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Tenth Edition

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Arnold Stern

Pharmacology

PreTest® Self-Assessment and Review

Tenth Edition

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Preface

In this tenth edition of *Pharmacology: PreTest® Self-Assessment and Review,* significant changes and improvements have been made. Questions that use clinical vignettes have been added; the responses require interpretation and data synthesis. The number of items per group of matching questions has been reduced in accordance with the new format used on United States Medical Licensing Examination (USMLE) Step 1. A High-Yield Facts section containing two sample Drug Classification Tables has been added; these tables serve as simple examples for collating and comparing information about various drug classes. References have been updated, and this section is preceded by a List of Abbreviations and Acronyms used throughout the book.

The author remains indebted to his students and colleagues at New York University Medical Center for their continuing support and encouragement.

Introduction

Each *PreTest® Self-Assessment and Review* allows medical students to comprehensively and conveniently assess and review their knowledge of a particular basic science—in this instance, pharmacology. The 490 questions parallel the format and degree of difficulty of the questions found in the United States Medical Licensing Examination (USMLE) Step 1. Practicing physicians who want to hone their skills before USMLE Step 3 or recertification may find this to be a good beginning in their review process.

Each question is accompanied by an answer, a paragraph explanation, and a specific page reference to an appropriate textbook. A bibliography listing sources can be found following the last chapter.

Before each chapter, a list of key terms or classifications of drugs or both is included to aid review. In addition, suggestions for effective study and review have been added afterward.

The most effective method of using this book is to complete one chapter at a time. Prepare yourself for each chapter by reviewing from your notes and favorite text the drugs classes listed at the beginning of each section and the drugs listed in the "High-Yield Facts" section. You should concentrate especially on the prototype drugs. Then proceed to indicate your answer by each question, allowing yourself not more than one minute for each question. In this way you will be approximating the time limits imposed by the examination.

After you finish going through the questions in the section, spend as much time as you need verifying your answers and carefully reading the explanations provided. Pay special attention to the explanations for the questions you answered incorrectly—but read *every* explanation. The editors of this material have designed the explanations to reinforce and supplement the information tested by the questions. If you feel you need further information about the material covered, consult and study the references indicated.

High-Yield Facts

SAMPLE DRUG CLASSIFICATION TABLES

TIPS FOR LEARNING PHARMACOLOGY

Pharmacology is best learned by comparing drugs within a particular class or by their specific use.

A chart highlighting the similarities and differences among the various agents can be a helpful tool. The charts included in this section are simple examples. More elaborate charts can be constructed that would include how the drug is administered, its pharmacological effects, its adverse effects, its mechanism of toxicity (if known), and significant drug-drug interactions. For infectious disease agents, the spectrum of antimicrobial activity and the basis of antibiotic resistance can be added.

Explanations for the abbreviations used in these charts are found in the List of Abbreviations and Acronyms, which appears before the Bibliography.

Drugs for Treating Bacterial Infectious Diseases

Drug Class	Prototype	Action	Spectrum
Penicillins		Inhibit bacterial cell-wall synthesis by binding to penicillin-binding proteins, inhibiting crosslinking enzymes, and activating autolytic enzymes that disrupt bacterial cell walls.	Streptococci, meningococci, pneumococci, gram-positive bacilli, gonococci, spirochetes.
Narrow spectrum			
Penicillinase-susceptible	Penicillin G		
Penicillinase-resistant	Methicillin		Staphylococci.
Wide spectrum	Ampicillin		Similar to penicillin G; also includes *E. coli, P. mirabilis,* and *H. influenzae.*
Penicillinase-susceptible	Carbenicillin		Gram-negative rods and especially useful for *Pseudomonas* spp.
Cephalosporins			
First-generation	Cephalothin		Gram-positive cocci, *E. coli,* and *K. pneumoniae.*
Second-generation	Cefamandole		Greater activity against gram-negative organisms than first-generation cephalosporins.
Third-generation	Cefoperazone		Broader activity against resistant gram-negative organisms; some derivatives penetrate the blood-brain barrier.
Carbapenem	Imipenem		Wide action against gram-positive cocci, gram-negative rods, and some anaerobes.
Monobactam	Aztreonam		Resistant to β-lactamases produced by gram-negative rods.

Macrolides	Erythromycin	Inhibits protein synthesis by binding to part of the 50S ribosomal . subunit	Gram-positive cocci, mycoplasma, corynebacteria, *Legionella, Ureaplasma, Bordetella.*
Vancomycin	Vancomycin	Inhibits synthesis of cell-wall mucopeptides (peptidoglycans).	Gram-positive bacteria, especially for resistant mutants.
Chloramphenicol	Chloramphenicol	Inhibits peptide bond formation by binding to the 50S ribosomal subunit, inhibiting peptidyl transferase.	*Salmonella* and *Haemophilus* infections and meningococcal and pneumococcal meningitis.
Aminoglycosides			
Systemic	Gentamicin	Inhibits protein synthesis by binding to the 30S subunit of ribosomes, which blocks formation of the initiation complex, causing misreading of the code on the mRNA template and disrupting polysomes.	*E. coli, Enterobacter, Klebsiella, Proteus, Pseudomonas,* and *Serratia* species.
Local	Neomycin		
Tetracycline	Tetracycline	Inhibits protein synthesis by binding to the 30S ribosomal subunit, which interferes with binding of aminoacyl-tRNA.	Mycoplasma, chlamydia, rickettsia, vibrio.
Sulfa drugs	Sulfonamides	Inhibit folic acid synthesis by competitive inhibition of dihydropteroate synthase.	Gram-positive and -negative organisms, including chlamydia and nocardia.
Trimethoprim	Trimethoprim	Inhibits folic acid synthesis by inhibition of dihydrofolate reductase.	Used in combination with sulfamethoxazole.
Fluoroquinolones	Norfloxacin	Inhibits topoisomerase II (DNA gyrase).	Gram-negative organisms, including gonococci, *E. coli, K. pneumoniae, C. jejuni, Enterobacter, Salmonella,* and *Shigella* species.

Drugs for Treating Hypertension

Drug Class	Prototype	Action
Sympathetic nervous system agents		
Central	Clonidine	α_2-agonist; causes decreased sympathetic outflow.
Peripheral	Guanethidine	Uptake by transmitter vesicles in nerve depletes and replaces norepinephrine in neurosecretory vesicles.
	Prazocin	α_1-antagonist.
	Propranolol	β-antagonist.
Central and peripheral	Reserpine	Binds tightly to storage vesicles, which consequently lose their ability to concentrate and store norepinephrine.
Vasodilators		
Arterial	Hydralazine	Unknown.
	Diazoxide	Opens K^+ channels and causes hyperpolarization of smooth muscle.
Arterial and venous	Nitroprusside	Releases NO, which binds to guanylyl cyclase to generate cGMP.
Ca^{++} channel-blockers	Nifedipine	Inhibits voltage-dependent "L-type" Ca^{++} channels.
ACE inhibitors	Captopril	Inhibits conversion of angiotensin I to angiotensin II.
Diuretics		
Thiazides (benzothiadiazides)	Hydrochlorothiazide	Inhibits Na^+ channels in luminal membrane in the proximal segment of the distal tubule.
Loop agents	Furosemide	Inhibits cotransporter of Na^+, K^+, Cl^- in the ascending limb of the loop of Henle.

HIGH-YIELD FACTS

General Principles

Serum concentration vs time graphs
- Relationship of drug elimination half-time ($t_{1/2}$)
- Apparent volume of distribution
- Drug clearance

Drug distribution
- Henderson-Hasselbalch equations
- Diffusion

Partition coefficients

Bioavailability

Log-dose response curves

Anti-Infectives

Cell-wall synthesis inhibitors
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenem
- Vancomycin
- Cycloserine

β-lactamase inhibitors

Protein synthesis inhibitors
- Chloramphenicol
- Tetracyclines
- Macrolides
- Lincosamides
- Aminoglycosides

Folic acid synthesis inhibitors
- Sulfonamides
- Trimethoprim

DNA synthesis inhibitors
- Fluoroquinolones

Antimycobacterials
- Isoniazid
- Rifampin
- Ethambutol
- Pyrizinamide
- Streptomycin

Antileprosy agents

Antifungals
- Amphotericin B
- Flucytosine
- Azoles
- Terbinafine

Antivirals
- Antiherpes agents

Antiretrovirals
- Nucleoside reverse transcriptase inhibitors
- Nonnucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Amantadine
- Interferons
- Ribavirin

Antiprotozoals

Antihelminthics

Organism	Drug
Pneumococcus	Penicillin G, ampicillin
Pneumococcus (penicillin-resistant)	Fluoroquinolones
Streptococcus	Penicillin G, macrolides (allergic patients)
Staphylococcus (penicillinase-resistant)	Penicillinase-resistant penicillin
Staphylococcus (methicillin-resistant)	Vancomycin
Enterococcus	Penicillin G and gentamycin
Enterococcus (vancomycin-resistant)	Linezolid
Gonococcus	Ceftriaxone, fluoroquinolones
Menigicoccus	Penicillin G, ampicillin, cephtriaxone
Escherichia coli, Proteus, Klebsiella	Second- and third-generation cephalosporin, trimethoprim-sulfamethoxazole, ampicillin, fluoroquinolones
Shigella	Fluoroquinolones
Enterobacter, Serratia	Imipenem, trimethoprim-sulfamethoxazole, fluoroquinolones, pipericillin/tazobactam
Hemophilus	Second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole, fluoroquinolones
Pseudomonas	Cephtazidime, cefepime, imipenem, aztreonam, ciprofloxacin, aminoglycoside, and extended-spectrum penicillin
Bacteroides	Metronidazole, clindamycin
Mycoplasma	Macrolide, tetracycline
Treponema	Penicillin G

Drug	Adverse Drug Reaction
Penicillins	Cross-allergenicity
Cephalosporins	Cross-allergenicity Contraindicated in patients with history of anaphylaxis to penicillins Disulfiram-like reaction with ethanol
Vancomycin	"Red person" syndrome
Chloramphenicol	"Gray baby syndrome," aplastic anemia
Macrolides	Arrhythmias with coadministration of astemizole

Drug	Adverse Drug Reaction
Clindamycin	Clostridium difficile colitis
Aminoglycosides	Ototoxicity and nephrotoxicity
Tetracycline	Discolored teeth, enamel dysplasia, and bone growth disturbances in children
Sulfa drugs	Cross-allergenicity with other sulfa drugs and with certain diuretics and hypoglycemics
Fluoroquinolones	Tendonitis, Achilles tendon rupture, contraindicated in patients less than 18 years old because of effects on cartilage development
Amphotericin B	Shocklike reaction
Azole antifungals	Arrhythmias with astemizole
Isoniazid	Hepatotoxicity prevented by coadministration of pyridoxine
Ethambutol	Visual disturbances
Pyrazinamide	Nongouty polyarthralgias
Dapsone	Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency

Antiviral Agent	Adverse Drug Reaction
Zidovudine (AZT)	Anemia
Didanosine (ddI)	Neuropathy, pancreatitis
Stavudine (d4T)	Neuropathy
Abacavir	Hypersensitivity reaction
Efavirenz	Central nervous system toxicity
Protease inhibitors	Hepatotoxicity, hyperlipidemia, nephrolithiasis, lipodystrophy
Acyclovir	Nephropathy
Ganciclovir	Neutropenia
Foscarnet	Renal toxicity
Ribavirin	Anemia
Interferons	Flulike symptoms
Lamivudine	Lactic acidosis
Rimantadine, amantadine	Central nervous system toxicity
Zanamavir	Bronchospasm

Cancer Chemotherapy and Immunology

Cell cycle kinetics

Antimetabolites
- Cell cycle sensitive (CCS)—primarily in the S phase

Plant alkaloids
- Vinblastine and vincristine—CCS—primarily in the M phase
- Ectoposide—CCS—S and early G2 phase
- Paclitaxel—spindle poison

Antibiotics
- Bleomycin—CCS—primarily in G2 phase
- Doxyrubicin, dactinomycin, and mitomycin—cell cycle non-sensitive

Alkylating agents and hormones—cell cycle nonspecific (CCNS)

Cardiovascular and Pulmonary Systems

Drugs used in congestive heart failure
- Positive inotropes
- Diuretics
- ACE inhibitors
- PDE inhibitors
- Vasodilators

Antianginals
- Calcium channel blockers
- Nitrates
- β-adrenergic blockers

Antiarrhythmics
- Sodium channel blockers
- β-adrenergic blockers
- Potassium channel blockers
- Calcium channel blockers
- Adenosine
- Digoxin

Antihypertensives
- Diuretics
- Adrenergic receptor blockers
- Vasodilators
- Angiotensin antagonists

Antihyperlipidemics
- Resins
- HMG-CoA reductase inhibitors
- Niacin
- Gemfibrozil

Drugs used in clotting disorders
- Clot reducers
  - Anticoagulants
  - Antiplatelet agents
  - Thrombolytics
- Clot facilitators
  - Replacement factors
  - Plasminogen inhibitors

Antiasthmatics
- Bronchodilators
- Anti-inflammatories
- Leukotriene antagonists

Drug	Adverse Drug Reaction
Digoxin	Arrythmias, visual aberrations
Nitrates	Tachycardia, headaches, and tolerance
Verapamil	Constipation
β-adrenergic blockers	Bradycardia and asthma
Quinidine and sotalol	Torsades-like arrhythmia
Procainamide	Lupus-like reaction
Amiodarone	Pulmonary fibrosis, thyroid dysfunction, and constipation
Prazosin	First-dose orthostatic hypotension
Clonidine	Rebound hypertension on acute drug cessation
Methyldopa	Positive Coombs test
Guanethidine	Orthostatic hypotension
Reserpine	Depression
Hydralazine	Lupus-like syndrome
Minoxidil	Hirsutism, marked salt and water retention
ACE inhibitors	Dry cough, contraindicated in renal disease
Resins	Bloating
HMG-CoA reductase inhibitors	Severe muscle pain
Niacin	Flushing

Central Nervous System

Antipsychotics
- Phenothiazines
- Thioxanthines
- Butyrophenones
- Heterocyclics
- Antimanics

Adverse Drug Reactions of Antipsychotics

Extrapyramidal effects—haloperidol, fluphenazine

Tardive dyskinesia

Atropine-like effects—thioridizine, chlorpromazine, clozapine

Orthostatic hypotension

Hyperprolactinemia

Amenorrhea-galactorrhea syndrome

Neuroleptic malignant syndrome

Agranulocytosis—clozapine

Nephrogenic diabetes insipidus—lithium

Antidepressants

Monoamine oxidase (MAO) inhibitors

Tricyclics

Heterocyclics

Selective serotonin reuptake inhibitors

α_2-adrenergic blockers

Adverse Drug Reactions of Antidepressants

Combination of MAO inhibitors and fluoxetine—serotonin syndrome

MAO inhibitors and foods containing tyramine—hypertensive crisis

Opiates
- Agonists
- Mixed agonists
- Antagonists

Anxiolytics
- Benzodiazepines
- Barbiturates
- Ethanol

Antiparkinsonians
- Dopamine antagonists
- MAO inhibitors
- Antimuscarinics

Adverse Drug Reactions of Antiparkinsonians

Levodopa, bromocryptine—choreoathetosis

Antiepileptics
- Phenytoin
- Carbamazepine
- Valproic acid
- Gabapentin
- Vigabatrin
- Ethosuximide
- Benzodiazepines

Drug	Use
Valproic acid, phenytoin, carbamazine	Grand mal seizures
Ethosuximide, valproic acid	Absence seizures
Valproic acid	Myoclonus
Diazepam, lorazepam	Status epilepticus

Drug	Adverse Drug Reaction
Valproic acid	Neural tube defects
Phenytoin	Nystagmus, gingival hyperplasia, ataxia, hirsutism
Carbamazepine	Diplopia, ataxia
Gabapentin	Movement disorders, behavioral aberrations in children
Vigabatrin	Agitation, confusion, psychosis

Autonomic Nervous System

Location and function of adrenergic and cholinergic receptors

Cholinergic agents
- Direct acting
  - Nicotinic
  - Muscarinic
- Indirect acting
  - Organophosphates
  - Carbamates
  - Quarternary alcohols

Anticholinergic agents
- Antimuscarinic
- Antinicotinic
- Ganglionic blockers
- Neuromuscular blockers

Adrenergic agents
- Direct acting
  - α-adrenergic agonists
  - β-adrenergic agonists
- Indirect acting
  - Releasers
  - Reuptake inhibitors

Antiadrenergic agents
- α-adrenergic blockers
- β-adrenergic blockers

Drug	Use
Edrophonium, pyridostigmine, neostigmine	Myasthenia gravis
Carbachol, pilocarpine, physostigmine, timolol	Glaucoma
Tacrine, donepezil	Alzheimer's disease
Pralidoxime	Organophosphate poisoning antidote
Scopalamime	Motion sickness
Ipratropium	Chronic obstructive pulmonary disease
Albuterol	Asthma
Dopamine	Cardiogenic shock
Dobutamine	Cardiogenic shock and congestive heart failure
Ephedrine, oxymetazoline, phenylephrine	Nasal congestion
Phentolamine, phenoxybenzamine	Pheochromocytoma
Prazosin	Hypertension
Beta blockers	Angina, hypertension, arrhythmias, and myocardial infarction
Epinephrine	Anaphylaxis
Tropicamide	Mydriasis and cycloplegia

Drug	Adverse Drug Reaction
Muscarinics	Nausea, vomiting, diarrhea, salivation, sweating, cutaneous vasodilation, and bronchial constriction
Nicotinics	Convulsions, respiratory paralysis, and hypertension
Cholinesterase inhibitors	Signs of muscarinic and nicotinic toxicities
Antimuscarinics	Hyperthermia due to blockage of sweating mechanisms, decreased salivation and lacrimation, acute-angle-closure glaucoma in the elderly, urinary retention, constipation, blurred vision, delirium, and hallucinations
Antinicotinics	Respiratory paralysis
Adrenergics	Marked increase in blood pressure, tachycardia
α-adrenergic blockers	Orthostatic hypotension, reflex tachycardia
β-adrenergic blockers	Bradycardia, atrioventricular blockade, negative inotropy, bronchiolar constriction, hypoglycemia

Local Control Substances

Histamine antagonists
- H_1
- H_2

Serotonin agonists
- 5-H_1
- Serotonin-selective reuptake inhibitors

Serotonin antagonists
- 5-HT_2
- 5-HT_3

Ergot alkaloids
- CNS
- Uterus
- Vessels

Eicosonoid agonists
- Prostaglandins
- Prostacyclins
- Thromboxanes
- Leukotrienes

Eicosonoid antagonists
- Corticosteroids
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Leukotriene antagonists

Drug	Use
Histamine antagonists	
H_1	Allergies
H_2	Acid-peptic disease
Serotonin agonists	
Sumatriptan	Acute migraine and cluster headaches
Serotonin antagonists	
Ketanserin, cyproheptadine, and phenoxybenzamine	Carcinoid tumors
Ondansetron	Postoperative vomiting and vomiting associated with cancer chemotherapy
Ergot alkaloids	
Ergotamine	Acute migraine headache
Methysergide and ergonovine	Prophylactic use for migraine headaches
Ergonovine and ergotamine	Reduction of postpartum bleeding
Bromocryptine and pergolide	Reduction of prolactin secretion
Eicosanoid agonists	
Misoprostol	Abortifacient, prevention of ulcers in combination with NSAIDs therapy
PGE_1	Maintain patency of ductus arteriosus
Alprostadil	Erectile dysfunction
Corticosteroids	Inhibition of arachidonic acid production
NSAIDs	Closure of patent ductus arteriosus
Indomethacin	Asthma
Leukotriene antagonists	

Drug	Adverse Drug Reaction
Histamine receptor antagonists	
H_1	Drowsiness
H_2-cimetidine	Inhibitor of drug-metabolizing enzymes
Serotonin antagonists	
Ketanserin	α and H_1 antagonism
Ondansetron	Diarrhea and headache
Ergot alkaloids	Ischemia and gangrene, fibroplasia of connective tissue, uterine contractions, and hallucinations

Renal System

Diuretics effecting salt and water excretion
- Osmotic
- Carbonic anhydrase inhibitors
- Loop diuretics
- Thiazides

Potassium-sparing diuretics

Drugs effecting water excretion
- Osmotic
- ADH agonists
- ADH antagonists

Drug	Use
Loop diuretics	Congestive heart failure and pulmonary edema, ascites
Thiazides	Hypertension, congestive heart failure, renal calcium stones
Osmotics	Increasing urine flow, decreasing intracranial pressure
Potassium-sparing diuretics	Diminishing potassium wasting from other diuretics
ADH	Pituitary diabetes insipidus

Drug	Adverse Drug Reaction
Loop diuretics	Hypokalemia, ototoxicity
Thiazides	Hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia
Potassium-sparing diuretics	Hyperkalemia
Spironolactone	Gynecomastia and antiandrogenic effects
ADH	Hyponatremia

Gastrointestinal System and Nutrition

Gastrointestinal tract ulcers
- Antacids
- Polymers (sucralfate)
- Proton pump inhibitors
- Antibiotics

Gastrointestinal motility promotors
- Antiemetics
- H_2 antagonists
- Phenothiazines
- 5-HT inhibitors

Pancreatic replacement enzymes
Laxatives
Irritants
Bulk formers
Stool softeners
Lubricants
Sulfasalazine
Antidiarrheals

Drug	Use
Ondansetron	Antiemetic in cancer chemotherapy
Omeprazole	Zollinger-Ellison syndrome

Endocrine System

- Androgens
  - Testosterone
- Antiandrogens
  - GnRH analogs
  - Steroid synthesis inhibitors
  - 5α reductase inhibitors
  - Testosterone receptor inhibitors
- Estrogens
- Progesterones
- Corticosteroids
  - Glucocorticoids
  - Mineralocorticoids
- Corticosteroid antagonists
  - Receptor antagonists
- Synthetic inhibitors
- Thyroid hormones
  - Thyroxine
  - Triiodothyronine
- Antithyroid hormones
  - Thioamides
  - Iodide
  - Radioactive iodide
  - Ipodate
- Antidiabetics
  - Insulin
  - Oral hypoglycemics
    - Sulfonylureas
    - Biguanides
    - Thiazolidinediones
    - Acarbose
- Hyperglycemics
- Bone mineral metabolism agents
  - Parathyroid hormone
  - Vitamin D
  - Calcitonin—Paget's disease and hypercalcemia
  - Estrogens
  - Glucocorticoids
  - Biphosphonates—post-menopausal osteoporosis
  - Fluoride
  - Plicamycin—Paget's disease

Drug	Adverse Drug Reaction
Androgens	Masculinizing effects
Estrogens	Breakthrough bleeding and breast tenderness
Thyroid hormones	Thyrotoxicosis
Glucocorticoids	Adrenal suppression, salt retention, diabetes, osteoporosis
Insulin	Hypoglycemia
Sulfonylureas	Hypoglycemia
Biguanides	Diarrhea, lactic acidosis in renal or hepatic insufficiency and anoxic states
Thiazolidinediones	Possible hepatotoxicity
Etidronate	Esophageal irritation
Fluoride	Ectopic bone formation, exostosis
Vitamin D	Nephrocalcinosis

Toxicology

Air pollutants
- Carbon monoxide
- Sulfur dioxide
- Nitrogen oxides
- Ozone

Solvents
- Halogenated hydrocarbons
- Aromatic hydrocarbons

Insecticides
- Chlorinated hydrocarbons
- Cholinesterase inhibitors
- Botanical insecticides

Herbicides

Environmental pollutants
- Dioxins
- Polychlorinated biphenyls

Heavy metals
- Lead
- Arsenic
- Mercury
- Iron

Toxin	Treatment
Carbon dioxide	Removal from exposure and administer oxygen
Sulfur dioxide	Removal from exposure
Aliphatic hydrocarbons	Removal from exposure
Aromatic hydrocarbons	Removal from exposure
Cholinesterase inhibitors	Atropine, pralidoxime
Paraquat	Gastric lavage and dialysis
Lead	Dimercaprol, penicillamine
Arsenic	Dimercaprol, penicillamine
Mercury	Dimercaprol (elemental), penicillamine, dimercaprol (inorganic salts)
Iron	Deferoxamine

General Principles

Drug-receptor interactions
Dose-response relationships
Molecular models of receptors and signal transduction mechanisms
Biotransformation
Pharmacokinetics
Pharmacodynamics
Dosage regimens and pharmacokinetic profiles
Factors affecting drug dosage
Development of new drugs
Regulation by the Food and Drug Administration

Questions

DIRECTIONS: Each item below contains a question or incomplete statement followed by suggested responses. Select the **one best** response to each question.

1. Of the many types of data plots that are used to help explain the pharmacodynamics of drugs, which plot is very useful for determining the total number of receptors and the affinity of a drug for those receptors in a tissue or membrane?

a. Graded dose-response curve
b. Quantal dose-response curve
c. Scatchard plot
d. Double-reciprocal plot
e. Michaelis-Menten plot

2. Which route of administration is most likely to subject a drug to a first-pass effect?

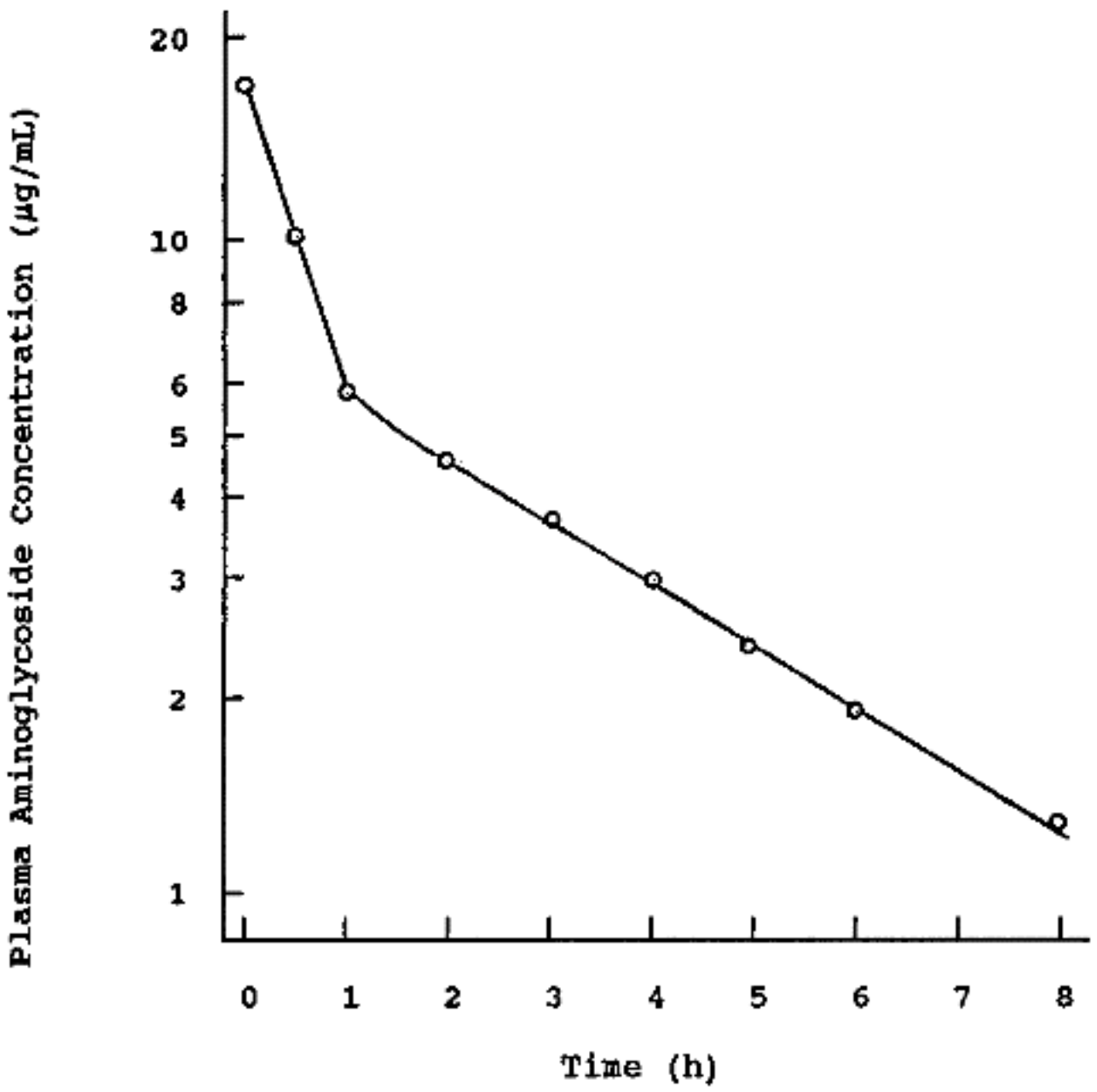
a. Intravenous
b. Inhalational
c. Oral
d. Sublingual (SL)
e. Intramuscular

3. Two drugs may act on the same tissue or organ through independent receptors, resulting in effects in opposite directions. This is known as

a. Physiologic antagonism
b. Chemical antagonism
c. Competitive antagonism
d. Irreversible antagonism
e. Dispositional antagonism

Questions 4–7

A new aminoglycoside antibiotic (5 mg/kg) was infused intravenously over 30 min to a 70-kg volunteer. The plasma concentrations of the drug were measured at various times after the end of the infusion, as recorded in the table and shown in the figure below.



Time After Dosing Stopped (h)	Plasma Aminoglycoside Concentration (mg/mL)
0.0	18.0
0.5	10.0
1.0	5.8
2.0	4.6
3.0	3.7
4.0	3.0
5.0	2.4
6.0	1.9
8.0	1.3

4. The elimination half-life ($t_{1/2}$) of the aminoglycoside in this patient was approximately

a. 0.6 h
b. 1.2 h
c. 2.1 h
d. 3.1 h
e. 4.2 h

5. The elimination rate constant (k_e) of the aminoglycoside in this patient was approximately

a. 0.15 h^{-1}
b. 0.22 h^{-1}
c. 0.33 h^{-1}
d. 0.60 h^{-1}
e. 1.13 h^{-1}

6. The apparent volume of distribution (V_d) of the drug in this patient was approximately

a. 0.62 L
b. 19 L
c. 50 L
d. 110 L
e. 350 L

7. The total body clearance (CL_{total}) of the drug in this patient was approximately

a. 11 L/h
b. 23 L/h
c. 35 L/h
d. 47 L/h
e. 65 L/h

8. If a drug is repeatedly administered at dosing intervals that are equal to its elimination half-life, the number of doses required for the plasma concentration of the drug to reach the steady state is

a. 2 to 3
b. 4 to 5
c. 6 to 7
d. 8 to 9
e. 10 or more

9. The pharmacokinetic value that most reliably reflects the amount of drug reaching the target tissue after oral administration is the

a. Peak blood concentration
b. Time to peak blood concentration
c. Product of the V_d and the first-order rate constant
d. V_d
e. Area under the blood concentration-time curve (AUC)

10. It was determined that 95% of an oral 80-mg dose of verapamil was absorbed in a 70-kg test subject. However, because of extensive biotransformation during its first pass through the portal circulation, the bioavailability of verapamil was only 25%. Assuming a liver blood flow of 1500 mL/min, the hepatic clearance of verapamil in this situation was

a. 60 mL/min
b. 375 mL/min
c. 740 mL/min
d. 1110 mL/min
e. 1425 mL/min

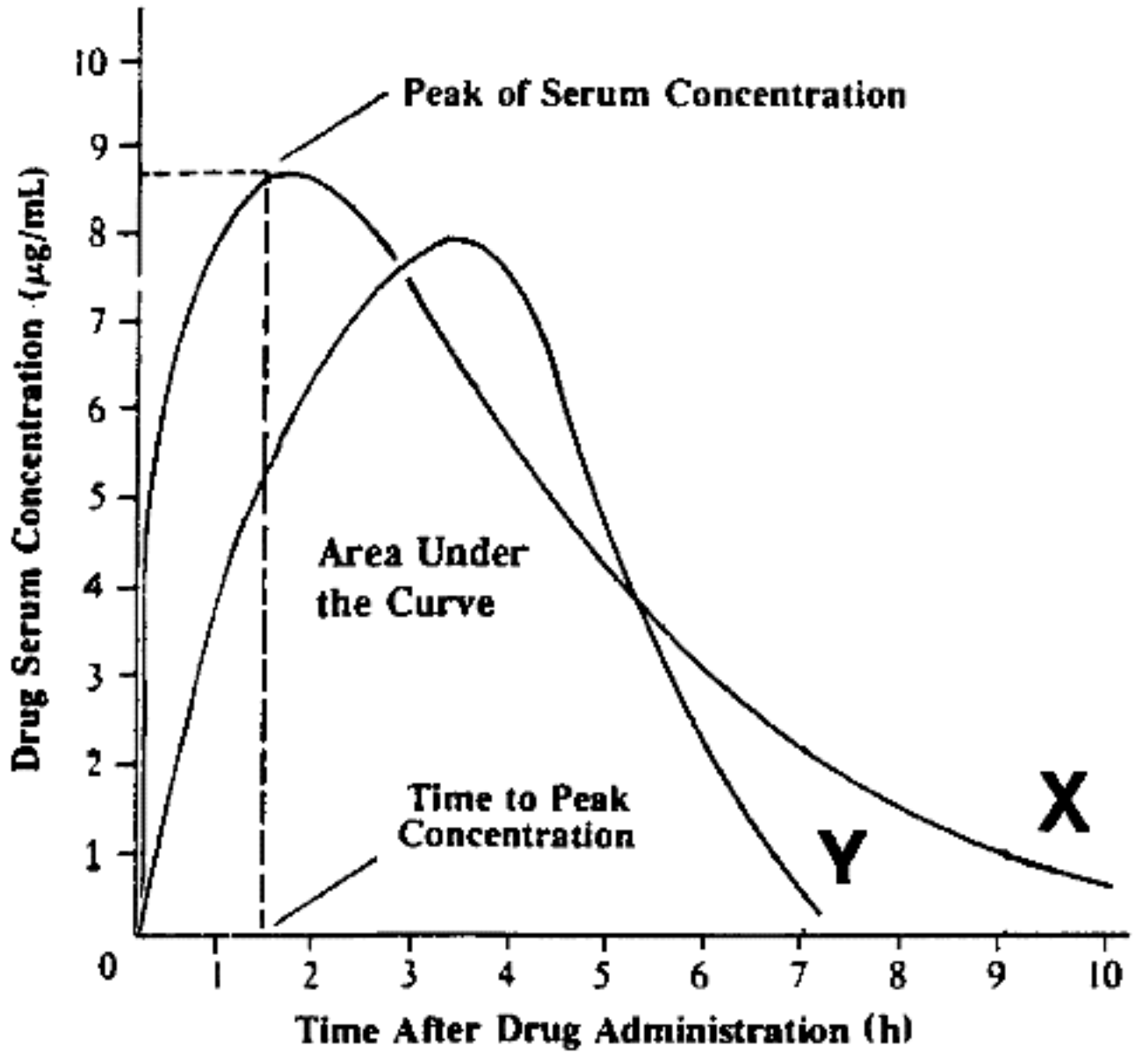
11. Drug products have many types of names. Of the following types of names that are applied to drugs, the one that is the official name and refers only to that drug and not to a particular product is the

a. Generic name
b. Trade name
c. Brand name
d. Chemical name
e. Proprietary name

12. Which of the following is classified as belonging to the tyrosine kinase family of receptors?

a. $GABA_A$ receptor
b. β-adrenergic receptor
c. Insulin receptor
d. Nicotinic II receptor
e. Hydrocortisone receptor

13. Identical doses of a capsule preparation (X) and a tablet preparation (Y) of the same drug were compared on a blood concentration-time plot with respect to peak concentration, time to peak concentration, and AUC after oral administration as shown in the figure below. This comparison was made to determine which of the following?



a. Potency
b. Extent of plasma protein binding
c. Bioequivalence
d. Therapeutic effectiveness
e. None of the above

14. Of the following characteristics, which is unlikely to be associated with the process of facilitated diffusion of drugs?

a. The transport mechanism becomes saturated at high drug concentrations
b. The process is selective for certain ionic or structural configurations of the drug
c. If two compounds are transported by the same mechanism, one will competitively inhibit the transport of the other
d. The drug crosses the membrane against a concentration gradient and the process requires cellular energy
e. The transport process can be inhibited noncompetitively by substances that interfere with cellular metabolism

15. In comparing the following possible routes, which is associated with the excretion of quantitatively small amounts of drugs or their metabolic derivatives?

a. Biliary tract
b. Kidneys
c. Lungs
d. Feces
e. Milk

16. Of the following, which is a phase II biotransformation reaction?

a. Sulfoxide formation
b. Nitro reduction
c. Ester hydrolysis
d. Sulfate conjugation
e. Deamination

17. Which of the following is unlikely to be associated with oral drug administration of an enteric-coated dosage form?

a. Irritation to the gastric mucosa with nausea and vomiting
b. Destruction of the drug by gastric acid or digestive enzymes
c. Unpleasant taste of the drug
d. Formation of nonabsorbable drug-food complexes
e. Variability in absorption caused by fluctuations in gastric emptying time

18. Of the following, which is unlikely to be associated with receptors bound to plasma membranes, their interaction with ligands, and the biologic response to this interaction?

a. Structurally, these receptors have hydrophobic amino acid domains, which are in contact with the membrane, and hydrophilic regions, which extend into the extracellular fluid and the cytoplasm
b. Chemical interactions of ligands with these receptors may involve the formation of many types of bonds, including ionic, hydrogen, van der Waals', and covalent
c. Ligand-receptor interactions are often stereospecific (i.e., one stereoisomer is usually more potent than the other)
d. In some cases, a ligand that acts as an agonist at membrane-bound receptors increases the activity of an intracellular second messenger
e. Activation of membrane-bound receptors and subsequent intracellular events elicit a biologic response through the transcription of DNA

19. Of the following, which is unlikely to be associated with the binding of drugs to plasma proteins?

a. Acidic drugs generally bind to plasma albumin; basic drugs preferentially bind to α_1-acidic glycoprotein
b. Plasma protein binding is a reversible process
c. Binding sites on plasma proteins are nonselective, and drugs with similar physicochemical characteristics compete for these limited sites
d. The fraction of the drug in the plasma that is bound is inactive and generally unavailable for systemic distribution
e. Plasma protein binding generally limits renal tubular secretion and biotransformation

20. Of the following, which is unlikely to be associated with drug distribution into and out of the central nervous system (CNS)?

a. The blood-brain barrier, which involves drug movement through glial cell membranes as well as capillary membranes, is the main hindrance to drug distribution to the CNS
b. Most drugs enter the CNS by simple diffusion at rates that are proportional to the lipid solubility of the nonionized form of the drug
c. Receptor-mediated transport allows certain peptides to gain access to the brain
d. Strongly ionized drugs freely enter the CNS through carrier-mediated transport systems
e. Some drugs leave the CNS by passing from the cerebrospinal fluid into the dural blood sinuses through the arachnoid villi

21. The greater proportion of the dose of a drug administered orally will be absorbed in the small intestine. However, on the assumption that passive transport of the nonionized form of a drug determines its rate of absorption, which of the following compounds will be absorbed to the least extent in the stomach?

a. Ampicillin ($pK_a = 2.5$)
b. Aspirin ($pK_a = 3.0$)
c. Warfarin ($pK_a = 5.0$)
d. Phenobarbital ($pK_a = 7.4$)
e. Propranolol ($pK_a = 9.4$)

DIRECTIONS: Each group of questions below consists of lettered options followed by a set of numbered items. For each numbered item, select the **one** lettered option with which it is **most** closely associated. Each lettered option may be used once, more than once, or not at all.

Questions 22–24

For each type of drug interaction below, select the pair of substances that illustrates it with a *reduction* in drug effectiveness:

a. Tetracycline and milk
b. Amobarbital and secobarbital
c. Isoproterenol and propranolol
d. Soap and benzalkonium chloride
e. Sulfamethoxazole and trimethoprim

22. Therapeutic interaction

23. Physical interaction

24. Chemical interaction

Questions 25–27

For each description of a drug response below, choose the term with which it is most likely to be associated:

a. Supersensitivity
b. Tachyphylaxis
c. Tolerance
d. Hyposensitivity
e. Anaphylaxis

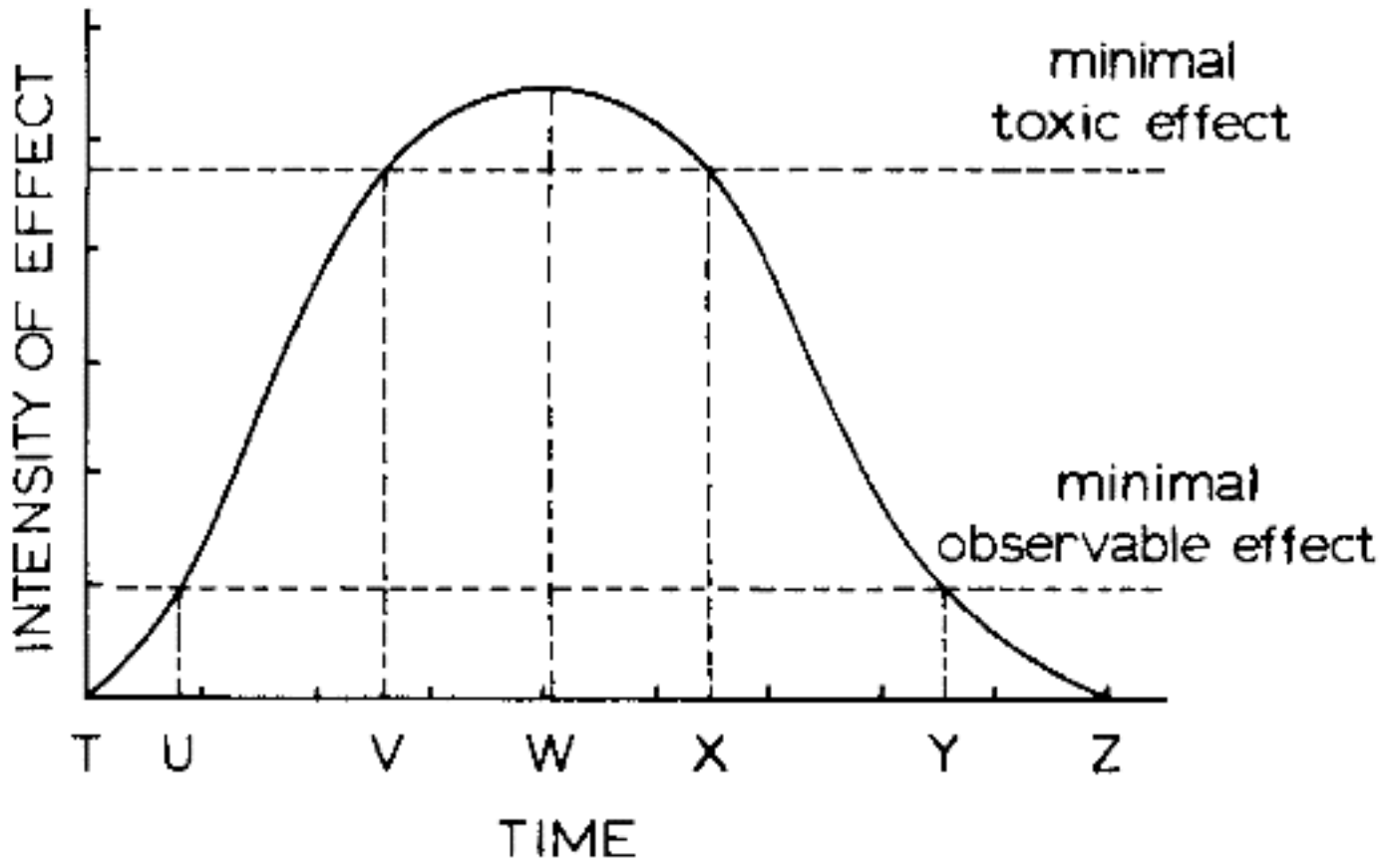
25. Immunologically mediated reaction to drug observed soon after administration

26. A rapid reduction in the effect of a given dose of a drug after only one or two doses

27. Hyperreactivity to a drug seen as a result of denervation

Questions 28–30

For each component of a time-action curve listed below, choose the lettered interval (shown on the diagram) with which it is most closely associated:



a. T to U
b. T to V
c. T to W
d. T to Z
e. U to V
f. U to W
g. U to X
h. U to Y
i. V to X
j. X to Y

28. Time to peak effect

29. Time to onset of action

30. Duration of action

Questions 31–33

For each description below, select the transmembranal transport mechanism it best defines:

a. Filtration
b. Simple diffusion
c. Facilitated diffusion
d. Active transport
e. Endocytosis

31. Lipid-soluble drugs cross the membrane at a rate proportional to the concentration gradient across the membrane and the lipid:water partition coefficient of the drug

32. Bulk flow of water through membrane pores, resulting from osmotic differences across the membrane, transports drug molecules that fit through the membrane pores

33. After binding to a proteinaceous membrane carrier, drugs are carried across the membrane (with the expenditure of cellular energy), where they are released

Questions 34–36

Lipid-soluble xenobiotics are commonly biotransformed by oxidation in the drug-metabolizing microsomal system (DMMS). For each description below, choose the component of the microsomal mixed-function oxidase system with which it is most closely associated:

a. Nicotinamide adenine dinucleotide phosphate (NADPH)
b. Cytochrome a
c. Adenosine triphosphate (ATP)
d. NADPH–cytochrome P450 reductase
e. Monoamine oxidase (MAO)
f. Cyclooxygenase
g. Cytochrome P450

34. A group of iron (Fe)-containing isoenzymes that activate molecular oxygen to a form that is capable of interacting with organic substrates

35. The component that provides reducing equivalents for the enzyme system

36. A flavoprotein that accepts reducing equivalents and transfers them to the catalytic enzyme

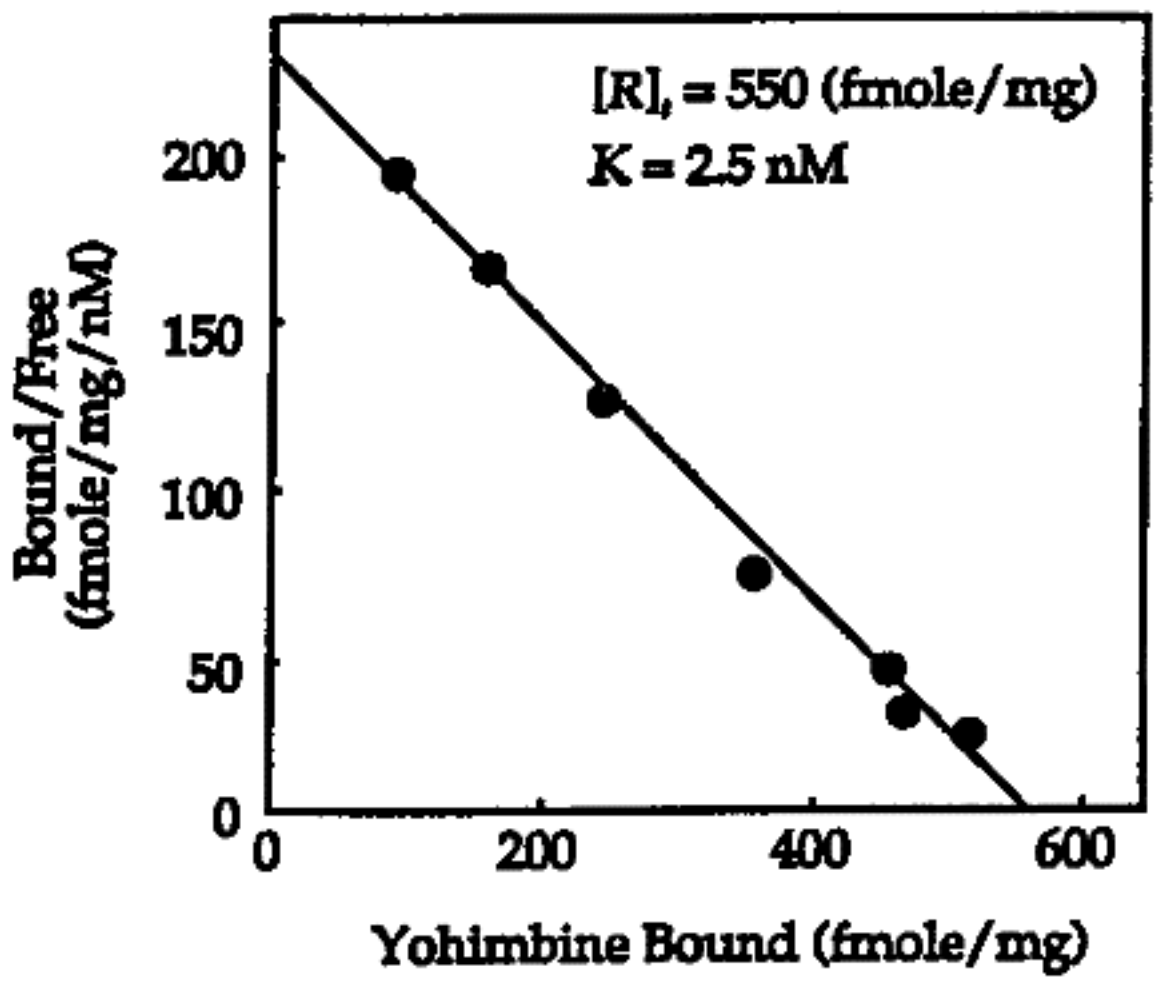
General Principles

Answers

1. The answer is c. *(Hardman, pp 37–38.)* Based on the concept that, for most situations, the association of a drug with its receptor is reversible, the following reaction applies:

$$D + R \underset{k_2}{\overset{k_1}{\rightleftarrows}} DR \rightarrow \text{Effect}$$

where D is the concentration of free drug, R is the concentration of receptors, DR is the concentration of drug bound to its receptors, and K_D (equal to k_2/k_1) is the equilibrium dissociation constant. The affinity of a drug for its receptor is estimated from the dissociation constant in that its reciprocal, $1/K_D$, is the affinity constant. All of the plots listed in the question can be used to quantitate some aspect of drug action. For example, K_D can be determined from the Michaelis-Menten relationship, graded dose-response curves, and the Scatchard plot. However, only the Scatchard plot can be



(From Neubig RR, Gantros RD, and Brasier RS: Mol Pharmacol *28:475–486, 1985, with permission.)*

used to determine the total number of receptors in a tissue or membrane. This is accomplished by measuring the binding of a radioactively labeled drug to a membrane or tissue preparation in vitro. A Scatchard plot of the binding of ^{3}H-yohimbine to α_2-adrenergic receptors on human platelet membranes is shown on the previous page as an example. A plot of DR/D (bound/free drug) vs. DR (bound drug) yields a slope of $1/K_D$ (the affinity constant) and an *x* intercept of R (total number of receptors).

Scatchard analysis is very useful in certain therapeutic situations. For example, this type of analysis is used to determine the number of estrogen receptors present in a biopsy of breast tissue prior to developing a drug treatment regimen for breast cancer in a patient.

2. The answer is c. *(Hardman, p 5.)* The first-pass effect is commonly considered to involve the biotransformation of a drug during its first passage through the portal circulation of the liver. Drugs that are administered orally and rectally enter the portal circulation of the liver and can be biotransformed by this organ prior to reaching the systemic circulation. Therefore, drugs with a high first-pass effect are highly biotransformed quickly, which reduces the oral bioavailability and the systemic blood concentrations of the compounds. Administration by the intravenous, intramuscular, and sublingual routes allows the drug to attain concentrations in the systemic circulation and to be distributed throughout the body prior to hepatic metabolism. In most cases, drugs administered by inhalation are not subjected to a significant first-pass effect unless the respiratory tissue is a major site for the drug's biotransformation.

3. The answer is a. *(Hardman, p 68.) Physiologic*, or *functional*, *antagonism* occurs when two drugs produce opposite effects on the same physiologic function, often by interacting with different types of receptors. A practical example of this is the use of epinephrine as a bronchodilator to counteract the bronchoconstriction that occurs following histamine release from mast cells in the respiratory tract during a severe allergic reaction. Histamine constricts the bronchioles by stimulating histamine H_1 receptors in the tissue; epinephrine relaxes this tissue through its agonistic activity on β_2-adrenergic receptors.

Chemical antagonism results when two drugs combine with each other chemically and the activity of one or both is blocked. For example, dimercaprol chelates lead and reduces the toxicity of this heavy metal. Competi-

tive antagonism, or inactivation, occurs when two compounds compete for the same receptor site; this is a reversible interaction. Thus, atropine blocks the effects of acetylcholine on the heart by competing with the neurotransmitter for binding to cardiac muscarinic receptors. Irreversible antagonism generally results from the binding of an antagonist to the same receptor site as the agonist by covalent interaction or by a very slowly dissociating noncovalent interaction. An example of this antagonism is the blockade produced by phenoxybenzamine on α-adrenergic receptors, resulting in a long-lasting reduction in the activity of norepinephrine.

Dispositional antagonism occurs when one drug alters the pharmacokinetics (absorption, distribution, biotransformation, or excretion) of a second drug so that less of the active compound reaches the target tissue. For example, phenobarbital induces the biotransformation of warfarin, reducing its anticoagulant activity.

4. The answer is d. *(Katzung, pp 35–41.)* The figure that accompanies the question shows an elimination pattern with two distinct components, which typifies a two-compartment model. The upper portion of the line represents the α phase, which is the distribution of the drug from the tissues that receive high rates of blood flow [the central compartment (e.g., the brain, heart, kidney, and lungs)] to the tissues with lower rates of blood flow [the peripheral compartment (e.g., skeletal muscle, adipose tissue, and bone)]. Once distribution to all tissue is complete, equilibrium occurs throughout the body. The elimination of the drug from the body (the β phase) is represented by the lower linear portion of the line; this part of the line is used to determine the elimination half-life of the drug.

At 2 h after dosing, the plasma concentration was 4.6 mg/mL; at 5 h, the concentration was 2.4 mg/mL. Therefore, the plasma concentration of this aminoglycoside decreased to one-half in approximately 3 h—its half-life. In addition, drug elimination usually occurs according to first-order kinetics (i.e., a linear relationship is obtained when the drug concentration is plotted on a logarithmic scale vs. time on an arithmetic scale (a semilogarithmic plot)].

5. The answer is b. *(Katzung, p 40.)* The fraction change in drug concentration per unit of time for any first-order process is expressed by k_e. This constant is related to the half-life ($t_{1/2}$) by the equation $k_e t_{1/2} = 0.693$. The units of k_e are time^{-1}, while the $t_{1/2}$ is expressed in units of time. By substi-