CHAPTER 7

Pharmacological Principles

KEY CONCEPTS

1. Drug molecules obey the law of mass action. When the plasma concentration exceeds the tissue concentration, the drug moves from the plasma into tissue. When the plasma concentration is less than the tissue concentration, the drug moves from the tissue back to plasma.
2. Most drugs that readily cross the blood–brain barrier (eg, lipophilic drugs like hypnotics and opioids) are avidly taken up in body fat.
3. Biotransformation is the chemical process by which the drug molecule is altered in the body. The liver is the primary organ of metabolism for drugs.
4. Small unbound molecules freely pass from plasma into the glomerular filtrate. The nonionized (uncharged) fraction of drug is reabsorbed in the renal tubules, whereas the ionized (charged) portion is excreted in urine.
5. Elimination half-life is the time required for the drug concentration to fall by 50%. For drugs described by multicompartment pharmacokinetics (eg, all drugs used in anesthesia), there are multiple elimination half-lives.
6. The offset of a drug's effect cannot be predicted from half-lives. The context-sensitive half-time is a clinically useful concept to describe the rate of decrease in drug concentration and should be used instead of half-lives to compare the pharmacokinetic properties of intravenous drugs used in anesthesia.

The clinical practice of anesthesiology is connected more directly than any other specialty to the science of clinical pharmacology. One would think, therefore, that the study of pharmacokinetics and pharmacodynamics would receive attention comparable to that given to airway assessment, choice of inhalation anesthetic for ambulatory surgery, or neuromuscular blockade in anesthesiology curricula and examinations. The frequent misidentification or misuse of pharmacokinetic principles and measurements suggests that this is not the case.

PHARMACOKINETICS

Pharmacokinetics defines the relationships among drug dosing, drug concentration in body fluids and tissues, and time. It consists of four linked

processes: absorption, distribution, biotransformation, and excretion.

Absorption

Absorption defines the processes by which a drug moves from the site of administration to the bloodstream. There are many possible routes of drug administration: oral, sublingual, rectal, inhalational, transdermal, transmucosal, subcutaneous, intramuscular, and intravenous. Absorption is influenced by the physical characteristics of the drug (solubility, pK_a, diluents, binders, and formulation), dose, and the site of absorption (eg, gut, lung, skin, muscle). Bioavailability is the fraction of the administered dose reaching the systemic circulation. For example, nitroglycerin is well absorbed by the gastrointestinal tract but has low bioavailability when administered orally. The reason is that nitroglycerin undergoes extensive first-pass hepatic metabolism as it transits the liver before reaching the systemic circulation.

Oral drug administration is convenient, inexpensive, and relatively tolerant of dosing errors. However, it requires cooperation of the patient, exposes the drug to first-pass hepatic metabolism, and permits gastric pH, enzymes, motility, food, and other drugs to potentially reduce the predictability of systemic drug delivery.

Nonionized (uncharged) drugs are more readily absorbed than ionized (charged) forms. Therefore, an acidic environment (stomach) favors the absorption of acidic drugs ($A^- + H^+ \rightarrow AH$), whereas a more alkaline environment (intestine) favors basic drugs ($BH^+ \rightarrow H^+ + B$). Most drugs are largely absorbed from the intestine rather than the stomach because of the greater surface area of the small intestine and longer transit duration.

All venous drainage from the stomach and small intestine flows to the liver. As a result, the bioavailability of highly metabolized drugs may be significantly reduced by first-pass hepatic metabolism. Because the venous drainage from the mouth and esophagus flows into the superior vena cava rather than into the portal system, sublingual or buccal drug absorption bypasses the liver and first-pass metabolism. Rectal administration partly bypasses the portal system, and represents an alternative route in small children or patients who are unable to tolerate oral ingestion. However, rectal absorption can be erratic, and many drugs irritate the rectal mucosa.

Transdermal drug administration can provide prolonged continuous administration for some drugs. However, the stratum corneum is an effective barrier to all but small, lipid-soluble drugs (eg, clonidine, nitroglycerin, scopolamine, fentanyl, and free-base local anesthetics [EMLA]).

Parenteral routes of drug administration include subcutaneous, intramuscular, and intravenous injection. Subcutaneous and intramuscular absorption depend on drug diffusion from the site of injection to the bloodstream. The rate at which a drug enters the bloodstream depends on both blood flow to the injected tissue and the injectate formulation. Drugs dissolved in solution are absorbed faster than those present in suspensions. Irritating preparations can cause pain and tissue necrosis (eg, intramuscular diazepam). Intravenous injections completely bypass the process of absorption.

Distribution

Once absorbed, a drug is distributed by the bloodstream throughout the body. Highly perfused organs (the so-called vessel-rich group) receive a disproportionate fraction of the cardiac output (Table 7–1). Therefore, these tissues receive a disproportionate amount of drug in the first minutes following drug administration. These tissues approach equilibration with the plasma concentration more quickly than less well perfused tissues due to the differences in

TABLE 7–1 Tissue group composition, relative body mass, and percentage of cardiac output.

Tissue Group	Composition	Body Mass (%)	Cardiac Output (%)
Vessel-rich	Brain, heart, liver, kidney, endocrine glands	10	75
Muscle	Muscle, skin	50	19
Fat	Fat	20	6
Vessel-poor	Bone, ligament, cartilage	20	0

blood flow. However, less well perfused tissues such as fat and skin may have enormous capacity to absorb lipophilic drugs, resulting in a large reservoir of drug following long infusions.

1 Drug molecules obey the law of mass action. When the plasma concentration exceeds the concentration in tissue, the drug moves from the plasma into tissue. When the plasma concentration is less than the concentration in tissue, the drug moves from the tissue back to plasma.

Distribution is a major determinant of end-organ drug concentration. The rate of rise in drug concentration in an organ is determined by that organ's perfusion and the relative drug solubility in the organ compared with blood. The equilibrium concentration in an organ relative to blood depends only on the relative solubility of the drug in the organ relative to blood, unless the organ is capable of metabolizing the drug.

Molecules in blood are either free or bound to plasma proteins and lipids. The free concentration equilibrates between organs and tissues. However, the equilibration between bound and unbound molecules is instantaneous. As unbound molecules of drug diffuse into tissue, they are instantly replaced by previously bound molecules. Plasma protein binding does not affect the rate of transfer directly, but it does affect relative solubility of the drug in blood and tissue. If the drug is highly bound in tissues, and unbound in plasma, then the relative solubility favors drug transfer into tissue. Put another way, a drug that is highly bound in tissue, but not in blood, will have a very large free drug concentration gradient driving drug into the tissue. Conversely, if the drug is highly bound in plasma and has few binding sites in the tissue, then transfer of a small amount of drug may be enough to bring the free drug concentration into equilibrium between blood and tissue. Thus, high levels of binding in blood relative to tissues increase the rate of onset of drug effect, because fewer molecules need to transfer into the tissue to produce an effective free drug concentration.

Albumin binds many acidic drugs (eg, barbiturates), whereas α_1-acid glycoprotein (AAG) binds basic drugs (local anesthetics). If the concentrations of these proteins are diminished or (typically less important) if the protein-binding sites are occupied by other drugs, then the relative solubility of the drugs in blood is decreased, increasing tissue uptake. Kidney disease, liver disease, chronic congestive heart failure, and malignancies decrease albumin production. Trauma (including surgery), infection, myocardial infarction, and chronic pain increase AAG levels. Pregnancy is associated with reduced AAG concentrations. Note that these changes will have very little effect on propofol, which is administered with its own binding molecules (the lipid in the emulsion).

Lipophilic molecules can readily transfer between the blood and organs. Charged molecules are able to pass in small quantities into most organs. However, the blood–brain barrier is a special case. Permeation of the central nervous system by ionized drugs is limited by pericapillary glial cells and endo-

2 thelial cell tight junctions. Most drugs that readily cross the blood–brain barrier (eg, lipophilic drugs like hypnotics and opioids) are avidly taken up in body fat.

The time course of distribution of drugs into peripheral tissues is complex and can only be assessed with computer models. Following intravenous bolus administration, rapid distribution of drug from the plasma into peripheral tissues accounts for the profound decrease in plasma concentration observed in the first few minutes. For each tissue, there is a point in time at which the apparent concentration in the tissue is the same as the concentration in the plasma. The redistribution phase (for each tissue) follows this moment of equilibration. During redistribution, drug returns from peripheral tissues back into the plasma. This return of drug back to the plasma slows the rate of decline in plasma drug concentration.

Distribution generally contributes to rapid emergence by removing drug from the plasma for many minutes following administration of a bolus infusion. Following prolonged infusions, *re*distribution generally delays emergence as drug returns from tissue reservoirs to the plasma for many hours.

The complex process of drug distribution into and out of tissues is one reason that half-lives are clinically useless. The offset of a drug's clinical actions are best predicted by computer models using the context-sensitive half-time or decrement times. The *context-sensitive half-time* is the time required

for a 50% decrease in plasma drug concentration to occur following a pseudo steady-state infusion (in other words, an infusion that has continued long enough to yield nearly steady-state concentrations). Here the "context" is the duration of the infusion. The *context-sensitive decrement time* is a more generalized concept referring to any clinically relevant decreased concentration in any tissue, particularly the brain or effect site.

The volume of distribution, V_d, is the *apparent* volume into which a drug has "distributed" (ie, mixed). This volume is calculated by dividing a bolus dose of drug by the plasma concentration at time 0. In practice, the concentration used to define the V_d is often obtained by extrapolating subsequent concentrations back to "0 time" when the drug was injected, as follows:

$$V_d = \frac{\text{Bolus dose}}{\text{Concentration}_{\text{time0}}}$$

The concept of a single V_d does not apply to any intravenous drugs used in anesthesia. All intravenous anesthetic drugs are better modeled with at least two compartments: a central compartment and a peripheral compartment. The behavior of many of these drugs is best described using three compartments: a central compartment, a rapidly equilibrating peripheral compartment, and a slowly equilibrating peripheral compartment. The central compartment may be thought of as including the blood and any ultra-rapidly equilibrating tissues such as the lungs. The peripheral compartment is composed of the other body tissues. For drugs with two peripheral compartments, the rapidly equilibrating compartment comprises the organs and muscles, while the slowly equilibrating compartment roughly represents distribution of the drug into fat and skin. These compartments are designated V_1 (central), V_2 (rapid distribution), and V_3 (slow distribution). The volume of distribution at steady state, V_{dss} is the algebraic sum of these compartment volumes. V_1 is calculated by the above equation showing the relationship between volume, dose, and concentration. The other volumes are calculated through pharmacokinetic modeling.

A small V_{dss} implies that the drug has high aqueous solubility and will remain largely within the intravascular space. For example, the V_{dss} of pancuronium is about 15 L in a 70-kg person, indicating that pancuronium is mostly present in body water, with little distribution into fat. However, the typical anesthetic drug is lipophilic, resulting in a V_{dss} that exceeds total body water (approximately 40 L). For example, the V_{dss} for fentanyl is about 350 L in adults, and the V_{dss} for propofol may exceed 5000 L. V_{dss} does not represent a real volume but rather reflects the volume into which the drug would need to distribute to account for the observed plasma concentration given the dose that was administered.

Biotransformation

3 Biotransformation is the chemical process by which the drug molecule is altered in the body. The liver is the primary organ of metabolism for drugs. The exception is esters, which undergo hydrolysis in the plasma or tissues. The end products of biotransformation are often (but not necessarily) inactive and water soluble. Water solubility allows excretion by the kidneys.

Metabolic biotransformation is frequently divided into phase I and phase II reactions. Phase I reactions convert a parent compound into more polar metabolites through oxidation, reduction, or hydrolysis. Phase II reactions couple (conjugate) a parent drug or a phase I metabolite with an endogenous substrate (eg, glucuronic acid) to form water-soluble metabolites that can be eliminated in the urine or stool. Although this is usually a sequential process, phase I metabolites may be excreted without undergoing phase II biotransformation, and a phase II reaction can precede or occur without a phase I reaction.

Hepatic clearance is the volume of blood or plasma (whichever was measured in the assay) cleared of drug per unit of time. The units of clearance are units of flow: volume per unit time. Clearance may be expressed in milliliters per minute, liters per hour, or any other convenient unit of flow.

If every molecule of drug that enters the liver is metabolized, then hepatic clearance will equal liver blood flow. This is true for very few drugs, although it is very nearly the case for propofol. For most drugs, only a fraction of the drug that enters the liver is removed. The fraction removed is called the *extraction ratio*. The hepatic clearance can therefore be expressed as the liver blood flow times the

extraction ratio. If the extraction ratio is 50%, then hepatic clearance is 50% of liver blood flow. The clearance of drugs efficiently removed by the liver (ie, having a high hepatic extraction ratio) is proportional to hepatic blood flow. For example, because the liver removes almost all of the propofol that goes through it, if the hepatic blood flow doubles, then the clearance of propofol doubles. Induction of liver enzymes has no effect on propofol clearance, because the liver so efficiently removes all of the propofol that goes through it. Even severe loss of liver tissue, as occurs in cirrhosis, has little effect on propofol clearance. Drugs such as propofol have flow-dependent clearance.

Many drugs have low hepatic extraction ratios and are slowly cleared by the liver. For these drugs, the rate-limiting step is not the flow of blood to the liver, but rather the metabolic capacity of the liver itself. Changes in liver blood flow have little effect on the clearance of such drugs. However, if liver enzymes are induced, then clearance will increase because the liver has more capacity to metabolize the drug. Conversely, if the liver is damaged, then less capacity is available for metabolism and clearance is reduced. Drugs with low hepatic extraction ratios thus have capacity-dependent clearance. The extraction ratios of methadone and alfentanil are 10% and 15% respectively, making these capacity-dependent drugs.

Excretion

Some drugs and many drug metabolites are excreted by the kidneys. Renal clearance is the rate of elimination of a drug from the body by kidney excretion. This concept is analogous to hepatic clearance, and similarly, renal clearance can be expressed as the renal blood flow times the renal extraction ratio.

4 Small unbound drugs freely pass from plasma into the glomerular filtrate. The nonionized (uncharged) fraction of drug is reabsorbed in the renal tubules, whereas the ionized (charged) portion is excreted in urine. The fraction of drug ionized depends on the pH; thus renal elimination of drugs that exist in ionized and nonionized forms depends in part on urinary pH. The kidney actively secretes some drugs into the renal tubules.

Many drugs and drug metabolites pass from the liver into the intestine via the biliary system. Some drugs excreted into the bile are then reabsorbed in the intestine, a process called *enterohepatic recirculation*. Occasionally metabolites excreted in bile are subsequently converted back to the parent drug. For example, lorazepam is converted by the liver to lorazepam glucuronide. In the intestine, β-glucuronidase breaks the ester linkage, converting lorazepam glucuronide back to lorazepam.

Compartment Models

Multicompartment models provide a mathematical framework that can be used to relate drug dose to changes in drug concentrations over time. Conceptually, the compartments in these models are tissues with a similar distribution time course. For example, the plasma and lungs are components of the central compartment. The organs and muscles, sometimes called the vessel-rich group, could be the second, or rapidly equilibrating, compartment. Fat and skin have the capacity to bind large quantities of lipophilic drug but are poorly perfused. These could represent the third, or slowly equilibrating, compartment. This is an intuitive definition of compartments, and it is important to recognize that the compartments of a pharmacokinetic model are mathematical abstractions that relate dose to observed concentration. A one-to-one relationship does not exist between any compartment and any organ or tissue in the body.

Many drugs used in anesthesia are well described by a two-compartment model. This is generally the case if the studies used to characterize the pharmacokinetics do not include rapid arterial sampling over the first few minutes (**Figure 7–1**). Without rapid arterial sampling the ultra-rapid initial drop in plasma concentration immediately after a bolus injection is missed, and the central compartment volume is blended into the rapidly equilibrating compartment. When rapid arterial sampling is used in pharmacokinetic experiments, the results are generally a three-compartment model. In these cases the number of identifiable compartments is a function of the experimental design and not a characteristic of the drug.

In compartmental models the instantaneous concentration at the time of a bolus injection is assumed to be the amount of the bolus divided by the central compartment volume. This is not

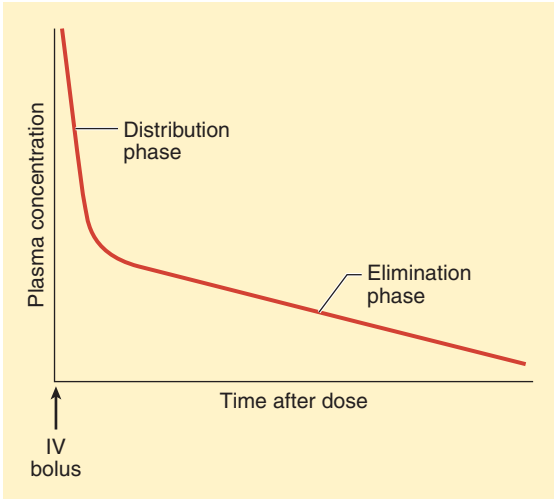

FIGURE 7–1 Two-compartment model demonstrates the distribution phase (α phase) and the elimination phase (β phase). During the distribution phase, the drug moves from the central compartment to the peripheral compartment. The elimination phase consists of metabolism and excretion.

correct. If the bolus is given over a few seconds, the instantaneous concentration is 0, because the drug is all in the vein, still flowing to the heart. It takes only a minute or two for the drug to mix in the central compartment volume. This misspecification is common to conventional pharmacokinetic models. More physiologically based models, sometimes called *front-end kinetic models*, can characterize the initial delay in concentration. These models are useful only if the concentrations over the first few minutes are clinically important. After the first few minutes, front-end models resemble conventional compartmental models.

In the first few minutes following initial bolus administration of a drug, the concentration drops very rapidly as the drug quickly diffuses into peripheral compartments. The decline is typically an order of magnitude over 10 minutes. For drugs with very rapid hepatic clearance (eg, propofol) or those that are metabolized in the blood (eg, remifentanil), metabolism contributes significantly to the rapid initial drop in concentration. Following this very rapid drop there is a period of slower decrease in plasma concentration. During this period, the rapidly equilibrating compartment is no longer removing drug from the plasma. Instead, drug returns to the plasma from the rapidly equilibrating compartment. The reversed role of the rapidly equilibrating tissues from extracting drug to returning drug accounts for the slower rate of decline in plasma concentration in this intermediate phase. Eventually there is an even slower rate of decrease in plasma concentration, which is log-linear until the drug is completely eliminated from the body. This terminal log-linear phase occurs after the slowly equilibrating compartment shifts from net removal of drug from the plasma to net return of drug to the plasma. During this terminal phase the organ of elimination (typically the liver) is exposed to the body's entire body drug load, which accounts for the very slow rate of decrease in plasma drug concentration during this final phase.

The mathematical models used to describe a drug with two or three compartments are, respectively:

$$Cp(t) = Ae^{-\alpha t} + Be^{-\beta t}$$

and

$$Cp(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where $Cp(t)$ equals plasma concentration at time t, and α, β, and γ are the exponents that characterize the very rapid (ie, very steep), intermediate, and slow (ie, log-linear) portions of the plasma concentration over time, respectively. Drugs described by two-compartment and three-compartment models will have two or three half-lives. Each half-life is calculated as the natural log of 2 (0.693), divided by the exponent. The coefficients A, B, and C represent the contribution of each of the exponents to the overall decrease in concentration over time.

The two-compartment model is described by a curve with two exponents and two coefficients, whereas the three-compartment model is described by a curve with three exponents and three coefficients. The mathematical relationships among compartments, clearances, coefficients, and exponents are complex. Every coefficient and every exponent is a function of every volume and every clearance.

5 Elimination half-life is the time required for the drug concentration to fall by 50%. For drugs described by multicompartment pharmacokinetics

(eg, all drugs used in anesthesia), there are multiple elimination half-lives, in other words the elimination half-time is context dependent. The offset of a drug's effect cannot be predicted from half-lives. Moreover, one cannot easily determine how rapidly a drug effect will disappear simply by looking at coefficients, exponents, and half-lives. For example, the terminal half-life of sufentanil is about 10 h, whereas that of alfentanil is 2 h. This does not mean that recovery from alfentanil will be faster, because clinical recovery from clinical dosing will be influenced by all half-lives, not just the terminal one. Computer models readily demonstrate that recovery from an infusion lasting several hours will be faster when the drug administered is sufentanil than it will be when the infused drug is alfentanil. The time required for a 50% decrease in concentration depends on the duration or "context" of the infusion. The context-sensitive half-time, discussed earlier, captures this concept and should be used instead of half-lives to compare the pharmacokinetic properties of intravenous drugs used in anesthesia.

PHARMACODYNAMICS

Pharmacodynamics, the study of how drugs affect the body, involves the concepts of potency, efficacy, and therapeutic window. Pharmacokinetic models can range from entirely empirical dose versus response relationships to mechanistic models of ligand–receptor binding. The fundamental pharmacodynamic concepts are captured in the relationship between exposure to a drug and physiological response to the drug, often called the *dose–response* or *concentration–response relationship*.

Exposure–Response Relationships

As the body is exposed to an increasing amount of a drug, the response to the drug similarly increases, typically up to a maximal value. This fundamental concept in the exposure versus response relationship is captured graphically by plotting exposure (usually dose or concentration) on the *x* axis as the independent variable, and the body's response on the *y* axis as the dependent variable. Depending on the circumstances, the dose or concentration may be plotted on a linear scale (Figure 7–2A) or a logarithmic scale (Figure 7–2B), while the response is typically plotted either as the actual measured response (Figure 7–2A) or as a fraction of the baseline or maximum physiological measurement (Figure 7–2B). For our purposes here, basic pharmacodynamic properties are described in terms of concentration, but any metric of drug exposure (dose, area under the curve, etc) could be used.

The shape of the relationship is typically sigmoidal, as shown in Figure 7–2. The sigmoidal

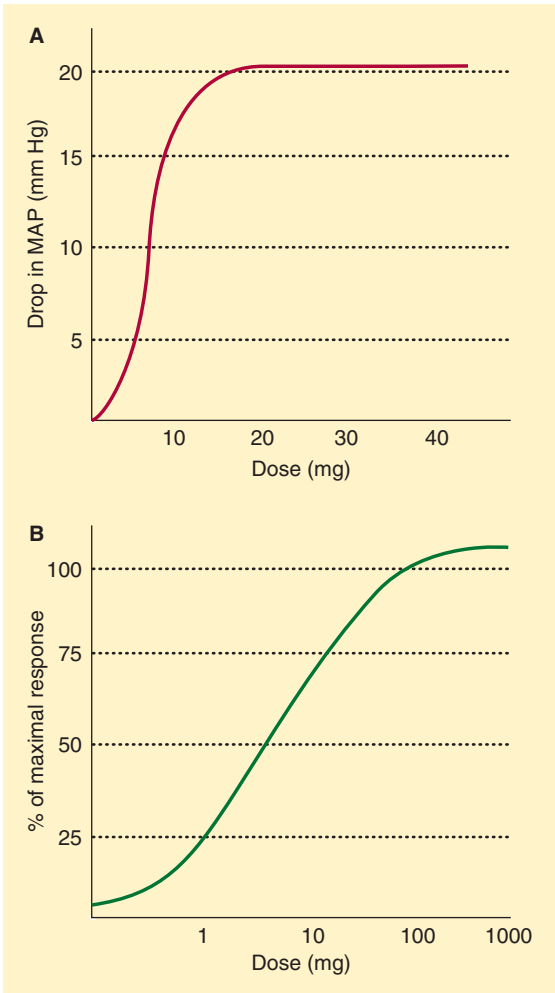

FIGURE 7–2 The shape of the dose–response curve depends on whether the dose or steady-state plasma concentration (C_{cpss}) is plotted on a linear **A**: or logarithmic **B**: scale. MAP, mean arterial pressure.

shape reflects the observation that often a certain amount of drug must be present before there is any measurable physiological response. Thus, the left side of the curve is flat until the drug concentration reaches a minimum threshold. The right side is also flat, reflecting the maximum physiological response of the body, beyond which the body simply cannot respond to additional drug (with the possible exception of eating and weight). Thus, the curve is flat on both the left and right sides. A sigmoidal curve is required to connect the baseline to the asymptote, which is why sigmoidal curves are ubiquitous when modeling pharmacodynamics

The sigmoidal relationship between exposure and response is defined by one of two interchangeable relationships:

$$\text{Effect} = E_0 + E_{\max} \frac{C^{\gamma}}{C_{50}{}^{\gamma} + C^{\gamma}}$$

or

$$\text{Effect} = E_0 + (E_{\max} - E_0) \frac{C^{\gamma}}{C_{50}{}^{\gamma} + C^{\gamma}}$$

In both cases, E_0 is the baseline effect in the absence of drug, C is drug concentration, C_{50} is the concentration associated with half-maximal effect, and γ describes the steepness of the concentration versus response relationship. For the first equation, $E_{\max}$ is the maximum change from baseline. In the second equation, $E_{\max}$ is the maximum physiological measurement, not the maximum change from baseline.

Once defined in this fashion, each parameter of the pharmacodynamic model speaks to the specific concepts mentioned earlier. $E_{\max}$ is related to the intrinsic efficacy of a drug. Highly efficacious drugs have a large maximum physiological effect, characterized by a large $E_{\max}$. For drugs that lack efficacy, $E_{\max}$ will equal E_0. C_{50} is a measure of drug potency. Highly potent drugs have a low C_{50}; thus small amounts produce the drug effect. Drugs lacking potency have a high C_{50}, indicating that a large amount of drug is required to achieve the drug effect. The parameter γ indicates steepness of the relationship between concentration and effect. A γ value less than 1 indicates a very gradual increase in drug effect with increasing concentration. A γ value greater than 4 suggests that once drug effect is observed, small increases in drug concentration produce large increases in drug effect until the maximum effect is reached.

The curve described above represents the relationship of drug concentration to a continuous physiological response. The same relationship can be used to characterize the probability of a binary (yes/no) response to a drug dose:

$$\text{Probability} = P_0 + (P_{\max} - P_0) \frac{C^{\gamma}}{C_{50}{}^{\gamma} + C^{\gamma}}$$

In this case, the probability (P) ranges from 0 (no chance) to 1 (certainty). P_0 is the probability of a "yes" response in the absence of drug. $P_{\max}$ is the maximum probability, necessarily less than or equal to 1. As before, C is the concentration, C_{50} is the concentration associated with half-maximal effect, and γ describes the steepness of the concentration versus response relationship. Half-maximal effect is the same as 50% probability of a response when P_0 is 0 and $P_{\max}$ is 1.

The *therapeutic window* for a drug is the range between the concentration associated with a desired therapeutic effect and the concentration associated with a toxic drug response. This range can be measured either between two different points on the same concentration versus response curve, or the distance between two distinct curves. For a drug such as sodium nitroprusside, a single concentration versus response curve defines the relationship between concentration and decrease in blood pressure. The therapeutic window might be the difference in the concentration producing a desired 20% decrease in blood pressure and a toxic concentration that produces a 60% decrease in blood pressure. However, for a drug such as lidocaine, the therapeutic window might be the difference between the C_{50} for local anesthesia and the C_{50} for lidocaine-induced seizures, the latter being a separate concentration versus response relationship. The therapeutic index is the C_{50} for toxicity divided by the C_{50} for the desired therapeutic effect. Because of the risk of ventilatory and cardiovascular depression (even at concentrations only slightly greater than those producing anesthesia), most inhaled and intravenous hypnotics are considered to have very low therapeutic indices relative to other drugs.

Drug Receptors

Drug receptors are macromolecules, typically proteins, that bind a drug (agonist) and mediate the drug response. Pharmacological antagonists reverse the effects of the agonist but do not otherwise exert an effect of their own. Competitive antagonism occurs when the antagonist competes with the agonist for the binding site, each potentially displacing the other. Noncompetitive antagonism occurs when the antagonist, through covalent binding or another process, permanently impairs the drug's access to the receptor.

The drug effect is governed by the fraction of receptors that are occupied by an agonist. That fraction is based on the concentration of the drug, the concentration of the receptor, and the strength of binding between the drug and the receptor. This binding is described by the law of mass action, which states that the reaction rate is proportional to the concentrations of the reactants:

$$[D][RU] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [DR]$$

where $[D]$ is the concentration of the drug, $[RU]$ is the concentration of unbound receptor, and $[DR]$ is the concentration of bound receptor. The rate constant k_{on} defines the rate of ligand binding to the receptor. The rate constant k_{off} defines the rate of ligand unbinding from the receptor. According to the law of mass action, the rate of receptor binding, $d[DR]/dt$ is:

$$\frac{d[DR]}{dt} = [D][RU]\, k_{on} - [DR]k_{off}$$

Steady state occurs almost instantly. Because the rate of formation at steady state is 0, it follows that:

$$[D][RU]\, k_{on} = [DR]k_{off}$$

In this equation, k_d is the dissociation rate constant, defined as k_{on}/k_{off}. If we define f, fractional receptor occupancy, as:

$$\frac{[DR]}{[DR] + [RU]}$$

then we can solve for receptor occupancy as:

$$f = \frac{[D]}{k_d + [D]}$$

The receptors are half occupied when $[D] = k_d$. Thus, k_d is the concentration of drug associated with 50% receptor occupancy.

Receptor occupancy is only the first step in mediating drug effect. Binding of the drug to the receptor can trigger a myriad of subsequent steps, including opening or closing of an ion channel, activation of a G protein, activation of an intracellular kinase, direct interaction with a cellular structure, or direct binding to DNA.

Like the concentration versus response curve, the shape of the curve relating fractional receptor occupancy to drug concentration is intrinsically sigmoidal. However, the concentration associated with 50% receptor occupancy and the concentration associated with 50% of maximal drug effect are not necessarily the same. Maximal drug effect could occur at very low receptor occupancy, or (for partial agonists) at greater than 100% receptor occupancy.

Prolonged binding and activation of a receptor by an agonist may lead to hyporeactivity ("desensitization") and tolerance. If the binding of an endogenous ligand is chronically blocked, then receptors may proliferate resulting in hyperreactivity and increased sensitivity.

SUGGESTED READING

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