DRUG PATENTS & GENERIC DRUGS

A patent application is usually submitted around the time that a new drug enters animal testing (Figure 1–5). In the United States, approval of the patent and completion of the NDA approval process give the originator the right to market the drug without competition from other firms for a period of 10–14 years from the NDA approval date. After expiration of the patent, any company may apply to the FDA for permission to market a generic version of the same drug if they demonstrate that their generic drug molecule is **bioequivalent** (ie, meets certain requirements for content, purity, and bioavailability) to the original product.

DRUG LEGISLATION

Many laws regulating drugs in the United States were passed during the 20th century. Refer to Table 1–4 for a partial list of this legislation.

ORPHAN DRUGS

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

TABLE 1–4 Selected legislation pertaining to drugs in the United States.

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of foods and drugs (but no requirement for efficacy or safety)
Harrison Narcotics Act of 1914	Established regulations for the use of opium, opioids, and cocaine (marijuana added in 1937)
Food, Drug, and Cosmetics Act of 1938	Required that new drugs be tested for safety as well as purity
Kefauver-Harris Amendment (1962)	Required proof of efficacy as well as safety for new drugs
Dietary Supplement and Health Education Act (1994)	Amended the Food, Drug, and Cosmetics Act of 1938 to establish standards for dietary supplements but prohibited the FDA from applying drug efficacy and safety standards to supplements

QUESTIONS

1. A 3-year-old is brought to the emergency department having just ingested a large overdose of chlorpropamide, an oral antidiabetic drug. Chlorpropamide is a weak acid with a pK_a of 5.0. It is capable of entering most tissues. On physical examination, the heart rate is 110/min, blood pressure 90/50 mm Hg, and respiratory rate 30/min. Which of the following statements about this case of chlorpropamide overdose is most correct?
   (A) Urinary excretion would be accelerated by administration of NH_4Cl, an acidifying agent
   (B) Urinary excretion would be accelerated by giving $NaHCO_3$, an alkalinizing agent
   (C) Less of the drug would be ionized at blood pH than at stomach pH
   (D) Absorption of the drug would be slower from the stomach than from the small intestine

2. Botulinum toxin is a large protein molecule. Its action on cholinergic transmission depends on an intracellular action within nerve endings. Which one of the following processes is best suited for permeation of very large protein molecules into cells?
   (A) Aqueous diffusion
   (B) Endocytosis
   (C) First-pass effect
   (D) Lipid diffusion
   (E) Special carrier transport

3. A 12-year-old child has bacterial pharyngitis and is to receive an oral antibiotic. She complains of a sore throat and pain on swallowing. The tympanic membranes are slightly reddened bilaterally, but she does not complain of earache. Blood pressure is 105/70 mm Hg, heart rate 100/min, temperature 37.8°C (100.1°F). Ampicillin is a weak organic acid with a pK_a of 2.5. What percentage of a given dose will be in the lipid-soluble form in the duodenum at a pH of 4.5?
   (A) About 1%
   (B) About 10%
   (C) About 50%
   (D) About 90%
   (E) About 99%

4. Ampicillin is eliminated by first-order kinetics. Which of the following statements best describes the process by which the plasma concentration of this drug declines?
   (A) There is only 1 metabolic path for drug elimination
   (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 distributed to only 1 compartment outside the vascular system

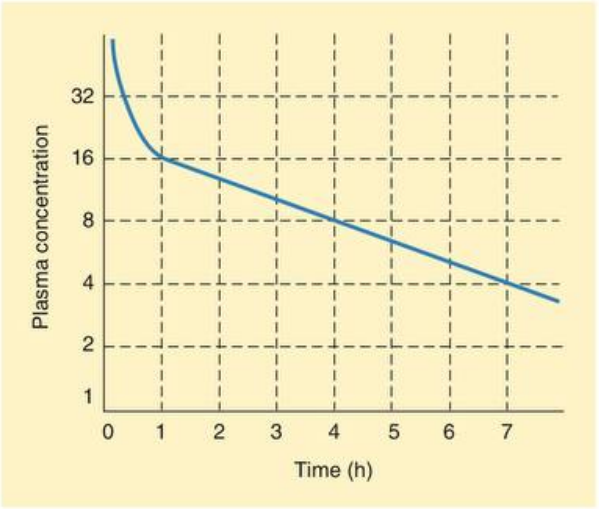
5. The pharmacokinetics of a new drug are under study in a phase 1 clinical trial. Which statement about the distribution of drugs to specific tissues is most correct?
(A) Distribution to an organ is independent of blood flow
(B) Distribution of a lipid-soluble drug will be to adipose tissue initially
(C) Distribution into a tissue depends on the unbound drug concentration gradient between blood and the tissue
(D) Distribution is increased for drugs that are strongly bound to plasma proteins
(E) Distribution has no effect on the half-life of the drug

6. The pharmacokinetic process or property that distinguishes the elimination of ethanol and high doses of phenytoin and aspirin from the elimination of most other drugs is called
(A) Distribution
(B) Excretion
(C) First-pass effect
(D) First-order elimination
(E) Zero-order elimination

7. Which of the following statements about animal testing of potential new therapeutic agents is *most* correct?
(A) Requires at least 3 years to discover late toxicities
(B) Requires at least 1 primate species (eg, rhesus monkey)
(C) Requires the submission of histopathologic slides and specimens to the FDA for evaluation by government scientists
(D) Has good predictability for drug allergy-type reactions
(E) May be abbreviated in the case of some very toxic agents used in cancer

8. 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) Teratogenicity
(B) Mutagenicity
(C) Carcinogenicity
(D) Sperm viability

9. In a phase 1 clinical trial, "Novexum," a new drug, was administered intravenously to 25 volunteers, and blood samples were taken for several hours. Several inactive metabolites were found as well as declining concentrations of Novexum. A graph was prepared as shown below, with the Novexum plasma levels plotted on a logarithmic ordinate and time on a linear abscissa. It was concluded that the drug has first-order kinetics. From this graph, what is the best estimate of the elimination half-life of Novexum?
(A) 0.5 h
(B) 1 h
(C) 3 h
(D) 4 h
(E) 7 h



10. A large pharmaceutical company has conducted extensive animal testing of a new drug for the treatment of advanced prostate cancer. The chief of research and development recommends that the company now submit an IND application in order to start clinical trials. Which of the following statements is *most* correct regarding clinical trials of new drugs?
(A) Phase 1 involves the study of a small number of normal volunteers by highly trained clinical pharmacologists
(B) Phase 2 involves the use of the new drug in a large number of patients (1000–5000) who have the disease to be treated under conditions of proposed use (eg, outpatients)
(C) Chronic animal toxicity studies must be complete and reported in the IND
(D) Phase 4 involves the detailed study of toxic effects that have been discovered in phase 3
(E) Phase 2 requires the use of a positive control (a known effective drug) and a placebo

11. Which of the following would probably *not* be included in an optimal phase 3 clinical trial of a new analgesic drug for mild pain?
(A) A negative control (placebo)
(B) A positive control (current standard analgesic therapy)
(C) Double-blind protocol (in which neither the patient nor immediate observers of the patient know which agent is active)
(D) A group of 1000–5000 subjects with a clinical condition requiring analgesia
(E) Prior submission of an NDA (new drug application) to the FDA

12. The Ames test is frequently carried out before clinical trials are begun. The Ames test is a method that detects
(A) Carcinogenesis in primates
(B) Carcinogenesis in rodents
(C) Mutagenesis in bacteria
(D) Teratogenesis in any mammalian species
(E) Teratogenesis in primates

13. Which of the following statements about new drug development is *most* correct?
    (A) If the need is great, drugs that test positive for teratogenicity, mutagenicity, or carcinogenicity can be tested in humans but the IND must specify safety measures to be taken
    (B) Food supplements and herbal (botanical) remedies must be shown to be effective for the target condition before marketing is approved by the FDA
    (C) All new drugs must be studied in at least 1 primate species before NDA submission
    (D) Orphan drugs are drugs that are no longer produced by the original manufacturer
    (E) Phase 4 (surveillance) is the most rigidly regulated phase of clinical drug trials

14. Which statement about the development of new drugs is most correct?
    (A) Because they may cause anaphylaxis, proteins cannot be used as drugs
    (B) Most drugs fall between 100 and 1000 in molecular weight
    (C) Drugs for systemic action that are to be administered orally should be highly water soluble and insoluble in lipids
    (D) Water solubility is minimal in highly polarized (charged) drug molecules

ANSWERS

1. Questions that deal with acid-base (Henderson-Hasselbalch) manipulations are common on examinations. Since absorption involves permeation across lipid membranes, we can in theory 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. Chlorpropamide is a weak acid, which means that it is less ionized when protonated, ie, at acid pH. Choice **C** suggests that the drug would be less ionized at pH 7.4 than at pH 2.0, which is clearly wrong for weak acids. Choice **D** says (in effect) that the more ionized form is absorbed faster, which is incorrect. **A** and **B** are opposites because NH_4Cl is an acidifying salt and sodium bicarbonate an alkalinizing one. (From the point of view of test strategy, opposites in a list of answers always deserve careful attention.) Because an alkaline environment favors ionization of a weak acid, we should give bicarbonate. The answer is **B.** Note that clinical management of overdose involves many other considerations in addition to trapping the drug in urine; manipulation of urine pH may be contraindicated for other reasons.

2. Endocytosis is an important mechanism for transport of very large molecules across membranes. Aqueous diffusion is not involved in transport across the lipid barrier of cell membranes. Lipid diffusion and special carrier transport are common for smaller molecules. The first-pass effect has nothing to do with the mechanisms of permeation; rather, it denotes drug metabolism or excretion before absorption into the systemic circulation. The answer is **B.**

3. U.S. Medical Licensing Examination (USMLE)-type questions often contain a lengthy clinical description in the stem. One can often determine the relevance of the clinical data by scanning the last sentence in the stem and the list of answers, see Appendix I. In this question, the emphasis is clearly on pharmacokinetic principles. Ampicillin is an acid, so it is more ionized at alkaline pH and less ionized at acidic pH. The Henderson-Hasselbalch equation predicts that the ratio changes from 50/50 at the pH equal to the pK_a to 1/10 (protonated/unprotonated) at 1 pH unit more alkaline than the pK_a and 1/100 at 2 pH units more alkaline. For acids, the protonated form is the nonionized, more lipid-soluble form. The answer is **A.**

4. "First-order" means that the elimination rate is proportional to the concentration perfusing the organ of elimination. The half-life is a constant. The rate of elimination is proportional to the rate of administration only at steady state. The order of elimination is independent of the number of compartments into which a drug distributes. The answer is **B**.

5. This is a straightforward question of pharmacokinetic distribution concepts. Choice B is incorrect because distribution depends on blood flow as well as solubility in the tissue; thus most drugs will initially distribute to high blood flow tissues and only later to larger, low-flow tissues, even if they are more soluble in them. From the list of determinants of drug distribution given on pages 5–6, choice **C** is correct.

6. The excretion of most drugs follows first-order kinetics. However, ethanol and, in higher doses, aspirin and phenytoin follow zero-order kinetics; that is, their elimination rates are constant regardless of blood concentration. The answer is **E.**

7. 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. Prediction of human drug allergy from animal testing is useful but not definitive (see answer 12). Testing may be abbreviated for drugs for which there is urgent need; the answer is **E.**

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

9. Drugs with first-order kinetics have constant half-lives, and when the log of the concentration in a body compartment is plotted versus time, a straight line results. The half-life is defined as the time required for the concentration to decrease by 50%. As shown in the graph, the concentration of Novexum decreased from 16 units at 1 h to 8 units at 4 h and 4 units at 7 h; therefore, the half-life is 7 h minus 4 h or 3 h. The answer is **C**.

10. Except for known toxic drugs (eg, cytotoxic cancer chemotherapy drugs), phase 1 is carried out in 25–50 normal volunteers. Phase 2 is carried out in several hundred closely monitored patients with the disease. Results of chronic toxicity studies in animals are required in the NDA and are usually underway at the time of IND submission. However, they do not have to be completed and reported in the IND. Phase 4 is the general surveillance phase that follows 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 placebos are often used in phase 2 and phase 3 studies. The answer is **A.**

11. The first 4 items (**A–D**) are correct; they *would* be included. An NDA cannot be acted upon until the first 3 phases of clinical trials have been completed. (The IND must be approved before clinical trials can be conducted.) The answer is **E.**

Which of the following statements about new drug development is *most* correct?

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11. The first 4 items (**A–D**) are correct; they *would* be included. An NDA cannot be acted upon until the first 3 phases of clinical trials have been completed. (The IND must be approved before clinical trials can be conducted.) The answer is **E.**

12. 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, a positive Ames test is often used to suggest that a particular agent may be a carcinogen. However, the test itself only detects mutations. The answer is **C.**

13. Food supplements and botanicals are much more loosely regulated than conventional drugs; they are not required to be shown effective before marketing. Primates are not required in any phase of new drug testing, although they are sometimes used. (Note the trigger word "all" in choice (C); answers claiming "all…" are almost always wrong.) Orphan drugs are those for which the anticipated patient population is smaller than 200,000 patients in the United States. Phase 4 surveillance is the most loosely regulated phase of clinical trials. Many drugs in current clinical use test positive for teratogenicity, mutagenicity, or carcinogenicity. Such drugs are usually labeled with warnings about these toxicities and, in the case of teratogenicity, are labeled as contraindicated in pregnancy. The answer is **A.**

14. Many peptide and protein drugs, eg, insulin, antibodies, are in use; if identical or sufficiently similar to the human molecules, anaphylaxis is uncommon. Most drugs *do* fall between 100 and 1000 in molecular weight. Drugs for systemic use should be at least minimally water soluble (so they do not precipitate in the intestine) and lipid soluble (so they can cross lipid barriers). Charged molecules attract a shell of water molecules, making them more water soluble. The answer is **B.**

Second, agonist-bound receptors may be internalized by endocytosis, removing them from further exposure to extracellular molecules. The internalized receptor molecule may then be either reinserted into the membrane (eg, morphine receptors) or degraded (eg, β adrenoceptors, epidermal growth factor receptors). In some cases, a cyclic internalization-reinsertion process may actually be necessary for normal functioning of the receptor-effector system.

Third, continuous activation of the receptor-effector system may lead to depletion of some essential substrate required for downstream effects. For example, depletion of endogenous thiol cofactors may be responsible for tolerance to nitroglycerin. In some cases, repletion of the missing substrate (eg, by administration of glutathione) can reverse the tolerance.

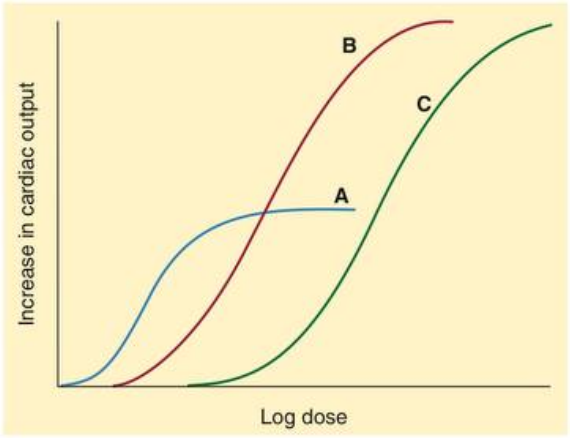
Long-term reductions in receptor number **(downregulation)** may occur in response to continuous exposure to agonists. The opposite change **(upregulation)** may occur when receptor activation is blocked for prolonged periods (usually several days) by pharmacologic antagonists or by denervation.

QUESTIONS

1. A 55-year-old man is seen in the clinic with hypertension of 150/95 mm Hg (millimeters of mercury). His personal medical history and physical examination are otherwise unremarkable but his family history is positive for early deaths due to cardiovascular disease. A decision is made to treat his hypertension, starting with a calcium channel blocker. Blocker A in a dose of 5 mg produces the same decrease in blood pressure as 500 mg of blocker B. Which of the following predictions is most accurate?
- **(A)** Blocker A will be more efficacious than blocker B
- **(B)** Blocker A will be about 100 times more potent than blocker B
- **(C)** Toxicity of blocker A will be less than that of blocker B
- **(D)** Blocker A will have a wider therapeutic window than blocker B
- **(E)** Blocker A will have a longer half-life than blocker B

2. Graded and quantal dose-response curves are being used for evaluation of a new analgesic drug in the animal laboratory and in clinical trials. Which of the following statements best describes *graded* dose-response curves?
- **(A)** More precisely quantitated than quantal dose-response curves
- **(B)** Obtainable from isolated tissue preparations but not from the study of intact subjects
- **(C)** Used to determine the maximal efficacy of the drug
- **(D)** Used to determine the therapeutic index of the drug
- **(E)** Used to determine the variation in sensitivity of subjects to the drug

3. Prior to clinical trials in patients with heart failure, an animal study was carried out to compare two new positive inotropic drugs (A and B) to a current standard agent (C). The results of cardiac output measurements are shown in the graph below.



Which of the following statements is correct?
- **(A)** Drug A is most effective
- **(B)** Drug B is least potent
- **(C)** Drug C is most potent
- **(D)** Drug B is more potent than drug C and more effective than drug A
- **(E)** Drug A is more potent than drug B and more effective than drug C

4. A study was carried out in isolated intestinal smooth muscle preparations to determine the action of a new drug "novamine," which in separate studies bound to the same receptors as acetylcholine, an agonist. In the absence of other drugs, acetylcholine caused contraction of the muscle. Novamine alone caused relaxation of the preparation. In the presence of a low concentration of novamine, the EC_{50} of acetylcholine was unchanged, but the E_{max} was reduced. In the presence of a high concentration of novamine, extremely high concentrations of acetylcholine had no effect. Which of the following expressions best describes novamine?
- **(A)** A chemical antagonist
- **(B)** An irreversible antagonist
- **(C)** A partial agonist
- **(D)** A physiologic antagonist
- **(E)** A spare receptor agonist

5. Beta adrenoceptors in the heart regulate cardiac rate and contractile strength. Several studies have indicated that in humans and experimental animals, about 90% of β adrenoceptors in the heart are spare receptors. 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 lasts longer than the intracellular effect
- **(C)** Spare receptors influence the maximal efficacy of the drug-receptor system
- **(D)** Spare receptors activate the effector machinery of the cell without the need for a drug
- **(E)** Spare receptors may be detected by finding that the EC_{50} is smaller than the K_d for the agonist

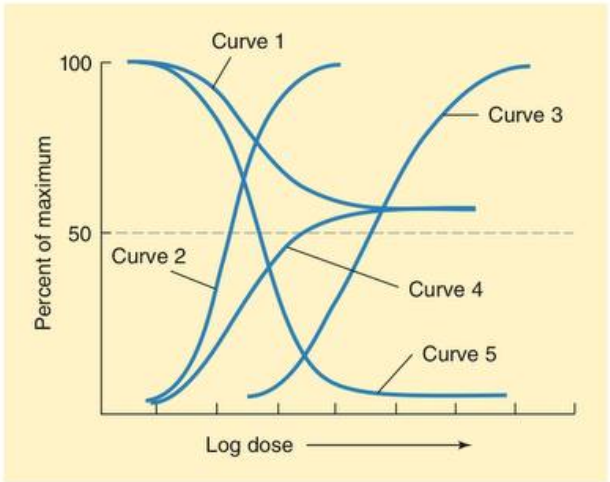
6. Two cholesterol-lowering drugs, X and Y, were studied in a large group of patients, and the percentages of the group showing a specific therapeutic effect (35% reduction in low-density lipoprotein [LDL] cholesterol) were determined. The results are shown in the following table.

Drug Dose (mg)	Percent Responding to Drug X	Percent Responding to Drug Y
5	1	10
10	5	20
20	10	50
50	50	70
100	70	90
200	90	100

Which of the following statements about these results is correct?
(A) Drug X is safer than drug Y
(B) Drug Y is more effective than drug X
(C) The 2 drugs act on the same receptors
(D) Drug X is less potent than drug Y
(E) The therapeutic index of drug Y is 10

7. Sugammadex is a drug that reverses the action of rocuronium and certain other skeletal muscle-relaxing agents (nondepolarizing neuromuscular blocking agents). It appears to interact directly with the rocuronium molecule and not at all with the rocuronium receptor. Which of the following terms best describes sugammadex?
(A) Chemical antagonist
(B) Noncompetitive antagonist
(C) Partial agonist
(D) Pharmacologic antagonist
(E) Physiologic antagonist

QUESTIONS: 8–10. Each of the curves in the graph below may be considered a concentration-effect curve or a concentration-binding curve.



8. Which of the curves in the graph describes the percentage of *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

9. Which of the curves in the graph describes the percentage *effect* observed 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

10. Which of the curves in the graph describes the percentage of *binding* of the partial agonist 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 maximal antihypertensive response to either drug. Similarly, no information about half-life or toxicity is provided. The fact that a given response is achieved with a smaller dose of blocker A indicates only that A is more potent than B in the ratio of 500:5. The answer is **B.**

2. Precise quantitation is possible with both types of dose-response curves. Quantal dose-response curves show the frequency of occurrence of a specified response, which may be therapeutically effective (ED) or toxic (TD). Thus, quantal studies are used to determine the therapeutic index and the variation in sensitivity to the drug in the population studied. Graded (not quantal) dose-response curves are used to determine maximal efficacy (maximal response). The answer is **C.**

3. Drug A produces 50% of its maximal effect at a lower dose than either B or C and thus is the most potent; drug C is the least potent. However, drug A, a partial agonist, is less efficacious than drugs B and C. The answer is **D.**

4. Choices involving chemical or physiologic antagonism are incorrect because novamine is said to act at the same receptors as acetylcholine. When given alone, the novamine effect is opposite to that of acetylcholine; so choice **C** is incorrect. "Spare receptor agonist" is a nonsense distracter. The answer is **B.**

5. There is no difference in location between "spare" and other receptors. Spare receptors may be defined as those that are not needed for binding drug to achieve the maximal effect. Spare 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 do not bind an

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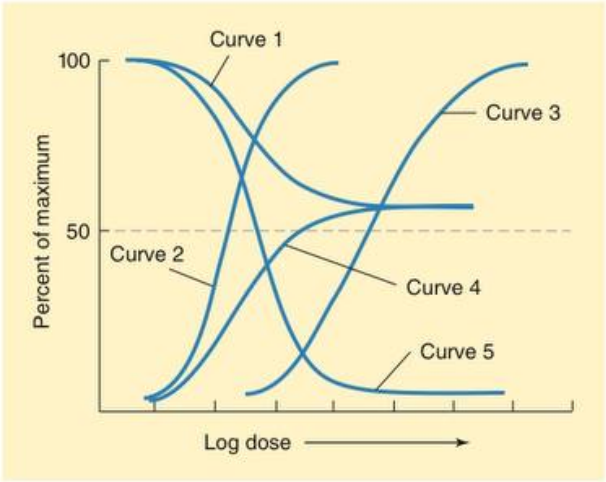

(E) Curve 5

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2. Precise quantitation is possible with both types of dose-response curves. Quantal dose-response curves show the frequency of occurrence of a specified response, which may be therapeutically effective (ED) or toxic (TD). Thus, quantal studies are used to determine the therapeutic index and the variation in sensitivity to the drug in the population studied. Graded (not quantal) dose-response curves are used to determine maximal efficacy (maximal response). The answer is **C.**
3. Drug A produces 50% of its maximal effect at a lower dose than either B or C and thus is the most potent; drug C is the least potent. However, drug A, a partial agonist, is less efficacious than drugs B and C. The answer is **D.**
4. Choices involving chemical or physiologic antagonism are incorrect because novamine is said to act at the same receptors as acetylcholine. When given alone, the novamine effect is opposite to that of acetylcholine; so choice **C** is incorrect. "Spare receptor agonist" is a nonsense distracter. The answer is **B.**
5. There is no difference in location between "spare" and other receptors. Spare receptors may be defined as those that are not needed for binding drug to achieve the maximal effect. Spare 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 do not bind an agonist molecule, spare receptors do not activate an effector molecule. EC_{50} *less* than K_d is an indication of the presence of spare receptors. The answer is **E.**
6. No information is presented regarding the safety of these drugs. Similarly, no information on efficacy (maximal effect) is presented; this requires graded dose-response curves. Although both drugs are said to be producing a therapeutic effect, no information on their receptor mechanisms is given. Since no data on toxicity are available, the therapeutic index cannot be determined. The answer is **D** because the ED_{50} of drug Y (20 mg/d) is less than that of drug X (50 mg/d).
7. Sugammadex interacts directly with rocuronium and not with the rocuronium receptor; therefore, it is a chemical antagonist. The answer is **A.**
8. The binding of a full agonist *decreases* 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 drops to zero, that is, Curve 5. The answer is **E.**
9. Curve 1 describes the *response* of the system when a full agonist is displaced by increasing concentrations of partial agonist. This is because the increasing percentage of receptors binding the partial agonist finally produce the maximal effect typical of the partial agonist. The answer is **A.**
10. Partial agonists, like full agonists, bind 100% of their receptors when present in a high enough concentration. Therefore, the binding curve (but not the effect curve) will go to 100%. If the effect curve is Curve 4 and many spare receptors are present, the binding curve must be displaced to the right of Curve 4 ($K_d > EC_{50}$). Therefore, Curve 3 fits the description better than Curve 2. The answer is **C.**

SKILL KEEPER ANSWER: ALLOSTERIC ANTAGONISTS

Allosteric antagonists do not bind to the agonist receptor site; they bind to some other region of the receptor molecule that results in inhibition of the response to agonists (see Figure 1–1). They do not prevent binding of the agonist. In contrast, pharmacologic antagonists bind to the agonist site and prevent access of the agonist. The difference can be detected experimentally by evaluating competition between the binding of radioisotopically labeled antagonist and the agonist. High concentrations of agonist displace or prevent the binding of a pharmacologic antagonist but not an allosteric antagonist.

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.

ADJUSTMENT OF DOSAGE WHEN ELIMINATION IS ALTERED BY DISEASE

Renal disease or reduced cardiac output often reduces the clearance of drugs that depend on renal elimination. Alteration of clearance by liver disease is less common but may also occur. Impairment of hepatic clearance occurs (for high extraction drugs) when liver blood flow is reduced, as in heart failure, and in severe cirrhosis and other forms of liver failure. Because it is important in the elimination of drugs, assessing renal function is important in estimating dosage in patients. The most important renal variable in drug elimination is glomerular filtration rate (GFR); and creatinine clearance (CL_{cr}) is a convenient approximation of GFR. The dosage in a patient with renal impairment may be corrected by multiplying the average dosage for a normal person times the ratio of the patient's altered creatinine clearance (CL_{cr}) to normal creatinine clearance (approximately 100 mL/min, or 6 L/h in a young adult).

$$\text{Corrected dosage} = \text{Average dosage} \times \frac{\text{Patient's } CL_{cr}}{100 \text{ mL/min}} \quad (6)$$

This simplified approach ignores nonrenal routes of clearance that may be significant. If a drug is cleared partly by the kidney and partly by other routes, Equation 6 should be applied to the 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 elimination rates are each 100 mg/d at steady state. Therefore, the corrected dosage in a patient with a creatinine clearance of 20 mL/min will be:

$$\begin{aligned}\text{Dosage} &= 100 \text{ mg/d (liver)} + 100 \text{ mg/d} \\ &\quad \times \frac{20 \text{ mL/min}}{100 \text{ mL/min}} \text{ (kidney)} \quad (7) \\ \text{Dosage} &= 100 \text{ mg/d} + 20 \text{ mg/d} = 120 \text{ mg/d}\end{aligned}$$

Renal function is altered by many diseases and is often decreased in older patients. CL_{cr} can be measured directly, but this requires careful measurement of both serum creatinine concentration and total urine creatinine over 12 or 24 hours. A common shortcut that requires only the serum (or plasma) creatinine measurement (S_{cr}) is the use of an equation. One such equation in common use is the Cockcroft-Gault equation:

$$CL_{cr} \text{ (mL/min)} = \frac{(140 - \text{Age}) \times \text{body weight (kg)}}{72 \times S_{cr}} \quad (8)$$

The result is multiplied by 0.85 for females. Similar equations (MDRD, CKD-EPI) are available online.

QUESTIONS

Mr Jones has zero kidney function and is undergoing hemodialysis 3 days per week while awaiting a kidney transplant. He takes metformin for type 2 diabetes mellitus and was previously stabilized (while his kidney function was adequate) at a dosage of 500 mg twice daily, given orally. The plasma concentration at this dosage with normal kidney function was found to be 1.4 mg/L. He has had 6 dialysis procedures and metformin toxicity is suspected. A blood sample now shows a metformin concentration of 4.2 mg/L. What was Mr Jones' clearance of metformin while his kidney function was normal?

(A) 238 L/d
(B) 29.8 L/h
(C) 3 L/d
(D) 238 L/h
(E) 30 L/min

Ms Smith, a 65-year-old woman with pneumonia, was given tobramycin, 150 mg, intravenously. After 20 minutes, the plasma concentration was measured and was found to be 3 mg/L. Assuming no elimination of the drug in 20 minutes, what is the apparent volume of distribution of tobramycin in Ms Smith?

(A) 3 L/min
(B) 3 L
(C) 50 L
(D) 7 L
(E) 0.1 mg/min

3. St. John's Wort, a popular botanical remedy, is a potent inducer of hepatic phase I CYP3A4 enzymes. 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 0.1 L/min. Based on this fact, which of the following is most correct?

(A) St. John's Wort will increase the half-life of phenytoin and verapamil
(B) St. John's Wort will decrease the volume of distribution of CYP3A4 substrates
(C) St. John's Wort will decrease the hepatic extraction of phenytoin
(D) St. John's Wort will decrease the first-pass effect for verapamil
(E) St. John's Wort will increase the clearance of phenytoin

4. A 45-year-old woman with small cell lung cancer has elected to participate in the trial of a new chemotherapeutic agent. It is given by constant intravenous infusion of 10 mg/h. Plasma concentrations (C_p) are measured with the results shown in the following table.

Time After Start of Infusion (h)	Plasma Concentration (mg/L)
1	0.7
4	3.0
8	3.6
16	3.84
24	4.0

What conclusion can be drawn from these data?
(A) Clearance is 2.0 L/h
(B) Doubling the rate of infusion would result in a plasma concentration of 16 mg/L at 40 h
(C) Elimination follows zero-order kinetics
(D) Half-life is 2 h
(E) Volume of distribution is 30 L

You are the only physician in a clinic that is cut off from the outside world by violent storms, flooding, and landslides. A 15-year-old girl is brought to the clinic with severe asthmatic wheezing. Because of the lack of other drugs, you decide to use intravenous theophylline for treatment. The pharmacokinetics of theophylline include the following average parameters: V_d 35 L; CL 48 mL/min; half-life 8 h. If an intravenous infusion of theophylline is started at a rate of 0.48 mg/min, how long would it take to reach 93.75% of the final steady-state concentration?
(A) Approximately 48 min
(B) Approximately 7.4 h
(C) Approximately 8 h
(D) Approximately 24 h
(E) Approximately 32 h

A 74-year-old retired mechanic is admitted with a myocardial infarction and a severe acute cardiac arrhythmia. You decide to give lidocaine to correct the arrhythmia. A continuous intravenous infusion of lidocaine, 1.92 mg/min, is started at 8 AM. The average pharmacokinetic parameters of lidocaine are: V_d 77 L; clearance 640 mL/min; half-life 1.4 h. What is the expected steady-state plasma concentration?
(A) 40 mg/L
(B) 3.0 mg/L
(C) 0.025 mg/L
(D) 7.2 mg/L
(E) 3.46 mg/L

A new drug is under study in phase 1 trials. It is found that this molecule is avidly taken up by extravascular tissues so that the final total amount in the extravascular compartment at steady state is 100 times the amount remaining in the blood plasma. What is the probable volume of distribution in a hypothetical person with 8 L of blood and 4 L of plasma?
(A) Insufficient data to calculate
(B) 8 L
(C) 14.14 L
(D) 100 L
(E) 404 L

A 63-year-old woman in the intensive care unit requires an infusion of procainamide. Its half-life is 2 h. The infusion is begun at 9 AM. At 1 PM on the same day, a blood sample is taken; the drug concentration is found to be 3 mg/L. What is the probable steady-state drug concentration after 16 or more hours of infusion?
(A) 3 mg/L
(B) 4 mg/L
(C) 6 mg/L
(D) 9.9 mg/L
(E) 15 mg/L

A 30-year-old man is brought to the emergency department in a deep coma. Respiration is severely depressed and he has pinpoint pupils. His friends state that he 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 V_d of morphine in this patient is 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) Not enough data to predict

Gentamicin, an aminoglycoside antibiotic, is sometimes given as a single large intravenous bolus dose of once a day to achieve a highly active peak plasma concentration. Gentamicin's volume of distribution is about 20 L in a 70 kg patient and, in your patient, the half-life is 4 h. If your patient is given an IV bolus dose of 360 mg, what will the trough concentration of gentamicin be 24 hours later just before the next intravenous bolus?
(A) 18 mg/L
(B) 4.5 mg/L
(C) 1.13 mg/L
(D) 0.56 mg/L
(E) 0. 28 mg/L

ANSWERS

1. Examination questions often provide more information than is needed—to test the student's ability to classify and organize data. In question 1, the data provided for Mr Jones on dialysis is irrelevant, even though choice **A,** 238 L/d, is the correct clearance while on dialysis. By definition, clearance is calculated by dividing the rate of elimination by the plasma concentration:

   Rate in = rate out (elimination rate) at steady state (ss)

   $$CL = \frac{\text{rate in}}{C_{p(ss)}}$$

   $$CL = \frac{1000\ \text{mg/24 h}}{1.4\ \text{mg/L}}$$

   $$CL = 29.8\ \text{L/h}$$

   The answer is **B.**

2. The volume of distribution (V_d) is the apparent volume into which the loading dose is distributed. It is calculated by dividing the dose by the resulting plasma concentration, C_p:

   $$V_d = \frac{\text{loading dose}}{C_p}$$

   $$V_d = \frac{150\ \text{mg}}{3\ \text{mg/L}}$$

   $$V_d = 50\ \text{L}$$

   The answer is **C.**

3. Induction of phase I metabolizing enzymes will *de*crease the half-life of substrates of these enzymes. P450 enzyme induction has *no effect* on volume of distribution. Hepatic extraction, the first-pass effect, and clearance for CYP3A4 substrates will be *in*creased by inducers. However, the extraction of verapamil is already equal to the hepatic blood flow, so further increase in metabolism will not increase clearance of this drug. The answer is **E.**

4. By inspection of the data in the table, it is clear that the steady-state plasma concentration is approximately 4 mg/L. None of the measured concentrations is equal to one half of the steady state value; so the half-life is not immediately apparent. However, according to the constant infusion principle (Figure 3–3), 2 half-lives are required to reach 75% of the final concentration; 75% (3.0 mg/L) of the final steady-state concentration was reached at 4 h. If 4 h equals 2 half-lives, the half-life must be 2 h. Rearranging the equation for maintenance dosing (dosing rate = CL × C_p), it can be determined that the clearance (CL) = dosing rate/plasma concentration (C_p), or 2.5 L/h. The volume of distribution (V_d) can be calculated from the half-life equation ($t_{1/2}$ = 0.693 × V_d/CL) and is equal to 7.2 L. This drug follows first-order kinetics, as indicated by the progressive approach to the steady-state plasma concentration. The answer is **D.**

5. For a drug with first-order kinetics, the approach of the drug plasma concentration to steady-state concentration during continuous infusion follows a stereotypical curve (Figure 3–3) that rises rapidly at first and gradually reaches a plateau. It reaches 50% of steady state at 1 half-life, 75% at 2 half-lives, 87.5% at 3, 93.75% at 4, and progressively halves the difference between its current level and 100% of steady state with each half-life. The answer is **E,** 32 h, or 4 half-lives.

6. The drug is being administered continuously and the steady-state concentration ($C_{p(ss)}$) for a continuously administered drug is given by the equation in question 1. Thus,

   $$\text{Dosage} = \text{Plasma level}_{ss} \times \text{Clearance}$$

   $$1.92\ \text{mg/min} = C_{p(ss)} \times CL$$

   Rearranging:

   $$C_{p(ss)} = \frac{1.92\ \text{mg/min}}{CL}$$

   $$C_{p(ss)} = \frac{1.92\ \text{mg/min}}{640\ \text{mL/min}}$$

   $$C_{p(ss)} = 0.003\ \text{mg/mL or } 3\ \text{mg/L}$$

   The answer is **B.**

7. Let Z be the amount in the blood plasma. If the amount in the rest of the body is 100 times greater, then the total amount in the body is 101Z. The concentration in the blood plasma (C_p) is Z/4 L. According to the definition:

   $$V_d = \frac{\text{amount in body}}{C_p}$$

   $$V_d = \frac{101Z}{Z/4\ \text{L}} = 101 \times 4\ \text{L} = 404\ \text{L}$$

   The answer is **E.**

8. According to the curve that relates plasma concentration to infusion time (Figure 3–3), a drug reaches 50% of its final steady-state concentration in 1 half-life, 75% in 2 half-lives, etc. From 9 AM to 1 PM is 4 h, or 2 half-lives. Therefore, the measured concentration at 1 PM is 75% of the steady-state value (0.75 × $C_{p(ss)}$). The steady-state concentration is 3 mg/L divided by 0.75, or 4 mg/L. The answer is **B.**

9. 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 morphine was 4 times higher immediately after administration than at the time of the measurement, which occurred 6 h, or 2 half-lives, later. Therefore, the initial plasma concentration was 1 mg/L. Since the amount in the body at any time is equal to V_d × plasma concentration (text Equation 1), the amount injected was 200 L × 1 mg/L, or 200 mg. The answer is **D.**

10. This problem requires, first, the calculation of the initial peak plasma concentration, and then the decline in concentration as the drug is eliminated by 50% in each half-life. The peak concentration = dose/V_d, or 360 mg/20 L or 18 mg/L. The trough concentration will be measured 24 hours or 6 half-lives later. After 1 half-life C_p will be 9; after 2, 4.5; after 3, 2.25; after 4 half-lives, 1.125 mg/L; after 5, 0.56; and after 6 half-lives, 0.28 mg/L. The answer is **E.**

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

The 3 important drugs that follow zero-order rather than first-order kinetics are ethanol, aspirin, and phenytoin.

QUESTIONS

Questions 1–2. You are planning to treat chronic major depression in a 35-year-old patient with recurrent suicidal thoughts. She has several comorbid conditions that require drug therapy, including rifampin for tuberculosis and amiodarone for arrhythmia. You are concerned about drug interactions caused by changes in drug metabolism in this patient.

1. Drug metabolism in humans usually results in a product that is
   (A) Less lipid soluble than the original drug
   (B) More likely to distribute intracellularly
   (C) More likely to be reabsorbed by kidney tubules
   (D) More lipid soluble than the original drug
   (E) Less water soluble than the original drug

2. If therapy with multiple drugs causes induction of drug metabolism in your depressed patient, it will
   (A) Be associated with increased smooth endoplasmic reticulum
   (B) Be associated with increased rough endoplasmic reticulum
   (C) Be associated with decreased enzymes in the soluble cytoplasmic fraction
   (D) Require 3–4 months to reach completion
   (E) Be irreversible

3. Which of the following factors is likely to increase the duration of action of a drug that is metabolized by CYP3A4 in the liver?
   (A) Chronic administration of rifampin during therapy with the drug in question
   (B) Chronic therapy with amiodarone
   (C) Displacement from tissue-binding sites by another drug
   (D) Increased cardiac output
   (E) Chronic administration of carbamazepine

4. Reports of cardiac arrhythmias caused by unusually high blood levels of 2 antihistamines, terfenadine, and astemizole, led to their removal from the market. Which of the following best explains these effects?
   (A) Concomitant treatment with rifampin
   (B) Use of these drugs by chronic alcoholics
   (C) Use of these drugs by chronic smokers
   (D) Treatment of these patients with ketoconazole, an azole antifungal agent

5. Which of the following agents, when used in combination with other anti-HIV drugs, permits dose reductions?
   (A) Cimetidine
   (B) Efavirenz
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

6. Which of the following drugs may inhibit the hepatic microsomal P450 responsible for warfarin metabolism?
   (A) Amiodarone
   (B) Ethanol
   (C) Phenobarbital
   (D) Procainamide
   (E) Rifampin

7. Which of the following drugs, if used chronically, is most likely to increase the toxicity of acetaminophen?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

8. Which of the following drugs has higher first-pass metabolism in men than in women?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

9. Which of the following drugs is an established inhibitor of P-glycoprotein (P-gp) drug transporters?
   (A) Cimetidine
   (B) Ethanol
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

10. Which of the following cytochrome isoforms is responsible for metabolizing the largest number of drugs?
    (A) CYP1A2
    (B) CYP2C9
    (C) CYP2C19
    (D) CYP2D6
    (E) CYP3A4

ANSWERS

1. Biotransformation usually results in a product that is *less* lipid-soluble. This facilitates elimination of drugs that would otherwise be reabsorbed from the renal tubule. The answer is **A.**

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

5. Which of the following agents, when used in combination with other anti-HIV drugs, permits dose reductions?
   (A) Cimetidine
   (B) Efavirenz
   (C) Ketoconazole
   (D) Procainamide
   (E) Quinidine
   (F) Ritonavir
   (G) Succinylcholine
   (H) Verapamil

(D) CYP2D6
(E) CYP3A4

ANSWERS

1. Biotransformation usually results in a product that is *less* lipid-soluble. This facilitates elimination of drugs that would otherwise be reabsorbed from the renal tubule. The answer is **A.**
2. The smooth endoplasmic reticulum, which contains the mixed-function oxidase drug-metabolizing enzymes, is selectively increased by inducers. The answer is **A.**

3. Rifampin and carbamazepine can induce drug-metabolizing enzymes and thereby may *reduce* the duration of drug action. Displacement of drug from tissue may transiently increase the intensity of the effect but decreases the volume of distribution. Amiodarone is recognized as an inhibitor of P450 and may decrease clearance of drugs metabolized by CYP2C9, CYP2D6, and CYP3A4. The answer is **B.**
4. Treatment with rifampin and chronic alcohol or tobacco use are associated with increased drug metabolism and lower, not higher, blood levels. Ketoconazole, itraconazole, erythromycin, and some substances in grapefruit juice slow the metabolism of certain older non-sedating antihistamines (Chapter 16). The answer is **D.**
5. Ritonavir inhibits hepatic drug metabolism, and its use at low doses in combination regimens has permitted dose reductions of other HIV protease inhibitors (eg, indinavir). The answer is **F.**
6. Amiodarone is an important antiarrhythmic drug and has a well-documented ability to inhibit the hepatic metabolism of many drugs. The answer is **A.**
7. Acetaminophen is normally eliminated by phase II conjugation reactions. The drug's toxicity is caused by an oxidized reactive metabolite produced by phase I oxidizing P450 enzymes. Ethanol and certain other drugs induce P450 enzymes and thus reduce the hepatotoxic dose. Alcoholic cirrhosis reduces the hepatotoxic dose even more. The answer is **B.**
8. Ethanol is subject to metabolism in the stomach as well as in the liver. Independent of body weight and other factors, men have greater gastric ethanol metabolism and thus a lower ethanol bioavailability than women. The answer is **B.**
9. Verapamil is an inhibitor of P-glycoprotein drug transporters and has been used to enhance the cytotoxic actions of methotrexate in cancer chemotherapy. The answer is **H.**
10. While CYP2D6 is responsible for metabolizing approximately 25% of drugs, CYP3A4 is involved in almost 50% of such reactions. The answer is **E.**