

Chapter 1

Introduction to pharmacology

I. Definition of terms

Absorption the movement of a drug from its site of administration (oral, topical, or injection) into the systemic circulation (bloodstream).

Adverse drug event (ADE) injury resulting from the use of a drug. It is an unfavorable and unintentional response resulting from an administered medication. Includes medication errors such as miscalculation of dosage or misreading a prescription.

Adverse drug reaction (ADR) harm to the body due to a medication that was properly prescribed (e.g., drug taken at normal doses and the correct route of administration). Examples of an ADR are allergy to penicillin or adverse (side) effect of a drug.

Affinity the ability of a drug to bind to the receptor to cause a therapeutic response.

Antibiotic prophylaxis antibiotic given to prevent an infection.

Bioavailability the amount of a drug (expressed as a percentage) that reaches the systemic circulation. For example, any drug administered intravenously has a 100% bioavailability

Biologics agents that are naturally produced in an animal or human body.

Clearance quantitative measure of the rate of drug elimination from the body divided by the concentration.

Creatinine a waste product in skeletal muscle by the breakdown of creatinine phosphate.

Creatinine clearance (CrCl) a test that compares the level of creatinine in the urine with that of creatinine in the blood and it determines normal functioning of the kidneys.

Cytochrome P450 (CYP) enzymes found primarily in the liver that are responsible for the metabolism of many drugs. Many drug interactions occur because some drugs are inhibitors or inducers of the substrate (drug being metabolized) resulting in high or low blood levels of one or the other drug.

Distribution movement of a drug through the body to the various target tissues/organs (site of action) after it enters the bloodstream.

Dose the amount of drug taken at any one time.

Drug any substance which changes a physiological function or modifies a disease process.

Drug action the response of living matter to administered chemicals. Levels of drug action include cellular or molecular. Cellular site of drug action is defined as all foreign parts that enter the body, will react with at least one portion of the cell. The initial reaction occurs here. At the molecular level the molecules of the drug will react with the molecules of the body.

Efficacy the ability of a drug to stimulate the receptor and produce the maximum response achievable by the drug. Two drugs can have the same efficacy but different potencies where one drug is more potent (stronger strength) than the first drug but both will have the same effect.

Elimination half-life ($t_{1/2}$): The time required to reduce the amount of drug in the body or concentration of drug in blood by 50%. However, once the first 50% is gone, it will take the body more time to clear 50% of the remaining medication. Usually it takes about 5 half-lives to clear 99% of the medication. To determine the time it takes for a drug to be 99% eliminated from the body multiply the half-life of the drug by 5.

First-pass effect (or first-pass metabolism) before an orally administered drug enters the systemic circulation it goes to the liver to be metabolized or biotransformed. Some oral drugs can undergo extensive first-pass effect that they are ineffective by the time of entering the bloodstream while other drugs undergo little first-pass effect and maintain the original efficacy. Drugs that undergo extensive first-pass effect cannot be given orally because it becomes pharmacologically ineffective by the time it enters the general circulation. Lidocaine is an example of a drug that cannot be given orally because it undergoes extensive first-pass effect.

First-order kinetics the rate of drug elimination decreases with time. That is, the rate of drug elimination falls as the concentration falls. Most drugs are removed from the body by first-order kinetics.

Loading dose (LD) an initial higher dose of a drug that may be given at the beginning of a course of treatment (to get initial quick plasma levels) before dropping down to a lower maintenance dose afterward. A loading dose is given on the first day of drug treatment.

Maintenance dose (MD) a lower drug dose allowing the dose that keeps the plasma drug concentration continuously within the therapeutic range. The maintenance dose is given starting after the loading dose on day 1 of drug therapy.

Metabolism (biotransformation) the primary mechanism of drug elimination from the body. Biotransformation will usually end the pharmacologic action of the drug.

Pharmacodynamics describes how the drug actually works; mechanism of action. How drugs interact with receptors and what happens once the drug binds to the receptor.

Pharmacokinetics study of the action of drug once it is in the patient. It describes the absorption, distribution, metabolism and elimination of the drug from the body.

Pharmacology is a Greek word defined as the science dealing with drugs and their interaction with the body's components.

Pharmacogenetics the convergence of pharmacology and genetics that deals with genetic factors that influence an organism's response to a drug.

Pharmacognosy study of drugs derived from herbal and other natural sources.

Pharmacotherapeutics the medical use of drugs in the prevention, diagnosis, treatment of diseases.

Polypharmacy many different medications including over-the-counter (OTC) and prescription drugs are taken by the patient.

Potency strength of the drug.

Prodrug a drug that becomes active only after it is ingested and metabolized in the liver. Codeine is converted from an inactive form to the pharmacologically active form, morphine, by first pass metabolism.

Protein binding attachment of a drug to proteins in the plasma. Drugs that are protein bound are inactive and become active in the free unbound form.

Steady state The point at which the rate of input of drug into the body is equal to the rate of elimination. As such, the amount or concentration in the body reaches a plateau.

Therapeutics branch of medicine that deals with the treatment of disease.

Therapeutic index (TI) (therapeutic ratio) a measure of the relative safety of a drug. Therapeutic index is expressed as the ratio of the lethal or toxic dose (LD) to the therapeutic dose (TD). For example, lithium has a narrow therapeutic index so if the dose is just slightly more than the therapeutic range toxicity can occur. Patients must be on chronic lithium maintenance treatment to avoid toxicity. On the other hand, penicillin has a wide therapeutic index so that slightly more than the usually dose will not cause toxicity.

Therapeutic range the dosage range of a drug that achieves the desired pharmacologic response.

Toxicology study of poisons and poisonings.

Zero-order kinetics the drug is removed at a constant rate regardless of the drug concentration; it is linear with time. The elimination from the body of a large concentration of alcohol is an example of a drug that follows zero-order kinetics. (Weinberg, 2002; Gossel, 1998a, b).

II. Pharmacokinetics

Q. What is the definition of pharmacokinetics and why is it important to know?

A. Pharmacokinetics describes the actions of the drug as it moves through the body and how the body influences drug concentrations. It is easiest to remember pharmacokinetics by the acronym: ADME (A=absorption into the systemic circulation; D=distribution to the target tissues and organs; M=metabolism or biotransformation; E=elimination from the body). It is important to know the basics of pharmacokinetics in order to understand the basic principles of prescribing medications. Pharmacokinetics (e.g., absorption of the drug into the blood) may be altered when certain antibiotics prescribed in dentistry are taken with food. Instructions must be verbally expressed to the patient and documented in the patient's chart on how to take medications that are prescribed by dentists (e.g., antibiotics, antimicrobial agents, analgesics, antifungal agents, antiviral agents, fluorides).

Q. What factors affect the rate of drug absorption?

A. In the gastrointestinal tract, many factors can influence the rate of drug absorption into the systemic circulation including acidity of the stomach and food in the stomach.

Some medications used in dentistry should be taken with food to reduce gastrointestinal irritation, some medications should be taken on an empty stomach because the food could delay the absorption of the drug and some medications can be taken with or without food because food would not interfere with absorption. Usually the absorption of the total amount of drug is not reduced but rather it will just take longer to get absorbed. Usually antibiotics have the most restrictions regarding taking with meals. Nonsteroidal anti-inflammatory drugs such as ibuprofen must be taken with food to avoid gastric irritation. Specific drugs will be discussed within the chapters.

Q. What does “take on an empty stomach” mean?

A. Take on an empty stomach means to take the drug within 1 hour before eating or 2 hours after eating. Take on an empty stomach is not interpreted as not eating.

Q. What is the pharmacokinetics of an orally administered drug?

A. The pharmacokinetics of a drug administered orally such as penicillin VK is as follows (Weinberg, 2002; Gossel 1998a, b):

1. An orally administered drug is swallowed and goes through the esophagus. It is important to take a tablet/capsule with a full glass of water to facilitate its passage through the esophagus into the stomach.
2. In the stomach the tablet/capsule must be released or liberated from its formulation. Once a tablet is “broken up” and a capsule is “opened” and the active ingredients are released there is dissolution of the drug from the liberated drug particles. Some acidic drugs are enteric-coated to protect the stomach lining. Dosage forms such as syrups or solutions are already a liquid which are immediately available for absorption and transport. A liquid gel capsule (Aleve, Advil) is formulated to dissolve quickly which allows the liquid inside the capsule to be absorbed fast.
3. Drug goes into the upper part of the small intestine (duodenum) where most absorption into the systemic circulation occurs because the small intestine has a large surface area due to microvilli on the surface which drugs may diffuse.
4. From the small intestine the drug molecules are *absorbed* into the bloodstream. Many factors can affect the rate and extent of absorption of the drug including foods and minerals. For example, tetracycline should not be given at the same time as dairy products or minerals (e.g., iron, calcium, magnesium) because insoluble complexes form in the intestinal tract, which slows down absorption. This can be avoided by taking the tetracycline one to two hours before or after the dairy/mineral product. Some antibiotics (e.g., tetracycline) must be taken on an empty stomach (one hour before or two hours after meals) which increases the rate of absorption. Most antibiotics can be taken without regard to meals (with or without food) but if stomach upset occurs food should be taken (Huang *et al.*, 2009).
5. Absorption occurs when a drug is nonionized or charged form and if it is more lipid-soluble. Most drugs are combined with a salt to enhance its absorption (e.g., lidocaine HCl, tetracycline HCl, doxycycline hyclate, amoxicillin trihydrate).

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6. Before an orally administered drug reaches the systemic circulation it goes to the liver via portal vein whereby it is immediately exposed to metabolism by liver enzymes (Huang *et al.*, 2009). This first exposure is referred to as **first-pass effect**. Some drugs such as lidocaine and morphine that undergo extensive first-pass metabolism will become inactive so they cannot be given orally. Diazepam (Valium) has close to 100% bioavailability (low first-pass metabolism) so it has similar oral and intravenous doses. Alternate routes of drug administration that bypass the first-pass effect include sublingual, rectal or parenteral (intravenous, intramuscular, and subcutaneous) (Pond & Tozer 1984; Fagerholm 2007).
7. Once reaching the systemic circulation, the drug is distributed in the blood to the various organs. Many drugs are bound to circulating proteins such as albumin (acidic drugs) and glycoproteins (basic drugs). Highly protein bound drugs are not active and only the free drug that is not bound to proteins is active.
8. Once the drug has exerted its actions it must be eliminated from the body. The first part of drug elimination involves **metabolism** or **biotransformation**, which occurs mostly in the liver. It may take a drug several passes through the liver before it is entirely metabolized. Biotransformation converts lipid-soluble drug molecules to metabolites or end products that are more water-soluble and easier to be eliminated from the body. Most of process of conversion of drugs occurs in the liver by metabolizing enzymes called microsomal enzymes. These enzymes, which are also called **cytochrome P450 (CYP)** enzymes are the primary enzymes responsible for the oxidation of many drugs. There are many different isoenzymes for different drugs (e.g., CYP3A4 is involved with many dental drugs). Many drug–drug and drug–food interactions occur via the microsomal enzymes. Some drugs called **prodrugs** (e.g., codeine is metabolized by the liver enzyme CYP2D6 to the active morphine), have no pharmacologic activity unless they are first metabolized to the active form in the body (Weinberg, 2002).
9. **Drug elimination**: now the more water-soluble metabolite must be eliminated from the body. The main route of drug elimination is excretion via the kidneys. Diseases of the kidney can significantly prolong the duration of drug action and dosage adjustment may be needed from the patient's physician. Some elimination occurs through the lungs, breast milk, sweat, tears, feces and bile. Some drugs (e.g., tetracycline) undergo biliary excretion whereby the drug is eliminated in the bile and enters the small intestine and eventually leaves the body in the feces. Most bile is then circulated back to the liver by **enterohepatic recirculation** and eventually metabolized by the liver and excreted via the kidneys. This route of reabsorption is helpful in prolonging the activity (increasing the half-life) of some antibiotics (Weinberg, 2002).

Q. What is the definition of drug absorption?

A. Drug **absorption** is the movement of a drug from the site of administration to the systemic circulation.

Q. What does it mean when a drug has 100% bioavailability?

A. **Bioavailability** describes the portion of an administered drug that reaches the systemic circulation. It is the rate and extent of absorption and how fast and how much of the drug is absorbed. It indicates that the drug is 100% absorbed into the blood. Only intravenously administered drugs have 100% bioavailability because 100% of the drug enters directly into the blood. A drug administered orally that undergo extensive first-pass metabolism (or first-pass effect) by traveling first to the liver, where it is metabolized and can become almost inactive by the time it reaches the systemic circulation. This drug would have low bioavailability.

Q. What is the first step involved in drug absorption?

A. Disintegration of the dosage formulation into a formulation that can easily be absorbed is the first step before a drug can be absorbed in the small intestine. The stomach should be the first site of absorption, but in reality, very little absorption occurs in the stomach because the surface area is very small. A tablet must break up to expose the active ingredient which takes some time. A capsule must open up which takes less time than a tablet. A solution is already in a liquid, easily absorbed form and takes the least time for disintegration and absorption of all dosage forms. The order of bioavailability is oral solution > oral suspension > capsule > tablet (Lloyd *et al.*, 1978).

Q. Is there any systemic absorption of a topical anesthetic applied on the surface of the gingiva?

A. Yes. The purpose of topical agents is to maximize the concentration of the drug at the target site while minimizing potential systemic adverse effects. Although drug absorption is not desired there could be some systemic absorption especially if the agent is applied on abraded gingiva or skin.

Because of its lipophilic nature, the stratum corneum of the skin may act as a reservoir for many drugs. Consequently, the local effects of the drug may be sufficiently long to allow once-daily application. For example, once-daily application of corticosteroid preparations is as effective as are multiple applications in most circumstances. Direct access to the skin may predispose the patient to frequent topical applications, increasing the risk of systemic adverse effects.

Q. How does a drug get absorbed into the systemic circulation?

A. A drug must pass through many cell membranes to get into the blood. A drug must have some water solubility to go through aqueous fluids and some lipid solubility to get through the cell membrane, which has 2 layers of phospholipids.

Q. What is the purpose of epinephrine added to local anesthetics?

A. Epinephrine is a vasoconstrictor that acts to constrict blood vessels to decrease blood flow in the area that the local anesthetic solution was injected. This allows the anesthetic solution to stay the site of action longer, which slows absorption of the anesthetic solution. Also acting as a vasoconstrictor reduces bleeding at the surgical site.

Q. What is drug distribution and what factors affect distribution?

A. Drug **distribution** is the movement of an agent through the blood or lymph to various sites of actions in the body. An important factor affecting drug distribution is **protein binding**. Many drugs in the blood are bound to circulating proteins such as albumin for acidic drugs (e.g., penicillin, barbiturates, aspirin, vitamin C) and acid glycoproteins and lipoproteins for basic drugs (e.g., narcotic analgesics, erythromycin). When drugs are bound to plasma proteins they are inactive circulating in the blood. This binding to proteins is temporary and reversible and can convert to free drug. Only drugs that are not bound to plasma proteins are “freely active” and bind to specific receptors on the target tissue/organ. Another factor that affects drug distribution is blood flow to the target organs.

Q. What is the definition of minimum effective concentration (MIC) of a drug?

A. The **minimum effective concentration (MIC)** is the amount of drug required to produce a therapeutic effect. This is important to know because a drug should not be given that is above the MIC that will produce toxic concentrations. The ideal concentration of a drug should be between the MIC and the toxic concentration. This is referred to as the **therapeutic range**. For example, after periodontal surgery the patient is recommended to take ibuprofen (Motrin, Nuprin). The patient decides to take only one 200mg tablet during the day. The patient still experiences pain because the therapeutic range was not reached. The patient should take two or three tablets which will increase the plasma level of ibuprofen into the therapeutic range. If the patient takes 5 or more tablets at one time then adverse effects may occur because the plasma level of ibuprofen is outside the therapeutic range and the maximum dose has been reached beyond which the analgesic effect does not increase.

Q. What does the term “dose” mean?

A. The **dose** of a drug is the amount of drug taken at any one time. Dose is expressed as the weight of drug (e.g., 500mg), the number of dosage forms (e.g., one capsule), or the volume of liquid (e.g., two drops).

Q. What is the definition of elimination half-life of a drug?

A. The **elimination half-life ($t_{1/2}$)** of a drug is essentially the duration of action of a drug. Also, it is used to determine the dosing of a drug. The elimination half-life of a drug is defined as the amount of time required for a drug to decrease its original concentration by 50% after it is administered. The second half-life is when it removes another 50%, leaving 25% in the blood. The third half-life is when it removes another 50%, leaving 12.5% in the blood. Drugs have different predetermined half-lives. The $t_{1/2}$ of a drug is used to determine the dosing of a drug and duration of drug action. As repeated doses of a drug are administered the plasma concentration builds up and reaches “**steady-state**”. Steady-state occurs when the amount of drug in the plasma builds up to a level that is considered to be therapeutically effective. In order to achieve steady state the amount of drug that is administered must balance the amount being cleared from the body. It usually takes about between four and five half-lives to reach clinical steady-state and about six half-lives before 98% of the drug is eliminated from the body. For example, if a drug has a $t_{1/2}$ of 2 hours it will take about 8 to 10 hours to reach the clinical steady state.

Drugs with a short $t_{1/2}$ are eliminated faster than drugs with a long $t_{1/2}$. For example, tetracycline HCl has a $t_{1/2}$ of 6–12 hours and doxycycline hyclate has a $t_{1/2}$ of 14–24 hours. Thus, tetracycline dosing is one capsule every 4 hours while doxycycline is dosed 100mg every 12 hours on day 1, then 100mg every day. On the average, doxycycline's half-life is around 19 hours. By multiplying 19 hours by 6 hours (average $t_{1/2}$ to be 98% eliminated from the body) ($19 \times 6 = 114$ hours) it takes 114 hours, or about 5 days, before 98% of the doxycycline has been removed from the body. Penicillin VK has a $t_{1/2}$ of 30 minutes and amoxicillin $t_{1/2}$ 1-1.3 hours. Thus, penicillin is doses every 6 hours and amoxicillin is dosed every 8 hours (Thomson, 2004a, b).

Ibuprofen has a short $t_{1/2}$ and is cleared from the body more rapidly than a drug with a longer $t_{1/2}$. Ibuprofen requires a more frequent, regular dosing regimen of 200 to 400mg every 4 to 6 hours in order to build up and maintain a high enough concentration in the plasma to be therapeutically effective.

Q. What is the definition of volume of distribution (V_D)?

A. **Volume of distribution (V_D)** refers to the distribution of the drug in the various body tissues. Volume of distribution is a calculated value referring to the volume of fluid [e.g., plasma, interstitial fluid (fluid between the cells), and lymph] in which a drug is able to distribute to the organs. The volume of distribution can be used to calculate the clearance of a drug (Aki *et al.*, 2010; Thomson, 2004a, b).

Q. What is drug biotransformation?

A. Drug biotransformation (or metabolism as it is sometimes referred to) is a method to terminate the action of a drug. Usually drug biotransformation occurs in the liver by enzymes, but can also occur in the plasma and kidney.

Q. What is the importance of drug clearance?

A. **Clearance** refers to the volume of fluid (e.g., plasma) that would be completely cleared of drug if the entire drug being excreted were removed from that volume of fluid. Essentially, clearance is the removal of a drug from the plasma. It is a calculated value and measured in liters/hour. Clearance indicates the ability of the liver and kidney to eliminate a drug. Clearance may be reduced in the elderly. Both clearance and V_D are important values in determining the half-life of a drug (Gossel, 1998a, b).

Q. What must happen in the body to a drug in order to have a drug effect to occur?

A. The rate of absorption must be greater than the rate of elimination in order for the drug to have an effect on the body. Usually the rate of elimination is slower than the rate of absorption so that it is the rate of elimination that is the controlling factor in the presence of the drug in the body (Fujimoto, 1979).

III. Pharmacodynamics

Q. What is the definition of pharmacodynamics and its significance in dentistry?

A. **Pharmacodynamics** deals with the mechanism of action of drugs or how the drug works in the body to produce a pharmacologic response and the relationship between drug concentration and response. It is important to know the mechanism of action of drugs because it will help with understanding the reason for prescribing the drug.

Q. What is the definition of drug affinity?

A. **Affinity** is the ability of a drug to bind to the receptor to elicit a therapeutic response. If one drug has a greater affinity than another drug it means that that drug binds more readily to the receptor. A drug with a “high affinity” means that even a small dose can produce a response.

Q. Do drugs bind strongly to a receptor?

A. Most drugs bind weakly to their receptors via hydrogen, hydrophobic and ionic bonds. Because it is a weak bond, the drug can come on and off the receptor. Some drugs do bind strongly to the receptor via covalent bonds.

Q. Can drugs bind to other receptors besides their specific receptors?

A. Yes. For example, atypical antipsychotic drugs bind to dopamine receptors for its antipsychotic response but also bind to alpha receptors which cause adverse effects such as weight loss and binding to muscarinic receptors causes xerostomia.

Q. How do most drugs cause a therapeutic response?

A. Most drugs have an affinity for a specific receptor. Most receptors are proteins. Once the drug binds to the receptor a therapeutic response occurs. Receptors have a steric or three-dimensional structure so that as the substrate or drug binds to that receptor the receptor undergoes steric realignment or changes which allows for the drug to bind more precisely to the receptor and have better efficacy.

Q. Do all drugs interact with receptors to cause a therapeutic response?

A. No. Epinephrine does bind to alpha and beta receptors on the organs but also it produces some of its effects by activating an enzyme called adenyl cyclase. Also, anesthetic gases do not bind to receptors in the central nervous system and antacids do not work by interacting with receptors.

Q. What are a drug agonist and antagonist?

A. Drugs produce their effects by altering the function of cells and tissues in the body or organisms such as bacteria. Most drugs have an affinity for a target receptor, which is usually a protein on the cell surface. Once a drug binds to a receptor it can act as either as an **agonist** (produces a stimulatory response) or an **antagonist** (sits on the receptor site and prevents an agonist from binding to the receptor; an antagonist does not produce a therapeutic response).

For example, epinephrine in low doses as used in dentistry is an agonist that when bound to β_2 -receptors results in vasodilation of skeletal muscle. This vasodilation tends to reduce peripheral resistance and therefore diastolic blood pressure. At the same time, the β_1 (and β_2)-receptors in the heart are activated to increase cardiac output and systolic blood pressure. These two influences cancel each other out regarding mean blood pressure.

An example of an antagonist is flumazenil (Romazicon), which is a benzodiazepine receptor antagonist that is used in benzodiazepine overdose. It will sit on the receptor and prevent the benzodiazepine from attaching. Naloxone (Narcan) is a narcotic receptor antagonist.

Q. What is the difference between drug potency and efficacy?

A. **Potency** is the relationship between the dose of a drug and the therapeutic effect; it refers to the drug's strength. **Efficacy** refers to the ability of a drug to exert an effect. For example, 500mg of acetaminophen and 200mg of ibuprofen both produce the same analgesia and have the same efficacy but ibuprofen is more potent because it requires a lower dosage.

Q. What is the therapeutic index of a drug?

A. The **therapeutic index** (TI) is the median effective dose (ED_{50}) is the dose required to produce a specific therapeutic response in 50% of patients. The median lethal dose (LD_{50}) refers to the dose of drug that will be lethal in 50% of a group of animals, not humans. To determine drug safety the drug's TI is calculated as the ratio of a drug's LD_{50} to its ED_{50} . Some drugs (e.g., lithium, digoxin) have a narrow TI whereby routine blood tests are necessary to assure the plasma drug level is within the therapeutic range.

Q. What is an adverse drug reaction and why is it important to know?

A. An **adverse drug reaction** (ADR) is defined by the World Health Organization (WHO) as any response to a drug that is noxious, unintended, and *occurs when a drug is properly prescribed at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease*. Medical errors are not included in this definition. Bisphosphonate-induced osteonecrosis of the jaws is an ADR. Other examples of adverse drug reactions include drug interactions, allergic reactions and irritating adverse effects of a drug such as gastrointestinal problems (nausea, diarrhea). A drug interaction

occurs when the effects of one drug are altered by the effects of another drug resulting in an increase or decrease of the drug. An allergic reaction due to a drug is an abnormal and unwanted response that range from a mild rash to life-threatening anaphylaxis. An allergic reaction does not often happen the first time you take a medication. A reaction is much more likely to occur the next time you take that medication.

Q. How does an ADR differ from an adverse effect or allergy?

A. An adverse effect is a type of adverse drug reaction mediated by an immune response and is not the intended therapeutic outcome. It has been suggested to avoid using the term “side effect” and use the term “adverse effect or adverse drug reaction” instead (VA Center for Medication Safety and VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. 2006; Riedl & Casillas, 2003).

Q. What is an adverse drug event?

A. An **adverse drug event** (ADE) is an unfavorable and unintended response to a drug that includes medical errors (e.g., miscalculations, confusion with handwritten prescriptions). The dentist has the responsibility to report any ADE that occurs through the FDA's Adverse Event Reporting System (MedWatch). (Mayer *et al.*, 2010). (<http://www.fda.gov/Safety/MedWatch/default.htm>)

Q. What is the definition of tolerance?

A. **Tolerance** to a drug is the development of resistance to the effects of a drug whereby in order to have the desired response more of the drug must be taken. Overdose is very common. Narcotics and alcohol are common examples of drugs that produce tolerance.

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