Katzung & Trevor's Pharmacology
Examination & Board Review
seventh edition

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INTRODUCTION

B. SINGLE-COMPARTMENT DISTRIBUTION

A few drugs may behave as if they are distributed to only 1 compartment (e.g., if they are restricted to the vascular compartment). Often there are more complex distributions that require more than 2 compartments for comparison of accurate mathematical models.

QUESTIONS

1. A 3-year-old child is brought to the emergency department having just ingested a large overdose of guaifenesin, an antitussive drug. Promethazine is a weak base with a pKa of 9.3. It is capable of entering most tissues, including the brain. On physical examination, the heart rate is 100/min, blood pressure 110/60 mm Hg, and respiratory rate 20/min. In this case of promethazine overdose,
   (A) Urinary excretion would be accelerated by administration of NH₄Cl, an acidifying agent
   (B) Urinary excretion would be accelerated by giving NaHCO₃, an alkalizing agent
   (C) More of the drug would be excreted at blood pH that is lower than stomach pH
   (D) Absorption of the drug would be faster from the stomach than from the small intestine
   (E) Hemodialysis is the only effective therapy

2. Which of the following is NOT a general mechanism of drug penetration?
   (A) Aquous diffusion
   (B) Aquous hydrolysis
   (C) Lipid diffusion
   (D) Penetration or dissolution
   (E) Special carrier transport

3. A patient with a history of epistaxis attacks of coughing, wheezing, and shortness of breath is being evaluated in the acute clinic. Several drug treatments with different routes of administration are under consideration. Which of the following questions about routes of administration is MOST correct?
   (A) Blood levels often rise more slowly after intramuscular injection than after oral dosing
   (B) The first-pass effect is the result of elimination of a drug after administration and before it enters the systemic circulation
   (C) Administration of an antimicrobial drug by inhaled aerosol is usually associated with more adverse effects (e.g., tachycardia, tremor) than is administration of the same drug by mouth
   (D) Bioavailability of some drugs is greater with rectal (suppository) administration than with sublingual administration
   (E) Administration of a drug by intradermal patch is often faster but is associated with more distal metastasis than self-administration

4. Aspirin is a weak organic acid with a pKa of 3.5. What percentage of a given dose will be in the lipid-soluble form at a stomach pH of 2.5?
   (A) About 1%
   (B) About 10%
   (C) About 50%
   (D) About 90%
   (E) About 99%

5. If the plasma concentration of a drug declines with “first-order kinetics,” this means that
   (A) There is only 1 metabolic path for drug disposition
   (B) The half-life is the same regardless of the plasma concentration
   (C) The drug is largely metabolized in the liver after oral administration and has low bioavailability
   (D) The rate of elimination is proportional to the rate of administration at all times
   (E) The drug is not distributed outside the vascular system

6. Regarding termination of drug action,
   (A) Drugs must be excreted from the body to terminate their action
   (B) Metabolism of drugs always increases their water solubility
   (C) Metabolism of drugs almost always abolishes their pharmacologic activity
   (D) Hepatic metabolism and renal excretion are the 2 most important mechanisms involved
   (E) Distribution of a drug out of the bloodstream terminates the drug’s effects

7. Distribution of drugs to specific tissues
   (A) Is independent of blood flow in the organ
   (B) Is independent of the solubility of the drug in that tissue
   (C) Depends on the unbound drug concentration gradient between blood and the tissue
   (D) Is increased for drugs that are strongly bound to plasma proteins
   (E) Has no effect on the half-life of the drug

8. Timox is being considered for the treatment of glaucoma in a 58-year-old patient. Except for elevated intracranial pressure, the patient’s history and physical examination are unremarkable. Timox is
a weak base of pH 9.2. Which of the following statements is FALSE?

(A) After parenteral administration, the concentration of timolol in the aqueous humor (pH 7.8) will be lower than the concentration in the duodenum (pH 5.5).

(B) When administered as eye drops, absorption into the eye will be faster if the drops are alkaline (pH 8.0) than if they are acidic (pH 5.0).

(C) Excretion in the urine will be faster if urine pH is alkaline (pH 8.0) than if the urine pH is acidic (pH 5.8).

(D) The proportion of timolol in the protonated form will be approximately 90% at pH 8.2.

(E) The proportion of timolol in the more lipid-soluble form will be approximately 90% at pH 10.2.

9. A physical process by which a weak acid becomes less water soluble and more lipid soluble at low pH is

(A) Distribution

(B) Elimination

(C) First-pass effect

(D) Permeation

(E) Protonation

10. The set of properties that characterize the effects of a drug on the body is called

(A) Lipid solubility

(B) Distribution

(C) Pharmacodynamics

(D) Pharmacokinetics

(E) Protonation

11. The set of properties that characterize the effects of the body on a drug is called

(A) Absorption

(B) Distribution

(C) Elimination

(D) First-order kinetics

(E) Pharmacokinetics

12. The most general term for the process by which the amount of active drug in the body is reduced after absorption into the systemic circulation is

(A) Distribution

(B) Elimination

(C) Excretion

(D) First-order elimination

(E) Metabolism

13. The process by which the amount of drug in the body is reduced after administration but before entering the systemic circulation is called

(A) Excretion

(B) First-pass effect

(C) First-order elimination

(D) Metabolism

(E) Pharmacokinetics

5. The kinetics that are characteristic of the elimination of ethanol and high doses of phenytoin and aspirin are called

(A) Distribution

(B) Excretion

(C) First-pass effect

(D) First-order elimination

(E) Zero-order elimination

ANSWERS

1. Questions that deal with acid-base (Henderson-Hasselbalch) manipulations are common. Since absorption involves permeation across lipid membranes, we can treat an overdose by decreasing absorption from the gut and reabsorption from the tubular urine by making the drug less lipid soluble. Ionization attracts water molecules and decreases lipid solubility. Phenothiazine is a weak base, which means that it will be more ionized (protonated) at acid pH than at basic pH. Choice C suggests that the drug would be more ionized at pH 7.4 than at pH 2.0; clearly wrong. Choice D says (in effect) that the more ionized form will be absorbed faster, which is incorrect. A and B are opposite because NH₄⁺ is an acidifying salt and sodium bicarbonate an alkalizing one. From the point of view of taste strategy, opposites always deserve attention and, in this case, encourage us to exclude E, a distractor. Because an acid environment favors ionization of a weak base, we should give NH₄⁺. The answer is A.

2. Hydrolysis has nothing to do with the mechanisms of permeation; rather, hydrolysis is one mechanism of drug metabolism. The answer is B.

3. Blood levels usually rise more rapidly after intramuscular injection than after oral administration. (C) is wrong: Delivering the drug directly to the target organ usually reduces adverse effects because the required total dose is smaller and the concentration reaching other organs is lower. Bioavailability is usually greater after sublingual than after rectal administration. Onset of effect is usually slower with transdermal administration than with any other route; but it does avoid the first-pass effect. The answer is B.

4. Aspirin is an acid, so it will be more ionized at alkaline pH and less ionized at acidic pH. The Henderson-Hasselbalch equation predicts that the ratio will change from 50/50 at the pH equal to the pKₐ to

5. "First-pass elimination" occurs when a drug or its metabolite is not absorbed, but is directly eliminated in the feces or urine. The answer is B.

6. None of the above choices are correct.

7. This is a question about the composition of the oral and intestinal tracts.

8. More basic drugs ionize less in the small intestine but ionize more in the large intestine.

CHECK YOUR ANSWERS

When you have finished:

☐ Predict the answer to each question.

☐ List and review the explanations to each answer.

☐ Draw a graph or table to order the answers.
5. "First-order" means that the elimination rate is proportional to the concentration permeating the organ of elimination. The half-life is a constant. The rate of elimination is proportionate to the rate of administration only at steady state. The answer is B.

6. Note the "trigger" words ("must," "always") in choices A, B, and C. All drugs that affect more than the blood or cellular endothelium are outside of the "bloodstream." The answer is D.

7. This is a straightforward question of distribution concepts. There are no trigger words to give the answer away, but it can be deduced without much trouble. From the list of determinants of drug distribution given previously, choice C is correct.

8. More Henderson-Hasselbalch concepts. Weak bases are more protonated in an acidic environment because more protons (hydrogen ions) are available. In the pronated acidic weak bases are ionized, polar, and less lipid soluble. Therefore, less tetracycl is lipid soluble and able to diffuse through the blood-brain barrier (pH 7.3) than is able to diffuse through the surface of the eye (pH 7.8). By the same reasoning, the drug diffuses faster if the eye drops are alkaline than if they are acidic. Less drug diffuses back into the body from the eye if the surface pH is acidic than if it is alkaline, so excretion will be faster in acidic urine. The answer is C.

9. Pronation (combination with a proton, H+) causes a weak acid to lose its negative electrical charge and become less polar and more lipid soluble. The answer is E.

10. More definitions. Pharmacodynamics is the term given to the properties of drug action on the body. The answer is C.

11. Pharmacokinetics is the general term that describes all of the body's actions on the drug. The answer is F.

12. The amount of active drug is reduced by excretion and metabolism processes that are included in the term "elimination." The answer is B.

13. "First-pass effect" is the term given to elimination of a drug before it enters the systemic circulation (ie, in first pass through the portal circulation and first). The answer is B.

14. The excretion of most drugs is determined by first-order kinetics. However, ethanol and, in higher doses, aspirin and phenytoin follow zero-order kinetics (ie, their elimination rates are constant regardless of blood concentration). The answer is E.

CHECKLIST

When you complete this chapter, you should be able to:

- Predict the relative ease of permeation of a weak acid or base from a knowledge of its pHc, the pH of the medium, and the Henderson-Hasselbalch equation.
- List and discuss the common routes of drug administration and excretion.
- Draw graphs of the blood level versus time for drugs subject to zero-order elimination and for drugs subject to first-order elimination. Label the axes appropriately.
channel's response to other agents (e.g., benzodiazepines at the GABA-activated chloride channel). The result is a change in transmembrane electrical potential.

**E. RECEPTORS LINKED TO EFFECTORS via G PROTEINS**

A very large number of drugs bind to receptors that are linked by coupling proteins to intracellular or membrane effectors. The best defined examples of this group are the sympathomimetic drugs, which activate or inhibit adenyl cyclase (formerly called adenylyl cyclase) by a multistep protein activation of the receptor by the drug result in activation of G proteins that either stimulate or inhibit the cyclase. Many types of G proteins have been identified. Of the most important are listed in Table 2-1. When G-coupled receptors bind agonists, the G protein is activated. This process involves dissociation of the GDP-bound G protein complex into an ATP-α-subunit moiety and a βγ-subunit moiety. The ATP-α-subunit is the primary player in most interactions with effector molecules, but in a few the βγ-guanine moiety is the active one.

**QUESTIONS**

1. A 55-year-old woman with heart failure is to be treated with a diuretic drug. Drugs X and Y have the same mechanism of diuretic action. Drug X in

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Coupling Protein</th>
<th>Effector</th>
<th>Effector Substrate</th>
<th>Second Messenger Response</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1, β1, δ1</td>
<td>Gi</td>
<td>Phospholipase C</td>
<td>Membrane lipids</td>
<td>IP3, DAG</td>
<td>Ca2+ and protein kinase activity</td>
</tr>
<tr>
<td>β2, δ2</td>
<td>Gi</td>
<td>Adenyl cyclase</td>
<td>ATP</td>
<td>Ca2+</td>
<td>Ca2+ influx and enzyme activity</td>
</tr>
<tr>
<td>α2, M2</td>
<td>Gi</td>
<td>Adenyl cyclase</td>
<td>ATP</td>
<td>Ca2+ influx and enzyme activity, K+ efflux</td>
<td></td>
</tr>
</tbody>
</table>
a dose of 3 mg produces the same magnitude of diuresis at 500 mg of drug X. This suggests that
(A) Drug Y is less effective than drug X
(B) Drug X is about 100 times more potent than drug Y
(C) Toxicity of drug X is less than that of drug Y
(D) Drug X is safer than drug Y
(E) Drug X will have a shorter duration of action than drug Y because less of drug X is present for a given effect.

2. Dose-response curves are used for drug evaluation in the animal laboratory and in the clinic. Quantitative dose-response curves are:
(A) Used for determining the absolute amount of a drug
(B) Used for determining the maximal effect of a drug
(C) More accurately quantitated than ordinary graded dose-response curves
(D) Obtained from the study of intact subjects but not from isolated tissue preparations
(E) Used to determine the statistical variation (standard deviation) of the maximal response to the drug.

3. The results shown in the graph below were obtained in a comparison of drugs that increase the force of cardiac contraction. Which of the following statements is MOST correct?
(A) Drug A is more effective.
(B) Drug B is less potent.
(C) Drug C is more potent than drug D and more effective than drug A.
(D) Drug A is more potent than drug B and more effective than drug C.

4. In the absence of other drugs, propranolol causes an increase in heart rate by activating beta adrenocep-
tors. In the presence of highly effective beta stimulants, however, propranolol causes a dose-dependent, reversible decrease in heart rate. Therefore, pro-
pranolol should be classified as
(A) An irreversible antagonist
(B) A physiologic antagonist
(C) A chemical antagonist
(D) A partial agonist
(E) A spare receptor antagonist.

5. Which of the following statements about spare receptors is MOST correct?
(A) Spare receptors, in the absence of drug, are sequestered in the cytoplasm.
(B) Spare receptors may be detected by finding that the drug-receptor interaction last longer than the intracellular effect.
(C) Spare receptors influence the maximal efficacy of the drug-receptor system.
(D) Spare receptors initiate the effect in the cell with the steady state.
(E) Spare receptors may be detected by the finding that the EC50 is smaller than the Kd of the agonist.

6. Two anthyroidogenic drugs, X and Y, were studied in large groups of patients with percent of the 
percentage of the group showing a specific therapeutic effect (30 mm Hg decrease in systolic blood pressure) were determined. The results are shown in the table.

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>Percent Responding to Drug X</th>
<th>Percent Responding to Drug Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>0.1 mg</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>0.05 mg</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

Which of the following statements about these results is MOST correct?
(A) Drug X is safer than drug Y.
(B) Drug Y is more effective than drug X.
(C) The two drugs act on the same receptors.
(D) Drug X is less potent than drug Y.
(E) The therapeutic index of drug X is 30.

7. Which of the following is true about the properties of the given drug?
(A) High affinity
(B) Low affinity
(C) High efficacy
(D) Low efficacy
(E) Both high affinity and high efficacy

8. Which of the following statements is MOST correct?
(A) The drug-receptor interaction first occurs at the plasma membrane.
(B) The drug-receptor interaction is not detectable in the cytoplasm.
(C) The drug-receptor interaction occurs in the nucleus of the cell.
(D) The drug-receptor interaction occurs in the mitochondria of the cell.

9. Which of the following statements about the regulation of gene expression is MOST correct?
(A) Transcription is regulated at the level of DNA binding sites.
(B) Transcription is regulated at the level of RNA splicing.
(C) Transcription is regulated at the level of RNA stability.
(D) Transcription is regulated at the level of RNA translation.

10. Which of the following statements about the regulation of gene expression is MOST correct?
(A) Transcription is regulated at the level of DNA binding sites.
(B) Transcription is regulated at the level of RNA splicing.
(C) Transcription is regulated at the level of RNA stability.
(D) Transcription is regulated at the level of RNA translation.

11. Which of the following statements about stress is MOST correct?
(A) Stress is a constant stimulus.
(B) Stress is a variable stimulus.
(C) Stress is a predictable stimulus.
(D) Stress is an unpredictable stimulus.

12. Which of the following statements about the effects of stress on the body is MOST correct?
(A) Stress increases the heart rate.
(B) Stress decreases the heart rate.
(C) Stress increases blood pressure.
(D) Stress decreases blood pressure.

13. Which of the following statements about the effects of stress on the body is MOST correct?
(A) Stress increases the heart rate.
(B) Stress decreases the heart rate.
(C) Stress increases blood pressure.
(D) Stress decreases blood pressure.
7. Which of the following terms best describes the antagonism of histamine's histamine receptor effect (mediated at histamine receptors) by cimetidine (acting at adrenergic receptors) in a patient with asthma?
(A) Pharmacologic antagonist
(B) Partial agonist
(C) Physiologic antagonist
(D) Chemical antagonist
(E) Noncompetitive antagonist

8. Which of the following terms best describes an antagonist that interacts directly with the agonist and not as acutely or only incidentally with the receptor?
(A) Pharmacologic antagonist
(B) Partial agonist
(C) Physiologic antagonist
(D) Chemical antagonist
(E) Noncompetitive antagonist

9. Which of the following terms best describes a drug that blocks the action of epinephrine at its receptors by occupying those receptors without activating them?
(A) Pharmacologic antagonist
(B) Partial agonist
(C) Physiologic antagonist
(D) Chemical antagonist
(E) Noncompetitive antagonist

10. Which of the following provides information about the variation in sensitivity to a drug within the population studied?
(A) Minimal efficacy
(B) Therapeutic index
(C) Drug potency
(D) Gradual dose-response curve
(E) Quantal dose-response curve

11. Which of the following most accurately describes the transmembrane signaling process involved in steroid hormone actions?
(A) Action on a membrane-spanning tyrosine kinase
(B) Activation of a G protein, which activates or inhibits adenyl cyclase
(C) Diffusion across the membrane and binding to an intracellular receptor
(D) Diffusion of STAT molecules across the membrane
(E) Opening of transmembrane ion channels

12. Which of the following provides information about the largest response a drug can produce, regardless of dose?
(A) Drug potency
(B) Maximal efficacy

13. Which of the curves in the graph describes the percentage binding of a large dose of full agonist to its receptors as the concentration of a partial agonist is increased from low to very high levels?
(A) Curve 1
(B) Curve 2
(C) Curve 3
(D) Curve 4
(E) Curve 5

14. Which of the curves in the graph describes the percentage effect when a large dose of full agonist is present throughout the experiment and the concentration of a partial agonist is increased from low to very high levels?
(A) Curve 1
(B) Curve 2
(C) Curve 3
(D) Curve 4
(E) Curve 5

15. Which of the curves in the graph describes the percentage binding of partial agonists whose effect is shown by curve 4 if the system has many spare receptors?
(A) Curve 1
(B) Curve 2
(C) Curve 3
(D) Curve 4
(E) Curve 5
ANSWERS

1. No information is given regarding the magnitude of the maximum kinetic response to the drug. Similarly, no information about toxicity is available. The fact that a given response is achieved with a smaller dose of drug A only indicates that X is more potent than Y in the range of 50/50%.

   The answer is B.

2. Graded (not quantal) dose-response curves must be used to determine maximum efficacy (maximal response). Quantal dose-response curves show only the frequency of occurrence of a specific response, which may be therapeutic (ED) or toxic (TD). Dividing the TD50 for the ED50 gives the therapeutic index. The answer is A.

3. These are straightened-out graded dose-response curves. Drug A is the most potent, drug C is the least. Drug A is too efficacious to be used alone, so choice A is incorrect. "Spine receptor agonist" is a nonsense statement. The answer is D.

4. Choice B and C are clearly incorrect because pindolol is said to act at beta receptors and to block beta-adrenergic stimulation. The drug effect is reversible, so choice A is incorrect. "Spine receptor agonist" is a nonsense statement. The answer is D.

5. While some types of receptors appear to be associated with the endoplasmic reticulum, since there is no difference between "spine" and other receptors, spine receptors may be defined as those which are not involved in binding drug to achieve the maximal effect. Spine receptors influence the sensitivity of the system to an agonist because the statistical probability of a drug-receptor interaction increases with the total number of receptors. They do not alter the maximal efficacy. If they are present, an agonist molecule (spine receptors) does not alter the binding affinity, Emax, for both Kd values in an indication of the presence of spine receptors. The answer is E.

6. No information is presented regarding the safety of these drugs. The percentage of the population showing the response. Similarly, no information on toxicity is presented and efficacy is not normally obtainable from spinal dose-response data. Although both drugs are said to be producing a therapeutic effect, an information on their receptor mechanism is given. Since no data on toxicity are available, the therapeutic index cannot be determined. The answer is D because the Emax of drug Y (1.0 mg) is less than that of drug X (3.0 mg).

7. Beta-blocking compounds interfere with adrenergic receptors and lower blood pressure due to the effects of beta-blocker receptor activation. Because the effects of adrenoreceptor agonists are receptor-mediated, beta-blockers must be a physiological antagonist. The answer is C.

8. A chemical antagonist interacts directly (chemically) with the agonist and not with a receptor. The answer is B.

9. A pharmacological antagonist occupies the receptors without activating them. The answer is A.

10. Quantal dose-response curves provide information about the statistical distribution of sensitivity to a drug. The answer is E.

11. Steroid hormones (e.g., cortisol, sex hormones, and aldosterone) diffuse through the membrane of the cell into the cytoplasm and bind to its intracellular receptor. The hormone-receptor complex then modulates gene expression. The answer is C.

12. Minimal efficacy represents the lower response a drug can produce. The answer is B.

13. The binding of a full agonist will decrease as the concentration of a partial agonist is increased to very high levels. As the partial agonist displaces more and more of the full agonist, the percentage of receptors that bind the full agonist will decrease, so the curve is E. Therefore, curve 3 for the description better than curve 2. The answer is C.
Note that clearance does not enter into this computation. If the loading dose is very large (4 times larger than blood volume), the dose should be given slowly so as to avoid excessively high peak plasma levels during the distribution phase.

**THERAPEUTIC WINDOW**

The therapeutic window is the safe "opening" between the minimum therapeutic concentration and the maximum toxic concentration of a drug. The concept is used to determine the range of plasma levels that is acceptable when designing a dosing regimen. Thus, the minimum effective concentration will usually determine the desired trough levels of a drug given intermit- tensely while the minimum toxic concentration determines the permissible peak plasma concentration. For example, the drug theophylline has a therapeutic concentration range of \(2-10\) mg/L and a toxic concentration range of \(15-20\) mg/L. The therapeutic window for a given patient might thus be fixed in the range of \(8-17\) mg/L (Figure 3, A). Unfortunately, for some drugs the therapeutic and toxic concentrations vary so greatly among patients that it is impossible to predict the therapeutic window in a given patient. Such drugs must be titrated individually in each patient.

![Figure 3.6: The therapeutic window for theophylline in a 13-year-old patient. The minimum effective concentration in the patient was found to be 8 mg/L; the minimum toxic concentration was found to be 16 mg/L. The therapeutic window is indicated by the colored area. To maintain the plasma concentration (Cp) within the window the drug must be given at least once every half life (7.5 hr in this patient) because the minimum effective concentration is half the minimum toxic concentration and is close to the half-life (Note: This concept applies to drugs given in the ordinary prompt-release form. Slow-release formulations can often be given at longer intervals.)](image)

**ADJUSTMENT OF DOSAGE WHEN ELIMINATION IS ALTERED BY DISEASE**

Readil disease or reduced cardiac output often reduces the clearance of drugs that depend on renal function. Alteration of clearance by liver disease is less common but may occur. Impairment of hepatic clearance occurs for high extraction drugs when liver blood flow is reduced, as in heart failure. The dose in a patient with renal impairment may be corrected by multiplying the average dose for a normal person times the ratio of the patient's altered creatinine clearance to normal creatinine clearance (approximately 100 mL/min. or 0.18). The corrected dose is:

\[
\text{Corrected dose} = \text{Average dose} \times \frac{\text{Patient's creatinine clearance}}{100 \text{ mL/min}}
\]

This simplified approach ignores several ranges of clearance that may be significant. If a drug is cleared partly by the kidney and partly by other routes, the above equation should be applied to that part of the dose that is eliminated by the kidney. For example, if a drug is 50% cleared by the kidney and 50% by the liver and the normal dosage is 200 mg/d, the hepatic and renal clearances are each 100 mg/d. Therefore, the corrected dosage in a patient with a creatinine clearance of 20 mL/min will be:

\[
\text{Dose} = \frac{100 \text{ mg/d} + 100 \text{ mg/d}}{100 \text{ mL/min}} = 20 \text{ mL/min} \times \frac{100 \text{ mL/min}}{100 \text{ mL/min}} = 20 \text{ mg/d}
\]

\[
\text{Corrected dose} = \frac{105 \text{ mg/d}}{20 \text{ mg/d} \times 120 \text{ mg/d}} = 120 \text{ mg/d}
\]

**QUESTIONS**

1. Mr. Jones is admitted to the hospital with pneumonia due to gram-negative bacteria. The antibiotic of choice is tetracycline. The Cl and Vf of tetracycline in Mr. Jones are 80 mL/min and 60 L, respectively.

1. What maintenance dose should be administered intravenously every 6 h to eventually obtain average steady-state plasma concentration of 4 mg/L?
   (A) 0.32 mg
   (B) 0.25 mg
   (C) 0.15 mg
   (D) 0.1 mg
   (E) 0.32 mg

2. If you wish to give Mr. Jones an intravenous loading dose to achieve the therapeutic plasma concentration of 4 mg/L, rapidly, how much should be given?
   (A) 0.1 mg
   (B) 0.25 mg
   (C) 0.15 mg
   (D) 0.1 mg
   (E) 0.32 mg
5. Despite your careful adherence to basic pharmacokinetic principles, your patient on digoxin therapy has developed digitalis toxicity. The plasma digoxin level is 4 ng/mL. Renal function is normal, and the plasma LDH for digoxin in this patient is 1.6. How long should you withhold digoxin in order to reach a safer yet probably therapeutic level of 1 ng/mL?
   (A) 1.6 days
   (B) 2.4 days
   (C) 3.2 days
   (D) 4.8 days
   (E) 6.4 days

6. Verapamil and phenytoin are both eliminated from the body by metabolism in the liver. Verapamil has a clearance of 1.5 L/min, approximately equal to liver blood flow, whereas phenytoin has a clearance of 0.3 L/min. When these compounds are administered along with rifampin, a drug that induces hepatic drug-metabolizing enzymes, which of the following is most likely?
   (A) The clearance of both verapamil and phenytoin will be increased
   (B) The clearance of both verapamil and phenytoin will be decreased
   (C) The clearance of verapamil will be unchanged, whereas the clearance of phenytoin will be increased
   (D) The clearance of phenytoin will be unchanged, whereas the clearance of verapamil will be increased

7. A 60-year-old man enters the hospital with a myocardial infarction and a severe ventricular arrhythmia. The antiarrhythmic drug chosen has a narrower therapeutic window: the minimum toxic plasma concentration is 1.5 times the minimum therapeutic plasma concentration. The half-life is 6 h. It is estimated to maintain the plasma concentration above the minimum therapeutic level to prevent a potentially lethal arrhythmia. Of the following, the most appropriate dosing regimen would be
   (A) Once a day
   (B) Twice a day
   (C) Three times a day
   (D) Four times a day
   (E) Constant intravenous infusion

8. A 50-year-old woman with metastatic breast cancer has elected to participate in the trial of a new chemo- therapeutic agent. It is given by constant intravenous infusion of 8 mg/h. Plasma concentrations (Cp) are measured with the results shown in the table at the bottom of this page. From these data, it may be concluded that
   (A) Volume of distribution is 30 L
   (B) Clearance is 2 L/h
   (C) Elimination follows zero-order kinetics
   (D) Half-life is 8 h
   (E) Doubling the rate of infusion would result in a plasma concentration of 15 mg/L at 40 h

9. A 50-year-old man who has been taking a medication for hypertension, C1, is admitted to the emergency room because of chest pain and diaphoresis. The emergency physician orders a creatinine level of 2 mg/dL.
   (A) 1
   (B) 2
   (C) 3
   (D) 4
   (E) 5

10. Your patient with diabetes mellitus is admitted to the hospital with a diagnosis of diabetic ketoacidosis. He takes a medication for hypertension, C1.
   (A) 1
   (B) 2
   (C) 3
   (D) 4
   (E) 5

11. A patient with hypertension and atrial fibrillation is on therapy with digoxin. The patient has just been discharged from the hospital following a 48 h hospitalization. The drug is prescribed at 0.5 mg twice daily.
   (A) 3
   (B) 4
   (C) 6
   (D) 5
   (E) 7

12. A patient with a known history of hypertension is started on a medication for cholesterol reduction.
   (A) 1
   (B) 2
   (C) 3
   (D) 4
   (E) 5

<table>
<thead>
<tr>
<th>Time After Start of Infusion (h)</th>
<th>Plasma Concentration (mg/L)</th>
<th>Time After Start of Infusion (h)</th>
<th>Plasma Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.8</td>
<td>16</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>20</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>25</td>
<td>3.9</td>
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<tr>
<td>8</td>
<td>3.0</td>
<td>30</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>3.6</td>
<td>40</td>
<td>4.0</td>
</tr>
</tbody>
</table>

13. A patient with diabetes mellitus is being admitted to the hospital for further evaluation. He has a history of type 2 diabetes mellitus, controlled with metformin. He is also taking aspirin for secondary prevention of cardiovascular disease.
   (A) 1
   (B) 2
   (C) 3
   (D) 4
   (E) 5
10. Your 74-year-old patient with myocardial infarction has a severe colic-like abdominl pain. You have decided to give lidocaine to control the pain. The recommended dose of lidocaine is 50 mg IV. However, the patient is hypertensive and has a history of angina. You should consider using a lower dose, such as 25 mg IV, to minimize the risk of hypotension and tachycardia.

11. A patient requires an infusion of procainamide. Its half-life is 2 h. The infusion is begun at 5 mg/h. At 10 am on the same day, a blood sample is taken; the drug concentration is found to be 3 mg/L. What is the possible steady-state drug concentration, mg, after 16 h of infusion?

A) 3 mg/L
B) 6 mg/L
C) 9 mg/L
D) 15 mg/L
E) 27 mg/L

12. A young woman is brought to the emergency room in a deep coma. Her friends state that she self-administered a large dose of morphine 6 h earlier. An immediate blood analysis shows a morphine blood level of 0.25 mg/L. Assuming that the pharmacokinetics of morphine in this patient are Vd = 200 L and the half-life is 3 h, how much morphine did the patient inject 6 h earlier?

A) 25 mg
B) 50 mg
C) 100 mg
D) 200 mg
E) Two more data to predict

13. A normal volunteer will receive a new drug in a phase I clinical trial. The efficacy and volume of distribution of the drug in the subject are 1,385 L/h and 80 L, respectively. The half-life of the drug at this subject will be approximately

A) 83 h
B) 77 h
C) 58 h
D) 49 h
E) 0.02 h

14. Gentamicin is often given in intermittent intravenous bolus doses of 100 mg 3 times a day to achieve target peak plasma concentrations of about 5 mg/L. Gentamicin's clearance (normally 5.4 L/hr/70 kg) is achieved entirely by glomerular filtration. Your patient, however, is found to have a creatinine clearance one third of normal. Your initial dosage regimen for this patient would probably be

A) 20 mg 3 times/day
B) 33 mg 3 times/day
C) 72 mg 3 times/day
D) 100 mg 2 times/day
E) 150 mg 3 times/day

15-17. A new drug was studied in 20 healthy volunteers to determine basic pharmacokinetic parameters. A dose of 100 mg was administered as an intravenous bolus to each volunteer, and blood samples were analyzed at intervals as shown in the graph on page 28. The average plasma concentrations at each time are shown by the solid circles at 90 and 30 minutes and at 1, 2, 3, 4, 6, and 18 hours after administration.

15. The elimination half-life of the new drug is approximately

A) 1.5 h
B) 2 h
C) 4 h
D) 6 h
E) 8 h
16. The volume of distribution of the new drug is approximately:
   (A) 0.05 L
   (B) 0.1 L
   (C) 1 L
   (D) 10 L
   (E) 20 L

17. The clearance of the new drug is approximately:
   (A) 0.43 L/h
   (B) 0.86 L/h
   (C) 1.15 L/h
   (D) 2.3 L/h
   (E) Too few data to answer

ANSWERS

1. Maintenance dose is a function of plasma level and clearance only:

   \[
   \text{Dosage} = \frac{\text{Plasma level} \times \text{Clearance}}{\text{Bioavailability (F)}}
   \]

   - Given: 4 mg/L · 0.08 L/min
   - \( F = 1.0 \)
   - \( \text{Dosage} = 0.32 \text{ mg/min} \)

   when given at 6-h intervals:
   - 0.32 mg/min \( \times 60 \text{ min/h} \times 6 \text{ h} \)
   - 115.2 mg/dose every 6 h

   The answer is C.

2. Loading dose is a function of volume of distribution and target plasma concentration:

   \[
   \text{Loading dose} = V_d \times \frac{\text{Target concentration}}{\text{Bioavailability}}
   \]

   \[
   \text{Loading dose} = 40 \text{L} \times \frac{4 \text{mg/L}}{1.0} = 160 \text{mg}
   \]

   The answer is D.

3. Since the blood level for a drug with first-order kinetics drops by 50% during each half-life, the level will be 2 mg/mL after 1.6 days and 1 mg/mL after 3.2 days. The answer is C.

4. Apparently verapamil is metabolized so readily that only the rate of delivery to the liver affects its disappearance, i.e., it is a blood flow-limited. Further increases in liver enzymes could not increase its elimination. However, the rate of elimination of phenytoin is apparently limited by its rate of metabolism since clearance is much less than hepatic blood flow. Therefore, the clearance of phenytoin can rise if some agent causes an increase in liver enzymes. (Commonly, heart failure, by reducing liver blood flow, may reduce verapamil clearance.) The answer is C.

5. From the description given, if the minimum therapeutic plasma concentration of the hypothetical drug X is 100 units, the minimum toxic concentration is 150 units. If a dose is given that brings the plasma concentration to 150 units, it will fall to 75 units in 1 half-life (6 h). Because 75 units is less than the minimum therapeutic concentration, this dosing interval is too long. Thus, none of the intermediate dosing schedules listed would meet the requirement of the question. Therefore, a constant intravenous infusion (which can be visualized as intermediate dosing at infinitely short intervals) would be more appropriate than any of the intermediate schedules. The answer is E.

6. By inspection of the data in the table, it is clear that the steady-state plasma concentration is approximately 4 mg/L. Further inspection shows that 50% of this concentration was achieved after 4 h of infusion. According to the constant infusion principle (Figure 3—3), 1 half-life is required to reach half of the final concentration; therefore, the half-life of the drug is 4 h. Rearranging the equation for maintenance dosing (dosing rate CL × \( C_p \)), it can be determined that the clearance = dosing rate/\( C_p \) or 2.1 L/h. The volume of distribution can be calculated from the half-life equation (\( V_d > 0.693 \times V_d \) and is equal to 11.5 L). This drug follows first-order kinetics as indicated by the progressive approach to the steady-state plasma concentration. The answer is B.
7. Bioavailability is calculated from the ratio of the area under the curve after oral administration (AUC_{oral}) to the AUC after intravenous administration (AUC_{IV}). The formula is given as: 

\[ \text{Bioavailability} = \frac{AUC_{oral}}{AUC_{IV}} \]

8. The approach to the drug plasma concentration to steady-state concentrations during continuous infusion follows a monoexponential curve (Figure 3-3) that rises rapidly at first and gradually levels off. It reaches 50% of steady state at 1 half-life, 75% at 2 half-lives, 97.5% at 3, 99.75% at 4, and progressively halves the difference between its current level and 100% with each half-life. The answer is E. 32 h or 4 half-lives.

9. The drug is being administered continuously; the steady-state concentration for a continuously administered drug is given by the equation in Question 1. Thus,

\[ \text{C_s} = \frac{\text{Dose}}{\text{Clearance}} \times C_L \]

Rearranging:

\[ C_L = \frac{\text{Dose}}{C_s \times 0.92} \]

\[ C_L = 0.92 \text{ mg/ml} \]

\[ C_L = 0.0209 \text{ mg/ml or 3 mg/l} \]

The answer is B.

10. If the half-life is 1.6 h, the plasma concentration should approach steady state about 8 h (more than 4 half-lives). As indicated by the equation used in question 5, the steady-state concentration is a function of dosage and clearance, or volume of distribution. If the plasma level is less than predicted, the clearance in this patient must be greater than normal. It is also possible that the patient may have a disease (type II disease) or not have normal volume of distribution. All other possible answers can be positively ruled out. The answer is B.

11. According to the curve that relates plasma concentration to infusion rate (Figure 3-3), a drug with each 50% of its final steady-state concentration in 1 half-life, 75% in 2 half-lives, etc. From 9.5 to 14.5 hr, 8 hr or 2 half-lives. Therefore, the measured concentration at 10 hr is 75% of the steady-state value (0.75 X C_s). The steady-state concentration will be 3 mg/l divided by 0.75, or 4 mg/l. The answer is B.

12. According to the curve that relates the decline of plasma concentration to time as the drug is eliminated (Figure 3-3), the plasma concentration of a morphine will be 5 times higher intravenously after administration than at the time of the measurement, which occurred 6 h or 2 half-lives later. Therefore, the initial plasma concentration was 5 mg/l. Since the amount in the body is equal to \( V_d \times C_L \) (see Equation 1), the amount remaining was 250 l x 1 mg/l, or 250 mg. The answer is D.

13. Half-life can be estimated from

\[ t_{1/2} = \frac{0.693}{C_L} \]

\[ = \frac{0.693}{1.386/\text{h}} \]

\[ = 0.5 \times \frac{1}{2.25/\text{h}} \]

\[ = 40 \text{ h} \]

The answer is D.

14. If the drug is cleared almost entirely by the kidney and excretion is constant, the drug daily dose should also be reduced to one third. The answer is B.

15. We are asked to determine the elimination half-life of the drug. The elimination phase of the graph of plasma concentration follows a straight line on the semilogarithmic graph, as we can conclude that the new drug follows first-order kinetics. For the first derivative, the first requirement for determining the half-life. The straight-line portion of the graph shows a decline of 50% from the 2-h point (4 mg/l) to the 4-h sample (2 mg/l). Therefore, the half-life must be 8 minus 2 h or 6 h. The answer is D, 6 h.

16. By definition, \( V_d \) is the amount of drug in the body divided by the plasma concentration. To determine the volume of distribution, the drug must be at equilibrium in its diffusion into the volume of distribution. Equilibrium is not reached until the distribution phase is complete. Therefore, we cannot use any of the data points preceding the start of the distribution phase. On the other hand,
the only point at which we know the amount of drug in the body within certainty is immediately after administration, when the amount is equal to the dose administered. This is the purpose of the extrapolated portion of the plasma concentration curve that extends to zero time. The dashed line shows the plasma concentration curve that would have been obtained if distribution were instantaneous. From the intercept of the extrapolated line with the plasma concentration axis, we see that the plasma concentration would have been 5 mg/L. Therefore, \( V_d = 100 \text{ mg} / 5 \text{ mg/L} = 20 \text{ L} \). The answer is E, 20 L.

17. By definition, CL is equal to the rate of elimination divided by the plasma concentration. However, we are given direct data for the rate of elimination. On the other hand, we have determined the half-life and the volume of distribution of the drug, so we can calculate the clearance from the relationship \( T_1/2 = \frac{0.693}{\text{CL}} \times \frac{V_d}{C_{pl}} \). Rearranging this equation, \( \text{CL} = \frac{0.693 \times V_d}{C_{pl} \times T_1/2} \). Using the data from questions 16 and 17, we obtain \( 0.693 \times 20 \text{ L} = 6 \text{ h} \), or 24 L/h (approximately). The answer is D.

CHECKLIST

When you complete this chapter, you should be able to:

- Compare the half-life of a drug based on its clearance and volume of distribution.
- Calculate loading and maintenance dosage regimens for oral or intravenous administration of a drug when given the following information: minimum therapeutic concentration; bioavailability; clearance; and volume of distribution.
- Calculate the dosage adjustment required for a patient with impaired renal function.

SKILL KEEPER 1 ANSWER:
ZERO-ORDER ELIMINATION (SEE CHAPTER 1)

The 3 important drugs that follow zero-order kinetics are ethanol, aspirin, and phenobarbital.

SKILL KEEPER 2 ANSWER:
FIRST-PASS EFFECT (SEE CHAPTER 1)

The oral route of administration entails passage of the drug through the liver before it enters the systemic circulation for distribution to the body. Therefore, this route results in the lowest bioavailability for most drugs.

THE NEPHROLOGY OF DRUG ACTION

Many cell membranes contain albumin and other plasma proteins that facilitate the absorption of drugs. Intrahepatic drug metabolism is generally considered to involve three steps: (1) activation, (2) inactivation or detoxification, and (3) excretion. Many drugs and their metabolites are excreted in the bile. This process is often the rate-limiting step in the elimination of many drugs, and it is subject to various physiological and pathological factors. The liver is an important site of drug metabolism, and the liver's ability to metabolize drugs is affected by many factors, including age, gender, and disease state.

All organ systems play a role in drug elimination, but the renal system is the most important. This is because the kidneys are responsible for removing many drugs and their metabolites from the body. The kidneys use a variety of mechanisms to eliminate drugs, including filtration, secretion, and reabsorption. The rate at which a drug is eliminated by the kidneys is often referred to as the renal clearance. The renal clearance is a measure of the amount of drug that is filtered by the kidneys and not reabsorbed. The renal clearance is a function of the glomerular filtration rate (GFR) and the fraction of the drug that is excreted unchanged in the urine. The GFR is the rate at which blood flows through the kidneys, and it is a measure of the kidneys' ability to filter blood. The GFR is affected by many factors, including age, gender, and disease state.

TYPE OF DRUG ACTION

A. Phase I

- Phase I reactions involve the oxidation, reduction, or hydrolysis of a drug.

B. Phase II

- Phase II reactions involve the conjugation of drugs with endogenous molecules, such as glucuronides, sulfates, or acetylated derivatives.
4. Which of the following is a phase II drug-metabolizing reaction?
   (A) Acetylation
   (B) Oxidation
   (C) Hydrolysis
   (D) Reduction
   (E) Sulfoxidation

5. Reports of cardiac arhythmias caused by unusually high blood levels of 2 antihistamines, terfenadine and astemizole, led to their removal from the market. These effects were best explained by
   (A) Concurrent treatment with phenothiazines
   (B) Use of these drugs by smokers
   (C) A generic predisposition to metabolic succinylcholine toxicity
   (D) Treatment of these patients with cimetidine, an antifungal agent
   (E) None of the above

6. Which of the following drugs is associated with decreased metabolism in Caucasion and African-Americans that in non-African:
   (A) Cimidine
   (B) Enalapril
   (C) Procainamide
   (D) Flecainide
   (E) Ketoconazole

7. Which of the following drugs may inhibit the hepatic enzymatic P450 responsible for warfarin metabolism?
   (A) Cimetidine
   (B) Enalapril
   (C) Procainamide
   (D) Ketoconazole
   (E) Sulfonamides

8. Which of the following drugs is hydrolyzed by a plasma esterase that is abnormally low in activity in about 1 of every 2500 humans?
   (A) Cimetidine
   (B) Enalapril
   (C) Procainamide
   (D) Flecainide
   (E) Sulfonamides

DIRECTIONS: 9-12. The matching questions in this section consist of a list of 8 lettered options followed by several numbered items. For each numbered item, select the ONE lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

(A) Cimetidine
(B) Enalapril
(C) Ketoconazole
(D) Procainamide

9. Which of the following is a drug that is partially metabolized by CYP2D6 in the liver?
   (A) Chaste
   (B) Cimetidine
   (C) Procainamide
   (D) Flecainide

10. Which of the following drugs is known to cause a decrease in hepatic detoxification of drugs?
    (A) Cimetidine
    (B) Enalapril
    (C) Ketoconazole
    (D) Procainamide

11. Which of the following drugs is known to increase the duration of action of a drug that is partially metabolized by CYP2D6 in the liver?
    (A) Chaste
    (B) Cimetidine
    (C) Procainamide
    (D) Flecainide

12. Which of the following drugs is known to increase the amount of drug in the body by inhibiting the renal clearance of drugs?
    (A) Cimetidine
    (B) Enalapril
    (C) Ketoconazole
    (D) Procainamide
(E) Quinidine
(F) Ritonavir
(G) Sucinylcholine
(H) Verapamil

9. Chronic use of this drug may increase the toxicity of acetaminophen.

10. A drug that has higher first-pass metabolism in men than in women.

11. This drug is an established inhibitor of P-glycoprotein (P-gp) drug transporters.

12. Use of this agent in combination with other anti-HIV drugs permit dose reductions.

ANSWERS

1. Biotransformation usually results in a product that is less lipid-soluble. The answer is B.

2. The smooth endoplasmic reticulum, which contains the mixed-function oxidase drug-metabolizing enzymes, is selectively increased by inducers. The answer is A.

3. Photoirradiation can induce drug-metabolizing enzymes and thereby reduce the duration of drug action. Displacement of drug from tissue can transiently increase the intensity of the effect, but will decrease the volume of distribution and thereby reduce the half-life. Cimetidine is recognized as an inhibitor of P450 and may also decrease hepatic blood flow under some circumstances. The answer is B.

4. Acetylation is a phase II conjugation reaction. The answer is A.

5. Treatment with photoirradiation and smoking are associated with increased drug metabolism and lower, not higher, blood levels. Ketoconazole, warfarin, erythromycin, and some substance in grapefruit juice slow the metabolism of cytochrome P450 and are inhibitors of CYP3A4 (Chapter 16). The answer is D.

6. Procainamide, like lidocaine and isoxazole, is metabolized by N-acetylation, an enzymatic process that is slow in about 20% of Asians and in about 60% of Caucasians and African-Americans. The answer is B.

7. Cimetidine is a commonly used drug that has well-documented ability to inhibit the hepatic metabolism of many drugs. The answer is A.

8. Sucinylcholine is normally hydrolyzed quickly rapidly by plasma cholinesterase (pseudo-cholinesterase). This enzyme is abnormal in about 1/25,000 of the human population, resulting in an unusually long duration of action of succinylcholine in those patients. The answer is C.

9. Acetaminophen is normally diminished by phase II conjugation reactions. The drug's toxicity is dependent on an oxidized reactive metabolite produced by phase I oxidizing P450 enzymes. Drugs that cause induction of P450 enzymes, such as rifampin (not listed), may increase the production of this toxic metabolite. Ethanol also does this and thus reduces the hepatotoxic dose. The answer is A.

10. Ethanol is subject to metabolism in the stomach as well as in the liver. Independently of weight and other factors, men have greater gastric alcohol metabolism than women. The answer is B.

11. Verapamil is an inhibitor of P-glycoprotein drug transporters and has been used to enhance the cytoxic actions of mechlorethamine in cancer chemotherapy. The answer is A.

12. Ritonavir induces hepatic drug metabolism, and its use as low doses in combination regimens has permitted dose reductions of other HIV protease inhibitors (eg, indinavir). The answer is B.

SAFETY

Because weight and body surface area are important factors in the metabolism of drugs, a weight index is sometimes used. The weight index is the weight divided by the body surface area. The body surface area can be calculated from the height, weight, and sex of the patient. The body surface area is estimated from several hundred formulae, but the following is widely used:

\[ \text{BSA} = \frac{0.457 \times \text{height} \times \text{weight}^{0.425}}{(\text{weight} + 0.375)^{0.625}} \]

For example, a 60-kg person who is 170 cm tall has a body surface area of approximately 1.73 m².

ANIMALS

The amount of drug that causes death in animals is generally higher than that required to cause death in humans. The therapeutic index is the ratio of the dose that causes death in animals to the dose that causes death in humans. A higher therapeutic index indicates a more favorable margin of safety.

A. Acute Toxicity

Acute toxicity occurs within minutes to 12 hours after ingestion of a single dose. The symptoms of acute toxicity may include nausea, vomiting, and diarrhea. In severe cases, convulsions and coma may occur. The treatment of acute toxicity includes supportive care, such as fluid and electrolyte replacement, and specific antidotes if available.

1. The compound in question is administered orally to a rat. The rat dies within 2 hours. The compound is:

   A. Acute toxic
   B. Moderate toxic
   C. Not toxic

2. The compound has a therapeutic index of 10. The compound is:

   A. High therapeutic index
   B. Moderate therapeutic index
   C. Low therapeutic index

3. The compound has a lethal dose of 10 mg/kg in mice. The compound is:

   A. Low lethal dose
   B. Moderate lethal dose
   C. High lethal dose

4. The compound has a therapeutic index of 5. The compound is:

   A. High therapeutic index
   B. Moderate therapeutic index
   C. Low therapeutic index
one that produces either a significant physiologic response or a very minor toxic effect.

**5. Phase II**

A phase II trial involves evaluation of a drug in a modest number of patients (e.g., 100–300) with the target disease. A placebo or positive control drug is included in a single-blind or double-blind design. The study is carried out under very carefully controlled conditions, and patients are very closely monitored, often in a hospital research ward. The goal is to determine whether the agent has the desired therapeutic effects at doses that are tolerated by sick patients.

**5. Phase III**

A phase III trial consists of a large design involving many patients (e.g., 1000–5000) or more in many centers and many clinicians who are using the drug in its usual general use (e.g., in patients). Such studies usually include placebos and more controls in a double-blind crossover design. The goal is to explore further the spectrum of beneficial properties of the new drug, to compare it with other therapies, and to decrease variability if any that occur scarily or are undesirable in phase II studies.

**5. Phase IV**

Phase IV represents the postmarketing surveillance of evaluation, in which it is hoped that reactions that occur very infrequently will be detected and reporting only enough to prevent major therapeutic disasters. Unlike the first 3 phases, phase IV is not rigidly regulated by the FDA.

**DRUG LEGISLATION**

In the United States, many laws regulating drugs have been passed during this century. Refer to Table 5–1 for a partial list of this legislation.

**ORPHAN DRUGS**

An orphan drug is a drug for a rare disease (one affecting fewer than 200,000 people in the United States). The study of such agents has often been neglected because the sales of an effective agent for an uncommon ailment might not pay for control development. In the United States, current legislation provides for tax relief and other incentives designed to encourage the development of orphan drugs.

**QUESTIONS**

1. With regard to clinical trials of new drugs, which of the following is MOST correct?

   (A) Phase I involves the study of a small number of normal volunteers by highly trained clinical pharmacologists...
### Table 5-1. Selected Legislation Pertaining to Drugs in the United States.

<table>
<thead>
<tr>
<th>Law</th>
<th>Purpose and Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Food &amp; Drug Act of 1906</td>
<td>Prohibited mislabeling and adulteration of drugs</td>
</tr>
<tr>
<td>Harrison Narcotics Act of 1914</td>
<td>Established regulations for the use of opium, opioids, and cocaine (marijuana added in 1937)</td>
</tr>
<tr>
<td>Food, Drug, &amp; Cosmetic Act of 1938</td>
<td>Required that new drugs be tested for safety as well as purity</td>
</tr>
<tr>
<td>Kelso-Harris Amendment (1962)</td>
<td>Required proof of efficacy as well as safety for new drugs</td>
</tr>
<tr>
<td>Comprehensive Drug Abuse Prevention &amp; Control Act (1970)</td>
<td>Outlined strict controls on the manufacture, distribution, and prescribing of habit-forming drugs; established programs for the treatment and prevention of addiction</td>
</tr>
<tr>
<td>Drug Price Competition &amp; Patent Restoration Act of 1984</td>
<td>Abbreviated new drug applications for generic drugs; required bioequivalence data; patent life extended by the amount of time drug was delayed by the review process; cannot exceed 5 years or extend to more than 14 years post NDA</td>
</tr>
<tr>
<td>Dietary Supplement Health and Education Act (1994)</td>
<td>Amended the Federal Food, Drug, &amp; Cosmetic Act of 1938 to establish standards with respect to dietary supplements; requires the establishment of specific ingredient and nutrition information labeling that defines dietary supplements and classifies them as part of the food supply.</td>
</tr>
<tr>
<td>Bioterrorism Act of 2002</td>
<td>Enhances controls on dangerous biologic agents and toxins; seeks to protect safety of food, water, and drug supply.</td>
</tr>
</tbody>
</table>


#### Questions

1. **A**. Phase II involves the use of the new drug in a large number of patients (1000–5000) who have the disease to be treated.  
   - **B**. Phase III involves the determination of the drug's therapeutic index by the cautious induction of toxicity.  
   - **C**. Phase IV involves the detailed study of toxic effects that have been discovered in phase III.  
   - **D**. Phase II requires the use of a positive control (a known effective drug) and a placebo.  

2. **A**. Animal testing of potential new therapeutic agents  
   - **B**. Requires the use of at least 2 primate species (e.g., monkey and baboon).  
   - **C**. Requires the submission of histopathologic slides and specimens to the FDA for government evaluation.  
   - **D**. Has good predictability for drug allergy-type reactions.  
   - **E**. May be abbreviated in the case of some very toxic agents used in cancer.

3. The "dominant lethal" test involves the treatment of a male adult animal with a chemical before mating; the pregnant female is later examined for fetal death and abnormalities. The dominant lethal test therefore is a test of:  
   - **A**. Transgenericity  
   - **B**. Matagenericy  
   - **C**. Carcinogenicity  
   - **D**. All of the above  
   - **E**. None of the above

4. An optimal phase III clinical trial of a new analgesic drug for mild pain would NOT include:  
   - **A**. A negative control (placebo)  
   - **B**. A positive control (current standard therapy)  
   - **C**. Double-blind protocol (neither the patient nor immediate observers of the patient know which agent is active)  
   - **D**. A group of 2000–3000 subjects with a clinical condition requiring analgesia  
   - **E**. Prior submission of an NDA (new drug application) to the FDA

5. In the testing of new compounds (e.g., antihyper- tension drugs) for potential therapeutic use  
   - **A**. Animal tests cannot be used to predict the types of toxicities that may occur because there is no correlation with human toxicity  
   - **B**. Human studies in normal individuals will be done before the drug is used in diseased individuals
6. The Ames test is a method for detecting
(A) Carcinogenesis in rodents
(B) Carcinogenesis in primates
(C) Teratogenesis in any mammalian species
(D) Teratogenesis in primates
(E) Mutagenesis in bacteria

ANSWERS

1. Except for known toxic drugs (e.g., cancer chemotherapy drugs), phase I is carried out in several hundred patients with the disease. The therapeutic index is rarely determined in any clinical trial. Phase IV is the general surveillance phase that follows general marketing of the new drug. It is not targeted at specific effects. Positive controls and placebos are not a rigid requirement of any phase of clinical trials, although they are often used in phase II and phase III studies. The answer is A.

2. Drugs proposed for short-term use may not require long-term chronic testing. For some drugs, no primates are used; for other agents, only 1 species is used. The data from the tests, not the evidence itself, must be submitted to the FDA. Preliminary data are not required for phase II clinical trials. The answer is A.

CHECKLIST
When you complete this chapter, you should be able to:

- Describe the major animal and clinical studies carried out in drug development.
- Describe the purpose of the Investigational New Drug (IND) Exemption and the New Drug Application (NDA).
- Define carcinogenesis, mutagenesis, and teratogenesis.

3. The description of the test indicates that a chromosomal change (picked from father to fetus) is the toxicity detected. This is a mutation. The answer is B.

4. The first 4 items (A-D) are correct. An NDA cannot be submitted unless the necessary clinical trials have been completed. The IND must be approved before clinical trials can be conducted. The answer is E.

5. Animal tests in a single species do not always predict human toxicities; however, when these tests are carried out in several species, most acute toxicities that occur in humans will also appear in at least 1 animal species. According to current FDA rules, the "degree of risk" must be determined in at least 2 species. Use of primates is not always required. The therapeutic index is not required. Except for cancer chemotherapeutic agents, phase I clinical trials are always carried out in normal subjects. The answer is B.

6. The Ames test is carried out in Salmonella and detects mutations in the bacterial DNA. Because mutagenic potential is associated with carcinogenic risk for many chemicals, the Ames test is often used to claim that a particular agent may be a carcinogen. However, the test itself only detects mutations. The answer is E.