General Pharmacologic Concepts

1 Pharmacokinetics: The Study of Drug Disposition

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Objectives

After completing this chapter, the reader should be able to

- Describe the role pharmacokinetics plays in determining drug movement between body tissues.
- Determine how various disease states affect the pharmacokinetic parameters of a drug.
- Calculate specific pharmacokinetic parameters such as volume of distribution, clearance, and half-life.
- Explain the differences between phase I and phase II metabolism.
- Describe how drug dosing regimens can be altered to maintain safe therapeutic drug levels.

Introduction

The word "pharmacology" is derived from the Greek word *Pharmakon* and the suffix *-logia* and is defined as the science or study of drugs.[1] As far back as recorded history, and undoubtedly before that, humans have used plant and animal materials to treat various ailments and disorders.[2] Studies have shown that humans are not alone in the use of natural substances to treat various disorders. Other primates, specifically gorillas and chimpanzees, have been observed ingesting certain plants in what is thought to be a self-treatment for intestinal parasites.[3,4] Indeed, even less-advanced animal species such as some arthropods and fish have been shown to collect materials from plants or other animals to use in their own chemical defense against predators.[4] Considering these findings, pharmacology may well be one of the oldest applied sciences known.

Pharmacology, like all other areas of science, comprises a series of basic principles and concepts that form the foundation of the science. The most basic of these principles arises from the chemical sciences. One could even argue that pharmacology is really just an applied chemical science because all drugs are chemical substances and the biologic systems on which they interact are nothing but a series of chemical molecules and reactions. These chemical principles are useful for describing how a drug interacts at the molecular level with various enzymes, receptors, and tissues throughout the body. These interactions form the basis for two important areas of study in pharmacology: pharmacokinetics and pharmacodynamics. In very simplistic terms, pharmacokinetics explains the effect of the body on a drug, whereas pharmacodynamics explains the effect of a drug on the body.[5] Combined, these areas help explain how a drug molecule moves through the body, elicits its effect at a specific site, and is subsequently inactivated and removed from the body. Understanding these key concepts is critical to the modern delivery of anesthesia. In a sense, today's anesthesia provider is a practicing clinical pharmacologist[6] whose daily practice involves the administration of drugs and the monitoring of his or her patient for effects.

Pharmacokinetics

One of the more important aspects of pharmacology deals with how drug molecules are handled by the body from the initial administration to the final elimination of the agent. It is the understanding of these principles and their mechanisms that allow the determination of various properties of specific drug molecules such as half-life, onset and duration of effects, and drug dosing, among many others. Together these concepts and principles form the basis of pharmacokinetics, which incorporates mathematical models to help explain and predict how a drug is handled by the body.

Routes of Administration

Drugs are administered to patients in several different ways depending on many different factors, such as available formulations, need for immediate action, patient compliance

and convenience, and the ability to get the drug to the site of action. In an outpatient environment, noninvasive routes (oral, topical) are usually preferred if possible, whereas in an inpatient setting, all routes of drug administration are common. In an operating room environment, administration of drugs by various parenteral and inhalational routes is more common. All routes of administration have specific advantages and disadvantages and must be considered based on patient needs and availability of dose forms.

Oral

Of all drug doses administered, drugs given by the oral route far outnumber any other route. This is mainly due to the noninvasive nature of the oral route and relatively good patient compliance. This is the route of choice for any drug that needs to be administered frequently or over an extended period of time. However, not all drugs can be given orally. Some drugs are not absorbed well after oral administration or are destroyed by stomach acid or enzymatic activity in the gastrointestinal (GI) tract. Other drugs are very irritating to the GI tract or may cause localized reactions that preclude their oral use. In addition, some drugs may need to be administered so frequently because of rapid elimination that oral dosing is just not practical. Compounds to be administered orally are usually produced in a tablet or capsule dose form that dissolves in the stomach or small intestine and is absorbed across GI membranes.

Topical

Many drugs are administered to the outer layers of the skin in dose forms that include creams, ointments, drops, powders, sprays, and transdermal patches. The topical route is most often used to treat a local disorder of the skin, eyes, and ears. However, drugs can also be applied to mucosal membranes such as the throat and vagina to treat localized disorders. Absorption of drug molecules across the skin is limited with most drugs; however, some drugs are absorbed into the general systemic circulation, allowing the use of the topical route to treat various systemic disorders. Transdermal patches and some creams/ointments are the most common means of supplying systemic therapy by the topical route.

Inhalational

Gaseous, volatile, and aerosolized compounds can be administered by inhalation. Although gaseous and volatile agents penetrate completely to the alveoli for absorption into the body, most aerosols are composed of particles that are too large to penetrate all the way to the alveoli. These drugs are therefore primarily used for localized therapy of airway and bronchial tissue.

Rectal

Rectal administration is particularly useful for patients that are unconscious or experiencing severe nausea and vomiting. The rectum comprises the last 6 inches of the large intestine and is usually devoid of stool. Solid dosage forms inserted into the rectum tend to be pulled back up into the lower regions of the large intestine. One of the primary functions of the large intestine is to remove excess water from the stool, and therefore the region contains an unpredictable volume of water in which to solubilize a drug for absorption. This makes rectal administration for systemic absorption unpredictable. However, because of the local blood flow, drugs absorbed rectally and through the lower portion of the large intestines do not travel to the liver before traveling back to the heart and thus avoid problems associated with first-pass metabolism.

Parenteral

Intravenous

This is the most common means of supplying a drug directly into the general systemic circulation. There is no absorptive phase with this route because the drug is supplied directly into the systemic circulation through an accessible vein. Drugs can be given rapidly (intravenous [IV] push) or more slowly (infusion). Local irritation of the vein in the region of administration is possible with some drugs. This can usually be mitigated by slower administration, thus allowing the drug to mix and dilute in the local venous blood as it is being injected.

Intra-arterial

This route is typically used to provide a drug to a specific target tissue in high concentration before it has a chance to dilute in the general circulation. Common uses are in chemotherapy and diagnostics. The arterial walls are not usually as sensitive as the veins, and so fewer local irritations are reported.

Epidural

This route is most commonly used to supply local anesthetic agents for pain relief during childbirth. The injection is made in a localized region inside the bony spine but external to the dura mater that surrounds the spinal cord.

Subcutaneous

Administration by this route is useful to provide a constant and relatively slow absorption of a drug. However, only nonirritating agents can be given by this route because localized irritation can lead to localized tissue necrosis. In addition, only relatively small volumes can be administered subcutaneously without excessive localized pain on injection. Some compounds and solid dose forms can be given as a depot injection, thus prolonging the duration of action of the supplied agent.

Intramuscular

Like the subcutaneous route, only nonirritating substances should be administered by this route. Irritating substances cause increased injection site pain and can cause localized necrosis. Although larger volumes can be injected intramuscularly than subcutaneously, the total volume at any one site is limited to approximately 5 mL to avoid excessive injection pain. Absorption into the general circulation is faster following intramuscular injection than after subcutaneous administration for most compounds. Depot injections, where the drug is usually prepared in oil, can be administered via this route to provide a slow absorption of the agent over a prolonged period, thus providing long-term therapy with fewer doses.

Solubility

To understand how a drug molecule can enter the body and move into different tissues, knowledge of that drug's physical properties is necessary. Drug molecules are chemical compounds and as such may be charged, uncharged, acidic, basic, or neutral structures. They may be gases, liquids, or solids at room temperature and thus require different dosage forms and routes for administration to a patient. These characteristics are critical in drug development and how the drug enters and interacts in the body.

One of the most important physical characteristics of a drug molecule is its solubility in various materials. Solubility of a drug affects drug dosage form design decisions and how the drug moves through various body tissues once administered. Most drug molecules cross tissue membranes by simple lipid diffusion. To enter a tissue, the drug must be able to move across cellular membranes that are composed of a lipid bilayer. To enter this hydrophobic layer, a drug molecule must have at least some lipid solubility or it cannot enter the cellular membrane and thus cannot cross biologic membranes by diffusion. However, if the drug is too lipid soluble it will not be able to move out of the membrane once it enters. The ratio of a drug's lipid solubility to water solubility at equilibrium is known as the oil-to-water partition coefficient, which is used as a predictor of how well a drug will cross biologic membranes to reach target tissues. Usually, the oil that is used for solubility determinations is octanol, an eight-carbon alcohol. Octanol is used because its oil solubility characteristics are very close to that of biologic membranes.[7,8] Although water is often used for the aqueous solubility measurement, an aqueous buffer solution similar in makeup to extracellular fluid may be used instead. Therefore the standard oil-to-water partition coefficient may also be seen as an octanol-to-water or octanol-to-buffer partition coefficient. The larger the value of this partition coefficient, the greater the lipid solubility of the drug.

Although the oil-to-water partition coefficient helps determine how well a drug molecule can cross biologic membranes, some drugs cross membranes by specialized transport molecules in the membrane. An example of this is the transport of the amino acids, which are charged molecules at physiologic pH. Because they are charged, they are not very lipid soluble and will not cross membranes by simple lipid diffusion. These transport molecules are proteins and are present in membranes to allow the movement of some compounds into or out of cells that do not cross easily by simple diffusion. Some drug molecules can use these specialized carriers to cross membranes and enter tissues even if the drug molecules cannot cross the membranes by lipid diffusion.

A different form of partition coefficient is used to describe the solubility of gases and volatile agents that are administered in gaseous mixtures. This is referred to as the blood-to-gas partition coefficient. Gases and volatile agents administered in air are administered to a patient via the inhalational route. For these compounds to cross the alveolar membranes and into the blood, they must possess some lipid solubility characteristics and some degree of blood solubility. However, unlike an oil-to-water partition coefficient, which is based on the concentration of the agent in each component, when discussing the partitioning of a gaseous or volatile molecule the partial pressure of the agent in each component is used. Therefore the blood-to-gas partition coefficient is the partial pressure of the gas or volatile agent in the blood divided by the partial pressure of the gas or volatile agent in the gas at the alveoli (P_A) once equilibrium has been reached. Partial pressures of the gases and volatile agents is similar (although not exactly

the same) to concentrations of nongaseous molecules. Gases or volatile agents move from a region of higher partial pressure to a region of lower partial pressure. Therefore the higher initial partial pressure of a gas or volatile agent being inhalationally administered at the alveoli is the driving force for movement of the molecules into the blood until equilibrium is reached.

Another form of partition coefficient is occasionally used to discuss the relative solubility of a drug in a tissue compared with the blood. This is known as the tissue-to-blood partition coefficient and is specific for the tissue being examined. These values are useful in determining what specific tissues a drug enters and to what extent. However, these values cannot be used to determine effect. Some drugs may only enter a tissue to a small extent compared with other agents but may still produce greater effects.

Many drug molecules are either weak acids or weak bases and as such may be charged at physiologic pH. These molecules will not cross biologic membranes by diffusion when they are in their charged form. However, as weak acids or bases they exist in a ratio of charged to uncharged molecules that is dependent on the pH of their environment and their specific acid or base character. An acidic group on a molecule is one that can give up a proton (H^+) and becomes charged once the proton has been removed from the molecule. A basic group on a molecule is one that can accept a proton and becomes charged once that proton binds to the molecule. Every acidic or basic group on a molecule has a particular propensity to gain or lose these protons determined by the relative hydrogen ion concentration in their environment. The pH where an acid or base exists 50% in the ionized form and 50% in the un-ionized form is known as the pK_a, or $-\log (K_a)$, where K_a is the acid dissociation constant. Every acidic or basic molecule has a specific pK_a value that is experimentally determined. From this pK_a it is possible to determine the relative ratio of charged to uncharged molecules that exists at a specific pH. The equation used to determine this is known as the Henderson-Hasselbalch equation,[9]

$$pH = pK_a + \log \frac{[UP]}{[P]} \ ,$$

where pH is the pH of the solution containing the drug (usually a physiologic pH if the drug is in the body), pK_a is the specific pK_a of the acidic or basic drug, [UP] is the concentration of the unprotonated form of the acid or base, and [P] is the concentration of the protonated form. It is important to remember that an acidic compound is charged when it is unprotonated and uncharged in the protonated form. A basic compound is uncharged in the unprotonated form and charged when protonated. By using this equation for a known acidic or basic compound, it is possible to determine the relative ratio of charged to uncharged molecules at a specific pH. Knowing this ratio provides information concerning how highly ionized (charged) the compound may be in the body. This is important because the ionized form does not normally cross membranes, and the higher the ratio of ionized to un-ionized, the slower the compound is to cross into tissues to exert its effect. An example of this is the local anesthetic lidocaine, which is a weak base with a $pK_a = 7.9$. At physiologic pH (7.4), the un-ionized-to-ionized ratio can be calculated as follows:

$$pH = pK_a + \log \frac{[UP]}{[P]}$$

$$7.4 = 7.9 + \log \frac{[UP]}{[P]}$$

$$-0.50 = \log \frac{[UP]}{[P]}$$

$$\text{antilog}(-0.50) = \frac{[UP]}{[P]}$$

$$0.32 = \frac{[UP]}{[P]}$$

Because the unprotonated (UP) form of a base is the un-ionized form and the protonated form (P) is the ionized form, this example demonstrates that at equilibrium there are approximately 32 un-ionized molecules of lidocaine for every 100 ionized molecules at pH 7.4. As the un-ionized molecules move across membranes in the body, a new equilibrium occurs among the remaining molecules to maintain the same ratio. Therefore even though there are ionized molecules present that cannot cross membranes initially, with time they will convert to un-ionized molecules and will be able to cross. Examination of another local anesthetic with a higher pK_a such as procaine, which has a pK_a of 8.9 at pH 7.4, the equilibrium ratio of approximately 32 un-ionized molecules is present for every 1000 ionized molecules. Because there are 10 times more ionized molecules in this case, it would be expected that procaine would exhibit a slower onset than lidocaine because it takes longer for the ionized molecules to be converted to the un-ionized form that can cross the cell membranes. These examples provide insight into how acidic or basic molecules can cross membranes by simple diffusion and how pK_a values of a molecule can influence the rate of onset of a drug's action.

Absorption, Distribution, Metabolism, and Elimination

Absorption

In biologic systems, drug absorption is considered to be the movement of drug molecules across membranes and into the bloodstream. Except for routes of administration that place the drug directly into the bloodstream (i.e., IV), all administered drugs have some absorptive phase if they need to enter the blood to reach a nonlocal site of action. Each route of administration or specific drug compound may have certain nuances associated with absorption, thereby requiring different dosage formulations to facilitate absorption.

The rate of absorption of drug molecules across membranes by passive diffusion is described by Fick's Law:

$$\text{Diffusion Rate} = \frac{(\Delta C)(\text{Membrane Area})(\text{Drug Solubility})}{\text{Membrane Thickness}\sqrt{\text{Drug Molecular Weight}}},$$

where the rate of diffusion across a specific membrane depends on the concentration (or partial pressure for a gaseous or volatile agent) differential or gradient across the membrane, the area of the membrane over which the drug may be absorbed, the solubility of the drug in the membrane, the thickness of the membrane, and the molecular weight of the drug, which is related to the size of the drug molecule. Therefore having a large difference in drug concentration from one side of the membrane to the other increases the diffusion rate, as does a large membrane area for absorption and a drug that is easily soluble into the membrane. However, thicker membranes or large molecules decrease the rate of diffusion.

Oral Drug Absorption

Most common oral dose forms are swallowed and rely on the stomach and/or small intestines for absorption. Solid dosage forms (i.e., tablets and capsules) must first undergo dissolution, which is the process by which the solid dosage form breaks down into individual molecules or very small absorbable particles. Liquid dose forms usually do not require this step unless they contain small suspended particles that need to dissolve further. Most drugs dissolve into their absorbable particles in the stomach; however, the acidic environment of the stomach may destroy acid labile substances. These drugs require a different dose form, usually composed of an enteric coating, which protects the drug from the stomach acidity and allows transport to the small intestines where the dose form then dissolves.

Once a drug has dissolved into individual molecules or very small particles, it may be absorbed across membranes and into the bloodstream. This process is driven by passive diffusion through the cellular membranes unless a specific carrier exists to carry the drug molecules across the membranes. Because passive diffusion requires the drug molecule to be in a lipid-soluble form, the ionization state of a weakly acidic or basic drug becomes important. Although most drugs are best absorbed in the small intestines, some drugs, especially weakly acidic drugs, are absorbed in the stomach. This again can be explained by the Henderson-Hasselbalch equation because in the acidic environment of the stomach, acidic drugs tend to exist more in their un-ionized form and are therefore better absorbed. Weakly basic drugs exist mainly in their ionized form in the acidic stomach contents and are therefore not well absorbed. In the small intestines, bicarbonate secreted with bile raises the pH of the GI contents and causes weakly basic drugs to convert more to their un-ionized, more lipid-soluble form, thereby facilitating their absorption from the small intestine. In addition, the small intestine wall is composed of small protrusions called microvilli that greatly increase the surface area for absorption of most compounds.

Although lipid solubility plays an important role in the rate of drug absorption across the small intestine, large octanol-to-buffer partition coefficients actually impede absorption. This is because the small intestine wall is covered with a more water-soluble polysaccharide layer known as the glycocalyx layer. This layer coats the epithelial cells of the small intestine and keeps very lipid-soluble compounds from crossing to the epithelial cells, thus limiting absorption. However, a certain degree of lipid solubility is required to cross the epithelial membranes by diffusion once the drug penetrates the glycocalyx layer. Highly lipid-soluble drugs may also bind to fats in the GI tract and can then be absorbed by epithelial endocytosis rather than passive diffusion.

Distribution

Once a drug is absorbed into the bloodstream it is transported throughout the body and may cross into tissues, where it may act. This is known as drug distribution. In the plasma some drugs bind to varying degrees to proteins located in the bloodstream. The two most common proteins to which drug molecules bind are plasma albumin and α_1-acid glycoproteins. These protein molecules are very large and have many sites on their structure to which drug molecules may attach. The binding to these sites is usually fairly weak, and the drug molecules attach and

detach readily. Although some drug molecules do not bind to plasma proteins to any appreciable extent, others are highly protein bound. An example of this is the anticoagulant drug warfarin, which is approximately 99% bound to plasma proteins.[10] Because only the free, unbound drug is available to cross membranes into tissues, a large amount of drug in the plasma that is bound to plasma proteins is unavailable to act. However, this protein binding is an equilibrium type of interaction, and as free drug leaves the plasma and moves into tissues, a new equilibrium maintains the relative bound-to-unbound ratio. Therefore the plasma protein binding can act as a depot or reservoir of drug, which can slowly supply additional free drug into the plasma as the free drug concentration decreases due to distribution into tissues or elimination.

Distribution of drug molecules into tissues from the bloodstream again depends on mechanisms of absorption. To enter a tissue there needs to be a specific transport protein capable of moving the drug into the tissue, or the drug may enter the tissue by endocytotic mechanisms or passive diffusion. Because the bloodstream is primarily an aqueous medium, lipophilic molecules are not very soluble and tend to cross lipid-soluble membranes into tissues readily by passive diffusion. The driving forces for diffusional distribution into a tissue are the relative solubility of the compound in a particular tissue, the concentration gradient, and the rate of blood flow to the particular tissue. A tissue that receives a high blood flow can absorb a drug faster because more drug molecules are being presented to this tissue per unit time than a tissue that receives a slower blood flow. This explains why the highly lipophilic anesthetic agents have short onset times. The brain has a high proportion of lipid, and thus lipophilic molecules readily cross from the bloodstream into the brain. In addition, the brain receives approximately 15% of cardiac output, which allows a large percentage of the anesthetic molecules in the plasma to be presented to the brain for absorption.

Like other processes, drug distribution into a tissue eventually reaches an equilibrium between the tissue concentration and plasma concentration. As the plasma concentration of the drug decreases due to elimination or distribution into other tissues, the equilibrium reached in some tissue shifts and the drug now begins to move back into the plasma to reestablish the equilibrium relationship. The movement of a drug from one tissue to another as equilibrium shifts in the body is known as redistribution and is the reason some of the highly lipophilic anesthetics exit the brain quickly and redistribute to body fat where they are more soluble, leading to a short duration of action.

Metabolism

Many drug molecules are converted in the body into other chemical compounds by a process known as metabolism or biotransformation. These processes normally produce more polar, water-soluble compounds, which are easier for the body to eliminate. Occasionally, however, a metabolic process may convert a drug molecule into a less polar compound that is more difficult to eliminate from the body. Unless this metabolite is further metabolized into a polar metabolite, it can build up and lead to potential toxicities. Drugs metabolized to less polar forms thus rarely make it to market. Although all tissues have the capability of metabolizing some drug molecules, the liver is the primary organ of metabolism in the body. Other important metabolizing tissues include the lung, kidney, skin, and epithelial cells of the GI tract. In addition, some metabolic reactions occur in the plasma. Drug metabolism is broken down into two types or phases of reactions based on how the compound is metabolized.

Phase I Metabolism

This type of metabolism involves primarily oxidation-reduction reactions and occurs mainly in hepatocytes by mixed function oxidase enzyme systems located on the smooth endoplasmic reticulum. These enzyme systems are linked to heme proteins and are referred to as the cytochrome P-450 system (CYPs). This is actually a family of enzymes, each of which may be responsible for the metabolism of different drug molecules. Although there are more than 50 known CYP enzymes, six are responsible for more than 90% of drug metabolism: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5.[11] The most common types of chemical reactions that occur by phase I metabolism are hydroxylation, oxidation, reduction, and hydrolysis. Some drug molecules undergo multiple phase I metabolic conversions. More polar metabolites may now enter the bloodstream and be removed from the body by the kidneys, or they may enter the biliary fluid and be excreted in bile. Some compounds may also be further metabolized by other enzyme systems. Because phase I metabolism is enzymatic, it is possible to saturate the ability of the enzymes to metabolize a particular compound. This can occur when too much of a single compound is administered or when multiple agents are administered that use the same enzymes for metabolism. This results in a buildup of the drug molecule and an increased half-life of the compound, potentially leading to toxicity. Some drugs or environmental exposures such as smoking may increase the number of active enzymes, a process known

as induction. In this case, because there are more enzymes present to metabolize a particular compound, any compound that depends on the induced system for biotransformation is converted more rapidly, resulting in a shorter half-life. Other drugs can inhibit these enzymes, leading to an increased half-life of any compound that is normally metabolized by the inhibited enzyme system.

Phase II Metabolism

These reactions are often referred to as synthetic reactions because large polar compounds are attached to the molecule being metabolized. Although some drug molecules may undergo phase II metabolism as the primary method of biotransformation, often a drug molecule that has already been biotransformed by a phase I metabolic reaction may be further metabolized by a phase II reaction (Figure 1-1). The attachment of large polar groups to the molecule greatly increases the compound's water solubility, making elimination by renal or biliary routes easy. In hepatocytes the enzymes responsible for phase II metabolism are located in the cytoplasm and on the smooth endoplasmic reticulum. The most common type of reaction is glucuronic acid conjugation, where a sugar group known as uridine diphosphoglucuronic acid (UDPGA) is attached to the drug molecule. Sugar groups are very water soluble, and the attachment of UDPGA greatly increases the water solubility of the molecule. Another common phase II metabolic process is the attachment of the tripeptide glutathione, which through several steps finally produces a mercapturic acid derivative of the drug molecule that can then be excreted. Other synthetic reactions include sulfate, glycine and glutamine conjugations, and acylation reactions. For many drug molecules phase II reactions are the most important means of inactivating a drug molecule and allowing it to be removed from the body.

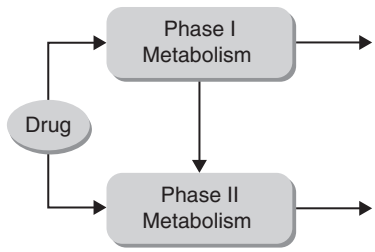

Figure 1-1 Metabolism of a drug molecule by either phase I or phase II metabolism. Many drugs that undergo phase I metabolism may be further metabolized by additional phase I or phase II reactions before being excreted.

First-Pass Metabolism

Drugs administered orally for absorption from the GI tract into the body are subject to a particular metabolic effect known as the first-pass effect. When a drug is absorbed across the GI membranes, it enters the hepatic portal system, which carries the drug molecules directly to the liver. If the drug is highly metabolized by the liver and exhibits a high extraction ratio, then a large percentage of the drug molecules may be destroyed (metabolized) before entering the general systemic circulation. Some drugs (e.g., lidocaine) are so highly metabolized that only a small portion of the absorbed drug reaches the general systemic circulation. The term "bioavailability" is used to help quantify the amounts of a drug that reach the general systemic circulation after absorption and is most commonly used to express the percentage of an oral drug that reaches the general systemic circulation. Bioavailability (F) is determined by dividing the amount of drug reaching the general systemic circulation (Amt_{oral}) by the amount entering the circulation after an IV dose of the same amount (Amt_{IV}) as was given orally:

$$F = \frac{Amt_{oral}}{Amt_{IV}}.$$

When the drug is given intravenously, there is no first-pass effect because the drug does not go directly to the liver before mixing throughout the circulation. Therefore the amount reaching the general systemic circulation is the most that a given dose can achieve. If the same dose given orally demonstrates the same amount entering the general systemic circulation as the IV dose, then the calculated bioavailability value would be 1.0, which means that no first-pass metabolism occurred. In reality, however, this is rarely the case because some of the oral drug is usually lost either due to some first-pass metabolism or failure of the dose to be completely absorbed. Lidocaine, if given orally, has a bioavailability of only 30%.[12]

Esterases

The body possesses many different enzymes that can split ester molecules. In the plasma an enzyme known as plasma esterase or pseudocholinesterase is responsible for metabolizing and inactivating many ester drug molecules, such as succinylcholine, etomidate, and procaine, among others. Other locations of esterases in the body are in cholinergic neuron synapses (acetylcholinesterase), on red blood cells, and in many other cells, including hepatocytes.

Metabolism in Other Tissues

As previously discussed, most tissues possess the ability to metabolize some drug molecules. The importance of a specific tissue on the overall metabolism of a particular compound varies with the compound, the tissue blood flow, and its penetration into the metabolizing tissue. The lung receives a high blood flow and is therefore good at metabolizing some drug molecules. One of the important lung metabolic reactions involves the conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme. This enzyme is the target of the angiotensin-converting enzyme inhibitors such as captopril. Other tissues are also capable of some drug metabolic reactions, which are usually secondary to liver metabolism.

Elimination

Drug elimination encompasses all processes by which a specific drug molecule is removed from the body. Metabolizing a drug molecule into a different form, whether the new form is active or not, is one type of drug elimination. Although the metabolite molecule may still be present, it is not the same chemical, and therefore the original drug molecule is no longer present in the body. In addition to drug metabolism, drug excretion comprises the remainder of normal drug elimination mechanisms. The primary excretory organ in the body is the kidney, and kidney blood flow and drug protein binding are important in determining the rate of drug elimination by renal mechanisms. Drug molecules of molecular weights up to approximately 5000 amu are freely filtered at the glomerulus of the renal nephron. Protein molecules, such as albumin, are normally excluded from the filtrate by their large size. However, because only free drug can be filtered at the glomerulus, plasma proteins play an important role in the filtration mechanism. Drugs that are highly protein bound are not as readily filtered. The structure of the filtration pores also plays a role in filtration selectivity. Because of negatively charged groups located inside the filtration pores, positively charged molecules are attracted to the pores and are more easily filtered, whereas negatively charged molecules, especially large molecules, are repulsed and are not filtered as readily. In addition to glomerular filtration, another mechanism by which drug molecules may enter the renal tubule is known as secretion and occurs primarily in the proximal tubule. Transport carrier molecules in this region move drug molecules by active transport from the blood into the proximal tubule. Examples of molecules secreted at the proximal tubule by specific carriers include organic acids, organic bases, and conjugated metabolites. Another important process that plays a role in drug excretion in the kidney is the reabsorption process. This occurs primarily in the proximal and distal regions of the nephron and occurs mainly by the movement of lipid-soluble drugs as they cross out of the renal tubular fluid back into the bloodstream by simple diffusion. Total renal excretion of a specific compound therefore is the amount filtered plus the amount secreted minus the amount reabsorbed. Because renal tubular fluid is an aqueous medium, polar water-soluble molecules will be retained in the fluid best. Also, because the pH of urinary fluid is usually in the range of 5–8, most weak acids and weak bases are somewhat ionized and thus easily excreted. Urinary acidifiers can be used to more fully ionize weakly basic drugs and enhance their excretion rate. Conversely, urinary alkalinizers enhance the elimination rate of weak acidic drugs.

Biliary excretion is another important mechanism of drug elimination. Active transport carriers in liver cells can secrete drug molecules and metabolites directly into bile. These molecules are then excreted into the GI tract where the molecules usually are eliminated in the fecal material. However, some glucuronide conjugates of drug molecules can undergo cleavage by enzymes produced by intestinal microorganisms. The attached glucuronide group is removed, thus releasing the original drug molecule. If this molecule is reabsorbed into the body, the duration of effect of the drug may be increased. This process is known as enterohepatic recycling and can greatly increase the effective half-life of the drug.

Lung excretion is mainly limited to the gaseous and volatile anesthetics. Most of these agents are almost entirely eliminated by lung excretion, with some being metabolized to a small extent.

Other excretion routes, including breast milk and sweat, are not significant means of drug excretion. Many different drugs may enter breast milk, but it is a small amount compared with other excretion mechanisms. Where it is important, however, is in the exposure of the infant to these molecules via the breast milk. Mothers must be aware that almost all drugs they take will be present to some degree in breast milk, and their child may be affected by exposure to those compounds.

Mathematical Modeling

Many of the pharmacokinetic concepts just discussed can be quantitatively approximated by using mathematical models. These models are designed based on specific characteristics

of individual drug molecules and the rates at which the various absorption, distribution, metabolism, and elimination processes in the body occur. Fortunately, most drugs can be adequately described through two basic models, known as the one-compartment and the two-compartment models.

In a one-compartment model (Figure 1-2) the entire body is viewed as a single compartment where the drug freely and evenly distributes to all tissues. Therefore the central compartment (also known as the plasma compartment) has a drug concentration equal to the drug concentration at the tissue site where the drug elicits its effects. The initial entry of the drug into the central compartment depends on the method of drug administration. Except for administrative techniques by which the drug is directly injected into the bloodstream (e.g., IV or intra-arterial), all other means of drug administration require drug molecules to cross cellular membranes to gain access to the central compartment and then be transported throughout the body. This initial movement from the site of administration into the central compartment is known as the absorptive phase, and the rate (k_a) of this movement can be quantitated. Drug molecules are then transported throughout the body and cross into other tissues where they may elicit their effects. The key to the one-compartment model is that once equilibrium is reached, the drug concentration at the site of action is approximately the same as in the plasma. Therefore if a plasma sample is taken and the drug concentration determined, that concentration would be the same as at the site of action of the drug. All drug molecules, no matter how they are administered, must be eliminated. This elimination can again be characterized by a rate (k_e) that takes into account the summation of rates for all routes of elimination for the particular drug (e.g., metabolism and excretion). Drugs well characterized by the one-compartment model are often small molecules and/or highly water-soluble molecules that tend to distribute through the body following total body water.

The two-compartment model (Figure 1-3) is similar in concept to a one-compartment model with the addition of a second compartment. Drugs that follow a two-compartment model do not demonstrate similar concentrations between the central compartment and the site of drug action at steady state. To adjust for these differences, consideration must be given to the rate of the drug moving into the tissue compartment from the central compartment (k_{12}) where the drug acts and the rate of back movement from the tissue to the central compartment (k_{21}). Many drugs can be characterized by two-compartment modeling. Although some drugs seem to follow more complex models (e.g., three- or four-compartment models), their behavior can often be adequately approximated by the two-compartment model.

The rates of drug movement for compartment models are determined experimentally from serial plasma samples (Figure 1-4). When administered by IV injection, there is

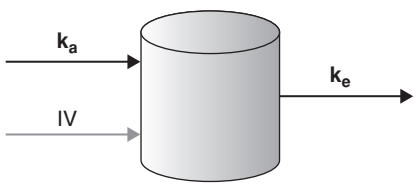

Figure 1-2 One-compartment model illustrating entry of drug by absorption (k_a) or direct injection (i.e., IV) and elimination from the body (k_e).

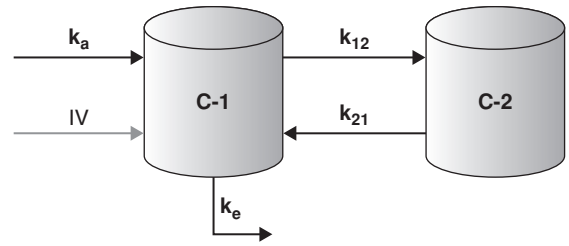

Figure 1-3 Two-compartment model illustrating entry of drug by absorption (k_a) or direct injection (i.e., IV) into the central compartment (C-1), distribution (k_{12}) into the tissue compartment (C-2), redistribution (k_{21}) from the tissue compartment back into the central compartment, and elimination from the central compartment (k_e).

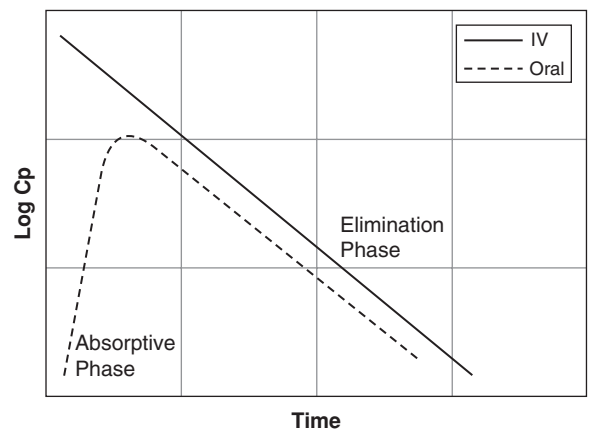

Figure 1-4 Comparison of oral and IV log (plasma concentration) versus time curves for the same drug. Elimination is via first-order kinetics. Note the lack of an absorptive phase with the IV dosing route and the same elimination rate by both routes.

no absorptive phase, and the only rate processes demonstrated are distribution and elimination. Of greatest interest is the rate of elimination (k_e). The elimination process begins as soon as the first drug molecule enters the central compartment and therefore is present during all phases of the plasma concentration curve. Once absorption (if any) is complete and the drug has reached steady-state distribution between tissue compartments and the central compartment, the steady decrease in the plasma concentration (Cp) seen with time is entirely due to elimination. Mathematically,

$$k_e = \frac{-d\mathrm{Cp}}{dt}, \text{ and}$$

$$k_e = \frac{-\Delta \mathrm{Cp}}{\Delta t}.$$

From this, the elimination rate constant for a drug can be determined.

In the human body, the elimination of drugs, whether by metabolism or excretion of unchanged drug molecules, is normally a first-order rate process. First-order rate kinetics is best understood as being dependent on the concentration of the agent being eliminated. As the concentration of the drug in the plasma decreases, less drug is available at the site of metabolism or excretion, and thus as the concentration decreases, the amount being eliminated is also decreasing. This change in the amount of drug being eliminated per unit time follows a logarithmic decline, and therefore the elimination of a drug following first-order kinetics is a logarithmic rate. Occasionally, another type of rate process is seen during elimination. This is known as a zero-order rate process and is seen when the metabolism or excretion processes become saturated. In this case the concentration of the drug is unrelated to the amount of the agent being eliminated. This occurs when the drug concentration is so high that all available metabolic enzymes or transport mechanisms are eliminating as many drug molecules as they can and altering the drug concentration does not change how many molecules can be eliminated per unit time. Therefore in zero-order elimination kinetics, a constant amount or number of drug molecules are eliminated per unit time. This is not a logarithmic decline as seen in first-order kinetics but is instead a linear elimination. Luckily, most therapeutic drug concentrations never reach saturation (zero-order) kinetics and are instead eliminated by first-order rate processes. Even if a drug concentration did reach levels high enough to saturate the normal elimination processes, as the concentration decreases it would move back into normal first-order rate elimination.

The elimination rate for a specific drug is not always the same in all patients. Factors, such as age, disease state, and genetics, can alter a patient's elimination rate of a specific agent. Fortunately, however, most drugs whose elimination rate is fairly consistent among individuals can be used to determine average elimination rates. These rates can then be used in other calculations to obtain commonly disseminated pharmacokinetic parameters for a specific drug.

Elimination Half-life

One of the most common pharmacokinetic parameters is the elimination half-life ($t_{1/2}$). Assuming the elimination rate is a first-order process, the elimination half-life can be calculated by

$$t_{1/2} = \frac{\ln 2}{k_e}.$$

In this equation, ln is the natural log required due to the logarithmic nature of first-order elimination kinetics and the value "2" refers to the change in the concentration by a factor of two (one-half). This equation can be further simplified by substituting the value of the natural log of 2, which is 0.693

$$t_{1/2} = \frac{0.693}{k_e}.$$

The elimination half-life is widely available for every marketed drug; however, published values for some drugs have a wide range of half-lives due to patient variability. It is important to remember that if a drug is eliminated primarily through liver metabolism, any hepatic disorder that diminishes the metabolic capacity of the liver may cause an increased half-life for that agent in a patient. The same holds for a patient with decreased renal function taking a drug that is primarily eliminated by renal excretion. In addition, some drug interactions are known to alter the half-life of some drugs. This is most commonly seen with drugs that induce liver metabolic enzymes (e.g., phenobarbital, rifampin, carbamazepine) or inhibit the metabolic enzymes (e.g., cimetidine, ciprofloxacin, isoniazid).[13]

Another common term associated with half-life is the half-life of effect. Some drugs (e.g., diazepam) are converted into metabolites in the body, which have the same effect as the parent compound. Looking at the half-life of the original compound only can then give a false idea of the duration of effects. Therefore the half-life of effect is used to encompass all possible active metabolites of the parent compound that may prolong the duration of the parent drug and thus provide a more accurate handle of the half-life of the expected effects, not just of the parent drug.

Volume of Distribution

The volume of distribution (Vd) is often referred to as the apparent volume of distribution because it is not necessarily a true volume but is instead a theoretical (apparent) volume of plasma in which the drug is dissolved. The values for the volume of distribution of a drug do not necessarily relate to the plasma volume. If a drug stays in the plasma compartment (e.g., heparin), then the volume of distribution is directly related to the plasma volume. However, if the drug leaves the plasma compartment to concentrate to a large extent in tissues, then the volume of distribution can be very large. This is because the amount of drug remaining in the plasma is small and its concentration is low, causing the apparent volume of distribution to appear very large. Apparent volumes of distribution for some drugs (e.g., propranolol) can reach hundreds of liters in a 70-kg patient. Values are commonly presented in liters per kilogram to allow for different patients. Obviously, their body volume is not that large. The main advantage of volume of distribution values is that they are useful to determine quickly whether the drug stays in the plasma, follows total body water, or concentrates in body tissues. For a one-compartment model, the apparent volume of distribution can be calculated from the dose of the drug (D_0) and the plasma concentration of the drug at time 0 (Cp_0):

$$Vd = \frac{D_0}{Cp_0} .$$

Although the initial dose of the drug is easy to obtain, the plasma concentration at time 0 is more difficult. It is impossible to actually sample the plasma compartment at time 0 even if the drug was given intravenously because a certain period of time is required for the drug to evenly disperse throughout the plasma compartment. Starting a serial plasma sample curve of drug concentration versus time at approximately 5 minutes allows time for initial mixing and can be used to back-extrapolate to time 0 to obtain the value. The volume of distribution is even more difficult to calculate for multicompartment models.[14] The volume of distribution can also be obtained from the clearance of a drug (see below).

Clearance

In pharmacokinetics, clearance is used to quantitate the rate by which a drug is removed from the body. Plasma clearance (Cl) is the volume of plasma that is *entirely* cleared of the drug per unit time, thereby giving clearance units of volume/time. Based on the definition, if 50% of a drug is removed from a given quantity of plasma from a particular organ, then that organ has only cleared 100% of the drug from half the volume of plasma. Total body clearance values are easily calculated from the elimination rate constant and volume of distribution for a specific drug:

$$Cl = k_e Vd .$$

Because a drug may be metabolized or excreted by multiple tissues in the body, each tissue has its own clearance rate that is calculated from each tissue's elimination rate constant for the drug. Therefore the sum of all these individual drug clearance values equals total body clearance:

$$Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{lung} + Cl \cdots .$$

As with other related pharmacokinetic parameters, the clearance of a drug is altered in cases of various disease states that affect the elimination rate of the drug. So, for example, if a drug is cleared to a large extent by the liver and the patient experiences hepatic insufficiency, the total body clearance of the drug decreases and the drug would tend to accumulate in the body. To maintain the proper drug concentration for effect may then require a dosage adjustment to lower the drug plasma concentration.

Drug Dosing

Determining proper drug dosages is critical to proper patient care and is one of the major advantages of understanding concepts such as drug clearance. Nowhere are these concepts more important than in anesthesia, where the drugs used to induce an anesthetized state are very toxic with little room for dosage errors.

Therapeutic Window

All drugs exhibit some concentration at their site of action at which the desired therapeutic effect is initially produced. In addition, most if not all drugs also demonstrate the initiation of side effects or toxicities at some specific concentration in a particular tissue. The sites of the desired therapeutic effects may or may not be the same site that produces the undesirable effects. If the undesirable effects are relatively minor and can be tolerated, they are usually referred to as side effects of the drug. However, some effects are intolerable or potentially life threatening and are referred to as toxicities. These concepts are actually pharmacodynamic principles because they are related to the effect of the drug on the body. However, the concept is important to introduce at this point because the basis for

proper patient dosing requires maintaining a therapeutic drug concentration while avoiding toxic concentrations. Because the plasma concentration is the only drug concentration readily accessible in the body, most therapeutic and toxic concentrations are based on the plasma concentration. Unfortunately, not all drugs elicit their tissue effects based directly on the tissue concentration. Other drugs (e.g., lithium carbonate) have well-defined therapeutic windows with strong relationships between the plasma concentration and the therapeutic and toxic concentrations. For drugs that exhibit a correlation between plasma concentration and effects, the goal of proper dosing is to keep the patient's plasma drug concentration above the minimum therapeutic concentration (Cp_{ther}) and below the plasma concentration associated with toxicity (Cp_{tox}) (Figure 1-5). Related to this idea is the therapeutic index or therapeutic ratio. The therapeutic index (TI) is the ratio of the toxic dose (D_{tox}) to the therapeutic dose (D_{ther})[15]:

$$TI = \frac{D_{tox}}{D_{ther}} .$$

Therefore drugs with large TI values are safer than drugs with smaller values. For example, diazepam, a fairly safe drug with a wide therapeutic window, has a TI greater than 100, whereas digoxin, which has a narrow therapeutic window, has a TI of approximately 2.[15] A new form of IV desflurane under study has a reported TI of approximately 3 in rats,[16] demonstrating the need for great care in its administration.

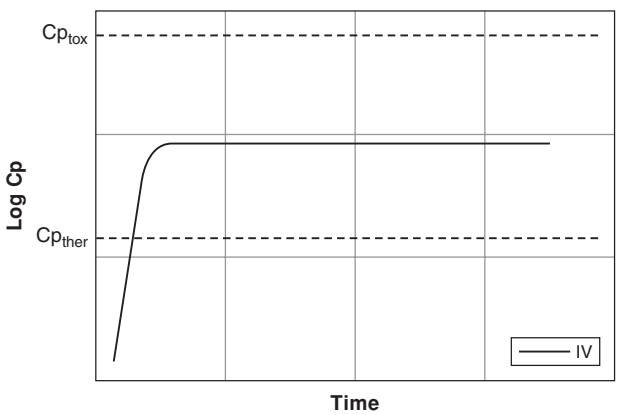

Figure 1-5 Graph illustrating the therapeutic window for a particular drug. Note the drug administered by IV infusion maintaining a safe plasma concentration above the minimum therapeutic concentration and below the toxic plasma concentration.

Dosing Calculations

To properly administer therapeutic drug doses requires that the purpose and method of drug administration are determined. It is a simple matter to determine the required dose of a drug that is to be administered in a single dose. It is more difficult and patient specific to determine dosing regimens for repeated IV dosing or IV infusions while trying to keep the patient's plasma concentration within the therapeutic window.

Intravenous Infusion Dosing

The goal when supplying a drug by IV infusion is to supply the exact amount of drug that is being eliminated by the patient to keep the patient's plasma concentration steady (steady state). The truth is that any dose supplied by IV infusion will meet this goal. Different infusion rates alter only the maintained plasma concentration as long as the drug concentration stays within first-order kinetics. This is because as the plasma concentration increases, first-order elimination states that a larger amount of the drug is removed per unit time. To calculate the infusion rate (k_{in}) (mg/min) required for IV infusion administration, only the steady-state plasma concentration (Cp_{ss}) (mg/mL) desired and the clearance of the drug (mL/min) are required:

$$K_{in} = CP_{ss}\ Cl .$$

However, using this approach requires approximately five drug half-lives to reach 95% of the eventual steady-state plasma concentration when administering a drug by continuous IV infusion. Therefore it may take a considerable period of time before steady state is achieved for drugs with long half-lives. A loading dose can be used to push the patient's plasma concentration to the eventual steady-state level more rapidly. The loading dose (D_{load}) (mg) is calculated from the volume of distribution of the drug in the patient (mL) and the steady-state plasma concentration desired to be reached (mg/mL):

$$D_{load} = Vd\ Cp_{ss} .$$

When the planned continuous IV infusion is preceded with a properly calculated loading dose, the desired steady-state plasma concentration will be reached immediately and then maintained for as long as the IV infusion is continued. However, if a new plasma steady state is desired in the patient, just changing the infusion rate will again take approximately five drug half-lives to reach the new steady state.

Intermittent Dosing

It is possible to maintain a patient's plasma drug concentration within the therapeutic window by supplying the drug in individual doses. This may even be preferred, especially for outpatient care. However, the drug being administered must have a reasonably long half-life to avoid requiring dosing intervals to be so short that they would require the patient to disrupt normal sleep periods if at all possible. Dosing should not be shorter than 6-hour intervals and should preferably be given every 12 or 24 hours to enhance patient compliance, especially if the drug is being self-administered. [17] Drugs to be dosed intermittently must have a therapeutic window wide enough to ensure that during the period between doses the plasma drug concentration does not fall below the minimum therapeutic concentration. Also, the plasma drug concentration cannot rise above the minimum toxic concentration when the dose is administered. Intermittent dosing can be accomplished by repeated IV dosing; however, the most common route is via oral administration. As in IV infusion dosing, without a loading dose it takes approximately five half-lives of the drug to reach 95% of the steady-state level in the plasma. The difference with repeated dosing is that no single steady-state concentration is reached. With each dose administered, the plasma level increases as the dose enters the plasma. The concentration then decreases at a rate based on the elimination rate of the drug until the next dose is administered. This creates a plasma concentration curve with peaks when the drug is given and troughs that bottom out just before the next dose is administered. Once steady state is reached, as long as neither the dose nor the dosing interval is changed, all peaks and troughs will occur at equal plasma concentrations. An average between the peak and trough concentrations is known as the average steady state. Although it is possible to calculate the required doses and dosing interval to reach a desired plasma concentration,[18] this information is usually supplied by the manufacturer and is rarely calculated today.

Key Points

- Routes of Drug Administration
- Drug Absorption, Distribution, Metabolism, and Elimination
- Pharmacokinetic Modeling
- Therapeutic Window
- Drug Half-life
- Volume of Distribution
- Clearance
- Drug Dosing

Chapter Questions

1. Explain what effect lowering the stomach pH would have on the ionized state of an acidic drug in the stomach.
2. What effect will increasing plasma protein binding of a drug have on the drug's ability to cross membranes into tissues?
3. Explain why doubling the dose of a constant IV infusion does not double the patient's plasma concentration of the drug.
4. What determines whether a drug can be modeled by a one-compartment model or a more complex multicompartment model?
5. What chemical characteristics increase and decrease the ability of a drug molecule to cross membranes?

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