Chapter Questions

Modern
Pharmacology With
Clinical Applications

Sixth Edition

Mechanism of Drug Action

Questions

1. Receptors are macromolecules that
   a. Are designed to attract drugs
   b. Are resistant to antagonists
   c. Exist as targets for physiological neurotransmitters and hormones
   d. Are only on the outer surface of cells
   e. Are only inside of cells
2. All of the following are capable of initiating a signal transduction process EXCEPT
   a. Combination of an agonist with its receptor
   b. Combination of an antagonist with its receptor
   c. Combination of a neurotransmitter with its receptor
   d. Combination of a hormone with its receptor
3. Which of the following chemical bonds would create an irreversible combination of an antagonist with its receptor?
   a. Ionic bond
   b. Hydrogen bond
   c. Van der Waals bond
   d. Covalent bond
4. Potency is determined by
   a. Affinity alone
   b. Efficacy alone
   c. Affinity and efficacy
   d. Affinity and intrinsic activity
   e. Efficacy and intrinsic activity

Answers

1. **C**
   There are a large number of receptors in the body. Although many drugs are attracted to receptors, the receptors are not designed for that purpose. Antagonists also are attracted to receptors. Some receptors are on the cell surface, while others are found inside the cell.
2. **B**
   An antagonist binds to a receptor and prevents the action of an agonist. Choice A is wrong because this combination does initiate a signal transduction process. C and D are incorrect because both neurotransmitters and hormones work through their appropriate receptor to initiate signal transduction.
3. **D**
   A covalent bond is a strong and stable bond that is essentially irreversibly formed at normal body temperature. The other bonds are much weaker.
4. **C**
   Potency is a useful measure of the comparison between two or more drugs. It does not equate to therapeutic superiority but rather is a measure of the size of the dose required to produce a particular level of response.

Drug Absorption & Distribution

Questions

1. Following oral administration, a drug is absorbed into the body, wherein it can exert its action. For a drug given orally, the primary site of drug absorption is:
    a. The esophagus
    b. The stomach
    c. The upper portion of the small intestine
    d. The large intestine
2. Patients can exhibit alterations in the rate and extent of drug absorption because of various factors. All of the following factors might affect the rate and/or extent of drug absorption EXCEPT:
    a. Gastric emptying time
    b. Intestinal motility
    c. The presence of food
    d. The formulation of the drug
    e. A generic form of the drug
3. The body has developed defense mechanisms that reduce the amount of foreign chemicals, such as drugs, that enter the body. One of the more prominent of these mechanisms is an efflux transport system that pumps some drugs back into the intestinal lumen following absorption into the enterocytes and that is responsible for the lack of complete absorption of some drugs. This efflux transport system is:
    a. Facilitated diffusion
    b. P glycoprotein
    c. Cytochrome P450 3A
    d. Pinocytosis
4. All of the following statements concerning the blood-brain barrier and the passage of drugs from the systemic circulation into the cerebrospinal fluid are TRUE EXCEPT:
    a. Ionized drugs are more likely to cross into the CSF than un-ionized drugs.
    b. The higher the lipid solubility of a drug, the more likely it will cross into the CSF.
    c. Inflammation of the meninges improves the likelihood that drugs will cross the blood-brain barrier as compared to the uninflamed state (i.e., normal condition).
    d. P glycoprotein serves to pump drugs back into the systemic circulation from endothelial cells lining the blood-brain barrier.
5. Which of the following organs or tissues is a potential site for drug accumulation of lead that has been ingested?
    a. Eyes
    b. Fat
    c. Bone
    d. Lungs
    e. Blood

Answers

1. **C**

   The primary site of absorption is the small intestine. Because of its large surface area and high blood perfusion rate, the small intestine is optimal for absorbing drugs. Some drug absorption occurs in the stomach and large intestine, but because of their reduced surface area in relative terms and for some drugs less than optimal physicochemical conditions, these tissues play a lesser role in drug absorption. Because of the tissue type, very little drug absorption occurs through the esophagus.

2. **E**

   To be approved, generic formulations must exhibit the same rate and extent of absorption as the trademark compound. All of the other choices can affect drug absorption. For example, slowing gastric emptying time may increase the absorption of a drug absorbed in the stomach. Alterations in gastric motility may affect the amount of time a drug spends in the region of the gastrointestinal tract, where it undergoes the most extensive absorption. The presence of food may cause decreased absorption through binding to the drug or may increase absorption through making a better local environment for absorption of particular drugs. Finally, changes in drug formulation can alter absorption by changing dissolution rates.

3. **B**

   P-glycoprotein transporters in the intestinal lumen serve as an efflux transporter for many drugs. This transporter pumps drugs out of the enterocytes into which they were absorbed and back into the intestinal lumen, reducing absorption. Facilitated diffusion and pinocytosis generally result in drug influx (absorption).The cytochrome P450 3A enzymes metabolize drugs; therefore, even though they may reduce the amount of drug absorbed, the reduction is due to drug metabolism, not efflux transport back into the intestinal lumen.

4. **A**

   Un-ionized drugs cross into the cerebrospinal fluid more readily than ionized drugs. All of the other choices are correct.

5. **C**

   Lead can substitute for calcium in the bone crystal lattice, resulting in bone brittleness. Bone may become a reservoir for other substances as well. Several drugs, such as chlorpromazine, may accumulate in the eye. Drugs with extremely high lipid–water partition coefficients tend to accumulate in fat, while basic amines tend to accumulate in the lungs. Many agents bind avidly to albumin in the blood.

Metabolism & Excretion of Drugs

Questions :

1. Concerning regulation of CYP-mediated drug metabolism, all of the following statements are true EXCEPT
   a. Drugs that competitively inhibit CYP enzymes cause a decrease in concentrations of the object (original) drug.
   b. Induction of drug-metabolizing enzymes results in a decrease in concentrations of the object (original) drug, thus potentially reducing efficacy.
   c. Induction of drug-metabolizing enzymes frequently requires the synthesis of new enzyme protein and thus may not occur immediately upon introduction of the inducing agent.
   d. Mechanism-based inactivation results in irreversible inactivation of the enzyme that lasts for the duration of the enzyme molecule.
2. Which of the following CYP enzymes is associated with metabolism of the greatest number of drugs and thus most likely to be involved in drug–drug interactions?
   a. CYP3A4
   b. CYP2C9
   c. CYP2D6
   d. CYP2E1
   e. CYP1A2
3. Conjugation of a drug with glucuronic acid via the glucuronosyl transferases will result in all of the following EXCEPT
   a. Production of a more water-soluble moiety that is more easily excreted
   b. A new compound that may also possess pharmacological activity
   c. A drug molecule that may be more susceptible to biliary elimination
   d. A drug molecule that may undergo enterohepatic recirculation and reintroduction into the bloodstream
   e. A drug with a different pharmacological mechanism of action
4. Concerning the renal excretion of drugs:
   a. Drugs that are ionized in the renal tubule are more likely to undergo passive reabsorption than those that are unionized
   b. Low-molecular-weight drugs are much more likely to be actively secreted than filtered.
   c. Only drug that is not bound to plasma proteins (i.e., free drug) is filtered by the glomerulus.
   d. Decreasing renal tubular fluid pH will increase elimination of weakly acidic drugs.
5. Drug presence in breast milk is most likely for:
   a. Drugs highly bound to plasma proteins
   b. Lipid-soluble molecules
   c. Large ionized water-soluble molecules
   d. Acidic compounds

Answers

1. **A**

   When one inhibits the action of a drug-metabolizing enzyme (A), one would expect an increase instead of a decrease in drug concentrations, since less is being metabolized. Induction of an enzyme (B) would have the opposite effect, since there would be more enzyme available to metabolize the drug. C is correct, since the most common mechanism of enzyme induction is through synthesis of new enzyme protein, which does not occur immediately. Finally, mechanism-based inactivation (D) is also correct, since this is irreversible, leaving the enzyme inactive and eventually it is degraded by the body.

2. **A**

   CYP3A4 is the predominant cytochrome P450 drug-metabolizing enzyme in the body, both in terms of amount of enzyme and the number of drugs that it metabolizes. It has been estimated to carry out approximately 50% of the cytochrome P450–mediated reactions observed. The other enzymes have been reported to carry out 30% (CYP2D6), 15–20% (CYP2C9) and 1–2% (both CYP2E1 and CYP1A2).

3. **E**

   Most glucuronic acid conjugates are less effective than the parent drug. The conjugate, however, usually maintains the same pharmacological mechanism of action, although frequently of a lesser magnitude. Conjugation with glucuronic acid makes a drug molecule more water soluble (A), and glucuronic acid conjugates are more likely to be eliminated by secretion into the bile (C) than are unconjugated compounds. These glucuronide conjugates, once secreted into the bile, may be cleaved by -glucuronidases to liberate the parent compound, which can then be reabsorbed (D). Several glucuronic acid conjugates of drugs (e.g., morphine 6- glucuronide) possess pharmacological activity (B).

4. **C**

   Plasma proteins are too large to be filtered by the glomerulus, so that any drug molecules bound to these plasma proteins will not undergo filtration. A is not correct: ionized drugs are less likely to undergo reabsorption, since this is generally thought to be a passive process. B is also not correct: low molecular- weight drugs are more likely to be filtered, since they can easily pass through the glomerulus filter. Finally, weakly acidic drugs will be un-ionized at a low (acidic) pH, hence more likely to undergo reabsorption, thus reducing the net elimination (D).

5. **B**

   Lipid-soluble molecules are more likely to be excreted in breast milk because it is primarily a passive diffusion process. A, C, and D are not correct because they are opposite of the typical characteristics of drugs excreted into breast milk.

Pharmacokinetics

Questions

1. Frequently it is useful to consider the overall exposure of a person to a drug during the dosing interval. Which of the following pharmacokinetic parameters defines the exposure of a person to a drug?
    a. C max
    b. T max
    c. AUC (area under the curve)
    d. Half-life
    e. Clearance

2. Organs such as the liver remove exogenous chemicals, such as drugs, from the body. For drugs such as phenytoin, for which the difference between the minimum effective concentration and the minimum toxic concentration is small, clinicians must calculate the rate at which a given individual removes drug from the body. The volume of fluid from which drug can be completely removed per unit of time (rate of drug removal) is termed:
    a. Distribution
    b. Clearance
    c. Metabolism
    d. Excretion

3. For a drug such as piroxicam with a 40-hour half-life and being dosed once daily (i.e., every 24 hours), steady state will be reached shortly following which DOSE (not which half-life)?
    a. 1st dose
    b. 3rd dose
    c. 5th dose
    d. 8th dose
    e. 12th dose

4. Volume of distribution (Vd), though not a physiological volume, helps a clinician to estimate drug distribution in the body. Drugs distribute throughout the body to differing degrees depending on a number of factors. Which of the following factors is TRUE concerning drug distribution?
    a. In general, a drug with a higher degree of plasma protein binding will have a lower volume of distribution.
    b. All drugs distribute to the same degree in all tissues.
    c. The binding of drugs to tissues has no relationship to the distribution of drug in the body.
    d. In general, lipophilic drugs distribute to a lesser extent than hydrophilic drugs.

5. A clinician must be concerned with the amount of a drug dose that reaches the systemic circulation, since this will affect the plasma concentration and therapeutic effects observed. The fraction of a dose reaching the systemic circulation as unchanged drug (i.e., intact) is defined as:
    a. Theoretical dose
    b. C max
    c. Bioavailability
    d. Ideal dose

Answers

1. **C**

   The AUC (area under the curve) best describes the overall exposure of a person to a given drug over the course of the dosing interval. It describes the concentration of drug integrated over the period assessed, usually the dosing interval. A (C max) is not correct, as C max gives the maximum concentration achieved but does not reveal how long measurable concentrations of the drug were present or how long until this concentration was achieved. B (T max) only refers to the time until the maximum concentration is achieved, again not giving a reference to overall exposure over time. D (half-life) simply describes how much time is required for the concentration to decrease by one-half. Finally, clearance (E) is the volume of fluid (usually plasma) from which drug can be removed per unit of time and as such does not define exposure.

2. **B**

   Clearance is defined as the volume of fluid from which drug is completely removed per unit of time and as such is a measure of the body's ability to remove drug by whatever manner (e.g., elimination, metabolism, excretion). Distribution is the theoretical volume to which the drug distributes and metabolism and excretion are simply methods of clearing drug.

3. **D**

   Approximately five half-lives are required for a drug to reach steady-state concentrations. Since piroxicam has a half-life of 40 hours, it will require approximately 200 hours before steady state is reached. If given every 24 hours, shortly after the 8th dose (192 hours at exactly the 8th dose) steady state will be reached.

4. **A**

   Drugs with a higher degree of plasma protein binding in general have a lower volume of distribution, since the plasma proteins (and thus the drug bound to the plasma protein) tend to stay in the plasma and not distribute to the extravascular tissues. Different drugs can have widely disparate volumes of distribution, so B is incorrect. Tissue binding of drugs is extremely important to drug distribution and can override plasma protein binding, so C is incorrect. Finally, D is incorrect, since in general the more lipophilic a drug is, the greater volume of distribution it has.

5. **C**

   Bioavailability describes the portion of the drug that reaches the systemic circulation without being metabolized or eliminated. Bioavailability is highly dependent on the drug and the route of administration. C max (B) is incorrect, since this is only the maximum concentration reached following a dose and gives no measure of the amount reaching the circulation. The other terms (ideal dose and theoretical dose) are fabricated.

<u>Case Studies</u>

1. **Drug Absorption & Distribution**

    Q : A 47-year-old man recently received a heart transplant and is being discharged home with oral medications, including cyclosporine. The physician also prescribed diltiazem, a calcium channel blocker used for the treatment of hypertension. Since he did not have hypertension, the patient wondered why this additional drug was being prescribed.

    A : Cyclosporine is an immunosuppressant drug used to prevent transplant rejections. Though an oral formulation is available, it has low bioavailability (very little reaches the systemic circulation as intact drug). Diltiazem will inhibit cytochrome P450 3A4 in the gut. CYP3A4 is the primary enzyme responsible for the presystemic metabolism of cyclosporine and has been implicated as the primary cause for the low amounts of orally administered cyclosporine reaching the systemic circulation. Coadministration of diltiazem greatly increases the bioavailability of cyclosporine, reducing the dose of drug needed. Furthermore, because cyclosporine is relatively expensive, a substantial cost savings is realized. Finally, a common adverse effect of cyclosporine therapy is the development of hypertension, and the diltiazem somewhat protects the patient from this adverse effect.

2. **Drug Metabolism & Excretion**

    Q : A 37-year-old woman visited her dentist for removal of her wisdom teeth. The teeth were found to be impacted, and removal necessitated extensive surgery. Following completion of the procedure on one side of the mouth, the patient was given a prescription for acetaminophen 300 mg with codeine 30 mg (combination product) for the relief of pain. The patient took the prescription as prescribed for approximately 2 days, but little pain relief was achieved. She called the dentist to get a prescription for another analgesic. What is a possible explanation for this lack of efficacy?

    A : Codeine itself is a very weak analgesic but is metabolized to morphine, which produces most of the analgesic effect following codeine administration. The metabolism of codeine to morphine is carried out by cytochrome P450 2D6, an enzyme that exhibits genetic polymorphism. The patient may be deficient in CYP2D6 and thus unable to convert codeine into its active metabolite, morphine; hence analgesic efficacy is lacking.

3. **Pharmacokinetics**

Q : A 67-year-old woman with atrial arrhythmia has been treated for 3 years with the antiarrhythmic amiodarone 200 mg and the anticoagulant warfarin 10 mg, both daily. The patient began having liver and ocular toxicity due to amiodarone. The physician decided to discontinue amiodarone therapy because of these adverse effects. Upon checkup, a month after discontinuation of amiodarone, the patient's international normalized ratio (INR), a measure of blood clotting, was greatly elevated, placing the patient at risk for bleeding. The physician reduced the dose of warfarin to 7.5 mg daily. The half-life of amiodarone is approximately 35 days. For how long should the physician continue to monitor the INR?

A : The half-life of amiodarone is 35 days. Approximately five half-lives are required for functionally complete drug elimination. Thus, it will take approximately 6 months (5 half-lives) before the amiodarone is eliminated from the body. Since amiodarone strongly inhibits metabolism of Swarfarin (active enantiomer), it will continue to affect warfarin metabolism for 6 months following discontinuation of amiodarone. Thus, the dose of warfarin will have to be monitored approximately every month and adjusted if necessary. This monthly monitoring should be continued for at least 6 months, until the metabolism of warfarin stabilizes and a constant dose of warfarin can again be maintained.

It was a few hours before our physiology midterm that I had completely lost hope in getting a good grade and went into a pathological state of despair. That was when my friend sent me a video of Aragorn's speech in LoTR at 5 in the morning in an attempt to raise my morale . I add the speech to this paper in hope it can cheer you up in times of darkness, ehem, I mean midterms.

"Sons of Gondor, of Rohan, my brothers! I see in your eyes the same fear that would take the heart of me. A day may come when the courage of men fails, when we forsake our friends, and break all bonds of fellowship; but it is not this day! An hour of woe, and shattered shields, when the Age of Men comes crashing down; but it is not this day! This day we fight! By all that you hold dear on this good earth, I bid you stand, Men of the West!"