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Pharmacokinetics and Pharmacodynamics

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Introduction

Pharmacokinetic studies describe the time course of drugs from administration to removal from the body, and pharmacodynamics evaluates the effects drugs have on the various body systems. The basic concepts of pharmacokinetics and pharmacodynamics with reference to drugs commonly used in the peri-anesthetic period will be reviewed in this chapter. The unique aspects of inhalant anesthetic pharmacokinetics are discussed in Chapter 10.

Pharmacokinetics

Drug disposition refers to the processes of absorption, distribution, metabolism and excretion within the body after the drug is administered. In order for drugs to exert their effects when given by routes other than intravenous administration (IV), they must first be absorbed into the central compartment (i.e. the systemic circulation), from where they are distributed to the site of action. Distribution is followed by metabolism (biotransformation) and, finally, the drug and/or its metabolites are eliminated from the body (Caldwell et al. 1995).

Absorption and Bioavailability

Absorption refers to the movement of a drug from its site of administration into the central compartment. Most anesthetic and other drugs given in the peri-anesthetic period are given IV, thus bypassing the absorption phase. Advantages to this include the ability to have an almost immediate effect, (e.g. IV induction of anesthesia with propofol allows for rapid tracheal intubation, thus protecting the airway), to titrate the dosage to effect, to administer large volumes, and for emergency treatment. A disadvantage is that an overdose can rapidly lead to serious side effects.

In order to be absorbed, drugs must cross cell membranes. Drugs that are weak acids or weak bases are typically ionizable. That is, in solution, they exist in two forms: the non-ionized form which is lipid soluble and readily diffusible, and the ionized form which has lower lipid solubility and is poorly diffusible. Distribution of ionizable drugs across cell membranes is related to the drug's pK_a, which is the pH at which 50% of the drug is ionized, and 50% is non-ionized. In the presence of a pH higher than a weak acidic drug's pK_a, dissociation will be favored, and in the presence of a pH lower than that drug's pK_a, non-ionization will be favored. The opposite is true for weak bases – at a pH below the pK_a, the drug will be more ionized, while a pH above the pK_a will result in more non-ionized drug (see Table 1.1). As an example, a weakly acidic drug will be readily absorbed in the highly acidic environment of the stomach as the pH favors non-ionization, whereas a weakly basic drug will be more non-ionized and readily absorbed in the alkaline environment of the small intestine.

Absorption can be a passive process (e.g. diffusion), or an active process (via active transporters). Most anesthetic drugs move across cell membranes by passive diffusion along a concentration gradient. The family of ABC transporters actively removes some drugs from cells and includes the P-glycoprotein (P-gp) transporter that is coded by the *ABCB1* (*MDR1*) gene. In dogs that have homozygous mutations of this gene, P-gp transporters are nonfunctional. This can result in toxicity with some drugs (e.g. ivermectin in Collies), as well as prolonged activity of acepromazine and opioids (Deshpande et al. 2016; Martinez et al. 2008).

Bioavailability is the fraction (F) of a drug that reaches the central compartment after administration, and can be expressed as follows:

$$F = \text{amount of drug entering the systemic circulation} / \text{amount of drug administered}$$

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Table 1.1 Impact of pH on ionization of weak acids and weak bases as it relates to a drug's pK_a, and the impact on absorption.

	pH = pK_a	**pH < pK_a**	**pH > pK_a**
Weak acid	Non-ionized = ionized $HA \rightleftharpoons A^- + H^+$	Non-ionized > ionized Absorption ↑	Non-ionized < ionized Absorption ↓
Weak base	Non-ionized = ionized $BA \rightleftharpoons B + H^+$	Non-ionized < ionized Absorption ↓	Non-ionized > ionized Absorption ↑

pK_a is the pH at which the drug is in equilibrium between the non-ionized and ionized form. The non-ionized form of the drug is more lipophilic and therefore more readily absorbed.
⇌ indicates that non-ionized and ionized forms are in equilibrium.

Bioavailability therefore ranges from 0 to 1, depending on route of administration. $F = 1$ after IV administration of drugs. Drugs given by the subcutaneous (SC) and intramuscular (IM) routes typically result in bioavailability above 0.75. Bioavailability after oral administration is highly variable, and dependent on multiple factors (e.g. impact of gastric enzymes on the drug, incomplete absorption in the presence of food, rate of gastric emptying, presence of enteric coating). Drugs absorbed in the gastrointestinal tract (GI) enter the hepatic portal circulation and can undergo first-pass biotransformation and elimination in the liver prior to entering the central compartment.

Drugs that can be absorbed via the oral mucosal surface (oral trans-mucosal, OTM), e.g. dexmedetomidine, buprenorphine, enter the central compartment via venous drainage from the head and neck to the cranial vena cava (Dent et al. 2019; Enomoto et al. 2022). Giving medication by this route has the advantage of being technically less challenging than giving injections, and therefore useful in minimizing stress in patients who are uncooperative for IM, IV, or SC administration. Absorption via the OTM route is determined by the Fick principle of diffusion, where the amount absorbed is directly proportional to drug concentration, drug lipophilicity, the surface area of and duration of contact with the tissue and is indirectly proportional to thickness of the tissue. The presence in the oral mucosa of enzymes that break down peptides can also limit drug absorption via this route (Zhang et al. 2002). Drugs delivered by this route can also be lost to the GI tract due to swallowing, which is likely to result in decreased bioavailability.

Intranasal (IN) administration offers similar advantages to the OTM route in that a large surface area with good blood supply is available for absorption. Naloxone given IN to dogs, for example, was rapidly absorbed with F = 0.32, and buprenorphine administered using a nasal atomization device had F = 0.57 (Wahler et al. 2019; Enomoto et al. 2022). Drawbacks to this route of administration include the drug being lost due to sneezing, head shaking or swallowing. Some animals actively resist placement of nasal drugs, making administration difficult. The presence of excess mucus in the nasal cavity may also decrease absorption.

Absorption of topical and transdermal formulations of drugs (e.g. the topical formulation of buprenorphine Zorbium®, fentanyl patches) occurs via the skin and, as a general rule, is determined by the lipid solubility of the drug and the surface area available (Kukanich and Clark 2012). In the case of fentanyl patches, other factors also play a role (location, body fat composition at the site of placement, body temperature). Damage to the skin surface can enhance absorption of drugs.

The formulation of a drug can impact its absorption. Several drugs with analgesic properties are available in sustained-release formulations that extend the period of absorption over time (e.g. fentanyl patch, liposome encapsulated bupivacaine) (Bartholomew and Smith 2023).

Distribution

After a drug is absorbed into the central compartment, it is distributed to the tissues. Distribution is impacted by regional blood flow and the tissue groups with high blood flow (the vessel rich group) such as the brain, heart, liver, and kidneys initially receive most of the drug. Delivery to the other tissues of the body (muscle, other viscera, skin, fat) takes longer.

Many drugs bind to plasma proteins. Acidic drugs typically bind to albumin, and basic drugs to α_1-acid glycoprotein. Plasma protein binding decreases free drug available for absorption. Decreases in plasma protein binding due to decreased number of binding sites, e.g. with hypoproteinemia, will result in increased drug being unbound in plasma. Many anesthetic drugs are given to effect, e.g. propofol which is highly protein bound (97%), thus, decreased protein binding has limited relevance clinically. The impact of decreased protein binding resulting in an increase in unbound drug may have relevance when the therapeutic index is narrow, e.g. IV lidocaine.

Drugs can accumulate in tissues through tissue binding. The tissue will then act as a reservoir for the drug. Commonly, lipophilic drugs accumulate in adipose tissue.

The endothelial cells of the brain have tight endothelial junctions, thus forming part of the blood-brain barrier. The more lipid soluble a drug is in its unbound, non-ionized form, the more likely it is to cross the blood-brain barrier. Similarly, highly lipid soluble drugs can cross the placenta. Ion trapping of basic drugs may occur in the fetus as the pH is slightly lower than 7.4.

Cessation of drug effect(s) usually occurs when the drug is cleared from the body via metabolism and excretion. In some cases, redistribution of a drug from its site of action to another tissue group can occur. For example, thiopental is cleared slowly, while anesthetic effects wear off relatively rapidly. Return to consciousness cannot be explained by metabolism alone, and is due in part to redistribution (Russo and Bressolle 1998).

Metabolism (Biotransformation)

Lipophilic drugs must be biologically transformed into hydrophilic metabolites in order to be excreted in urine. Metabolism of most drugs occurs via first-order kinetics, i.e. a fraction (or percentage) of the drug is metabolized per unit time. Some drugs, e.g. ethanol (alcohol), are metabolized via zero-order kinetics, i.e. a fixed amount of drug is metabolized per unit time.

The main site of metabolism is the liver, and biotransformation occurs in two steps via microsomal enzyme activity. Firstly, phase 1 reactions change the parent drug via oxidation, reduction, or hydrolysis. Phase 1 enzymes include cytochrome P450 (CYP) enzymes, non-CYP enzymes, and flavin-containing monooxygenase (FMO) enzymes. Metabolism via these enzymes results in exposure of, or addition of, a functional group, e.g. -OH, —COOH, —SH, -O-, or NH_2 to the drug molecule. Functional group addition usually makes the drug inactive, but does not make the drug less lipophilic. Some inactive drugs (called prodrugs) can be activated by phase 1 reactions. Metabolites of active drugs are usually inactive; however, some may have biological effects. Additionally, some drugs can induce activity in phase 1 enzymes, resulting in increased clearance of other drugs biotransformed in the same pathway, e.g. pentobarbital increases the clearance of propranolol (Branch and Herman 1984). Secondly, enzymes involved in phase 2 reactions conjugate the products of phase 1 with another molecule (e.g. an acetyl group, glucuronic acid, glutathione, sulfate), resulting in metabolites that are more hydrophilic, which makes them pass more easily into the aqueous environment of urine or bile. Phase 2 enzymes include glucuronosyltransferases, glutathione-S-transferases (GST), methyltransferases, N-acetyl-transferases (NAT), and sulfotransferases (SULT).

The lung is a site for drug metabolism, with the most important enzymes being CYP, FMO, carboxyl esterase, GST, NAT, and SULT (Enlo-Scott et al. 2021). Drugs can also be metabolized in the kidneys and the GI tract (e.g. biotransformation by transferases) (Rowland et al. 2013). In plasma, drugs can undergo Hoffman elimination, e.g. atracurium, and ester hydrolysis, e.g. remifentanil (Neill et al. 1983; Egan et al. 1993).

Elimination

The kidney is the main organ of drug elimination, and both unchanged drug and drug metabolites can be excreted into the urine. Compounds that are highly lipophilic are less readily eliminated compared to water soluble (polar) molecules, which move into the aqueous urine more easily. The process of renal elimination involves glomerular filtration, active tubular secretion, and passive tubular reabsorption. Glomerular filtration rate (GFR) and whether or not a drug is protein bound determines how much drug enters the proximal renal tubular lumen. Only compounds that are not bound to proteins are available for filtration. Non-ionized forms of drug (i.e. more lipophilic) can be reabsorbed from the distal renal tubular lumen via passive diffusion. The pH of the urine will influence reabsorption in the same way that pH influences absorption. Acidic urine will favor reabsorption of weak acids and excretion of weak bases, whereas alkaline urine will favor reabsorption of weak bases and excretion of weak acids.

Drugs can also be excreted by the liver into bile, which then enters the intestinal tract. Parent compounds and metabolites can be reabsorbed from the intestines. This is referred to as enterohepatic recycling, and can lead to extended drug activity.

Pharmacokinetic Models

Mathematical modeling of pharmacokinetics is used to describe the time course of a drug's disposition in the various body compartments. Drug disposition is comprised of drug distribution and elimination. Key parameters affecting drug disposition include bioavailability (defined above), apparent volume of distribution (often abbreviated to volume of distribution), elimination half-life and clearance.

Apparent Volume of Distribution

Apparent volume of distribution (V) is the theoretical fluid volume that would be required to produce a given plasma (or blood) concentration (C) for the amount of drug in the body (A).

$$V = A/C \tag{1.1}$$

If a drug is administered IV, then A is equal to the dose administered

$$V = \text{Dose}/C \tag{1.2}$$

The apparent volume of distribution can vastly exceed the body's total fluid volume for highly lipophilic drugs. For example, V for propofol is reported as 6.5l/kg in dogs (Nolan and Reid 1993). In other words, V does not usually correspond to a physiologic volume of the body like blood volume. If V is known for a drug, Eq. (1.2) can be used to calculate the dose needed to achieve a specific C.

$$\text{Dose} = \text{V} \cdot \text{C} \tag{1.3}$$

Elimination Half-Life

The concentration immediately after a dose is administered IV, C(0), can be extrapolated from a C versus time (t) plot. Anesthetic and analgesic drugs are commonly eliminated by first-order kinetics. When a semilogarithmic plot of C is graphed against time (Figure 1.1a), the straight line obtained is described by the following equation, where k is the slope of the line:

$$\ln \text{C} = \ln \text{C}\left(0\right) - \text{kt} \tag{1.4}$$

Equation (1.4) can be transformed by taking the antilogarithm of both sides.

$$\text{C} = \text{C}\left(0\right) \cdot \text{e}^{-\text{kt}} \tag{1.5}$$

Both sides can be multiplied by V, giving:

$$\text{V} \cdot \text{C} = \text{V} \cdot \text{C}\left(0\right) \cdot \text{e}^{-\text{kt}} \tag{1.6}$$

Since V · C represents the amount of drug in the body (A), and V · C(0) is the dose, then:

$$\text{A} = \text{Dose} \cdot \text{e}^{-\text{kt}} \tag{1.7}$$

Equations (1.5) and (1.7) can be used to estimate C and A at any point in time. Elimination half-life ($t_{½}$) is defined as the time it takes for C to decrease by half (Figure 1.1a, b). It follows that one half-life would be the time taken for C(0) to decrease to ½ of C(0). Equation (1.5) can therefore be expressed as:

$$½ \cdot \text{C}\left(0\right) = \text{C}\left(0\right) \cdot \text{e}^{-\text{kt}½} \tag{1.8}$$

This can be simplified to:

$$½ = \text{e}^{-\text{kt}½} \tag{1.9}$$

Inverting yields:

$$2 = \text{e}^{\text{kt}½} \tag{1.10}$$

The natural logarithm of both sides gives:

$$0.693 = \text{kt}_{½} \tag{1.11}$$

This can be rearranged as follows to give $t_{½}$:

$$\text{t}_{½} = 0.693/\text{k} \tag{1.12}$$

The constant, k, represents the slope of the line from Eq. (1.4) and can also be calculated using Eq. (1.12) if the

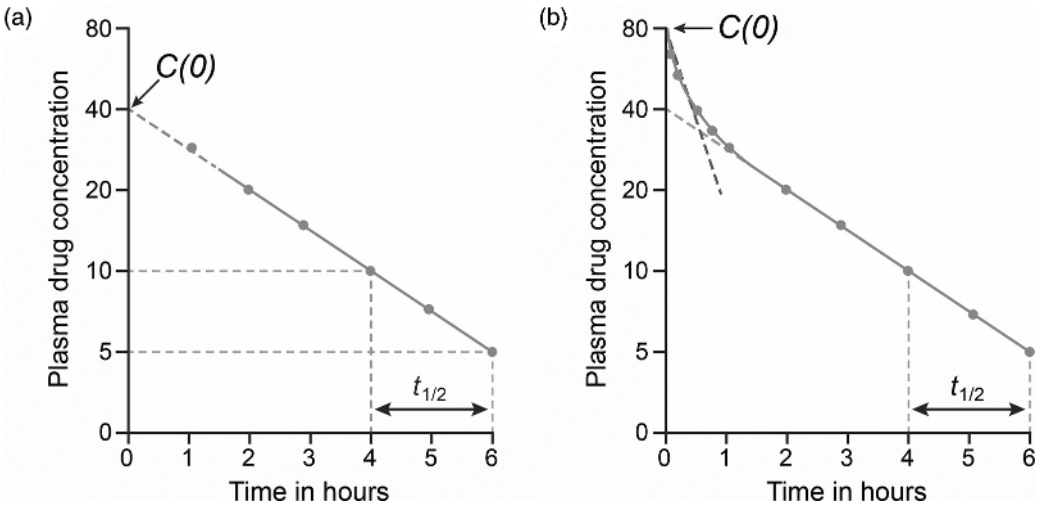

Figure 1.1 Semilogarithmic plots of plasma concentration of drug vs time. (a) Plasma concentrations plotted over time yield a straight line. The first plasma sample is taken at one hour after IV administration. Extrapolation of the line (the dashed portion of the line) yields the plasma concentration at time 0: C(0). Elimination half-life ($t_{1/2}$) is the time required for plasma concentration to decrease by 50%. If the extrapolated C(0) matched the measured C(0), this plot would represent a one-compartment pharmacokinetic model, where the drug does not distribute outside of the central compartment. The log of plasma concentration vs time relationship can be described by the equation for a single straight line. (b) Increased frequency of plasma sampling between 0 and 1 hour results in the line obtained becoming curved between those time points. In this theoretical example, the latter part of the curve is identical to 1.1a, however C(0) is not accurately predicted by extrapolation of this terminal part of the curve. This shows that the drug distributes into more than one compartment, i.e. the central compartment and a tissue compartment. In a two-compartment model, the equation describing the curve is comprised of two lines, one for each compartment.

value for $t_{½}$ is known. It can also be related to the amount of drug in the body (A) as it changes over time by differentiating Eq. (1.7):

$$dA/dt = -k \cdot dose \cdot e^{-kt½} \quad (1.13)$$

Since $A = Dose \cdot e^{-kt}$,

$$dA/dt = -k \cdot A \quad (1.14)$$

dA/dt is the rate of change of a drug in the body and is equal to the rate of elimination. Rearranging Eq. (1.14) yields:

$$k = \text{rate of drug elimination / amount of drug in the body} \quad (1.15)$$

The rate constant k in Eq. (1.15) describes elimination and is known as the elimination rate constant. Equation (1.7) can be arranged to show that the fraction of drug remaining in the body (A/dose) equals e^{-kt}.

$$A/dose = e^{-kt} \quad (1.16)$$

From Eq. (1.11), $k = 0.693/t_{½}$, therefore:

$$A/dose = e^{-0.693/t_{½}} \quad (1.17)$$

The right side of Eq. (1.17) can also be expressed in general terms of the number of half-lives, n, that have passed since the drug was given, where $n = t/t_{½}$.

$$A/dose = e^{-0.693n} \quad (1.18)$$

The value of $e^{-0.693}$ is ½, giving:

$$A/dose = \left(½\right)^{n} \quad (1.19)$$

The fraction of drug remaining in the body for different values of n can be determined (Table 1.2). After five half-lives approximately 3% of the original dose is left, i.e. 97% has been eliminated. While a drug will continue to be in the body in evermore declining fractions of the original dose, in practical terms, it can be considered to have been effectively eliminated after five half-lives.

Table 1.2 Fraction of the drug as a percentage remaining in the body as it relates to the number of elapsed half-lives.

Number of half-lives (*n* in Eq. (1.20))	Fraction of drug remaining (%)	Fraction of drug eliminated (%)
0	100	0
1	0.5 × 100 = 50	50
2	0.5 × 50 = 25	75
3	0.5 × 25 = 12.5	87.5
4	0.5 × 12.5 = 6.25	93.75
5	0.5 × 6.25 = 3.125	96.875
6	0.5 × 3.125 = 1.5625	98.4375

A drug is considered to have been effectively eliminated after five half-lives.

Clearance

Total body, i.e. systemic, clearance (CL) relates the concentration of a drug to its rate of elimination. When clearance is at a constant rate:

$$\text{Rate of elimination} = CL \cdot C \quad (1.20)$$

Since the rate of elimination = k · A (Eq. (1.15)), and A = V · C (Eq. (1.3)),

$$\text{Rate of elimination} = k \cdot V \cdot C \quad (1.21)$$

Rearranging Eq. (1.20) gives:

$$CL = \text{rate of elimination}/C \quad (1.22)$$

Substituting rate of elimination = k · V · C from Eq. (1.21) yields:

$$CL = k \cdot V \quad (1.23)$$

From Eq. (1.12), $t_{½} = 0.693/k$, and from Eq. (1.23), k = CL/V. Half-life can therefore be related to the independent variable's clearance and volume of distribution as follows:

$$t_{½} = 0.693 \cdot V/CL \quad (1.24)$$

Clearance can be determined independently of the elimination half-life. Equation (1.22) can be used to express the amount of drug eliminated in a period of time (dt) as follows:

$$\text{Amount eliminated during dt} = CL \cdot C \cdot dt \quad (1.25)$$

If dt represents a short interval of time, e.g. one minute, C · dt is equal to the area under the drug concentration versus time curve (AUC) for that short period of time. The AUC for the entire time course of elimination is given by mathematical integration of the whole drug concentration vs time curve such that:

$$AUC = \text{amount of drug eliminated}/CL \quad (1.26)$$

When a drug is administered IV, the amount of drug eliminated is equal to the dose. Rearranging Eq. (1.26) yields:

$$Dose = CL \cdot AUC \quad (1.27)$$

Clearance can therefore be determined independently of volume of distribution and $t_{½}$. Equations (1.23) and (1.27) can be used to determine volume of distribution. Rearranging Eq. (1.23) gives V = CL/k. Substituting for clearance gives:

$$V = Dose/\left(AUC \cdot k\right) \quad (1.28)$$

Equation (1.28) shows that volume of distribution can be calculated without extrapolating to time zero from the concentration versus time curve that was described earlier.

The most important organs involved in eliminating drugs are the liver and kidneys. Other organs can also contribute to clearance e.g. the lungs. Total body clearance is therefore given by:

$$CL = CL_{hepatic} + CL_{renal} + CL_{other} \quad (1.29)$$

Hepatic Clearance The amount of drug that enters the liver via the arterial blood supply equals hepatic blood (Q_H) × the drug concentration in arterial blood (C_A). Similarly, the amount of drug exiting the organ is Q_H × the drug concentration in venous blood (C_V). Rate of elimination is therefore:

$$\begin{aligned} \text{Rate of elimination} &= Q_H \cdot C_A - Q_H \cdot C_V \\ &= Q_H \cdot \left(C_A - C_V\right) \end{aligned} \quad (1.30)$$

Since clearance equals rate of elimination/drug concentration, Eq. (1.30) can be related to clearance by dividing both sides by C_A.

$$CL_H = Q_H \cdot \left(C_A - C_V\right)/C_A \quad (1.31)$$

In Eq. (1.31), $(C_A - C_V)/C_A$ is termed the extraction ratio (ER), giving:

$$CL_H = Q_H \cdot ER \quad (1.32)$$

The processes responsible for drug elimination that occur in the liver, indeed, in any organ, do not have infinite capacity, and can become saturated. This occurs when the rate at which a drug is presented to the liver exceeds the liver's capacity to clear the drug. The maximum capacity of an organ to clear a drug is referred to as the intrinsic clearance (CL_i) of that organ. ER and CL_i are related as follows:

$$ER = CL_i/\left(Q + CL_i\right) \quad (1.33)$$

Combining Equations (1.33) and (1.31) gives the relationship between hepatic clearance and intrinsic clearance:

$$CL_H = Q_H \cdot CL_i/\left(Q_H + CL_i\right) \quad (1.34)$$

When intrinsic clearance is very small compared to hepatic blood flow, CL_i in the denominator of Eq. (1.34) can be ignored, giving:

$$CL_H = Q_H \cdot CL_i/Q_H \quad (1.35)$$

Equation (1.35) can then be expressed as:

$$CL_H = CL_i \quad (1.36)$$

In this case, clearance depends on the intrinsic clearance of the liver and not hepatic blood flow.

When the amount of drug presented to the liver is much less than the intrinsic clearance for that drug, clearance is a function of hepatic blood flow. CL_i in the denominator of Eq. (1.34) can be ignored, giving:

$$CL_H = Q_H \cdot CL_i/CL_i \quad (1.37)$$

This can then be written as:

$$CL_H = Q_H \quad (1.38)$$

As an example, lidocaine is cleared very efficiently by the liver, and therefore clearance is determined by hepatic blood flow. This is demonstrated in a study by Feary et al. (2005) which showed that clearance of lidocaine administered as an infusion to awaken horses was 29 ml/min/kg, whereas in sevoflurane anesthetized horses clearance was 15 ml/min/kg, a reduction of approximately 50% (Feary et al. 2005). The decrease in clearance is attributed to decreased liver blood flow as a result of the significant decrease in cardiac output that occurs under inhalant anesthesia in horses.

Renal Clearance Renal clearance (CL_R) is defined as the rate of change of drug in the urine compared to the plasma concentration of drug.

$$CL_R = \text{excretion rate}/C \quad (1.39)$$

Renal clearance is determined by renal filtration, renal tubular secretion and renal tubular reabsorption.

$$\begin{aligned} CL_R = (&\text{filtration rate} + \text{secretion rate} \\ &- \text{reabsorption rate})/C \end{aligned} \quad (1.40)$$

If secretion and reabsorption rates are low, renal clearance is then a function of GFR.

$$CL_R = GFR/C \quad (1.41)$$

Additionally, only a drug that is free (i.e. not protein bound) is available for renal clearance. The unbound fraction of drug (fu) is given by the following, where C_u is the concentration of unbound drug:

$$fu = C_u/C \quad (1.42)$$

Renal filtration rate is then:

$$\text{Filtration rate} = GFR \cdot fu \cdot C \quad (1.43)$$

If there is no renal secretion or reabsorption, the filtration rate in Eq. (1.41) can be replaced using Eq. (1.43), giving:

$$CL_R = GFR \cdot fu \cdot C/C \quad (1.44)$$

Renal clearance is therefore:

$$CL_R = GFR \cdot fu \quad (1.45)$$

In cases were fu = 1, i.e. when a drug does not bind to proteins, renal clearance is equal to the GFR. When renal

clearance exceeds or is less than the GFR, this indicates that the drug is being actively secreted by, or is being reabsorbed from, the renal tubules.

Compartmental Models

Compartmental models of drug disposition are used to obtain pharmacokinetic variables that help to predict drug concentration, and therefore drug effect(s). Statistical pharmacokinetic software uses drug plasma concentrations over time to predict the model that fits best. Most drugs can be modeled as one-, two- or three-compartment models. The first compartment is referred to as the central compartment, and the others are peripheral compartments.

A one-compartment model is shown in Figure 1.2a. A dose of drug given directly into, or absorbed into, the compartment (I represents input) distributes into the volume (V) of the compartment, and is eliminated over time (k is the elimination constant). In the case of a one-compartment model, the change in plasma concentration over time [C(t)] is described by the following exponential equation:

$$C(t) = e^{-kt} \tag{1.46}$$

The semilogarithmic plot of plasma concentration vs time yields a single straight line, like the one shown in Figure 1.1a. The dose required to reach a target plasma concentration for a one-compartment model can be calculated using Eq. (1.3), clearance can be determined from Eq. (1.23), and $t_{½}$ from Eq. (1.24).

In the case of a two-compartment model, the drug is eliminated from the central compartment and distributed to (and can return from) a peripheral compartment (Figure 1.2b). The semilogarithmic plasma concentration vs time plot will yield a curve comprised of two overlapping straight lines (Figure 1.1b). The initial phase has a steeper slope compared to the second phase. Change of plasma drug concentration over time in a two-compartment model is given by:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} \tag{1.47}$$

A three-compartment model has two peripheral compartments connected to the central compartment with different equilibration rates (rapid and slow) (Figure 1.2c). This model's semilogarithmic plasma concentration vs time plot will be comprised of three overlapping straight lines. The equation for change of plasma concentration over time contains three exponential terms:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \tag{1.48}$$

Compartmental pharmacokinetic analysis is a simplification of how drugs are distributed within the body, as each organ has its own specific blood flow. Physiologic-based models can be used to give a clearer picture of a drug's pharmacokinetics. Pharmacokinetic parameters can also be determined using non-compartmental analysis. A discussion of pharmacokinetics of these models is outside the scope of this chapter.

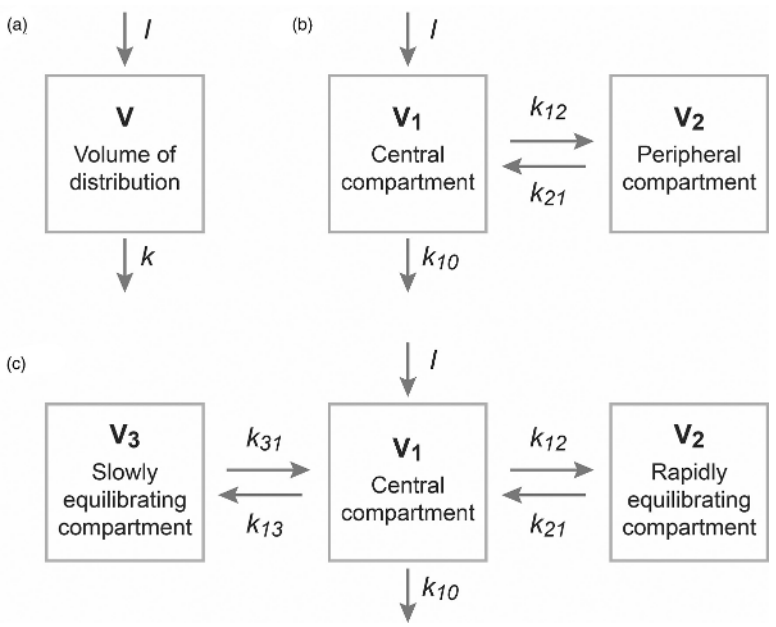

Figure 1.2 Compartmental pharmacokinetic models. (a) A one-compartmental model, where the compartment is the central compartment, i.e. the drug does not move out of the blood into the tissues. *I* represents input, i.e. IV drug dose or a drug that enters the compartment via absorption. V represents volume of distribution, and k is the elimination constant. (b) A two-compartment model showing a central compartment and a peripheral tissue compartment with their own volumes of distribution, V_1 and V_2. k_{12} and k_{21} are the equilibrium constants between the compartments, and k_{10} is the elimination constant. (c) A three-compartment model showing two peripheral compartments connected to the central compartments. The two peripheral tissue compartments are a more rapidly equilibrating one and a more slowly equilibrating one. Each compartment will have its own volume of distribution, with multiple constants describing drug equilibration between compartments.

Infusion Pharmacokinetics

Up to this point, the pharmacokinetics of a single dose have been discussed. For a continuous drug effect, repeated boluses can be given, with peaks and troughs of drug plasma concentration stabilizing after about 5 half-lives (Figure 1.3). A true steady state plasma concentration (C_{ss}) can be achieved by administering a drug by infusion. This is useful for drugs with a narrow therapeutic range, and for those with very short half-lives, e.g. catecholamines like norepinephrine where $t_{½}$ is measured in minutes. Use of infusions is commonplace in veterinary anesthesia, e.g. to provide analgesia and/or reduce inhalant requirements (opioids, lidocaine, ketamine), for cardiovascular support (inotropes) or as total IV anesthesia (propofol).

Since it takes about 5 half-lives to reach steady state, a bolus or loading dose can be given for drugs that have relatively long half-lives (Figure 1.4). This can be determined using Eq. (1.3). If V_{SS} equals volume of distribution at steady state, then:

$$\text{Loading dose} = C \cdot V_{SS} \tag{1.49}$$

Loading doses are useful when the half-life of a drug is relatively long, so that the desired plasma concentration at steady state can be reached sooner. In a one-compartment model, once steady state has been reached, the rate at which a drug needs to be added is equal to the desired plasma concentration × clearance.

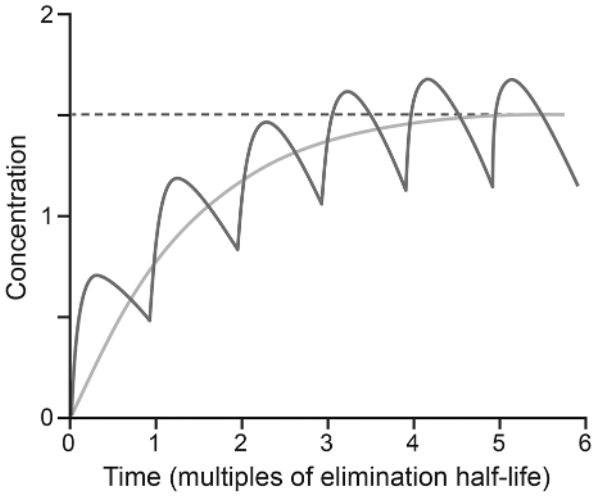

Figure 1.3 Semilogarithmic plot of drug concentration vs time comparing intermittent dosing to constant rate infusion. Time is given in multiples of elimination half-life, the time it takes drug concentration to increase (or decrease) by 50% from a previous value. It takes approximately 5 half-lives to reach steady state. The blue curve demonstrates peaks and troughs of drug concentration observed with intermittent dosing. Administration of a drug by constant rate infusion (orange curve) smooths out the peaks and valleys, allowing a drug to reach a steady state (dashed line).

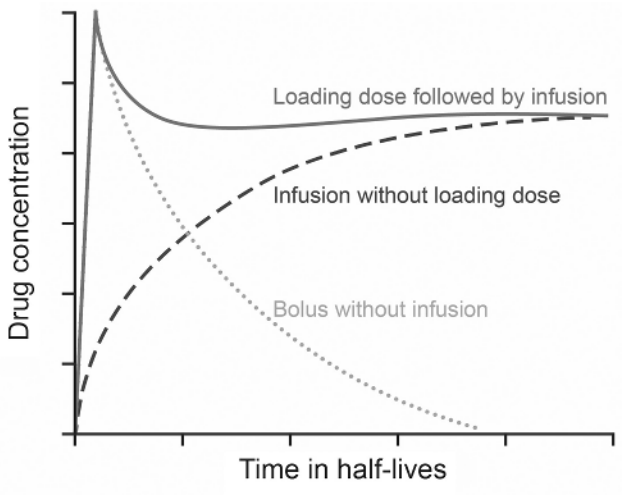

Figure 1.4 Semilogarithmic plot of drug concentration vs time for a constant rate infusion with and without a loading dose. The blue line (dotted) represents the plasma concentration vs time course of a loading dose. The red line (dashed) represents the time taken to reach steady state after starting a constant rate infusion. To reach steady state earlier, a loading dose can be given (purple solid line).

$$\text{Maintenance infusion rate} = C \cdot CL \tag{1.50}$$

Note that once a true plasma concentration steady state has been reached, kinetics can be characterized as a zero-order process, i.e. a fixed amount of drug is added and removed per unit time. This concept also applies to the pharmacokinetics of fentanyl patches, where a specific dose per unit time is delivered (Lötsch et al. 2013). Equation (1.50) is also valid for two- and three-compartment models once all compartments have reached equilibrium. This may not occur for some time, particularly with slowly equilibrating tissue compartments. Under circumstances where it takes hours to reach equilibration, using this equation will underestimate the plasma concentration, since the drug will still be moving into the third compartment. The following equation is used for an infusion where the drug distributes in a three-compartment model, where C_T is the target plasma concentration:

$$\text{Maintenance infusion rate} = C_T \cdot V_1 \cdot \left(k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t}\right) \tag{1.51}$$

For example, in dogs, after an IV bolus of propofol (4 mg/kg), use of a constant rate infusion of propofol (0.4 mg/kg/min) for maintenance of anesthesia for

60 minutes resulted in a steady rise in plasma concentration (Nolan and Reid 1993). This rise in plasma concentration can be ameliorated by decreasing the rate of infusion in a stepwise fashion over time. This is most commonly achieved in veterinary anesthetic practice by manually changing the rate of delivery of an infusion (or syringe) pump. Pharmacokinetic data can be used in conjunction with computer programing to create devices that can deliver a drug to target a specific plasma concentration, i.e. target-controled infusion systems. The operator chooses the target plasma concentration, and the device alters the infusion rate in accordance with pharmacokinetic data to achieve that concentration. Target-controled infusion systems have been evaluated for propofol in dogs and cats, and for ketamine in ponies, however, this anesthetic delivery technique remains a research tool in veterinary anesthesia (Beths et al. 2001; Cattai et al. 2016; Levionnois et al. 2010).

The concept of elimination half-life was previously discussed in the context of administering a single bolus with minimal distribution to peripheral compartments. When a drug is given by infusion over a period of time long enough to allow significant distribution to peripheral compartments, the concept of context-sensitive half time is useful. Context-sensitive half-time is the time for drug plasma concentration to decrease by 50% when the drug is being administered by infusion such that plasma concentration is at steady state. Context-sensitive half-time is not a fixed value, instead, it increases as the duration of infusion administration increases until equilibrium among compartments is reached.

Pharmacodynamics

Pharmacodynamics is the study of the effect of drugs on the body, with the vast majority of drugs acting via interaction with receptors. Molecules, both endogenous (e.g. natural hormones) and exogenous (e.g. drugs), that bind to receptors (R) are referred to as ligands (L).

Receptors

Receptors can be grouped into families based on shared structure and similarity of function. Major receptor families relevant to drugs used in the peri-anesthetic period include ion channels, transmembrane enzymes and G protein-coupled receptors (GPCR). Ion channels include voltage-gated channels, e.g. sodium channels which are a target for local anesthetics, and ligand-gated channels, e.g. neurotransmitter receptors like gamma-aminobutyric acid (GABA), a target for some injectable anesthetics such as propofol. Transmembrane receptors that are linked to intracellular enzymes include receptor tyrosine kinases like the insulin receptor. The family of GCPRs is large, and includes opioid, adrenergic and muscarinic receptors. In the basal state, GPCR consist of seven membrane-spanning helixes coupled with an intracellular G protein consisting of three subunits (Gα, Gβ, and Gγ) that forms a complex connected to the intracellular helix loops, with GDP connected to the Gα subunit (Figure 1.5). Binding of a ligand to the receptor results in a conformational change that stimulates GDP release and binding of GTP to the Gα subunit. The activated Gα unit and Gβγ complex are now able to bind to effectors, resulting in actions, or signals, via second

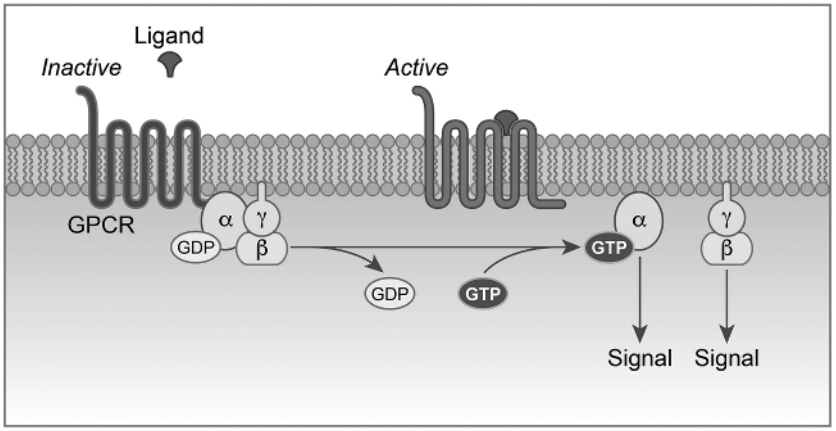

Figure 1.5 G protein-coupled receptor. In the basal state, G protein-coupled receptors consist of seven membrane-spanning helixes coupled with an intracellular G protein. The G protein consists of three subunits (Gα, Gβ, and Gγ) that forms a trimeric complex connected to the intracellular helix loops, with GDP connected to the Gα subunit. Binding of a ligand to the receptor results in a conformational change that stimulates GDP release and binding of GTP to the Gα subunit. The activated Gα unit and Gβγ dimer are now able to bind to effectors, resulting in actions, or signals, via second messengers. Ligands can be endogenous (e.g. hormones, neurotransmitters, opioids) or exogenous (e.g. drugs, toxins).

messengers like cyclic AMP. Traditionally, GPCRs were thought to be inactive in the basal state, only becoming active through ligand binding. More recently, it has been shown that these receptors can exist in two states in the absence of ligand binding: they can be inactive (R) or have some basal level of activity (R*). This two state model can be expressed as follows:

$$R \rightleftharpoons R^*$$

When a ligand is present, the ligand-receptor relationship is:

$$L + R \rightleftharpoons LR \rightleftharpoons LR^*$$

Drug-receptor Interactions

Drug action at a receptor is influenced by the degree to which it binds to the receptor (affinity) as well as the drug's ability to cause a response once bound to the receptor (efficacy).

A drug with high affinity for a receptor will bind more readily to a receptor than a drug with low affinity. Therefore at equilibrium, a greater fraction (or percent) of a high affinity drug will be bound to receptors compared to a low affinity drug.

Ligands (drugs) that produce an increased response when they bind to receptors are called agonists (Figure 1.6). The ability of a drug to produce an effect is known as its efficacy. A full agonist is a ligand that can activate a receptor to a maximal extent (e.g. morphine). Agonists that produce a submaximal response are referred to as partial agonists (e.g. buprenorphine). Morphine is therefore more efficacious than buprenorphine. Ligands are said to be antagonists when they effectively occupy the receptor and do not change its level of activity (e.g. naloxone). Antagonism can be competitive or non-competitive. Antagonism from a competitive antagonist can be overcome by increasing the concentration (i.e. dose) of an agonist. In contrast, non-competitive antagonism cannot be overcome by increasing the concentration of an agonist. Some drugs can have agonist activity at one receptor, and antagonist activity at another (e.g. butorphanol, which is a kappa opioid receptor agonist and a mu opioid receptor antagonist). Such drugs are referred to as agonist-antagonists. Ligands can also decrease the level of activity when binding to a receptor that has a basal level of activity, i.e. receptors in the R* state, in which they are referred to as inverse agonists (Sato et al. 2016).

Potency refers to the amount of drug required to exert an effect. If less drug (lower plasma concentration) is required to produce an effect compared to another drug, the first drug is more potent, i.e. as potency increases, the more a dose/effect curve moves to the left (Figure 1.7). Note that in Figure 1.7, all three drugs are able to reach maximum

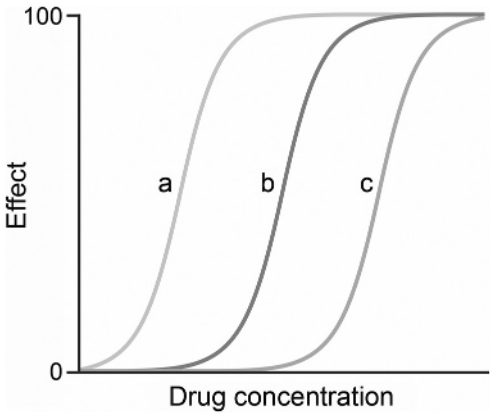

Figure 1.7 Potency. Potency is the amount of a drug required to exert an effect. Drug *a* is more potent than drugs *b* and *c* because a lower plasma concentration is required to exert the same effect as either *a* or *b*. Note that all three drugs shown here have the same efficacy.

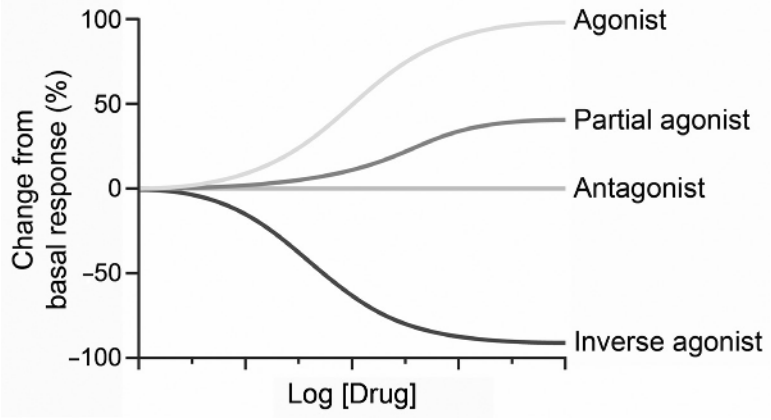

Figure 1.6 Efficacy. The ability of a ligand (drug) to bind to a receptor and produce an effect is known as its efficacy. A full agonist is a ligand that can activate a receptor to a maximal extent. Agonists that produce a submaximal response are referred to as partial agonists. Antagonists are ligands that occupy a binding site on a receptor and prevent changes to the basal level of activity of that receptor. Ligands that decrease basal receptor activity are termed inverse agonists, which can have partial or full activity. Note that all four of the ligands shown in this figure have the same potency and different efficacies.

effect, and therefore have equal efficacy. Compare this to Figure 1.6 where the full agonist, partial agonist, antagonist and inverse agonist have equal potency, but different efficacy.

Receptor populations, and therefore response to drugs, is not always uniform within a species, often as a result of genetic mutation. The study of inherited variability in response to drugs is termed pharmacogenomics and is discussed in Chapter 2.

Pharmacokinetic/Pharmacodynamic Modeling

Studies that relate pharmacokinetics to pharmacodynamics (PK/PD) studies are used to provide information relating plasma concentration to drug effect. In an ideal world, the veterinary anesthetist would have access to PK/PD models for all drugs used in the perioperative period, in both awake and anesthetized animals, that also take important disease states (e.g. hepatopathy, renal insufficiency, hypovolemia) into account. This would inform decision making when selecting drug dosages and rates of administration in healthy and ill animals, as well as expectations for drug effects, both wanted and unwanted. In reality this is not the case, particularly when it comes to disease states. When this information is unavailable, it is prudent to give drugs to effect where possible, and to monitor patients closely for side effects.

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Further Reading

Basic pharmacodynamic and pharmacokinetic concepts have been discussed in this chapter. An expanded discussion of these and more advanced pharmacologic concepts can be found in the following texts.

Brunton, L.L., Hilal-Dandan, R., and Knollman, B.C. (ed.) (2018). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, *13*e. Wolters Kluwer.

Derendorf, H. and Schmidt, S. (ed.) (2020). *Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*, *5*e. McGraw-Hill Education.