ROBERT K. STOELTING

PHARMACOLOGY and PHYSIOLOGY in ANESTHETIC PRACTICE

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The author and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

PREFACE

Anesthesiology is a medical specialty that requires daily application of principles of pharmacology and physiology in the care of patients. Reference textbooks of pharmacology and physiology often serve as the repository of information that is pertinent to all medical aspects of pharmacology and physiology. Clearly, only portions of these textbooks are relevant to the clinical practice of anesthesia. In this regard, the goal of *Pharmacology and Physiology in Anesthetic Practice* is to provide students as well as practicing anesthesiologists with an in-depth but concise and current presentation of those aspects of pharmacology and physiology that are relevant either directly or indirectly to the perioperative anesthetic management of patients.

Preparation of a textbook of this scope requires unique and reliable support from others. In this regard, special accolades go to my secretary, Deanna Walker, for her skillful preparation of the many revisions that preceded the final manuscript. Ellyn Traub receives my appreciation for her skillful preparation of the original art work. Lewis Reines, president of J. B. Lippincott Company, again earned my admiration for his professionalism and constant ability to provide encouragement and resources for the evolution of this textbook. Finally, my wife and daughters deserve my special thanks for again enduring the time commitment required for another textbook.

Robert K. Stoelting, M.D.

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SECTION I

PHARMACOLOGY

CHAPTER 1

Pharmacokinetics and Pharmacodynamics of Injected and Inhaled Drugs

INTRODUCTION

Pharmacokinetics is the quantitative study of the absorption, distribution, metabolism, and excretion of injected or inhaled drugs and their metabolites (*i.e.,* what the body does to a drug) (Hug, 1978; Stanski and Watkins, 1982). Coupled with the dose of drug administered, pharmacokinetics determines the concentration of drug at its sites of action (*i.e.,* receptors) and, thus, the intensity of the drug's effects with time. Pharmacokinetics also determines variations in plasma concentrations of a drug among patients resulting from differences in its absorption, distribution, and elimination. Selection and adjustment of drug dosage schedules and interpretation of measured plasma concentrations of drugs are facilitated by an understanding of pharmacokinetic principles.

Pharmacodynamics is the study of the intrinsic sensitivity or responsiveness of receptors to a drug and the mechanisms by which these effects occur (*i.e.,* what the drug does in the body) (Hull, 1979; Maze, 1981; Stanski and Watkins, 1982). Structure activity relationships relate the actions of drugs to their chemical structure and facilitate design of drugs with more desirable pharmacologic properties. Intrinsic sensitivity of receptors is determined by measuring plasma concentrations of a drug required to evoke specific pharmacologic responses (Kauffman, 1981). Variability exists in the intrinsic sensitivity of receptors among patients. As a result, at similar plasma concentrations of drug, some patients show a therapeutic response, others show no response, and, in others, toxicity develops.

DESCRIPTION OF DRUG RESPONSE

Hyperreactive is the term used for people in whom an unusually low dose of drug produces its expected pharmacologic effects. *Hypersensitive* is the term usually reserved for people who are allergic to a drug. *Hyporeactive* describes people who require unusually large doses of drug to evoke expected pharmacologic effects. Hyporeactivity acquired from chronic exposure to a drug is better termed *tolerance*. Cross-tolerance frequently develops between drugs of different classes that produce similar pharmacologic effects (*e.g.,* alcohol and inhaled anesthetics). Tolerance that develops acutely with only a few doses of a drug, such as thiopental, is termed *tachyphylaxis*. The most important factor in the development of tolerance to drugs such as the opioids, barbiturates, and alcohol is neuronal adaptation referred to as cellular tolerance. Other mechanisms of tolerance may include enzyme induction and depletion of neurotransmitters by virtue of sustained stimulation. Immunity is present when hyporeactivity is due to formation of antibodies. Idiosyncrasy is present when an unusual effect of a drug occurs in a small percentage of patients regardless of the dose of drug. More appropriately, unusual effects of drugs should be described precisely in terms of their documented or likely mechanisms (*e.g.,* allergy, genetic difference).

An *additive effect* means that a second drug acting with the first drug will produce an effect equal to an algebraic summation. For example, the anesthetic effects of two different inhaled anesthetics are additive as reflected by MAC equivalents (Quasha *et al,* 1980) (see the section entitled Minimum Alveolar Concentration). Synergistic means two drugs interact to produce an effect that is greater than algebraic summation. Antagonism is when two drugs interact to produce an effect less than algebraic summation.

A drug that activates a receptor by binding to the receptor is called an *agonist.* An *antagonist* is a drug that binds to the receptor without activating the receptor and at the same time prevents an agonist from stimulating the receptor. Competitive antagonism is present when increasing concentrations of the antagonist progressively inhibit the response to an unchanging concentration of agonist. Noncompetitive antagonism is present when, after administration of an antagonist, even high concentrations of agonist cannot completely overcome the antagonism.

Termination of drug effect is by metabolism, excretion, or redistribution. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug is administered rapidly intravenously.

PHARMACOKINETICS OF INJECTED DRUGS

Compartmental Models

Pharmacokinetics of injected drugs has been simplified by considering the body to be comprised of a number of compartments representing theoretical spaces. This approach permits a mathematical modeling of the disposition of a drug within the body based on its pharmacokinetics. In this regard, it is essential that the analytical procedures used in pharmacokinetic studies measure the parent drug and its metabolites separately.

A two-compartment model can be used to illustrate basic concepts of pharmacokinetics that also apply to more complex models (Fig. 1-1) (Stanski and Watkins, 1982). In the two-compartment model, drug is introduced by intravenous injection directly into the central compartment. Drug subsequently distributes to a peripheral compartment only to return eventually to the central compartment where clearance from the body occurs.

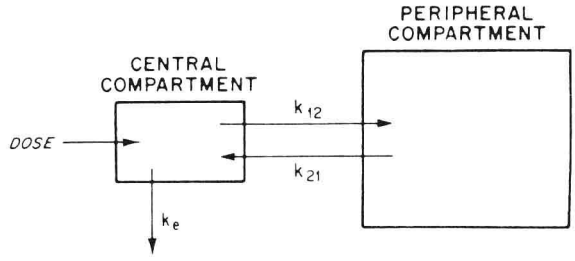

FIGURE 1-1. A two-compartment pharmacokinetic model as derived from a biexponential plasma decay curve (see Fig. 1-2). K_{12} and k_{21} are the rate constants that characterize intercompartmental transfer of drugs, and k_e is the rate constant for overall drug elimination from the body. (From Stanski DR, Watkins WD. Drug Disposition in Anesthesia. New York, Grune and Stratton, 1982. Reproduced by permission of the authors and publisher.)

The central compartment includes intravascular fluid and highly perfused tissues (*e.g.,* heart, brain, lungs, liver, kidneys) into which uptake of drug is rapid (see the section entitled Distribution). In an adult, these tissues represent about 10% of body mass but receive almost 75% of the cardiac output. This central compartment is defined only in terms of its apparent volume, which is calculated and does not necessarily correspond to actual anatomic volumes (see the section entitled Volume of Distribution). Likewise, the peripheral compartment is defined in terms of its apparent volume. A large calculated volume for the peripheral compartment suggests extensive uptake of drug by those tissues that constitute the peripheral compartment. Any residual drug present in the peripheral compartment at the time of repeat injection will diminish the effect of distributive processes on the reduction of the plasma concentration and lead to exaggerated effects of the repeat dose (*i.e.,* cumulative drug effect). The degree of cumulative drug effect can be calculated knowing the drug's volume of distribution, elimination half-time, and dosing interval.

Despite the usefulness of compartmental models to depict the pharmacokinetics of drugs, it must be appreciated that these pharmacokinetic characteristics are most often derived from healthy and ambulatory adults with a low fat-to-lean body ratio. Conversely, drugs are most likely to be administered to patients with chronic disease at various extremes of age, hydration, and nutrition.

Plasma Concentration Curves

A graphic plot of the logarithm of the plasma concentration of drug versus time following a rapid (bolus) intravenous injection characterizes the distribution and elimination half-times of that drug (Fig. 1-2) (Stanski and Watkins, 1982). Logarithms provide a convenient means for managing the large range in the plasma concentrations encountered after an intravenous injection of drug. In addition, logarithms are appropriate for depiction of the first-order kinetics characteristic of the distribution and elimination of most drugs.

Distribution and Elimination Phases

Two distinct phases (*i.e.,* biexponential) are present on the graphic plot of the decline in the plasma concentration of a drug (Fig. 1-2) (Stanski and Watkins, 1982). The first phase is designated the distribution (alpha) phase. This phase begins immediately after intravenous injection of the drug and reflects its distribution from the circulation to peripheral tissues. The second phase is designated the elimination (beta) phase. This phase is characterized by a gradual decline in the plasma concentration of the drug and reflects its elimination from the central vascular compartment by renal and hepatic clearance mechanisms (see Fig. 1-1) (Stanski and Watkins, 1982).

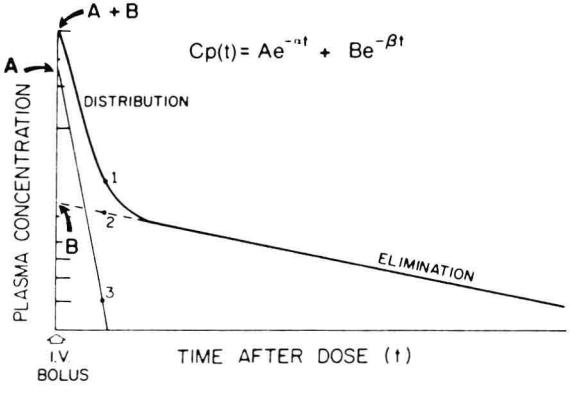

FIGURE 1-2. Schematic depiction of the decline in the plasma concentration of drug with time following rapid intravenous injection into the central compartment (see Fig. 1-1). Two distinct phases (*e.g.,* biexponential) characterize this curve, being designated the distribution and elimination phases. (From Stanski DR, Watkins WD. Drug Disposition in Anesthesia. New York, Grune and Stratton, 1982. Reproduced by permission of the authors and publisher.)

ELIMINATION HALF-TIME. The rate of drug elimination can be characterized by the slope of the line representing the log plasma concentration of drug plotted against time during the elimination phase. The numerical value of the slope of the elimination phase is defined as the first-order rate constant. The concept of elimination half-time, however, is used more frequently than the rate constant. *Elimination half-time* is the time necessary for the plasma concentration of drug to decline 50% during the elimination phase. Conversely, *half-life* refers to the total amount of drug in the body and the time necessary for elimination of 50% of this total from the body. Half-time and half-life are not equal when the decline of drug concentrations in all tissues does not parallel the decline in the plasma concentration.

Elimination half-time of a first-order process can be estimated graphically by selecting any point on the straight line portion of the elimination phase and measuring the time interval to the point on the same line that represents one-half the original concentration (Fig. 1-2) (Stanski and Watkins, 1982). The elimination half-time can also be calculated as 0.63 divided by the elimination rate constant for that drug.

Elimination half-time of a drug is directly proportional to its volume of distribution and inversely proportional to its clearance. For this reason, renal or hepatic disease that alters volume of distribution and/or clearance will alter the elimination half-time.

The amount of drug remaining in the body is related to the number of elimination half-times that have elapsed. For example, if 50% of a drug is eliminated in 10 minutes, another 10 minutes will be required for elimination of one-half the remaining drug. About five elimination half-times are required for almost complete (96.9%) elimination of a drug (Table 1-1) (Hug, 1978). For this reason, drug accumulation is predictable if dosing intervals are less than this period of time. Drug accumulation continues until the rate of drug elimination equals the rate of drug administration. As with drug elimination, the time necessary for a drug to achieve a steady state plasma concentration (Cpss) with intermittent dosing is about five elimination half-times.

Table 1-1
Relationship of Half-Times to Amount of Drug Eliminated

Number of Half-Times	*Fraction of Initial Amount Remaining*	*Percent of Initial Amount Eliminated*
0	1	0
1	1/2	50
2	1/4	75
3	1/8	87.5
4	1/16	93.8
5	1/32	96.9
6	1/64	98.4

(Adapted from Hug CC. Pharmacokinetics of drugs administered intravenously. Anesth Analg 1978; 57:704–23 with permission of the author and publisher)

Route of Administration and Systemic Absorption of Drugs

The choice of route of administration for a drug should be based on an appreciation of factors that influence the systemic absorption of drugs. The rate of systemic absorption of a drug determines its intensity and duration of action. Changes in the rate of systemic absorption may necessitate an adjustment in the dose or time interval between repeated drug doses (Azarnoff and Huffman, 1976).

Systemic absorption, regardless of the route of drug administration, is dependent on drug solubility. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Circulation to the site of absorption is also important in the rapidity of absorption. For example, increased blood flow by external massage or local application of heat enhances systemic absorption, whereas decreased blood flow due to vasoconstriction impedes drug absorption. Finally, the area of absorbing surface to which a drug is exposed is an important determinant of drug absorption.

Oral Administration

Oral administration of a drug is the most convenient and economic route of administration. Disadvantages of the oral route of administration include (1) emesis because of irritation of the gastrointestinal mucosa by the drug, (2) destruction of the drug by digestive enzymes or low gastric fluid *p*H, and (3) irregularities in absorption in the presence of food or other drugs. Furthermore, drugs may be metabolized by enzymes or bacteria in the gastrointestinal tract before systemic absorption can occur.

Following oral administration, the onset of drug effect is largely determined by the rate and extent of absorption from the gastrointestinal tract. The principal site of drug absorption after oral administration is from the small intestine, reflecting the large surface area of this portion of the gastrointestinal tract. Lipid solubility is necessary to facilitate drug absorption across epithelial cells lining the gastrointestinal tract. Changes in gastrointestinal *p*H that favor the lipid-soluble nonionized fraction of drug thus favor systemic absorption. Drugs, such as aspirin, which are weak acids, become more highly ionized in the alkaline environment of the small intestine, but absorption is still great because of the large surface area. Furthermore, absorption also occurs in the stomach, where gastric fluid *p*H is low.

FIRST-PASS HEPATIC EFFECT. Drugs absorbed from the gastrointestinal tract enter the portal venous blood and thus pass through the liver before entering the systemic circulation for delivery to tissue receptors (Fig. 1-3). This is known as the *first-pass hepatic effect,* and, for drugs that undergo extensive hepatic extraction and metabolism (*e.g.,* propranolol, lidocaine), this is the reason for large differences between effective oral and intravenous doses (Routledge and Shand, 1979).

Sublingual Administration

The sublingual route of administration permits rapid onset of drug effect by virtue of bypassing

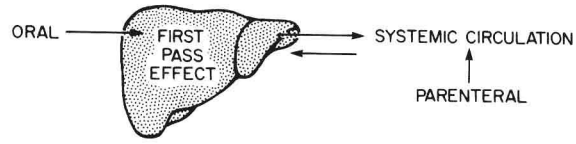

FIGURE 1-3. Drugs administered orally are absorbed from the gastrointestinal tract into the portal venous blood and pass through the liver (*e.g.,* first-pass hepatic effect) before entering the systemic circulation for distribution to receptors. Conversely, intravenously administered drugs gain rapid access to the systemic circulation without an initial impact of metabolism in the liver.

the liver and thus preventing the first-pass hepatic effect on the initial plasma concentration of drug. For example, venous drainage from the sublingual area is into the superior vena cava. Evidence of the value of bypassing the first-pass hepatic effect is the efficacy of sublingual nitroglycerin. Conversely, oral administration of nitroglycerin is ineffective because extensive first-pass hepatic metabolism prevents achievement of a therapeutic plasma concentration. Buccal administration is an alternative to sublingual placement of drug, being better tolerated and less likely to stimulate salivation. Salivation speeds solution of a tablet so that it is more easily swallowed and rendered less active (Bell *et al,* 1985).

Drugs administered rectally also bypass the liver and enter directly into the systemic circulation. Nevertheless, rectal absorption is often unpredictable, and irritation of the rectal mucosa may occur.

Transdermal Administration

Transdermal administration of drugs provides sustained therapeutic plasma concentrations of the drug with a low total dosage that results in minimal associated drug-induced side effects (Shaw and Chandrasekaran, 1978; Shaw and Urquhart, 1980). This route of administration is devoid of the complexity of continuous intravenous infusion techniques, and the low incidence of side effects owing to the minimal total dose administered contributes to high patient compliance and acceptance. Characteristics of drugs that favor predictable transdermal absorption include (1) combined water and lipid solubility, (2) molecular weight less than 1000, and (3) *p*H 5 to 9 in a saturated aqueous solution. Scopolamine, clonidine, and nitroglycerin are examples of drugs that undergo predictable transdermal absorption (see Chapters 10, 15, and 16).

The rate-limiting step in transdermal absorption of drugs is diffusion across the stratum corneum of the epidermis. Significant differences in the thickness and chemistry of the stratum corneum are reflected in the skin's permeability. For example, skin may be 10 to 20 μm thick on the back and abdomen compared with 400 to 600 μm on the palmar surfaces on the hands. Likewise, skin permeation studies have shown substantial regional differences for systemic absorption of scopolamine (Shaw and Chandrasekaran, 1978). The postauricular zone, because of its thin epidermal layer and somewhat higher temperature, is the only area that is sufficiently permeable for predictable and sustained absorption of scopolamine. Systemic absorption is least when scopolamine is applied to the thigh and intermediate when applied to the back or chest.

It is likely that transdermal absorption of drug initially occurs along sweat ducts and hair follicles (*i.e.,* diffusion shunts). Following saturation of skin binding sites with drug, diffusion through the stratum corneum becomes the dominant pathway for absorption. The stratum corneum sloughs and regenerates at a rate such that 7 days of adhesion appears to be the duration limit for one application of a transdermal system. There is no evidence for active transport of drugs across the skin.

Parenteral Administration

Parenteral administration may be required to ensure absorption of the active form of the drug. Systemic absorption after parenteral injection is usually more rapid and more predictable than after oral administration. The effective administered dose can be more precisely determined when absorption is predictable. Parenteral administration is the only acceptable route of drug administration in an unconscious or otherwise uncooperative patient.

Systemic absorption from subcutaneous and intramuscular injection sites occurs by simple diffusion along the concentration gradient from the site of drug deposition to plasma. Rate of systemic absorption is limited by the area of the absorbing capillary membranes and by solubility of the drug in interstitial fluid. Large aqueous channels in vascular endothelium account for the unimpeded diffusion of drug molecules, regardless of their lipid solubility (see Chapter 39).

Intravenous administration avoids those factors that limit systemic absorption by other routes. As a result, the desired concentration of drug in the blood can be more rapidly and precisely acheived by this route of administration. Irritant drugs are more comfortably administered by this route because blood vessel walls are relatively insensitive and the injected drug is rapidly diluted in the blood.