toxicity includes decreased heme synthesis, anemia, nephropathy, and peripheral neuropathy, the last leading to foot drop or wrist drop. Garlic breath and watery stools are associated with arsenic poisoning. Chronic gingivitis and loose teeth are features of mercury poisoning.

18. **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 other oral agents used in diabetes insipidus. Metformin is "euglycemic," 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.

19. **Answer: E.** Trastuzumab is a monoclonal antibody specific for blocking the HER2/neu receptors associated with breast cancers that are genotypically linked. Abciximab binds to the glycoprotein IIb/IIIa receptor and is used postangioplasty; alpha interferon is used in hepatitis B and C. Aldesleukin is a recombinant form of IL-2 that activates interleukin receptors; filgrastim is a granulocyte colony stimulating factor (G-CSF).

20. **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 (mesna), which inactivates acrolein, is available for protection against hemorrhagic cystitis in patients treated with cyclophosphamide and related drugs.

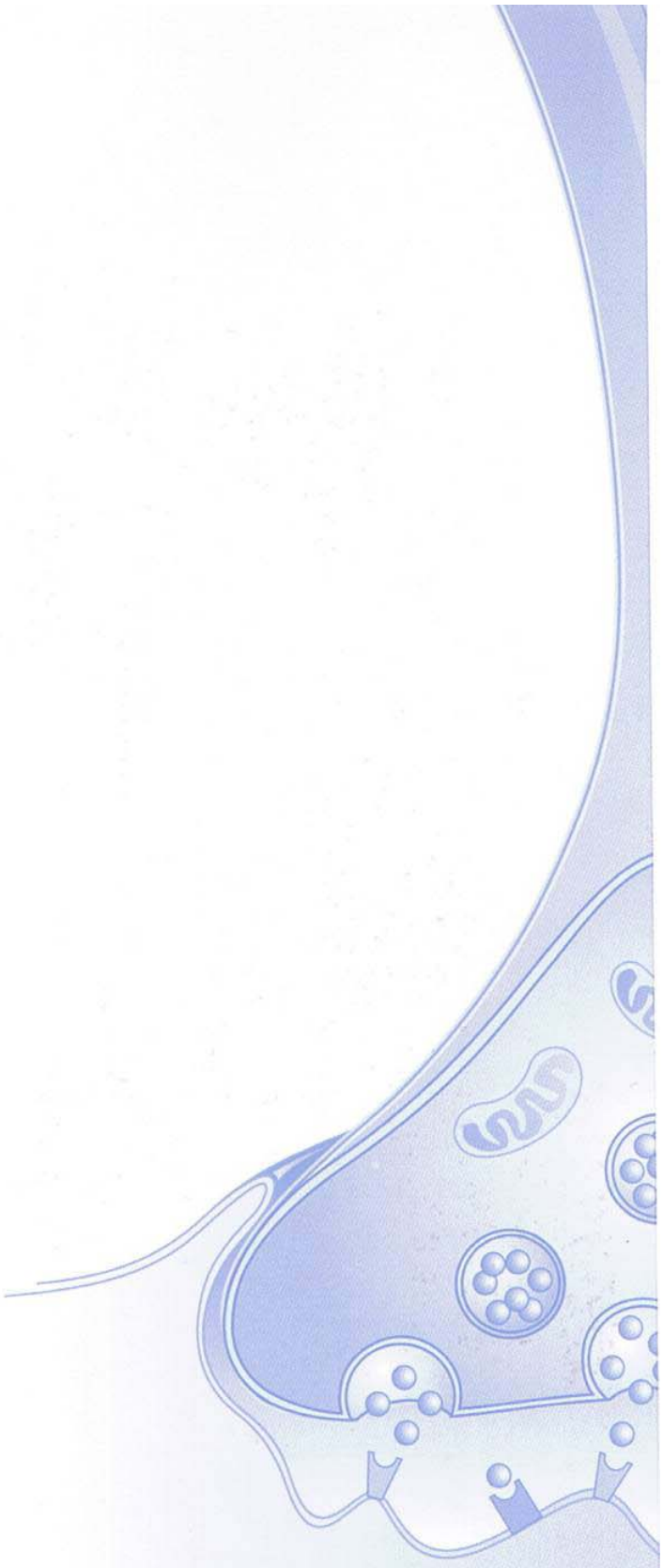
21. **Answer: D.** Drugs that decrease extracellular potassium such as the thiazide and loop diuretics and adrenal glucocorticoids will lead to an increased requirement for insulin by making it more difficult to release the hormone from the B cells of the pancreas. Spironolactone is K sparing, tends to cause hyperkalemia, and does not interfere with the release of insulin. Stress conditions such as examinations also increase insulin requirement.

22. **Answer: A.** Alendronate is currently the drug of choice to prevent osteoporosis in patients who must be maintained on steroids for their anti-inflammatory 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.

23. **Answer: A.** It can help 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.

24. **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.

25. **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.



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