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Basic Pharmacology: Part I – Pharmacodynamic and Pharmacokinetic Principles

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Clinicians and patients recognize the major role played by drugs in modern healthcare. Hence, it is important for practitioners to have a solid understanding of pharmacology. Participants in this course will be introduced to general pharmacological principles as they relate to the use of drugs in dental practice. Pharmacodynamic and pharmacokinetic concepts will be reviewed.

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- The authors report no conflicts of interest associated with this course.

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Overview

Clinicians and patients recognize the major role played by drugs in modern healthcare. Hence, it is important for practitioners to have a solid understanding of pharmacology. Participants in this course will be introduced to general pharmacological principles as they relate to the use of drugs in dental practice. Pharmacodynamic and pharmacokinetic concepts will be reviewed.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Understand basic principles of pharmacodynamics related to drug-receptor interactions.
- Apply pharmacodynamic principles to clinical practice as they relate to efficacy, potency, and toxicity of drugs.
- Understand basic principles of pharmacokinetics related to the faith of drugs in the body.
- Apply pharmacokinetic principles to clinical practice as they relate to drug absorption, distribution, metabolism, clearance, and dosing requirements.

Course Contents

Introduction

The science of pharmacology is the study of drugs. Understanding how drugs affect physiological homeostatic mechanisms at the molecular level forms the basis for developing sound therapeutic strategies. Consequently, the use of therapeutic agents requires an understanding of basic pharmacological principles. These principles apply to all drugs and are predicated on pharmacodynamic and pharmacokinetic variables.[1-5]

Pharmacodynamics

Pharmacodynamic principles relate to molecular interactions between body constituents and drugs.[1-3] They are concerned with issues related to biochemical and physiological mechanisms of drug actions and are based on the concept of drug-receptor interactions. Pharmacodynamics describes the effect of drugs quantitatively in order to determine efficacy, potency, and toxicity.

Drug Receptors

The first step in initiating a drug-induced effect is the formation of a complex between a drug and a cell component generally known as the ***drug receptor***. Drug receptors are cellular macromolecules (Figure 1). They may be metabolic or regulatory enzymes or co-enzymes; proteins or glycoproteins associated with transport mechanisms; and structural and functional components of lipid membranes or nucleic acids.

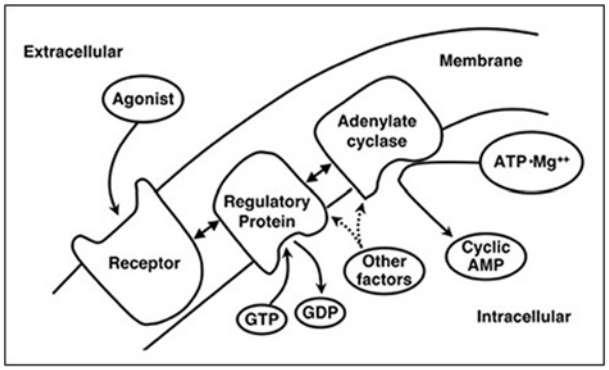

Figure 1. Drug receptors are cellular macromolecules.

Drugs bind to receptors by covalent, ionic, hydrogen, hydrophobic, and Van der Waals forces (Figure 2). It is of note, however, that not all drugs interact with specific receptors. Some form chemical bonds with small molecules, chelating agents, or metallic cations; others act by still obscure physiochemical mechanisms. Most drug-receptor bonds are weak, allowing the drug to disassociate from its receptor as a function of the drug's concentration at the receptor site.

To form a drug-receptor bond, the drug must have ***affinity*** for the receptor. A drug's affinity to a particular receptor and the type of bond formed is related to the drug's chemical structure. Affinity is expressed as the ***dissociation constant*** or K_d of the drug, i.e., the concentration of a drug required to achieve 50 percent occupancy of its receptors. The molecular events that follow drug-receptor interactions reflect the drug's ***mechanisms of action***.

Agonists

Following the formation of a drug-receptor complex, the ability of a drug to initiate a response is predicated on the drug's ***intrinsic activity***. A drug, which interacts with the active binding site of a receptor and has a direct stimulatory effect on that receptor, is called an ***agonist***. A ***strong agonist*** produces a significant physiological/ pharmacological response when only a relatively small number of receptors are occupied, i.e. the drug has high intrinsic activity.

A ***weak agonist*** must interact with the agonist-binding domain of the drug on many more receptors to produce the same effect as a strong agonist, i.e., the drug has lower intrinsic activity. A ***partial agonist*** will never produce the same effect

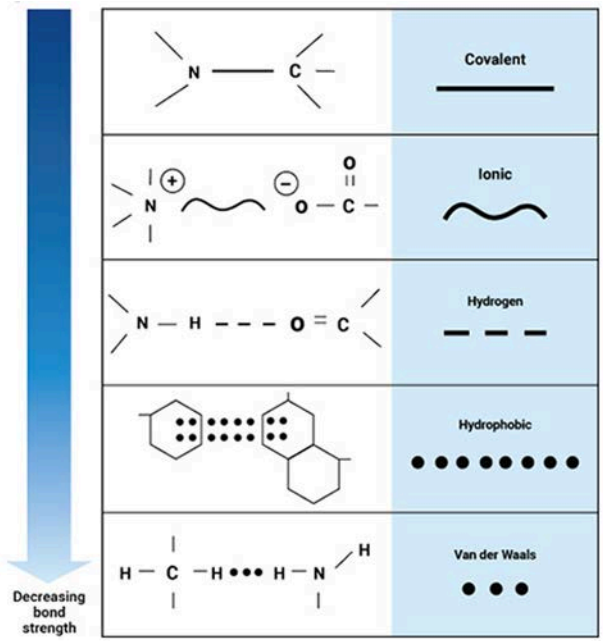

Figure 2. Hydrogen and ionic bonds are the most common, they require little energy and may be easily broken.

as a strong or a weak agonist even when all active binding-sites are occupied by the drug. While a partial agonist has affinity for a receptor, it has low intrinsic activity.

Antagonists

An ***antagonist*** interacts with the agonist-binding domain of a receptor and blocks the agonist from interacting with it. Antagonism may be reversible or irreversible. A ***reversible antagonist*** binds to the agonist-binding domain of the receptor, but high concentrations of the agonist can overcome the antagonism. Naloxone is a reversible (competitive) antagonist at opioid receptor sites. An ***irreversible antagonist*** also blocks the agonist-binding domain, but forms a permanent drug-receptor bond (i.e., covalent bond), which is irreversible (noncompetitive).

An ***allosteric antagonist*** binds to a receptor at a site other than the agonist-binding domain and produces a conformational change in the receptor. This either alters the K_d for the agonist or inhibits the receptor from responding to the agonist. There are also two non-receptor-related mechanisms of antagonism. A chemical antagonist sequesters the agonist and prevents it from interacting with its receptor. A ***physiologic antagonist*** blocks the action of an agonist by a molecular mechanism that does not involve the receptor for that agonist.

Receptor Classification

Receptors may be classified according to the type of drug that they interact with or according to the specific physiologic response produced by the drug-receptor complex. By evaluating the effects of different agonists in the presence of a given antagonist, receptor sites may also be subclassified. For example, cholinergic receptors can be activated either by muscarine or nicotine. However, only the response to muscarine is antagonized by atropine, while curare will only antagonize the response to nicotine.

This evidence suggests that acetylcholine can bind to and activate at least two different receptor-subtypes, which are either muscarinic or nicotinic. Similarly, receptors and receptor subtypes exist for other agents. The number of any given receptor type or subtype on a cell may also vary. Certain disease states or drugs taken in large doses and/or chronically may increase (up-regulate) or decrease (down regulate) the number of receptors and reflect a degree of receptor adaptability in the face of a changing physiologic environment.

Efficacy

The magnitude of a physiological/pharmacological response obtained from optimal receptor occupancy by a drug reflects its ***efficacy***. The efficacy of a drug is related to its chemical structure and is predicated on the drug's intrinsic activity. The ***graded dose-response relationship*** is the quantification of a specific response elicited by a drug over a range of dosages. It is expressed visually and mathematically by a ***dose-response curve*** (Figure 3).

The slope of the dose-response curve reflects the effect of a drug associated with increasing dosages. The dose of a drug that produces ***maximal effect*** (E_{max}) is the ***ceiling dose*** of that drug. For example, the analgesic ceiling dose of ibuprofen is 800 mg three times a day (i.e., a total daily dose of 2400 mg); the administration of higher daily doses of ibuprofen would not provide any additional therapeutic (analgesic) benefit and may increase toxicity.

Potency

Potency of a drug is defined as that concentration at which the drug elicits 50 percent of its E_{max}, i.e., EC_{50}. It reflects both the affinity of a drug to its receptors as well as its intrinsic activity. Note in

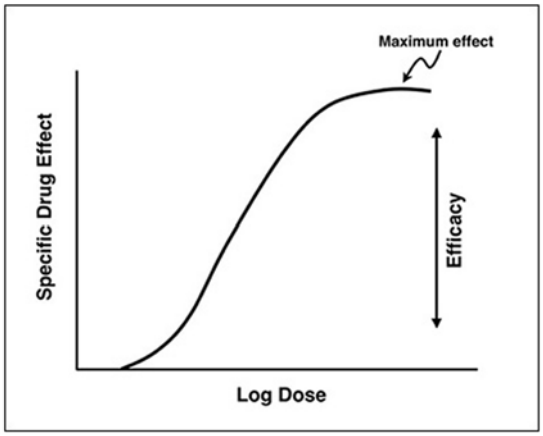

Figure 3. The dose-response curve is established by placing the logarithmic value for dosage on the x-axis and the quantified response on the y-axis.

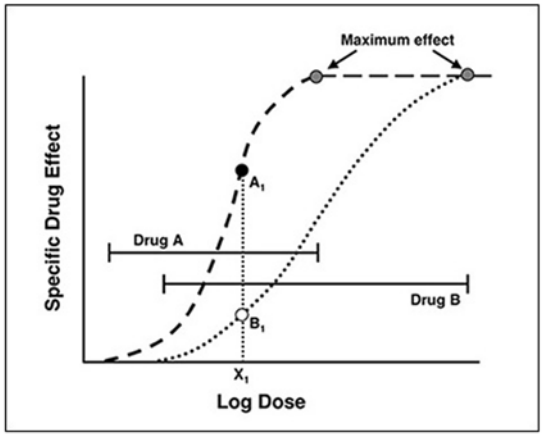

Figure 4. The concept of potency is important in determining drug dosage, however, high or low potency is significant only if the administration of an effective dose becomes impractical.

Figure 4 that for a given dose (x_1), the effect of drug B at B_1 is smaller than the effect of drug A at A_1. Drug A also reaches the upper plateau (E_{max}) of the dose-response curve at a smaller dose, i.e., drug A is more potent than drug B, yet they have the same efficacy (Figure 4).

Toxicity

Toxic effects may be (1) exaggerations of direct effects of a drug seen at higher dosages, e.g., a barbiturate may produce sedation and drowsiness at therapeutic levels, but cause death at increased dosage levels; or (2) multiple concurrent "side" effects that occur at therapeutic dosages, e.g., an antihistamine, intended to antagonize histamine action in peripheral tissues may also bind to receptors in the CNS and cause drowsiness.

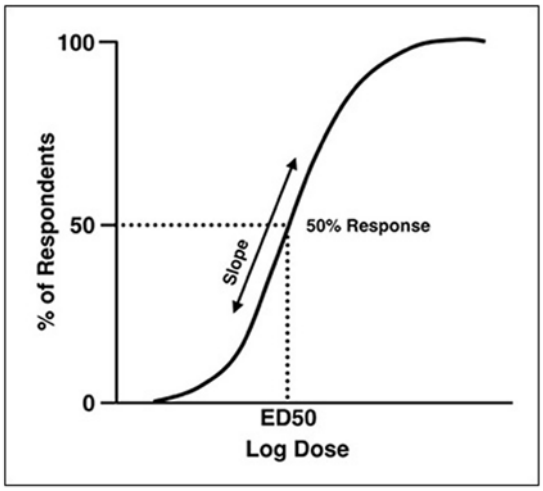

Figure 5. The dose of a drug required to produce a specific response in 50 percent of the individuals within the same population is the median effective dose (ED_{50}).

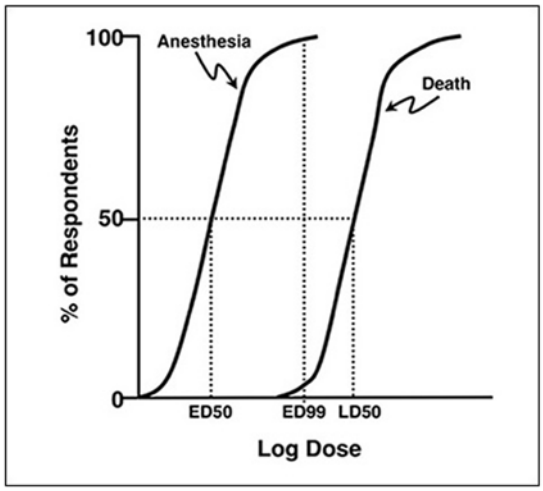

Figure 6. The margin of safety of a drug may be determined by comparing the 99% dose-response curve for the therapeutic effect with the curve for a toxic or lethal effect.

The dose of a drug required to produce a specific response in 50 percent of the individuals within the same population (Figure 5) is the ***median effective dose*** (ED_{50}). If the measured endpoint is a toxic effect, the ***median toxic dose*** is expressed as TD_{50}. If death is the measured endpoint, the ***median lethal dose*** is expressed as LD_{50}. A steep dose-response curve indicates a narrow range between therapeutic, toxic, and lethal dosages.

The ***margin of safety*** of a drug is expressed as its ***therapeutic index***, i.e., the ratio of LD_{50}/ED_{50}). The margin of safety may also be established by comparing the ***99 percent dose-response curve*** for the therapeutic effect with the curve for a particular toxic or the lethal effect (Figure 6). The farther apart these curves are the wider the margin of safety. The ***therapeutic window*** is the range of doses at which a drug is effective without causing significant adverse effects.

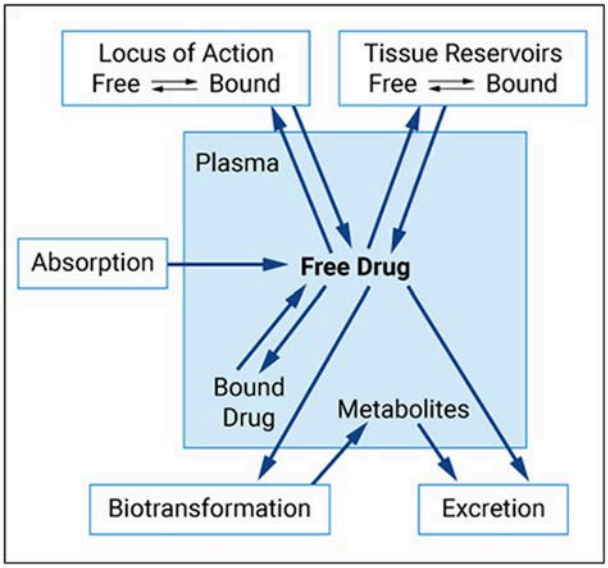

Figure 7. Pharmacokinetic factors that affect a drug's ability to reach and maintain therapeutic concentrations in the body for optimum efficacy without causing toxicity.

Pharmacokinetics

Pharmacokinetic principles relate to the fate of drugs within the body.[4,5] They are concerned with mechanisms of absorption, distribution (redistribution), metabolism (biotransformation), and excretion or clearance (Figure 7). Pharmacokinetic variable are important determinants of the dosing regimen required for a drug to reach and maintain therapeutic concentrations in the body for optimum efficacy without causing toxicity.

Absorption

To gain access to their receptors most drugs must first be absorbed into the systemic circulation. This requires that drugs translocate across biological membranes. There are several mechanisms by which this can be achieved, but the most important one is ***passive diffusion***. Primary determinants of passive diffusion include the drug's molecular weight; its concentration gradient, pKa, and lipid solubility; and, to some extent, the drug's formulation and route of administration.

Most drugs are weak acids or weak bases. In an aqueous environment they exist as a mixture of protonated (positively charged) and deprotonated (neutral) molecules. Only the deprotonated or neutral (unionized) form of drug molecules can translocate across biological membranes. The ratio of protonated (ionized) to deprotonated (unionized) forms of a drug is predicated on the drugs' ***dissociation constant*** (pKa) and the pH of the drug's milieu (environment).

The pKa is that pH at which a drug is 50% ionized and 50% unionized (Figure 8). When the pH of the environment is increased above the pKa of a weak acid, over 50% of the drug will be ionized. Conversely, when the pH of the environment is decreased below the pKa of a weak acid, over 50% of the drug will be unionized. Generally, the pKa of weak acids (e.g., aspirin, penicillin) is 3 to 5; and the pKa of weak bases (e.g., local anesthetics) is 6 to 10.

When lidocaine with a pKa of 7.9 is deposited into an infected (acidic) site more than 50% of its molecules will be ionized. Since only the neutral form of the drug can translocate across biological membranes, the protonated or charged forms of the drug will accumulate at the site. This phenomenon is known as ***ion trapping***. Ion trapping also explains the accumulation of weak acids (e.g., aspirin) in an alkaline environment, i.e., when placed in the mucobuccal fold.

The ***oral route*** is the most common, convenient, and economical method of drug administration. It is also the least predictable. When a drug is administered orally (an enteral route) its rate of absorption into the systemic circulation is greatly influenced by the pH of the gastrointestinal tract, gastric motility, splanchnic blood flow, the presence of food in the stomach, and importantly, patient adherence to the prescribed drug regimen.

Gastric motility (emptying) moves a drug from the stomach into the upper small intestine. The larger surface area of the small intestine and its more specialized epithelial lining promote absorption. Consequently, rapid gastric emptying leads to more rapid drug absorption. Conversely, factors that slow gastric motility (e.g., fatty foods in the stomach) tend to delay gastric emptying, slow the rate of absorption, and, predictably, delay a drug's onset of action.

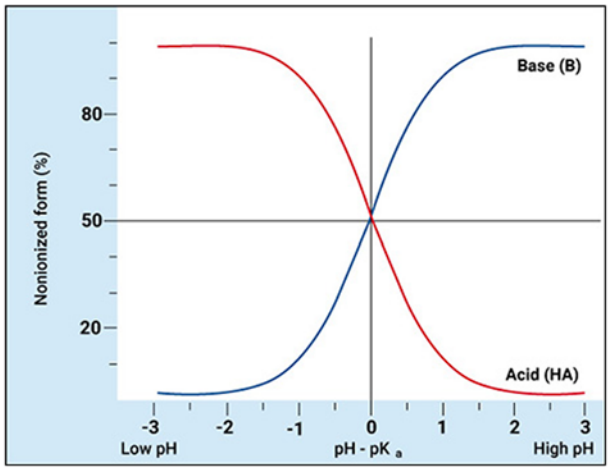

Figure 8. The pKa is that pH at which a drug is 50% ionized and 50% unionized.

Following oral administration of a drug, an important determinant of its ***bioavailability*** is ***first-pass metabolism*** by the liver. Bioavailability is the extent and rate at which the active drug or its active metabolite enters the systemic circulation and becomes available for distribution to the drug's site of action. In general, drugs given enterically that are efficiently removed and/or extensively metabolized by the liver at the time of first-pass will have low bioavailability.

Intravenous (IV) administration (a parenteral route) provides for accurate and immediate deposition of drugs into the systemic circulation unaffected by hepatic first-pass metabolism. The dose can be adjusted to patient response; however, once a drug is injected into the circulation there is no recall. Sterile formulations of soluble substances and an aseptic technique are required. Local irritation and thromboembolic complications may occur with some drugs.

Subcutaneous (SC) injections provide for a rate of drug absorption that is sufficiently constant to maintain steady-state concentrations. Local tissue irritation such as sloughing, necrosis, and severe pain may occur. ***Intramuscular*** (IM) injections allow for rapid absorption of aqueous solutions, while oily or other nonaqueous vehicles provide for slow, constant absorption. Drugs that are too irritating when administered IV or SC may be given IM.

Gaseous, volatile agents administered by ***inhalation*** may act locally, cross the alveoli, or

travel in the systemic circulation and then act at distant receptor sites. Concentration is controlled at the alveolar level, since most of these drugs are exhaled immediately. The rectal route of drug administration may be useful in young children and for unconscious or vomiting patients, however, absorption, as with the oral route of drug administration, is unpredictable.

Following ***topical*** application, drugs are absorbed across skin and mucosa by passive diffusion as a function of their concentration, molecular size, lipid solubility, and pKa. ***Sublingual*** drug administration, because of venous drainage from the mouth is via the superior vena cava, allows for direct absorption into the systemic circulation and has the advantage of circumventing first-pass metabolism in the liver.

Distribution

Following the absorption into the systemic circulation, drugs are distributed both into the extracellular and intracellular milieu. However, the determinants that affect a drug's diffusion across biological membranes and the drug's ***plasma protein binding*** limit its ability to leave the vascular compartment. Even so, lipid soluble drugs will reach their receptors in highly perfused organs such as the heart, liver, kidney, and brain within minutes of absorption.

Since only the free form of a drug is capable of diffusion, plasma protein binding reduces a drug's availability to cross biological membranes. Albumin is the most abundant protein in plasma and it is responsible for most plasma protein binding of drugs. Highly protein bound drug tends to remain in the vascular compartment and have a low ***volume of distribution*** (V_d). Plasma protein binding is also an important mechanism for drug-drug interactions.

The V_d represents the fluid volume that would be required to contain the total amount of absorbed drug in the body at a uniform concentration equivalent to that in plasma at steady state, i.e., V_d = Dose / $[Drug]_{plasma}$. Thus, for two drugs of equal potency, the drug that is more highly distributed among body tissues will generally require a higher initial dose to establish a therapeutic plasma concentration than the drug that is less highly distributed.

The distribution of drugs to the central nervous system (CNS) and cerebral spinal fluid is restricted by the ***blood-brain barrier***. However, the only limiting factor associated with highly lipid-soluble drugs is cerebral blood flow. ***Redistribution*** may affect the duration of a drug effect, for example, when a drug of high lipid solubility, which first acts on the brain or cardiovascular system after administration is redistributed to other tissues.

Metabolism

Weak acids and bases are not readily eliminated from the body. Metabolism fosters drug clearance by biotransformation into more polar, i.e., more water-soluble fractions. The main site of drug metabolism is the liver. The lungs, skin, kidneys, gastrointestinal mucosa, and plasma enzymes may play minor roles. Metabolism or biotransformation is also responsible for converting some drugs (pro-drugs), which are inactive, into their active metabolites.

The chemical reactions associated with metabolism or biotransformation of drugs is classified into two types: Phase I or Phase II reactions. ***Phase I reactions*** are mediated by the hepatic microsomal CYP450 enzyme system and involve metabolic modification of a drug by oxidation or reduction. This system can be "induced" to increase or reduce the rate of a drug's metabolism and is responsible for many drug-drug interactions.

There is much genetic variability (polymorphism) with the CYP450 enzyme system. For example, the demethylation of codeine (a pro-drug) by the CYP450 isoenzyme 2D6 is subject to genetic polymorphism. Up to 10% of the general population metabolize codeine poorly and do not experience analgesia in response to treatment with codeine, while another 10% rapidly convert codeine to morphine and experience potentially severe toxicity (including death).

In ***Phase II reactions*** drugs are either hydrolyzed or conjugated to endogenous macromolecules (e.g., glucuronic acid, sulphate, glycine, glutamine, or acetate) in order to facilitate the drugs' clearance. The terminology Phase I and Phase II does not imply a hierarchy in sequential steps. For example, acetaminophen, which is primarily

metabolized by Phase II reactions, with higher doses may undergo Phase I and then another Phase II reaction (Figure 9).

Excretion (Clearance)

Drugs are excreted (cleared) from the body either unchanged or as metabolites. The kidney is the most important organ responsible for clearance. Renal clearance may involve three processes: glomerular filtration which depends on fractional plasma protein binding and filtration rate; active tubular excretion, a non-selective carrier system for organic ions; and passive tubular reabsorption of unionized drugs.

Some drugs are cleared via the bile into the intestinal tract. These agents may subsequently be reabsorbed from the gut (enterohepatic recirculation), which contributes to higher bioavailability and prolonged drug action. Pulmonary excretion is important for the clearance of anesthetic gases and vapors. Drugs excreted in milk are potential sources of unwanted adverse effects in nursing infants. Other routes, such as saliva, sweat, and tears are quantitatively unimportant.

Drug clearance may be by first-order or zero-order kinetics. Most drugs are excreted by ***first-order kinetics***, implying that a constant fraction of the drug is eliminated per unit time from the body. The clearance of some drugs (e.g., alcohol) follows ***zero-order kinetics***, implying that a constant amount of the drug is eliminated per unit time. Zero-order kinetics tend to predominate in overdose as a result of saturation of metabolic and/or elimination pathways.

Drug Dosing

Following drug administration, the initial rapid clearance of the drug from the vascular compartment reflects the distribution of the drug to various tissues. The time it takes to distribute 50% of a drug from the circulation throughout the body is the drug's ***distribution half-life*** ($t_{½}$). The time required for metabolizing and clearing 50 percent of the drug from the body is the drug's ***elimination half-life*** ($t_{½}$). The elimination half-life determines the dosing interval.

Assuming first-order kinetics, dosage intervals shorter than the drug's elimination half-life lead to ***steady-state concentration*** (accumulation) of the drug in approximately four half-lives (Figure 10). At steady-state concentration, the rate of drug administration is equal to the rate of drug elimination. Predictably, after the administration of a single dose or the last dose of a drug, it will take approximately four half-lives to eliminate the drug from the body as follows (Figure 10):

- After 1 half-life 50% of the drug is remaining in the body and 50% has been eliminated
- After 2 half-lives 25% of the drug is remaining in the body and 75% has been eliminated
- After 3 half-lives 12.5% of the drug is remaining in the body and 87.5% has been eliminated
- After 4 half-lives 6.25% of the drug is remaining in the body and 93.75% has been eliminated

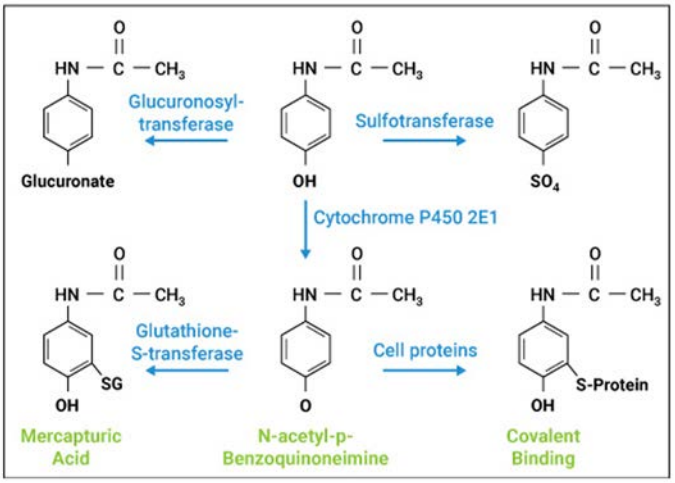

Figure 9. The metabolism of acetaminophen.

Steady-state plasma concentration of a drug may be achieved faster than four half-lives by the administration of an initial ***loading-dose*** (LD). By convention, the LD is twice the usual dose. However, when administering a LD caution must be exercised because too high a dose may cause adverse effects. After the administration of an initial LD, the dose recommended to maintain optimal therapeutic levels is defined as the ***maintenance dose*** (MD) of the drug.

Summary

Effective and safe drug therapy is predicated on pharmacodynamic and pharmacokinetic variable. Pharmacodynamics relates to drugs-receptor interactions and provides quantitative information that is the basis for determining efficacy, potency, and toxicity of drugs. Pharmacokinetics underlies the faith of drugs within the body, i.e., provides the basis for understanding the mechanisms responsible for a drug's ability to reach its receptor and factors essential to maintain therapeutic concentration for optimum efficacy and safety.

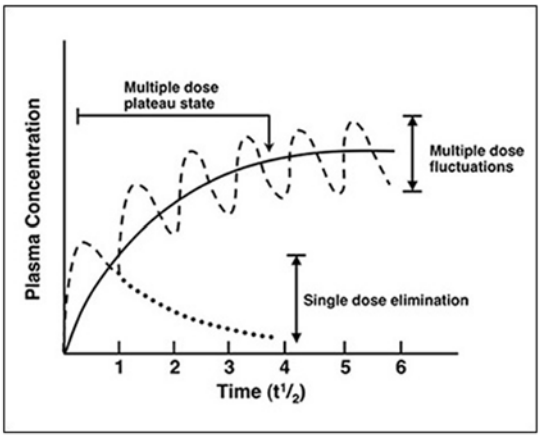

Figure 10. The effect of dosing on plasma concentrations.

Course Test Preview

1. Pharmacodynamics describes the effect of drugs quantitatively in order to determine _____.

a. efficacy
b. potency
c. toxicity
d. All of the above are correct.

2. Which of the following statements is correct with respect to the relationship between drugs and their receptors?

a. The first step in initiating a drug-induced effect is the formation of a complex between the drug and a cell component known as the drug receptor.
b. Drug receptors may be metabolic or regulatory enzymes or co-enzymes; proteins or glycoproteins associated with transport mechanisms; and structural and functional components of lipid membranes or nucleic acids.
c. The molecular events that follow drug-receptor interactions are called the mechanisms of action of drugs.
d. All of the above are correct.

3. Which of the following statements is correct with respect to the relationship between drugs and their affinity for their receptors?

a. Drugs attach to their receptors by covalent, ionic, hydrogen, hydrophobic, and Van der Waals binding.
b. The affinity of a drug for a particular receptor and the type of bond formed is intimately related to the drug's chemical structure.
c. Affinity is expressed as the drug's dissociation constant (K_d), i.e., the concentration of the drug required in solution to achieve 50 percent occupancy of its receptors.
d. All of the above are correct.

4. Which of the following types of chemical bonding is the least likely to be involved in a drug-receptor interaction?

a. Covalent bonding
b. Hydrogen bonding
c. Electrostatic bonding
d. Van der Wall's forces

5. Which of the following statements is correct with respect to a drug, which has a direct stimulatory effect on a receptor?

a. A strong agonist produces a significant physiologic response when only a relatively small number of receptors are occupied, i.e. the drug has good intrinsic activity.
b. A weak agonist must be bound to many more receptors to produce the same effect, i.e., the drug has low intrinsic activity.
c. A partial agonist will never produce the same effect as a strong or a weak agonist even when all receptors are occupied, i.e., the drug has very low intrinsic activity.
d. All of the above are correct.

6. All of the following statements related to antagonists are correct EXCEPT which one?

a. An antagonist interacts with the agonist-binding domain of a receptor and blocks the agonist from interacting with it.
b. A chemical antagonist either alters the K_d for the agonist or inhibits the receptor from responding to the agonist.
c. A reversible antagonist binds to the agonist-binding domain of the receptor, but high concentrations of the agonist can overcome the antagonism.
d. An allosteric antagonist binds to a receptor at a site other than the agonist-binding domain and produces a conformational change in the receptor.

7. Which of the following statements is correct with respect to the efficacy of a drug?

a. The magnitude of a physiological/pharmacological response obtained from optimal receptor occupancy by a drug reflects its efficacy.
b. The graded dose-response relationship is the quantification of a specific response elicited by a drug over a range of dosages.
c. The dose of a drug that produces maximal effect (E_{max}) is the ceiling dose of that drug.
d. All of the above are correct.

8. Which of the following statements is correct with respect to a drug's potency?

a. Potency of a drug is defined as that concentration at which the drug elicits 50 percent of its E_{max}, i.e., EC_{50}.
b. Potency reflects the affinity of a drug to its receptor as well as its intrinsic activity.
c. The concept of potency is important in determining drug dosage.
d. All of the above are correct.

9. The Therapeutic Index of a drug is defined as the _____.

a. median effective dose (ED_{50}) of the drug
b. LD_1/ED_{99}
c. the ratio of LD_{50}/ED_{50}
d. the therapeutic window of the drug

10. There are several mechanisms by which drugs translocate across biological membranes, but the most important one is _____.

a. active transport
b. facilitated transport
c. passive diffusion
d. pinocytosis

11. Primary determinants of passive diffusion include the drug's _____.

a. molecular weight
b. concentration gradient
c. pKa and lipid solubility
d. All of the above are correct.

12. Which of the following statements related to the dissociation constant (pKa) is correct?

a. The pKa is that pH at which a drug is 50% ionized and 50% unionized.
b. When the pH of the environment is increased above the pKa of a weak acid, over 50% of the drug will be ionized.
c. When lidocaine with a pKa of 7.9 is deposited into an infected (acidic) milieu more than 50% of its molecules will be ionized.
d. All of the above are correct.

13. Which of the following is an example of an enteral route of drug administration?

a. Oral
b. Sublingual
c. Subcutaneous
d. Intramuscular

14. All of the following statements related to plasma protein binging of drugs are correct EXCEPT which one?

a. Only the free form of a drug is capable of diffusion, plasma protein binding reduces a drug's availability to cross biological membranes.
b. Albumin is the most abundant protein in plasma and it is responsible for most plasma protein binding of drugs.
c. Highly protein bound drug have a high volume of distribution (V_d).
d. Plasma protein binding is also an important mechanism for drug-drug interactions.

15. All of the following statements relate to metabolism/biotransformation are correct EXCEPT which one?

a. Phase I reactions are mediated by the hepatic microsomal CYP450 enzyme system and involve metabolic modification of a drug by oxidation and reduction.
b. In Phase II reactions drugs are either hydrolyzed or conjugated to endogenous macromolecules.
c. Phase II reactions can be "induced" to increase or reduce the rate of a drug's metabolism and is responsible for many drug-drug interactions.
d. There is much genetic variability (polymorphism) with the CYP450 enzyme system.

16. Renal excretion may involve _____.

a. glomerular filtration which depends on fractional plasma protein binding and filtration rate
b. active tubular excretion, a non-selective carrier system for organic ions
c. passive tubular reabsorption of unionized drugs, which result in net passive reabsorption
d. All of the above are correct.

17. All of the statements relative to the excretion of drugs are correct EXCEPT which one?

a. Most drugs are excreted by zero-order kinetics.
b. First-order kinetics implies that a constant fraction of the drug is eliminated per unit time.
c. Zero-order kinetics, implying that a constant amount of the drug is eliminated per unit time.
d. Zero-order kinetics tend to predominate in overdose as a result of saturation of metabolic and/or elimination pathways.

18. All of the following statements about drug clearance and/or dosing requirements are correct EXCEPT which one?

a. Following drug administration, the initial rapid clearance of the drug from the vascular compartment reflects the distribution of the drug to various tissues.
b. The time it takes to distribute 50% of a drug from the circulation throughout the body is the drug's distribution half-life ($t_{½}$).
c. The time required for metabolizing and clearing 50 percent of the drug from the body is the drug's elimination half-life ($t_{½}$).
d. The distribution half-life ($t_{½}$) determines the dosing interval.

19. Assuming first-order kinetics, _____.

a. dosage intervals shorter than the drug's elimination half-life lead to steady-state concentration (accumulation) of the drug in approximately four half-lives
b. at steady-state concentration, the rate of drug administration is equal to the rate of drug clearance
c. after the administration of a single dose or the last dose of a drug, it will take approximately four half-lives to eliminate the drug from the body
d. All of the above are correct.

20. All of the following statements about drug dosing are correct EXCEPT which one?

a. Steady-state plasma concentration of a drug may be achieved faster than four half-live by the administration of an initial loading-dose (LD).
b. By convention, the LD is four times the usual dose.
c. When administering a LD caution must be exercised because too high a dose may cause adverse effects.
d. After the administration of an initial LD, the dose recommended to maintain optimal therapeutic levels is defined as the maintenance dose (MD) of the drug.

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