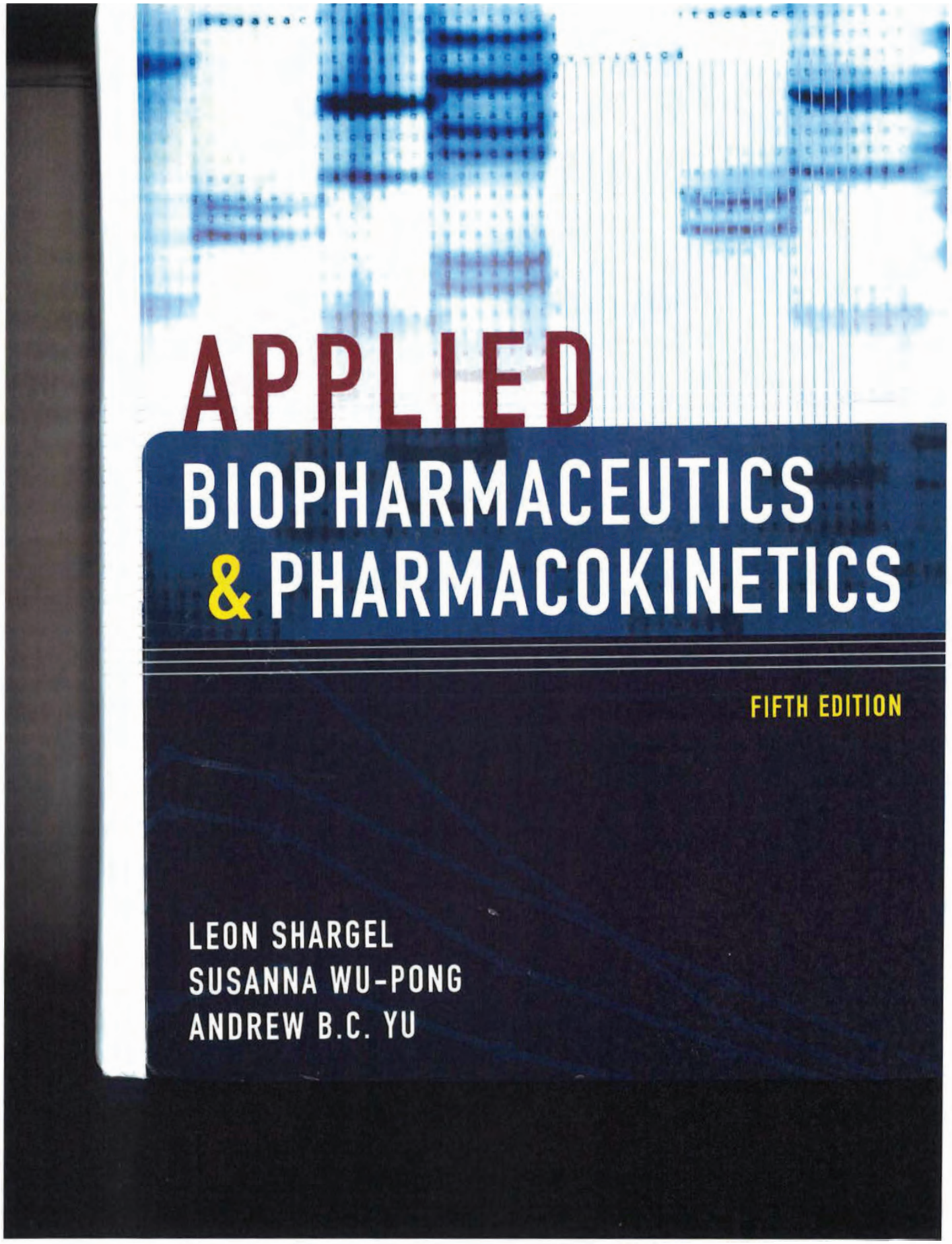


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1

INTRODUCTION TO BIOPHARMACEUTICS AND PHARMACOKINETICS

BIOPHARMACEUTICS

All pharmaceuticals, from the generic analgesic tablet in the community pharmacy to the state-of-the-art immunotherapy in specialized hospitals, undergo extensive research and development prior to approval by the U.S. Food and Drug Administration (FDA). The physicochemical characteristics of the active pharmaceutical ingredient (API, or drug substance), the dosage form or the drug, and the route of administration are critical determinants of the *in-vivo* performance, safety and efficacy of the drug product. The properties of the drug and its dosage form are carefully engineered and tested to produce a stable drug product that upon administration provides the desired therapeutic response in the patient. Both the pharmacist and the pharmaceutical scientist must understand these complex relationships to comprehend the proper use and development of pharmaceuticals.

To illustrate the importance of the drug substance and the drug formulation on absorption, and distribution of the drug to the site of action, one must first consider the sequence of events that precede elicitation of a drug's therapeutic effect. First, the drug in its dosage form is taken by the patient either by an oral, intravenous, subcutaneous, transdermal, etc., route of administration. Next, the drug is released from the dosage form in a predictable and characterizable manner. Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue, into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. If the drug concentration at the site of action exceeds the *minimum effective concentration* (MEC), a pharmacologic response results. The actual dosing regimen (dose, dosage form, dosing interval) was carefully determined in clinical trials to provide the correct drug concentrations at

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the site of action. This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form, the drug itself, or both.

Historically, pharmaceutical scientists have evaluated the relative drug availability to the body *in vivo* after giving a drug product to an animal or human, and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. In addition, the *bioavailability* (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products. In other words, the nature of the drug molecule, the route of delivery, and the formulation of the dosage form can determine whether an administered drug is therapeutically effective, toxic, or has no apparent effect at all.

Biopharmaceutics is the science that examines this interrelationship of the physicochemical properties of the drug, the dosage form in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. Thus, biopharmaceutics involves factors that influence (1) the stability of the drug within the drug product, (2) the release of the drug from the drug product, (3) the rate of dissolution/release of the drug at the absorption site, and (4) the systemic absorption of the drug. A general scheme describing this dynamic relationship is described in Figure 1-1.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. Studies in biopharmaceutics use both *in-vitro* and *in-vivo* methods. *In-vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. *In-vivo* methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 14. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability, and large-scale production of the drug and drug product on the biologic performance of the drug. Moreover, biopharmaceutics considers the properties of the drug and dosage form in a physiologic environment, the drug's intended therapeutic use, and the route of administration.

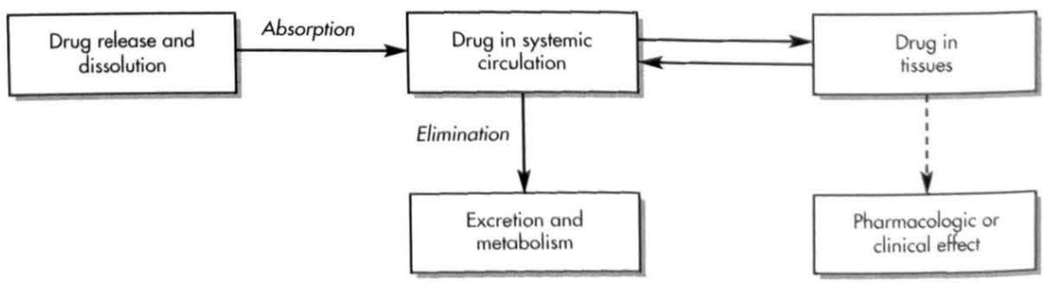


Figure 1-1. Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

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PHARMACOKINETICS

After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both. The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics. *Pharmacokinetics* is the science of the kinetics of drug absorption, distribution, and elimination (ie, excretion and metabolism). The description of drug distribution and elimination is often termed *drug disposition*. Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.

The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biologic sampling techniques, analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation ultimately for the purpose of designing and predicting optimal dosing regimens for individuals or groups of patients. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

CLINICAL PHARMACOKINETICS

During the drug development process, large numbers of patients are tested to determine optimum dosing regimens, which are then recommended by the manufacturer to produce the desired pharmacologic response in the majority of the anticipated patient population. However, intra- and interindividual variations will frequently result in either a subtherapeutic (drug concentration below the MEC) or toxic response (drug concentrations above the *minimum toxic concentration,* MTC), which may then require adjustment to the dosing regimen. *Clinical pharmacokinetics* is the application of pharmacokinetic methods to drug therapy. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.

The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 1.1 is a list of 10 age-adjusted rates of death from 10 leading causes of death in the United States, 2003. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy. The study of pharmacokinetic differences of drugs in various population groups is termed *population pharmacokinetics* (Sheiner and Ludden, 1992).

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TABLE 1.1 Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death in the USA, 2003

DISEASE	RANK	MALE:FEMALE
Disease of heart	1	1.5
Malignant neoplasms	2	1.5
Cerebrovascular diseases	3	4.0
Chronic lower respiration diseases	4	1.4
Accidents and others*	5	2.2
Diabetes mellitus	6	1.2
Pneumonia and influenza	7	1.4
Alzheimers	8	0.8
Nephrotis, nephrotic syndrome and nephrosis	9	1.5
Septicemia	10	1.2

*Death due to adverse effects suffered as defined by CDC.

Source: National Vital Statistics Report Vol 52, No. 3, 2003

Pharmacokinetics is also applied to *therapeutic drug monitoring* (TDM) for very potent drugs such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity. For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (eg, theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (eg, warfarin). Pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the *clinical pharmacokinetic service* (CPKS). Some drugs frequently monitored are the aminoglycosides and anticonvulsants. Other drugs closely monitored are those used in cancer chemotherapy, in order to minimize adverse side effects (Rodman and Evans, 1991).

PHARMACODYNAMICS

Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response. Pharmacokinetic-pharmacodynamic models are constructed to relate plasma drug level to drug concentration in the site of action and establish the intensity and time course of the drug. Pharmacodynamics and pharmacokinetic-pharmacodynamic models are discussed more fully in Chapter 19.

TOXICOKINETICS AND CLINICAL TOXICOLOGY

Toxicokinetics is the application of pharmacokinetic principles to the design, conduct, and interpretation of drug safety evaluation studies (Leal et al, 1993) and in validating dose-related exposure in animals. Toxicokinetic data aids in the interpretation of toxicologic findings in animals and extrapolation of the resulting

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data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.

Clinical toxicology is the study of adverse effects of drugs and toxic substances (poisons) in the body. The pharmacokinetics of a drug in an overmedicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in lower therapeutic doses. At very high doses, the drug concentration in the body may saturate enzymes involved in the absorption, biotransformation, or active renal secretion mechanisms, thereby changing the pharmacokinetics from linear to nonlinear pharmacokinetics. Nonlinear pharmacokinetics is discussed in Chapter 9. Drugs frequently involved in toxicity cases include acetaminophen, salicylates, morphine, and the tricylic antidepressants (TCAs). Many of these drugs can be assayed conveniently by fluorescence immunoassay (FIA) kits.

MEASUREMENT OF DRUG CONCENTRATIONS

Because drug concentrations are an important element in determining individual or population pharmacokinetics, drug concentrations are measured in biologic samples, such as milk, saliva, plasma, and urine. Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic matrices. Such measurements are generally validated so that accurate information is generated for pharmacokinetic and clinical monitoring. In general, chromatographic methods are most frequently employed for drug concentration measurement, because chromatography separates the drug from other related materials that may cause assay interference.

Sampling of Biologic Specimens

Only a few biologic specimens may be obtained safely from the patient to gain information as to the drug concentration in the body. *Invasive methods* include sampling blood, spinal fluid, synovial fluid, tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient. In contrast, *noninvasive methods* include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention. The measurement of drug and metabolite concentration in each of these biologic materials yields important information, such as the amount of drug retained in, or transported into, that region of the tissue or fluid, the likely pharmacologic or toxicologic outcome of drug dosing, and drug metabolite formation or transport.

Drug Concentrations in Blood, Plasma, or Serum

Measurement of drug concentration (levels) in the blood, serum, or plasma is the most direct approach to assessing the pharmacokinetics of the drug in the body. Whole blood contains cellular elements including red blood cells, white blood cells, platelets, and various other proteins, such as albumin and globulins. In general, serum or plasma is most commonly used for drug measurement. To obtain serum, whole blood is allowed to clot and the serum is collected from the

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supernatant after centrifugation. Plasma is obtained from the supernatant of centrifuged whole blood to which an anticoagulant, such as heparin, has been added. Therefore, the protein content of serum and plasma is not the same. Plasma perfuses all the tissues of the body, including the cellular elements in the blood. Assuming that a drug in the plasma is in dynamic equilibrium with the tissues, then changes in the drug concentration in plasma will reflect changes in tissue drug concentrations.

Plasma Level–Time Curve

The plasma level–time curve is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered. The concentration of drug in each plasma sample is plotted on rectangular-coordinate graph paper against the corresponding time at which the plasma sample was removed. As the drug reaches the general (systemic) circulation, plasma drug concentrations will rise up to a maximum. Usually, absorption of a drug is more rapid than elimination. As the drug is being absorbed into the systemic circulation, the drug is distributed to all the tissues in the body and is also *simultaneously* being eliminated. Elimination of a drug can proceed by excretion, biotransformation, or a combination of both.

The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in Figure 1-2. MEC and MTC represent the *minimum effective concentration* and *minimum toxic concentration* of drug, respectively. For some drugs, such as those acting on the autonomic nervous system, it is useful to know the concentration of drug that will just barely produce a pharmacologic effect (ie, MEC). Assuming the drug concentration in the plasma is in equilibrium with the tissues, the MEC reflects the minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect. Similarly, the MTC represents the drug concentration needed to just barely produce a toxic effect. The *onset time* corresponds to the time required for the drug to reach the MEC. The

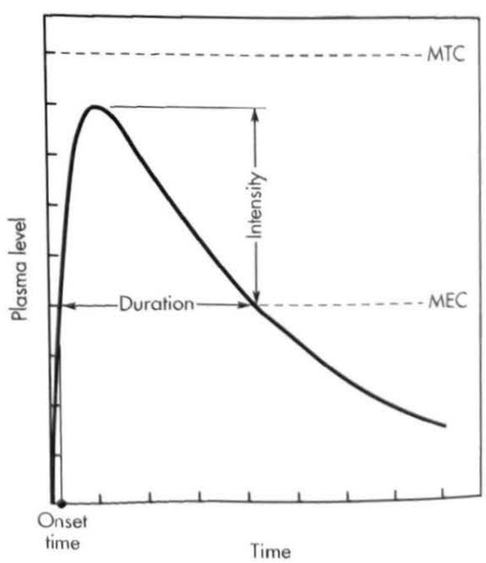


Figure 1-2. Generalized plasma level–time curve after oral administration of a drug.

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intensity of the pharmacologic effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response, up to a maximum. The *duration of drug action* is the difference between the onset time and the time for the drug to decline back to the MEC.

In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as *peak plasma level, time for peak plasma level,* and *area under the curve,* or AUC (Fig. 1-3). The time of peak plasma level is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption. The peak plasma level or maximum drug concentration is related to the dose, the rate constant for absorption, and the elimination constant of the drug. The AUC is related to the amount of drug absorbed systemically. These and other pharmacokinetic parameters are discussed in succeeding chapters.

Drug Concentrations in Tissues

Tissue biopsies are occasionally removed for diagnostic purposes, such as the verification of a malignancy. Usually, only a small sample of tissue is removed, making drug concentration measurement difficult. Drug concentrations in tissue biopsies may not reflect drug concentration in other tissues nor the drug concentration in all parts of the tissue from which the biopsy material was removed. For example, if the tissue biopsy was for the diagnosis of a tumor within the tissue, the blood flow to the tumor cells may not be the same as the blood flow to other cells in this tissue. In fact, for many tissues, blood flow to one part of the tissues need not be the same as the blood flow to another part of the same tissue. The measurement of the drug concentration in tissue biopsy material may be used to ascertain if the drug reached the tissues and reached the proper concentration within the tissue.

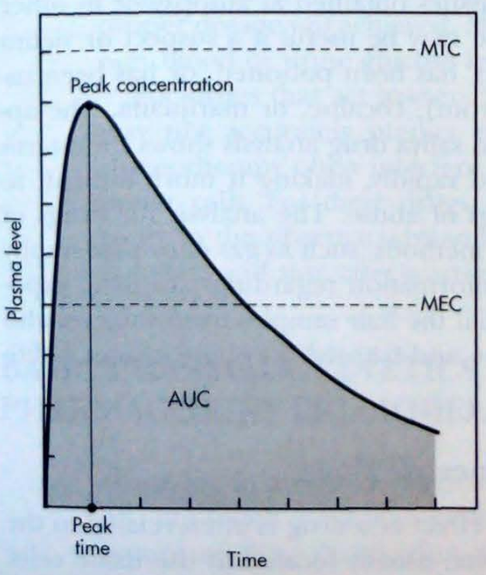


Figure 1-3. Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

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Drug Concentrations in Urine and Feces

Measurement of drug in urine is an indirect method to ascertain the bioavailability of a drug. The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption. The use of urinary drug excretion measurements to establish various pharmacokinetic parameters is discussed in Chapter 15.

Measurement of drug in feces may reflect drug that has not been absorbed after an oral dose or may reflect drug that has been expelled by biliary secretion after systemic absorption. Fecal drug excretion is often performed in mass balance studies, in which the investigator attempts to account for the entire dose given to the patient. For a mass balance study, both urine and feces are collected and their drug content measured. For certain solid oral dosage forms that do not dissolve in the gastrointestinal tract but slowly leach out drug, fecal collection is performed to recover the dosage form. The undissolved dosage form is then assayed for residual drug.

Drug Concentrations in Saliva

Saliva drug concentrations have been reviewed for many drugs for therapeutic drug monitoring (Pippenger and Massoud, 1984). Because only free drug diffuses into the saliva, saliva drug levels tend to approximate free drug rather than total plasma drug concentration. The saliva/plasma drug concentration ratio is less than 1 for many drugs. The saliva/plasma drug concentration ratio is mostly influenced by the pKa of the drug and the pH of the saliva. Weak acid drugs and weak base drugs with pKa significantly different than pH 7.4 (plasma pH) generally have better correlation to plasma drug levels. The saliva drug concentrations taken after equilibrium with the plasma drug concentration generally provide more stable indication of drug levels in the body. The use of salivary drug concentrations as a therapeutic indicator should be used with caution and preferably as a secondary indicator.

Forensic Drug Measurements

Forensic science is the application of science to personal injury, murder, and other legal proceedings. Drug measurements in tissues obtained at autopsy or in other bodily fluids such as saliva, urine, and blood may be useful if a suspect or victim has taken an overdose of a legal medication, has been poisoned, or has been using drugs of abuse such as opiates (eg, heroin), cocaine, or marijuana. The appearance of social drugs in blood, urine, and saliva drug analysis shows short-term drug abuse. These drugs may be eliminated rapidly, making it more difficult to prove that the subject has been using drugs of abuse. The analysis for drugs of abuse in hair samples by very sensitive assay methods, such as gas chromatography coupled with mass spectrometry, provides information regarding past drug exposure. A study by Cone et al (1993) showed that the hair samples from subjects who were known drug abusers contained cocaine and 6-acetylmorphine, a metabolite of heroine (diacetylmorphine).

Significance of Measuring Plasma Drug Concentrations

The intensity of the pharmacologic or toxic effect of a drug is often related to the concentration of the drug at the receptor site, usually located in the tissue cells.

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Because most of the tissue cells are richly perfused with tissue fluids or plasma, measuring the plasma drug level is a responsive method of monitoring the course of therapy.

Clinically, individual variations in the pharmacokinetics of drugs are quite common. Monitoring the concentration of drugs in the blood or plasma ascertains that the calculated dose actually delivers the plasma level required for therapeutic effect. With some drugs, receptor expression and/or sensitivity in individuals varies, so monitoring of plasma levels is needed to distinguish the patient who is receiving too much of a drug from the patient who is supersensitive to the drug. Moreover, the patient's physiologic functions may be affected by disease, nutrition, environment, concurrent drug therapy, and other factors. Pharmacokinetic models allow more accurate interpretation of the relationship between plasma drug levels and pharmacologic response.

In the absence of pharmacokinetic information, plasma drug levels are relatively useless for dosage adjustment. For example, suppose a single blood sample from a patient was assayed and found to contain 10 mg/mL. According to the literature, the maximum safe concentration of this drug is 15 mg/mL. In order to apply this information properly, it is important to know when the blood sample was drawn, what dose of the drug was given, and the route of administration. If the proper information is available, the use of pharmacokinetic equations and models may describe the blood level–time curve accurately.

Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order to individualize and optimize therapeutic drug regimens. In the presence of alteration in physiologic functions due to disease, monitoring plasma drug concentrations may provide a guide to the progress of the disease state and enable the investigator to modify the drug dosage accordingly. Clinically, sound medical judgment and observation are most important. Therapeutic decisions should not be based solely on plasma drug concentrations.

In many cases, the *pharmacodynamic response* to the drug may be more important to measure than just the plasma drug concentration. For example, the electrophysiology of the heart, including an electrocardiogram (ECG), is important to assess in patients medicated with cardiotonic drugs such as digoxin. For an anticoagulant drug, such as dicumarol, prothrombin clotting time may indicate whether proper dosage was achieved. Most diabetic patients taking insulin will monitor their own blood or urine glucose levels.

For drugs that act irreversibly at the receptor site, plasma drug concentrations may not accurately predict pharmacodynamic response. Drugs used in cancer chemotherapy often interfere with nucleic acid or protein biosynthesis to destroy tumor cells. For these drugs, the plasma drug concentration does not relate directly to the pharmacodynamic response. In this case, other pathophysiologic parameters and side effects are monitored in the patient to prevent adverse toxicity.

BASIC PHARMACOKINETICS AND PHARMACOKINETIC MODELS

Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often

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happen simultaneously. Yet such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events require the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

A *model* is a hypothesis using mathematical terms to describe quantitative relationships concisely. The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process. The key parameters in a process are commonly estimated by fitting the model to the experimental data, known as *variables*. A *pharmacokinetic parameter* is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as k depend on the method of tissue sampling, the timing of the sample, drug analysis, and the predictive model selected.

A pharmacokinetic function relates an *independent variable* to a *dependent variable*, often through the use of parameters. For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time. In this case, the drug concentration depends on the time after the administration of the dose, where the time:concentration relationship is defined by a pharmacokinetic parameter, k, the elimination rate constant.

Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination to describe and *predict* drug concentrations in the body as a function of time. Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions

Simplifying assumptions are made in pharmacokinetic models to describe a complex biologic system concerning the movement of drugs within the body. For example, most pharmacokinetic models assume that the plasma drug concentration reflects drug concentrations globally within the body.

A model may be empirically, physiologically, or compartmentally based. The model that simply interpolates the data and allows an empirical formula to estimate drug level over time is justified when limited information is available. *Empirical models* are practical but not very useful in explaining the mechanism of the actual process by which the drug is absorbed, distributed, and eliminated in the body. Examples of empirical models used in pharmacokinetics are described in Chapter 22.

Physiologically based models also have limitations. Using the example above, and apart from the necessity to sample tissue and monitor blood flow to the liver *in vivo*, the investigator needs to understand the following questions. What does liver

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drug concentration mean? Should the drug concentration in the blood within the tissue be determined and subtracted from the drug in the liver tissue? What type of cell is representative of the liver if a selective biopsy liver tissue sample can be collected without contamination from its surroundings? Indeed, depending on the spatial location of the liver tissue from the hepatic blood vessels, tissue drug concentrations can differ depending on distance to the blood vessel or even on the type of cell in the liver. Moreover, changes in the liver blood perfusion will alter the tissue drug concentration. If heterogeneous liver tissue is homogenized and assayed, the homogenized tissue represents only a hypothetical concentration that is an *average* of all the cells and blood in the liver at the time of collection. Since tissue homogenization is not practical for human subjects, the drug concentration in the liver may be estimated by knowing the liver extraction ratio for the drug based on knowledge of the physiologic and biochemical composition of the body organs.

A great number of models have been developed to estimate regional and global information about drug disposition in the body. Some physiologic pharmacokinetic models are also discussed in Chapter 22. Individual pharmacokinetic processes are discussed in separate chapters under the topics of drug absorption, drug distribution, drug elimination, and pharmacokinetic drug interactions involving one or all the above processes. Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered. Practical considerations have limited the growth of new pharmacokinetic models.

A very simple and useful tool in pharmacokinetics is *compartmentally based models*. For example, assume a drug is given by intravenous injection and that the drug dissolves (distributes) rapidly in the body fluids. One pharmacokinetic model that can describe this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug. The concentration of the drug in the tank after a given dose is governed by two parameters: (1) the fluid volume of the tank that will dilute the drug, and (2) the elimination rate of drug per unit of time. Though this model is perhaps an overly simplistic view of drug disposition in the human body, a drug's pharmacokinetic properties can frequently be described using a fluid-filled tank model called the *one-compartment open model* (see below). In both the tank and the one-compartment body model, a fraction of the drug would be continually eliminated as a function of time (Fig. 1-4). In pharmacokinetics, these parameters are assumed to be constant for a given drug. If drug concentrations in the tank are determined at various time intervals following administration of a known dose, then the volume of fluid in the tank or compartment (V_D, volume of distribution) and the rate of drug elimination can be estimated.

In practice, pharmacokinetic parameters such as k and V_D are determined experimentally from a set of drug concentrations collected over various times and known as *data*. The number of parameters needed to describe the model depends on the complexity of the process and on the route of drug administration. In

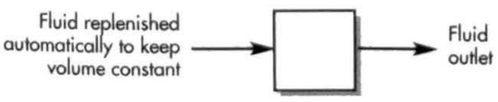


Figure 1-4. Tank with a constant volume of fluid equilibrated with drug. The volume of the fluid is 1.0 L. The fluid outlet is 10 mL/min. The fraction of drug removed per unit of time is 10/1000, or 0.01 min^{-1}.

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general, as the number of parameters required to model the data increases, accurate estimation of these parameters becomes increasingly more difficult. With complex pharmacokinetic models, computer programs are used to facilitate parameter estimation. However, for the parameters to be valid, the number of data points should always exceed the number of parameters in the model.

Because a model is based on a hypothesis and simplifying assumptions, a certain degree of caution is necessary when relying totally on the pharmacokinetic model to predict drug action. For some drugs, plasma drug concentrations are not useful in predicting drug activity. For other drugs, an individual's genetic differences, disease state, and the compensatory response of the body may modify the response of a drug. If a simple model does not fit all the experimental observations accurately, a new, more elaborate model may be proposed and subsequently tested. Since limited data are generally available in most clinical situations, pharmacokinetic data should be interpreted along with clinical observations rather than replacing sound judgment by the clinician. Development of pharmacometric statistical models may help to improve prediction of drug levels among patients in the population (Sheiner and Beal, 1982; Mallet et al, 1988). However, it will be some time before these methods become generally accepted.

Compartment Models

If the tissue drug concentrations and binding are known, physiologic pharmacokinetic models, which are based on actual tissues and their respective blood flow, describe the data realistically. Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay. On the other hand, tissue samples are often not available for human subjects, so most physiological models assume an average set of blood flow for individual subjects.

In contrast, because of the vast complexity of the body, drug kinetics in the body are frequently simplified to be represented by one or more tanks, or compartments, that communicate reversibly with each other. A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity. Within each compartment, the drug is considered to be uniformly distributed. Mixing of the drug within a compartment is rapid and homogeneous and is considered to be "well stirred," so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment. Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment. The model is an *open system* because drug can be eliminated from the system. Compartment models are based on linear assumptions using linear differential equations.

Mammillary Model

A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment. The *mammillary model* is the most common compartment model used in pharmacokinetics. The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug

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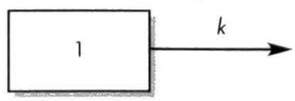
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is introduced into a given compartment. In the one-compartment model, drug is both added to and eliminated from a central compartment. The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with drug. When an intravenous dose of drug is given, the drug enters directly into the central compartment. Elimination of drug occurs from the central compartment because the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

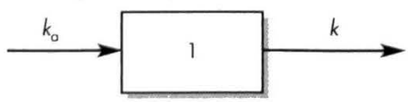
In a two-compartment model, drug can move between the central or plasma compartment to and from the tissue compartment. Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues. In this model, the total amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment. Knowing the parameters of either the one- or two-compartment model, one can estimate the amount of drug left in the body and the amount of drug eliminated from the body at any time. The compartmental models are particularly useful when little information is known about the tissues.

Several types of compartment models are described in Figure 1-5. The pharmacokinetic rate constants are represented by the letter k. Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue compartment. The drawing of models has three functions. The model (1) enables the pharmacokineticist to write differential equations to describe drug concentration changes in each compartment, (2) gives a visual representation of the rate processes, and (3) shows how many pharmacokinetic constants are necessary to describe the process adequately.

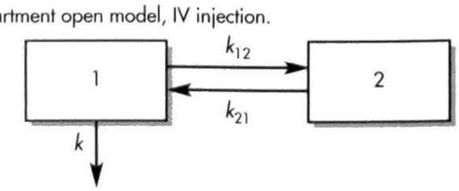
MODEL 1. One-compartment open model, IV injection.



MODEL 2. One-compartment open model with first-order absorption.



MODEL 3. Two-compartment open model, IV injection.



MODEL 4. Two-compartment open model with first-order absorption.

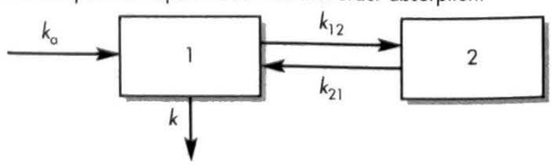


Figure 1-5. Various compartment models.

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EXAMPLE

Two parameters are needed to describe model 1 (Fig. 1-5): the volume of the compartment and the elimination rate constant, k. In the case of model 4, the pharmacokinetic parameters consist of the volumes of compartments 1 and 2 and the rate constants—k_a, k, k_{12}, and k_{21}—for a total of six parameters.

In studying these models, it is important to know whether drug concentration data may be sampled directly from each compartment. For models 3 and 4 (Fig. 1-5), data concerning compartment 2 cannot be obtained easily because tissues are not easily sampled and may not contain homogeneous concentrations of drug. If the amount of drug absorbed and eliminated per unit time is obtained by sampling compartment 1, then the amount of drug contained in the tissue compartment 2 can be estimated mathematically. The appropriate mathematical equations for describing these models and evaluating the various pharmacokinetic parameters are given in the succeeding chapters.

Catenary Model

In pharmacokinetics, the mammillary model must be distinguished from another type of compartmental model called the catenary model. The *catenary model* consists of compartments joined to one another like the compartments of a train (Fig. 1-6). In contrast, the mammillary model consists of one or more compartments around a central compartment like satellites. Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

Physiologic Pharmacokinetic Model (Flow Model)

Physiologic pharmacokinetic models, also known as blood flow or perfusion models, are pharmacokinetic models based on known anatomic and physiologic data. The models describe the data kinetically, with the consideration that blood flow is responsible for distributing drug to various parts of the body. Uptake of drug into organs is determined by the binding of drug in these tissues. In contrast to an estimated tissue volume of distribution, the actual tissue volume is used. Because there are many tissue organs in the body, each tissue volume must be obtained and its drug concentration described. The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do. Unfortunately, much of the information required for adequately describing a physiologic pharmacokinetic model are experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how

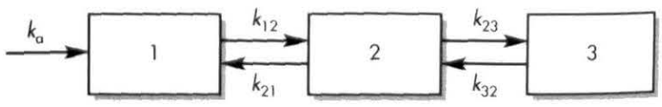


Figure 1-6. Example of caternary model.

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physiologic factors may change drug distribution from one animal species to another. Other major differences are described below.

First, no data fitting is required in the perfusion model. Drug concentrations in the various tissues are predicted by organ tissue size, blood flow, and experimentally determined drug tissue–blood ratios (ie, partition of drug between tissue and blood).

Second, blood flow, tissue size, and the drug tissue–blood ratios may vary due to certain pathophysiologic conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models.

Third, and most important of all, physiologically based pharmacokinetic models can be applied to several species, and, for some drugs, human data may be extrapolated. Extrapolation from animal data is not possible with the compartment models, because the volume of distribution in such models is a mathematical concept that does not relate simply to blood volume and blood flow. To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models. Tissue levels of some of these drugs cannot be predicted successfully with compartment models, although they generally describe blood levels well. An example of a perfusion model is shown in Figure 1-7.

The number of tissue compartments in a perfusion model varies with the drug. Typically, the tissues or organs that have no drug penetration are excluded from consideration. Thus, such organs as the brain, the bones, and other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs. To describe each organ separately with a differential equation would make the model very complex and mathematically difficult. A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single compartment.

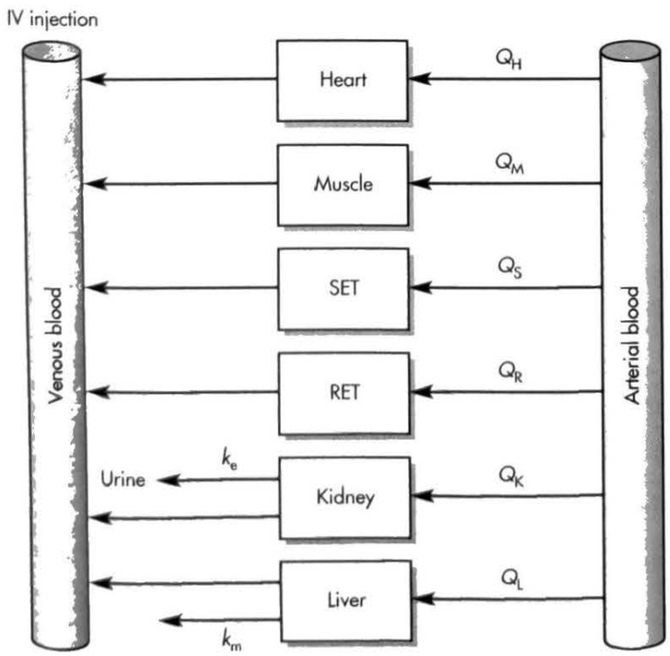


Figure 1-7. Pharmacokinetic model of drug perfusion. The *k*'s represent kinetic constants: k_e is the first-order rate constant for urinary drug excretion and k_m is the rate constant for hepatic elimination. Each "box" represents a tissue compartment. Organs of major importance in drug absorption are considered separately, while other tissues are grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue). The size or mass of each tissue compartment is determined physiologically rather than by mathematical estimation. The concentration of drug in the tissue is determined by the ability of the tissue to accumulate drug as well as by the rate of blood perfusion to the tissue, represented by *Q*.

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A perfusion model has been used successfully to describe the distribution of lidocaine in blood and various organs. In this case, organs such as lung, liver, brain, and muscle were individually described by differential equations, whereas other tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue), as shown in Figure 1-7. Figure 1-8 shows that the blood concentration of lidocaine declines biexponentially and was well predicted by the physiologic model based on blood flow. The tissue lidocaine level in the lung, muscle, and adipose and other organs is shown in Figure 1-9. The model shows that adipose tissue accumulates drugs slowly because of low blood supply. In contrast, vascular tissues, like the lung, equilibrate rapidly with the blood and start to decline as soon as drug level in the blood starts to fall. The physiologic pharmacokinetic model provides a realistic means of modeling tissue drug levels. Unfortunately, the simulated tissues levels in Figure 1-9 cannot be verified in humans because drug levels in tissues are not available. A criticism of physiologic pharmacokinetic models in general has been that there are fewer data points than parameters that one tries to fit. Consequently, the projected data are not well *constrained.*

The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data (Sawada et al, 1985). The mass of various body organs or tissues, extent of protein binding, drug metabolism capacity, and blood flow in humans and other species are often known or can be determined. Thus, physiologic and anatomic parameters can be used to predict the effects of drugs on humans from the effects on animals in cases where human experimentation is difficult or restricted.

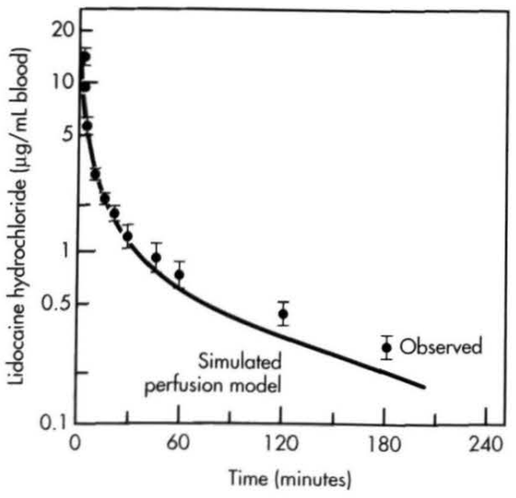


Figure 1-8. Observed mean (●) and simulated (—) arterial lidocaine blood concentrations in normal volunteers receiving 1 mg/kg per min constant infusion for 3 minutes.
(From Benowitz et al 1974, with permission; data from Tucker GT, Boas RA: *Anesthesiology* **34:**538, 1971.)

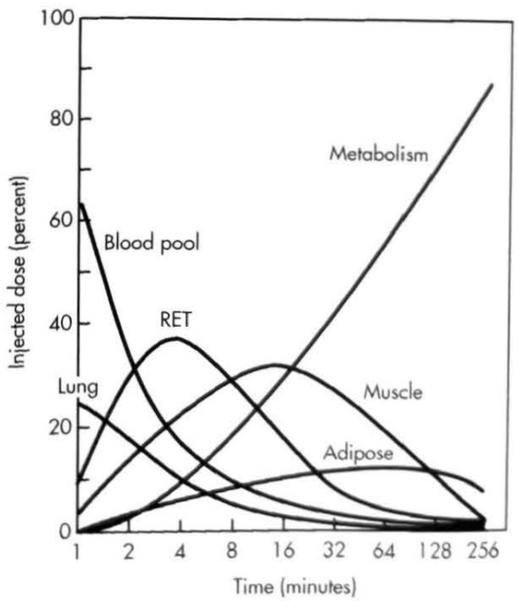


Figure 1-9. Perfusion model simulation of the distribution of lidocaine in various tissues and its elimination from humans following an intravenous infusion for 1 minute.
(From Benowitz et al 1974, with permission.)

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FREQUENTLY ASKED QUESTIONS

1. Why is plasma or serum drug concentration, rather than blood concentration, used to monitor drug concentration in the body?
2. What are reasons to use a multicompartment model instead of a physiologic model?
3. At what time should plasma drug concentration be taken in order to best predict drug response and side effects?



LEARNING QUESTIONS

1. What is the significance of the plasma level–time curve? How does the curve relate to the pharmacologic activity of a drug?
2. What is the purpose of pharmacokinetic models?
3. Draw a diagram describing a three-compartment model with first-order absorption and drug elimination from compartment 1.
4. The pharmacokinetic model presented in Figure 1-10 represents a drug that is eliminated by renal excretion, biliary excretion, and drug metabolism. The metabolite distribution is described by a one-compartment open model. The following questions pertain to Figure 1-10.
   a. How many parameters are needed to describe the model if the drug is injected intravenously (ie, the rate of drug absorption may be neglected)?
   b. Which compartment(s) can be sampled?
   c. What would be the overall elimination rate constant for elimination of drug from compartment 1?
   d. Write an expression describing the rate of change of drug concentration in compartment 1 (dC_1/dt).

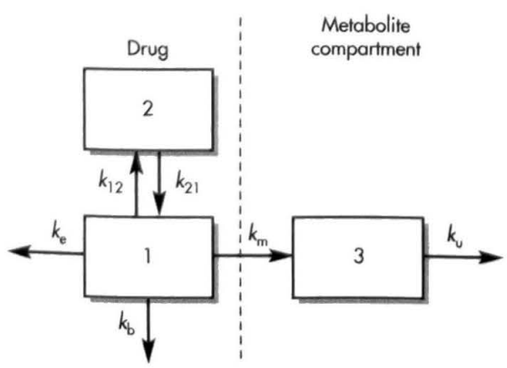


Figure 1-10. Pharmacokinetic model for a drug eliminated by renal and biliary excretion and drug metabolism. k_m = rate constant for metabolism of drug; k_u = rate constant for urinary excretion of metabolites; k_b = rate constant for biliary excretion of drug; and k_e = rate constant for urinary drug excretion.

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5. Give two reasons for the measurement of the plasma drug concentration, C_p assuming (a) the C_p relates directly to the pharmacodynamic activity of the drug and (b) the C_p does not relate to the pharmacodynamic activity of the drug.
6. Consider two biologic compartments separated by a biologic membrane. Drug A is found in compartment 1 and in compartment 2 in a concentration of c_1 and c_2, respectively.
   a. What possible conditions or situations would result in concentration $c_1 > c_2$ at equilibrium?
   b. How would you experimentally demonstrate these conditions given above?
   c. Under what conditions would $c_1 = c_2$ at equilibrium?
   d. The total amount of Drug A in each biologic compartment is A_1 and A_2, respectively. Describe a condition in which $A_1 > A_2$, but $c_1 = c_2$ at equilibrium.

Include in your discussion, how the physicochemical properties of Drug A or the biologic properties of each compartment might influence equilibrium conditions.

REFERENCES

Benowitz N, Forsyth R, Melmon K, Rowland M: Lidocaine disposition kinetics in monkey and man. *Clin Pharmacol Ther* **15:**87–98, 1974

Cone EJ, Darwin WD, Wang W-L: The occurrence of cocaine, heroin and metabolites in hair of drug abusers. *Forensic Sci Int* **63:**55–68, 1993

Leal M, Yacobi A, Batra VJ: Use of toxicokinetic principles in drug development: Bridging preclinical and clinical studies. In Yacobi A, Skelly JP, Shah VP, Benet LZ (eds), *Integration of Pharmacokinetics, Pharmacodynamics and Toxicokinetics in Rational Drug Development.* New York, Plenum Press, 1993, pp 55–67

Mallet A, Mentre F, Steimer JL, Lokiec F: Pharmacometrics: Nonparametric maximum likelihood estimation for population pharmacokinetics, with application to cyclosporine. *J Pharm Biopharm* **16:**311–327, 1988

Pippenger CE and Massoud N: Therapeutic drug monitoring. In Benet LZ, et al (eds). *Pharmacokinetic Basis for Drug Treatment.* New York, Raven, 1984, chap 21

Rodman JH and Evans WE: Targeted systemic exposure for pediatric cancer therapy. In D'Argenio DZ (ed), *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis.* New York, Plenum Press, 1991, pp 177–183

Sawada Y, Hanano M, Sugiyama Y, Iga T: Prediction of the disposition of nine weakly acidic and six weekly basic drugs in humans from pharmacokinetic parameters in rats. *J Pharmacokinet Biopharm* **13:**477–492, 1985

Sheiner LB and Beal SL: Bayesian individualization of pharmacokinetics. Simple implementation and comparison with nonBayesian methods. *J Pharm Sci* **71:**1344–1348, 1982

Sheiner LB and Ludden TM: Population pharmacokinetics/dynamics. *Annu Rev Pharmacol Toxicol* **32:**185–201, 1992

BIBLIOGRAPHY

Benet LZ: General treatment of linear mammillary models with elimination from any compartment as used in pharmacokinetics. *J Pharm Sci* **61:**536–541, 1972

Bischoff K and Brown R: Drug distribution in mammals. *Chem Eng Med* **62:**33–45, 1966

Bischoff K, Dedrick R, Zaharko D, Longstreth T: Methotrexate pharmacokinetics. *J Pharm Sci* **60:**1128–1133, 1971

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Chiou W: Quantitation of hepatic and pulmonary first-pass effect and its implications in pharmacokinetic study, I: Pharmacokinetics of chloroform in man. *J Pharm Biopharm* **3:**193–201, 1975

Colburn WA: Controversy III: To model or not to model. *J Clin Pharmacol* **28:**879–888, 1988

Cowles A, Borgstedt H, Gilles A: Tissue weights and rates of blood flow in man for the prediction of anesthetic uptake and distribution. *Anesthesiology* **35:**523–526, 1971

Dedrick R, Forrester D, Cannon T, et al: Pharmacokinetics of 1-β-d-arabinofurinosulcytosine (ARA-C) deamination in several species. *Biochem Pharmacol* **22:**2405–2417, 1972

Gerlowski LE and Jain RK: Physiologically based pharmacokinetic modeling: Principles and applications. *J Pharm Sci* **72:**1103–1127, 1983

Gibaldi M: *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd ed. Philadelphia, Lea & Febiger, 1984

Gibaldi M: Estimation of the pharmacokinetic parameters of the two-compartment open model from post-infusion plasma concentration data. *J Pharm Sci* **58:**1133–1135, 1969

Himmelstein KJ and Lutz RJ: A review of the applications of physiologically based pharmacokinetic modeling. *J Pharm Biopharm* **7:**127–145, 1979

Lutz R and Dedrick RL: Physiologic pharmacokinetics: Relevance to human risk assessment. In Li AP (ed), *Toxicity Testing: New Applications and Applications in Human Risk Assessment.* New York, Raven, 1985, pp 129–149

Lutz R, Dedrick R, Straw J, et al: The kinetics of methotrexate distribution in spontaneous canine lymphosarcoma. *J Pharm Biopharm* **3:**77–97, 1975

Metzler CM: Estimation of pharmacokinetic parameters: Statistical considerations. *Pharmacol Ther* **13:**543–556, 1981

Montandon B, Roberts R, Fischer L: Computer simulation of sulfobromophthalein kinetics in the rat using flow-limited models with extrapolation to man. *J Pharm Biopharm* **3:**277–290, 1975

Rescigno A and Beck JS: The use and abuse of models. *J Pharm Biopharm* **15:**327–344, 1987

Ritschel WA and Banerjee PS: Physiologic pharmacokinetic models: Applications, limitations and outlook. *Meth Exp Clin Pharmacol* **8:**603–614, 1986

Rowland M, Thomson P, Guichard A, Melmon K: Disposition kinetics of lidocaine in normal subjects. *Ann N Y Acad Sci* **179:**383–398, 1971

Rowland M and Tozer T: *Clinical Pharmacokinetics—Concepts and Applications*, 3rd ed. Philadelphia, Lea & Febiger, 1995

Segre G: Pharmacokinetics: Compartmental representation. *Pharm Ther* **17:**111–127, 1982

Tozer TN: Pharmacokinetic principles relevant to bioavailability studies. In Blanchard J, Sawchuk RJ, Brodie BB (eds), *Principles and Perspectives in Drug Bioavailability.* New York, S Karger, 1979, pp 120–155

Wagner JG: Do you need a pharmacokinetic model, and, if so, which one? *J Pharm Biopharm* **3:**457–478, 1975

Welling P and Tse F: *Pharmacokinetics.* New York, Marcel Dekker, 1993

Winters ME: *Basic Clinical Pharmacokinetics*, 3rd ed. Vancouver, WA, Applied Therapeutics, 1994

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15

BIOAVAILABILITY AND BIOEQUIVALENCE

A *multisource drug product* is a drug product that contains the same active drug substance in the same dosage form and is marketed by more than one pharmaceutical manufacturer. *Single-source drug products* are drug products for which the patent has not yet expired or has certain exclusivities so that only one manufacturer can make it. Single-source drug products are usually brand-name (innovator) drug products. After the patent and other exclusivities for the brand-name drug expires, a pharmaceutical firm may manufacture a generic drug product that can be substituted for the branded drug product. Since the formulation and method of manufacture of the drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the brand-name drug product.

Drug product selection and generic drug product substitution are major responsibilities for physicians, pharmacists, and others who prescribe, dispense, or purchase drugs. To facilitate such decisions, the U.S. Food and Drug Administration (FDA) publishes annually, in print and on the Internet, *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the *Orange Book* (www.fda.gov/cder/ob/default.htm). The *Orange Book* identifies drug products approved on the basis of safety and effectiveness by the FDA and contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. The following definitions are from the *2003 Orange Book, Code of Federal Regulations*, 21 CFR 320, and other sources.

DEFINITIONS

- *Bioavailability.* Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at

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the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

- *Bioequivalence requirement.* A requirement imposed by the FDA for *in-vitro* and/or *in-vivo* testing of specified drug products, which must be satisfied as a condition for marketing.
- *Bioequivalent drug products.* This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. For systemically absorbed drugs, the test (generic) and reference listed drug (brand-name) shall be considered bioequivalent if: (1) the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (2) the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

  When the above methods are not applicable (eg, for drug products that are not intended to be absorbed into the bloodstream), other *in-vivo* or *in-vitro* test methods to demonstrate bioequivalence may be appropriate. Bioequivalence may sometimes be demonstrated using an *in-vitro* bioequivalence standard, especially when such an *in-vitro* test has been correlated with human *in-vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

  Bioequivalent drug products may contain different inactive ingredients, provided the manufacturer identifies the differences and provides information that the differences do not affect the safety or efficacy of the product.
- *Brand name.* The trade name of the drug. This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor's products (eg, Tylenol, McNeil Laboratories).
- *Chemical name.* The name used by organic chemists to indicate the chemical structure of the drug (eg, N-acetyl-*p*-aminophenol).
- *Abbreviated New Drug Application* (ANDA). Drug manufacturers must file an ANDA for approval to market a generic drug product. The generic manufacturer is not required to perform clinical efficacy studies or nonclinical toxicology studies for the ANDA.
- *Drug product.* The finished dosage form (eg, tablet, capsule, or solution) that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.
- *Drug product selection.* The process of choosing or selecting the drug product in a specified dosage form.

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- *Drug substance.* A drug substance is the active pharmaceutical ingredient (API) or component in the drug product that furnishes the pharmacodynamic activity.
- *Equivalence.* Relationship in terms of bioavailability, therapeutic response, or a set of established standards of one drug product to another.
- *Generic name.* The established, nonproprietary, or common name of the active drug in a drug product (eg, acetaminophen).
- *Generic substitution.* The process of dispensing a different brand or an unbranded drug product in place of the prescribed drug product. The substituted drug product contains the same active ingredient or therapeutic moiety as the same salt or ester in the same dosage form but is made by a different manufacturer. For example, a prescription for Motrin brand of ibuprofen might be dispensed by the pharmacist as Advil brand of ibuprofen or as a nonbranded generic ibuprofen if generic substitution is permitted and desired by the physician.
- *Pharmaceutical alternatives.* Drug products that contain the same therapeutic moiety but as different salts, esters, or complexes. For example, tetracycline phosphate or tetracycline hydrochloride equivalent to 250 mg tetracycline base are considered pharmaceutical alternatives. Different dosage forms and strengths within a product line by a single manufacturer are pharmaceutical alternatives (eg, an extended-release dosage form and a standard immediate-release dosage form of the same active ingredient). The FDA currently considers a tablet and capsule containing the same active ingredient in the same dosage strength as pharmaceutical alternatives.
- *Pharmaceutical equivalents.* Drug products in identical dosage forms that contain the same active ingredient(s), ie, the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration (eg, chlordiazepoxide hydrochloride, 5-mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (ie, strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling. When applicable, pharmaceutical equivalents must meet the same content uniformity, disintegration times, and/or dissolution rates. Modified-release dosage forms that require a reservoir or overage or certain dosage forms such as prefilled syringes in which residual volume may vary must deliver identical amounts of active drug ingredient over an identical dosing period.
- *Pharmaceutical substitution.* The process of dispensing a pharmaceutical alternative for the prescribed drug product. For example, ampicillin suspension is dispensed in place of ampicillin capsules, or tetracycline hydrochloride is dispensed in place of tetracycline phosphate. Pharmaceutical substitution generally requires the physician's approval.
- *Reference listed drug.* The reference listed drug (RLD) is identified by the FDA as the drug product on which an applicant relies when seeking approval of an Abbreviated New Drug Application (ANDA). The RLD is generally the brand-name drug that has a full New Drug Application (NDA). The FDA designates a

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single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent. The FDA hopes to avoid possible significant variations among generic drugs and their brand-name counterparts. Such variations could result if generic drugs were compared to different reference listed drugs.

- *Therapeutic alternatives.* Drug products containing different active ingredients that are indicated for the same therapeutic or clinical objectives. Active ingredients in therapeutic alternatives are from the same pharmacologic class and are expected to have the same therapeutic effect when administered to patients for such condition of use. For example, ibuprofen is given instead of aspirin; cimetidine may be given instead of ranitidine.
- *Therapeutic equivalents.* Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. The FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in-vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. The FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.
- *Therapeutic substitution.* The process of dispensing a therapeutic alternative in place of the prescribed drug product. For example, amoxicillin is dispensed instead of ampicillin or ibuprofen is dispensed instead of naproxen. Therapeutic substitution can also occur when one NDA-approved drug is substituted for the same drug which has been approved by a different NDA, eg, the substitution of Nicoderm (nicotine transdermal system) for Nicotrol (nicotine transdermal system).

PURPOSE OF BIOAVAILABILITY STUDIES

Bioavailability studies are performed for both approved active drug ingredients and therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients must be approved by the FDA before marketing. In approving a drug product for marketing, the FDA ensures that the drug product is safe and effective for its labeled indications for use. Moreover, the drug product must meet all applicable standards of identity, strength, quality, and purity. To ensure that these standards are met, the FDA requires bioavailability/pharmacokinetic studies and, where necessary, bioequivalence studies for all drug products (*FDA Guidance for Industry,* 2003). Bioavailability may be considered as one aspect of drug product quality that links *in-vivo* performance of the drug product used in clinical trials to studies demonstrating evidence of safety and efficacy.

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For unmarketed drugs that do not have full NDA approval by the FDA, *in-vitro* and/or *in-vivo* bioequivalence studies must be performed on the drug formulation proposed for marketing as a generic drug product. Furthermore, the essential pharmacokinetics of the active drug ingredient or therapeutic moiety must be characterized. Essential pharmacokinetic parameters, including the rate and extent of systemic absorption, elimination half-life, and rates of excretion and metabolism, should be established after single- and multiple-dose administration. Data from these *in-vivo* bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

In-vivo bioavailability studies are also performed for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and to characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation.

In summary, clinical studies are useful in determining the safety and efficacy of drug products. *Bioavailability* studies are used to define the effect of changes in the physicochemical properties of the drug substance and the effect of the drug product (dosage form) on the pharmacokinetics of the drug. *Bioequivalence* studies are used to compare the bioavailability of the same drug (same salt or ester) from various drug products. Bioavailability and bioequivalence can also be considered as performance measures of the drug product *in-vivo*. If the drug products are bioequivalent and therapeutically equivalent (as defined above), then the clinical efficacy and the safety profile of these drug products are assumed to be similar and may be substituted for each other.

RELATIVE AND ABSOLUTE AVAILABILITY

The area under the drug concentration–time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation. The AUC is dependent on the total quantity of available drug, FD_0, divided by the elimination rate constant, k, and the apparent volume of distribution, V_D. F is the fraction of the dose absorbed. After IV administration, F is equal to unity, because the entire dose enters the systemic circulation. Therefore, the drug is considered to be completely available after IV administration. After oral administration of a drug, F may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption).

Relative Availability

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard. The fraction of dose systemically available from an oral drug product is difficult to ascertain. The availability of drug in the formulation is compared to the availability of drug in a standard dosage formulation, usually a solution of the pure drug evaluated in a crossover study. The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained using the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A}{[\text{AUC}]_B} \tag{15.1}$$

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where drug product B is the recognized reference standard. This fraction may be multiplied by 100 to give percent relative availability.

When different doses are administered, a correction for the size of the dose is made, as in the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A/\text{dose A}}{[\text{AUC}]_B/\text{dose B}} \tag{15.2}$$

Urinary drug excretion data may also be used to measure relative availability, as long as the total amount of intact drug excreted in the urine is collected. The percent relative availability using urinary excretion data can be determined as follows:

$$\text{Percent relative availability} = \frac{[D_u]_A^\infty}{[D_u]_B^\infty} \times 100 \tag{15.3}$$

where $[D_u]^\infty$ is the total amount of drug excreted in the urine.

Absolute Availability

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing. The absolute availability of a drug is generally measured by comparing the respective AUCs after extravascular and IV administration. This measurement may be performed as long as V_D and k are independent of the route of administration. Absolute availability after oral drug administration using plasma data can be determined as follows:

$$\text{Absolute availability} = F = \frac{[\text{AUC}]_{PO}/\text{dose}_{PO}}{[\text{AUC}]_{IV}/\text{dose}_{IV}} \tag{15.4}$$

Absolute availability, F, may be expressed as a fraction or as a percent by multiplying $F \times 100$. Absolute availability using urinary drug excretion data can be determined by the following:

$$\text{Absolute availability} = \frac{[D_u]_{PO}^\infty/\text{dose}_{PO}}{[D_u]_{IV}^\infty/\text{dose}_{IV}} \tag{15.5}$$

The absolute bioavailability is also equal to F, the fraction of the dose that is bioavailable. Absolute availability is sometimes expressed as a percent, ie, $F = 1$, or 100%. For drugs given intravascularly, such as by IV bolus injection, $F = 1$ because all of the drug is completely absorbed. For all extravascular routes of administration, such as the oral route (PO), the absolute bioavailability F may not exceed 100% ($F > 1$). F is usually determined by Equation 15.4 or 15.5, where PO is the oral route or any other extravascular route of drug administration.

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PRACTICE PROBLEM

The bioavailability of a new investigational drug was studied in 12 volunteers. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. Plasma samples were obtained periodically up to 48 hours after the dose and assayed for drug concentration. The average AUC values (0–48 hours) are given in the table below. From these data, calculate (a) the relative bioavailability of the drug from the tablet compared to the oral solution and (b) the absolute bioavailability of the drug from the tablet.

Drug Product	Dose (mg)	AUC (μg hr/mL)	Standard Deviation
Oral tablet	200	89.5	19.7
Oral solution	200	86.1	18.1
IV bolus injection	50	37.8	5.7

Solution

The relative bioavailability of the drug from the tablet is estimated using Equation 15.1. No adjustment for dose is necessary.

$$\text{Relative bioavailability} = \frac{89.5}{86.1} = 1.04 \quad \text{or} \quad 104\%$$

The relative bioavailability of the drug from the tablet is 1.04, or 104%, compared to the solution. In this study, the difference in drug bioavailability between tablet and solution was not statistically significant. It is possible for the relative bioavailability to be greater than 100%.

The absolute drug bioavailability from the tablet is calculated using Equation 15.4 and adjusting for the dose.

$$F = \text{absolute bioavailability} = \frac{89.5/200}{37.8/50} = 0.592 \quad \text{or} \quad 59.2\%$$

Because F, the fraction of dose absorbed from the tablet, is less than 1, the drug is not completely absorbed systemically, as a result of either poor absorption or metabolism by first-pass effect. The relative bioavailability of the drug from the tablet is approximately 100% when compared to the oral solution.

Results from bioequivalence studies may show that the relative bioavailability of the test oral product is greater than, equal to, or less than 100% compared to the reference oral drug product. However, the results from these bioequivalence studies should not be misinterpreted to imply that the absolute bioavailability of the drug from the oral drug products is also 100% unless the oral formulation was compared to an intravenous injection of the drug.

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METHODS FOR ASSESSING BIOAVAILABILITY

Direct and indirect methods may be used to assess drug bioavailability. The *in-vivo* bioavailability of a drug product is demonstrated by the rate and extent of drug absorption, as determined by comparison of measured parameters, eg, concentration of the active drug ingredient in the blood, cumulative urinary excretion rates, or pharmacological effects. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. The design of the bioavailability study depends on the objectives of the study, the ability to analyze the drug (and metabolites) in biological fluids, the pharmacodynamics of the drug substance, the route of drug administration, and the nature of the drug product. Pharmacokinetic and/or pharmacodynamic parameters as well as clinical observations and *in-vitro* studies may be used to determine drug bioavailability from a drug product (Table 15.1).

Plasma Drug Concentration

Measurement of drug concentrations in blood, plasma, or serum after drug administration is the most direct and objective way to determine systemic drug bioavailability. By appropriate blood sampling, an accurate description of the plasma drug concentration–time profile of the therapeutically active drug substance(s) can be obtained using a validated drug assay.

t_{max}. The *time of peak plasma concentration*, t_{max}, corresponds to the time required to reach maximum drug concentration after drug administration. At t_{max}, peak drug absorption occurs and the rate of drug absorption exactly equals the rate of drug elimination (Fig. 15-1). Drug absorption still continues after t_{max} is reached, but at a slower rate. When comparing drug products, t_{max} can be used as an approximate indication of drug absorption rate. The value for t_{max} will become smaller (indicating less time required to reach peak

TABLE 15.1 Methods for Assessing Bioavailability and Bioequivalence

Plasma drug concentration
Time for peak plasma (blood) concentration (t_{max})
Peak plasma drug concentration (C_{max})
Area under the plasma drug concentration–time curve (AUC)
Urinary drug excretion
Cumulative amount of drug excreted in the urine (D_u)
Rate of drug excretion in the urine (dD_u/dt)
Time for maximum urinary excretion (t)
Acute pharmacodynamic effect
Maximum pharmacodynamic effect (E_{max})
Time for maximum pharmacodynamic effect
Area under the pharmacodynamic effect–time curve
Onset time for pharmacodynamic effect
Clinical observations
Well-controlled clinical trials
***In-vitro* studies**
Drug dissolution

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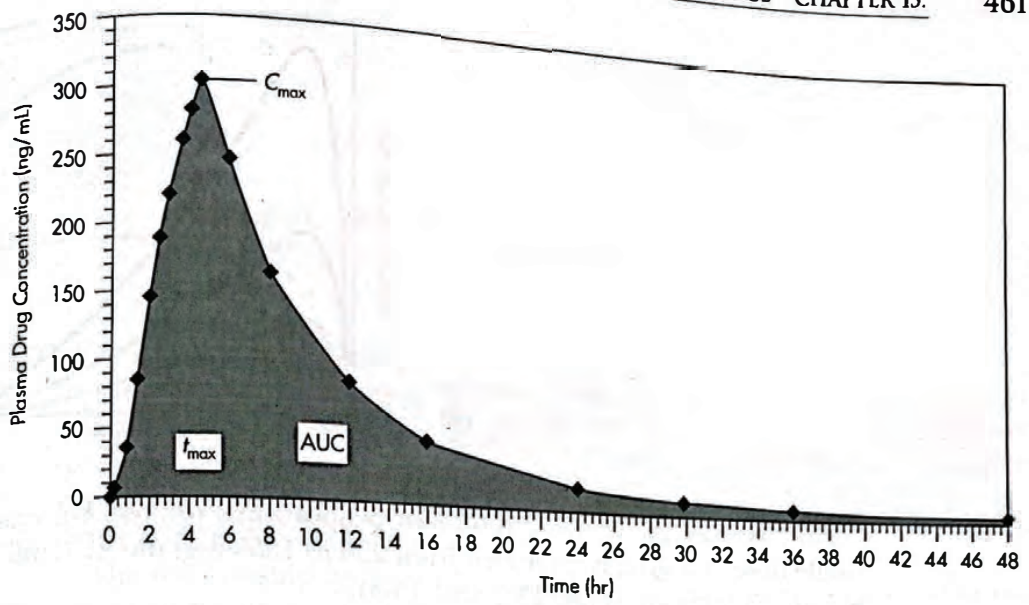


Figure 15-1. Plasma drug concentration–time curve.

plasma concentration) as the absorption rate for the drug becomes more rapid. Units for t_{max} are units of time (eg, hours, minutes).

C_{max}. The *peak plasma drug concentration*, C_{max}, represents the maximum plasma drug concentration obtained after oral administration of drug. For many drugs, a relationship is found between the pharmacodynamic drug effect and the plasma drug concentration. C_{max} provides indications that the drug is sufficiently systemically absorbed to provide a therapeutic response. In addition, C_{max} provides warning of possibly toxic levels of drug. The units of C_{max} are concentration units (eg, mg/mL, ng/mL). Although not a unit for rate, C_{max} is often used in bioequivalence studies as a surrogate measure for the rate of drug bioavailability.

AUC. The *area under the plasma level–time curve*, AUC, is a measurement of the *extent* of drug bioavailability (Fig. 15-1). The AUC reflects the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma level–time curve from $t = 0$ to $t = \infty$, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

$$[\text{AUC}]_0^\infty = \int_0^\infty C_p\,dt \tag{15.6}$$

$$[\text{AUC}]_0^\infty = \frac{FD_0}{\text{clearance}} = \frac{FD_0}{kV_D} \tag{15.7}$$

where F = fraction of dose absorbed, D_0 = dose, k = elimination rate constant, and V_D = volume of distribution. The AUC is independent of the route of administration and processes of drug elimination as long as the elimination processes do not change. The AUC can be determined by a numerical integration procedure, such as the trapezoidal rule method. The units for AUC are concentration time (eg, μg hr/mL).

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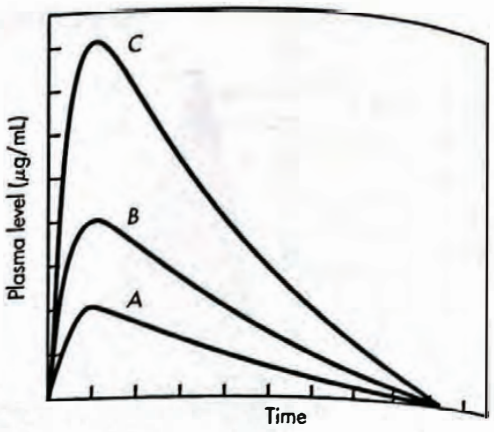


Figure 15-2. Plasma level–time curve following administration of single doses of **(A)** 250 mg, **(B)** 500 mg, and **(C)** 1000 mg of drug.

For many drugs, the AUC is directly proportional to dose. For example, if a single dose of a drug is increased from 250 to 1000 mg, the AUC will also show a fourfold increase (Figs. 15-2 and 15-3).

In some cases, the AUC is not directly proportional to the administered dose for all dosage levels. For example, as the dosage of drug is increased, one of the pathways for drug elimination may become saturated (Fig. 15-4). Drug elimination includes the processes of metabolism and excretion. Drug metabolism is an enzyme-dependent process. For drugs such as salicylate and phenytoin, continued increase of the dose causes saturation of one of the enzyme pathways for drug metabolism and consequent prolongation of the elimination half-life. The AUC thus increases disproportionally to the increase in dose, because a smaller amount of drug is being eliminated (ie, more drug is retained). When the AUC is not directly proportional to the dose, bioavailability of the drug is difficult to evaluate because drug kinetics may be dose dependent.

Urinary Drug Excretion Data

Urinary drug excretion data is an indirect method for estimating bioavailability. The drug must be excreted in significant quantities as unchanged drug in the urine. In addition, timely urine samples must be collected and the total amount of urinary drug excretion must be obtained (see Chapter 3).

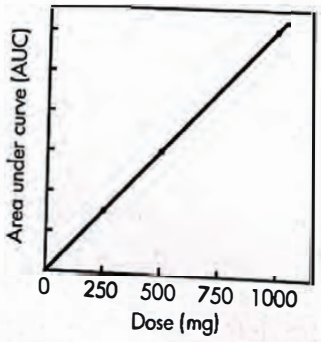


Figure 15-3. Linear relationship between AUC and dose (data from Fig. 15-2).

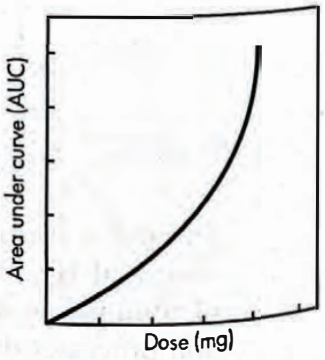


Figure 15-4. Relationship between AUC and dose when metabolism is saturable.

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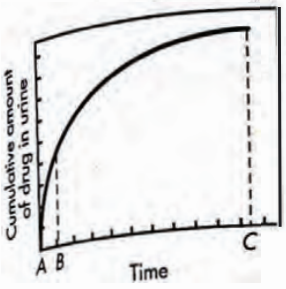


Figure 15-5. Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

D_u^∞. The *cumulative amount of drug excreted in the urine*, D_u^∞, is related directly to the total amount of drug absorbed. Experimentally, urine samples are collected periodically after administration of a drug product. Each urine specimen is analyzed for free drug using a specific assay. A graph is constructed that relates the cumulative drug excreted to the collection-time interval (Fig. 15-5).

The relationship between the cumulative amount of drug excreted in the urine and the plasma level–time curve is shown in Figure 15-6. When the drug is almost completely eliminated (point *C*), the plasma concentration approaches zero and the maximum amount of drug excreted in the urine, D_u^∞, is obtained.

dD_u/dt. The *rate of drug excretion.* Because most drugs are eliminated by a first-order rate process, the rate of drug excretion is dependent on the first-order elimination rate constant k and the concentration of drug in the plasma C_p. In Figure 15-6, the *maximum rate of drug excretion*, $(dD_u/dt)_{max}$, is at point *B*, whereas the minimum rate of drug excretion is at points *A* and *C*. Thus, a graph comparing the rate of drug excretion with respect to time should be similar in shape as the plasma level–time curve for that drug (Fig. 15-7).

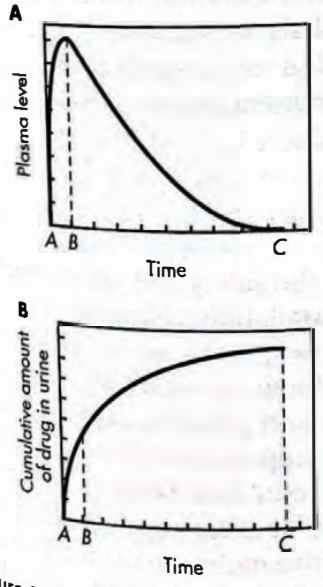


Figure 15-6. Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

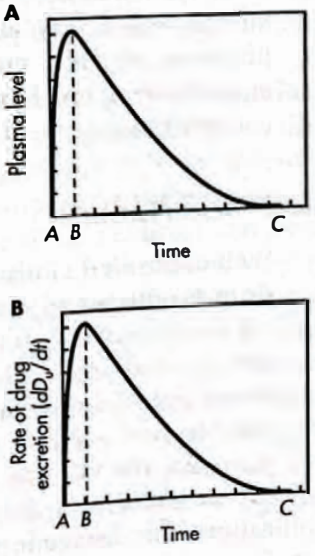


Figure 15-7. Corresponding plots relating the plasma level–time curve and the rate of urinary drug excretion.

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t^{∞}. The *total time for the drug to be excreted.* In Figures 15-6 and 15-7, the slope of the curve segment *A–B* is related to the rate of drug absorption, whereas point *C* is related to the total time required after drug administration for the drug to be absorbed and completely excreted $t = \infty$. The t^{∞} is a useful parameter in bioequivalence studies that compare several drug products, as will be described later in this chapter.

Acute Pharmacodynamic Effect

In some cases, the quantitative measurement of a drug in plasma or urine lacks an assay with sufficient accuracy and/or reproducibility. For locally acting, nonsystemically absorbed drug products, such as topical corticosteroids, plasma drug concentrations may not reflect the bioavailability of the drug at the site of action. An acute pharmacodynamic effect, such as an effect on forced expiratory volume, FEV_1 (inhaled bronchodilators) or skin blanching (topical corticosteroids) can be used as an index of drug bioavailability. In this case, the acute pharmacodynamic effect is measured over a period of time after administration of the drug product. Measurements of the pharmacodynamic effect should be made with sufficient frequency to permit a reasonable estimate for a time period at least three times the half-life of the drug (Gardner, 1977). This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

The use of an acute pharmacodynamic effect to determine bioavailability generally requires demonstration of a dose–response curve (see Chapter 19). Bioavailability is determined by characterization of the dose–response curve. For bioequivalence determination, pharmacodynamic parameters including the total area under the acute pharmacodynamic effect–time curve, peak pharmacodynamic effect, and time for peak pharmacodynamic effect are obtained from the pharmacodynamic effect–time curve. The onset time and duration of the pharmacokinetic effect may also be included in the analysis of the data. The use of pharmacodynamic endpoints for the determination of bioavailability and bioequivalence is much more variable than the measurement of plasma or urine drug concentrations.

Clinical Observations

Well-controlled clinical trials in humans establish the safety and effectiveness of drug products and may be used to determine bioavailability. However, the clinical trials approach is the least accurate, least sensitive, and least reproducible of the general approaches for determining *in-vivo* bioavailability. The FDA considers this approach only when analytical methods and pharmacodynamic methods are not available to permit use of one of the approaches described above. Comparative clinical studies have been used to establish bioequivalence for topical antifungal drug products (eg, ketoconazole) and for topical acne preparations. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the other approaches

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In Vitro Studies

Drug dissolution studies may under certain conditions give an indication of drug bioavailability. Ideally, the *in-vitro* drug dissolution rate should correlate with *in-vivo* drug bioavailability (see Chapters 7 and 14 on *in-vivo–in-vitro* correlation, IVIVC). Dissolution studies are often performed on several test formulations of the same drug. The test formulation that demonstrates the most rapid rate of drug dissolution *in vitro* will generally have the most rapid rate of drug bioavailability *in vivo*.

The FDA may also use other *in-vitro* approaches for establishing bioequivalence. For example, cholestyramine resin is a basic quaternary ammonium anion-exchange resin that is hydrophilic, insoluble in water, and not absorbed in the gastrointestinal tract. The bioequivalence of cholestyramine resin is performed by equilibrium and kinetic binding studies of the resin to bile acid salts (www.fda.gov/cder/guidance/cholesty.pdf).

BIOEQUIVALENCE STUDIES

Differences in the predicted clinical response or an adverse event may be due to differences in the pharmacokinetic and/or pharmacodynamic behavior of the drug among individuals or to differences in the bioavailability of the drug from the drug product. Bioequivalent drug products that have the same systemic drug bioavailability will have the same predictable drug response. However, variable clinical responses among individuals that are unrelated to bioavailability may be due to differences in the pharmacodynamics of the drug. Differences in pharmacodynamics, ie, the relationship between the drug and the receptor site, may be due to differences in receptor sensitivity to the drug. Various factors affecting pharmacodynamic drug behavior may include age, drug tolerance, drug interactions, and unknown pathophysiologic factors.

The bioavailability of a drug may be more reproducible among fasted individuals in controlled studies who take the drug on an empty stomach. When the drug is used on a daily basis, however, the nature of an individual's diet and lifestyle may affect the plasma drug levels because of variable absorption in the presence of food or even a change in the metabolic clearance of the drug. Feldman and associates (1982) reported that patients on a high-carbohydrate diet have a much longer elimination half-life of theophylline, due to the reduced metabolic clearance of the drug ($t_{1/2}$, 18.1 hours), compared to patients on normal diets ($t_{1/2}$ = 6.76 hours). Previous studies demonstrated that the theophylline drug product was completely bioavailable. The higher plasma drug concentration resulting from a carbohydrate diet may subject the patient to a higher risk of drug intoxication with theophylline. The effect of food on the availability of theophylline has been reported by the FDA concerning the risk of higher theophylline plasma concentrations from a 24-hour sustained-release drug product taken with food. Although most bioavailability drug studies use fasted volunteers, the diet of patients actually using the drug product may increase, decrease, or have no affect on the bioavailability of the drug (Hendles et al, 1984).

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Bases for Determining Bioequivalence

Bioequivalence is established if the *in-vivo* bioavailability of a test drug product (usually the generic product) does not differ significantly (ie, statistically insignificant) in the product's rate and extent of drug absorption, as determined by comparison of measured parameters (eg, concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacodynamic effects), from that of the *reference listed drug* (usually the brand-name product) when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.

In a few cases, a drug product that differs from the reference listed drug in its rate of absorption, but not in its extent of absorption, may be considered bioequivalent if the difference in the rate of absorption is intentional and appropriately reflected in the labeling and/or the rate of absorption is not detrimental to the safety and effectiveness of the drug product.

Drug Products with Possible Bioavailability and Bioequivalence Problems

Lack of bioavailability or bioequivalence may be suspected when evidence from well-controlled clinical trials or controlled observations in patients of various marketed drug products do not give comparable therapeutic effects. These drug products need to be evaluated either *in vitro* (eg, drug dissolution/release test) or *in vivo* (eg, bioequivalence study) to determine if the drug product has a bioavailability problem (see also U.S. Code of Federal Regulations, 21 CFR 320.33).

In addition, during the development of a drug product, certain biopharmaceutical properties of the active drug substance or the formulation of the drug product may indicate that the drug may have variable bioavailability and/or a bioequivalence problem. Some of these biopharmaceutic properties include:

- The active drug ingredient has low solubility in water (eg, less than 5 mg/mL).
- The dissolution rate of one or more such products is slow (eg, less than 50% in 30 minutes when tested with a general method specified by the FDA).
- The particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability.
- Certain structural forms of the active drug ingredient (eg, polymorphic forms, solvates, complexes, and crystal modifications) dissolve poorly, thus affecting absorption.
- Drug products that have a high ratio of excipients to active ingredients (eg, greater than 5:1).
- Specific inactive ingredients (eg, hydrophilic or hydrophobic excipients and lubricants) either may be required for absorption of the active drug ingredient or therapeutic moiety or may interfere with such absorption.
- The active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the GI tract or is absorbed from a localized site.

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- The degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor (eg, less than 50%, ordinarily in comparison to an intravenous dose), even when it is administered in pure form (eg, in solution).
- There is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the absorption process (first-order metabolism), so that the rate of absorption is unusually important in the therapeutic effect and/or toxicity of the drug product.
- The therapeutic moiety is rapidly metabolized or excreted, so that rapid dissolution and absorption are required for effectiveness.
- The active drug ingredient or therapeutic moiety is unstable in specific portions of the GI tract and requires special coatings or formulations (eg, buffers, enteric coatings, and film coatings) to ensure adequate absorption.
- The drug product is subject to dose-dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence.

DESIGN AND EVALUATION OF BIOEQUIVALENCE STUDIES

Bioequivalence studies are performed to compare the bioavailability of the generic drug product to the brand-name product. Statistical techniques should be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability. Once bioequivalence is established, it is likely that both the generic and brand-name dosage forms will produce the same therapeutic effect. The FDA publishes guidances for bioequivalence studies (www.fda.gov/cder/guidance; see also 21 CFR 320.25). Sponsors may also request a meeting with the FDA to review the study design for a specific drug product.

Design

The design and evaluation of well-controlled bioequivalence studies require cooperative input from pharmacokineticists, statisticians, clinicians, bioanalytical chemists, and others. The basic design for a bioequivalence study is determined by (1) the scientific questions to be answered, (2) the nature of the reference material and the dosage form to be tested, (3) the availability of analytical methods, and (4) benefit–risk and ethical considerations with regard to testing in humans. For some generic drugs, the FDA offers general guidelines for conducting these studies. For example, *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* is available from the FDA; the publication addresses three specific aspects, including (1) logarithmic transformation of pharmacokinetic data, (2) sequence effect, and (3) outlier consideration. However, even with the availability of such guidelines, the principal investigator should prepare a detailed protocol for the study. Some of the elements of a protocol for an *in-vivo* bioavailability study are listed in Table 15.2. Bioavailability studies for controlled-release dosage forms are discussed in Chapter 17.

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TABLE 15.2 Elements of a Bioavailability Study Protocol

- I. Title
  - A. Principal investigator (study director)
  - B. Project/protocol number and date
- II. Study objective
- III. Study design
  - A. Design
  - B. Drug products
    - 1. Test product(s)
    - 2. Reference product
  - C. Dosage regimen
  - D. Sample collection schedule
  - E. Housing/confinement
  - F. Fasting/meals schedule
  - G. Analytical methods
- IV. Study population
  - A. Subjects
  - B. Subject selection
    - 1. Medical history
    - 2. Physical examination
    - 3. Laboratory tests
  - C. Inclusion/exclusion criteria
    - 1. Inclusion criteria
    - 2. Exclusion criteria
  - D. Restrictions/prohibitions
- V. Clinical procedures
  - A. Dosage and drug administration
  - B. Biological sampling schedule and handling procedures
  - C. Activity of subjects
- VI. Ethical considerations
  - A. Basic principles
  - B. Institutional review board
  - C. Informed consent
  - D. Indications for subject withdrawal
  - E. Adverse reactions and emergency procedures
- VII. Facilities
- VIII. Data analysis
  - A. Analytical validation procedure
  - B. Statistical treatment of data
- IX. Drug accountability
- X. Appendix

For bioequivalence studies, the test and reference drug formulations must contain the pharmaceutical equivalent drug in the same dose strength, in similar dosage forms (eg, immediate release or controlled release), and be given by the same route of administration. Both a single-dose and/or a multiple-dose (steady-state) study may be required. Before beginning the study, the *Institutional Review Board* (IRB) of the clinical facility in which the study is to be performed must approve the study. The IRB is composed of both professional and lay persons with diverse backgrounds, who have clinical experience and expertise as well as sensitivity to ethical issues and community attitudes. The IRB is responsible for safeguarding the rights and welfare of human subjects.

The basic guiding principle in performing studies is *do not do unnecessary human research.* Generally, the study is performed in normal, healthy male and female volunteers who have given informed consent to be in the study. Critically ill patients are not included in an *in-vivo* bioavailability study unless the attending physician determines that there is a potential benefit to the patient. The number of subjects in the study will depend on the expected intersubject and intrasubject variability. Patient selection is made according to certain established criteria for inclusion into, or exclusion from, the study. For example, the study might exclude any volunteers who have known allergies to the drug, are overweight, or have taken any medication within a specified period (often 1 week) prior to the study. Smokers are often included in these studies. The subjects are generally fasted for 10 to 12 hours (overnight) prior to drug administration and may continue to fast for a 2- to 4-hour period after dosing.

Analytical Methods

The analytical method used in an *in-vivo* bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or

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its active metabolite(s), in body fluids or excretory products, or the method used to measure an acute pharmacological effect, must be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body. For bioavailability studies, both the parent drug and its major active metabolites are generally measured. For bioequivalence studies, the parent drug is measured. The active metabolite might be measured for some very high hepatic clearance (first-pass metabolism) drugs when the parent drug concentrations are too low to be reliable.

Reference Standard

For bioequivalence studies, one formulation of the drug is chosen as a reference standard against which all other formulations of the drug are compared. The reference drug product should be administered by the same route as the comparison formulations unless an alternative route or additional route is needed to answer specific pharmacokinetic questions. For example, if an active drug is poorly bioavailable after oral administration, the drug may be compared to an oral solution or an intravenous injection. For bioequivalence studies on a proposed generic drug product the reference standard is the *reference listed drug* (RLD), which is listed in *Approved Drug Products with Therapeutic Equivalence Evaluations*—the *Orange Book* (www.fda.gov/cder/ob/default.htm), and the proposed generic drug product is often referred to as the "Test" drug product. The RLD is generally a formulation currently marketed with a fully approved NDA for which there are valid scientific safety and efficacy data. The RLD is usually the innovator's or original manufacturer's brand-name product and is administered according to the dosage recommendations in the labeling.

Before beginning an *in-vivo* bioequivalence study, the total content of the active drug substance in the test product (generally the generic product) must be within 5% of that of the reference product. Moreover, *in-vitro* comparative dissolution or drug-release studies under various specified conditions are usually performed for both test and reference products before performing the *in-vivo* bioequivalence study.

Extended-Release Formulations

The purpose of an *in-vivo* bioavailability study involving an extended-release drug product is to determine if (1) the drug product meets the controlled-release claims made for it, (2) the bioavailability profile established for the drug product rules out the occurrence of any *dose dumping*, (3) the drug product's steady-state performance is equivalent to that of a currently marketed non-extended-release formulation, and (4) the drug product's formulation provides consistent pharmacokinetic performance between individual dosage units. A comparison bioavailability study is used for the development of a new extended release drug product in which the reference drug product may be either a solution or suspension of the active ingredient or a currently marketed non-controlled release drug product such as a tablet or capsule. For example, the bioavailability of a non-controlled-release (immediate-release) drug product given at a dose of 25 mg every 8 hours is compared to an extended-release

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product containing 75 mg of the same drug given once daily. For a bioequivalence study of a new generic extended release drug product, the reference drug product is the currently marketed extended release drug product listed as the RLD in the Orange Book and is administered according to the dosage recommendations in the approved labeling.

Combination Drug Products

Generally, the purpose of an *in-vivo* bioavailability study involving a combination drug product containing more than one active drug substance is to determine if the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations. The reference material in such a bioavailability study should be two or more currently marketed, single-ingredient drug products, each of which contains one of the active drug ingredients in the combination drug product. The FDA may, for valid scientific reasons, specify that the reference material be a combination drug product that is the subject of an approved NDA.

STUDY DESIGNS

For many drug products, the FDA, Division of Bioequivalence, Office of Generic Drugs, provides guidance for the performance of *in-vitro* dissolution and *in-vivo* bioequivalence studies. Similar guidelines appear in the United States Pharmacopeia NF. Currently, three different studies may be required for solid oral dosage forms, including (1) a fasting study, (2) a food intervention study, and/or (3) a multiple-dose (steady-state) study. Other study designs have been proposed by the FDA. For example, the FDA published two draft guidelines in October and December 1997 to consider the performance of individual bioequivalence studies using a replicate design and a two-way crossover food intervention study. Proper study design and statistical evolution are important considerations for the determination of bioequivalence. Some of the designs listed above are summarized here.

Fasting Study

Bioequivalence studies are usually evaluated by a single-dose, two-period, two-treatment, two-sequence, open-label, randomized crossover design comparing equal doses of the test and reference products in fasted, adult, healthy subjects. This study is required for all immediate-release and modified-release oral dosage forms. Both male and female subjects may be used in the study. Blood sampling is performed just before (zero time) the dose and at appropriate intervals after the dose to obtain an adequate description of the plasma drug concentration–time profile. The subjects should be in the fasting state (overnight fast of at least 10 hours) before drug administration and should continue to fast for up to 4 hours after dosing. No other medication is normally given to the subject for at least 1 week prior to the

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study. In some cases, a parallel design may be more appropriate for certain drug products, containing a drug with a very long elimination half-life. A replicate design may be used for a drug product containing a drug that has high intrasubject variability.

Food Intervention Study

Co-administration of food with an oral drug product may affect the bioavailability of the drug. Food intervention or food effect studies are generally conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. The test meal is a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. A typical test meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of brown potatoes, and 8 ounces of milk. This test meal derives approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively (www.fda.gov/cder/guidance/4613dft.pdf).

For bioequivalence studies, drug bioavailability from both the test and reference products should be affected similarly by food. The study design uses a single-dose, randomized, two-treatment, two-period, crossover study comparing equal doses of the test and reference products. Following an overnight fast of at least 10 hours, subjects are given the recommended meal 30 minutes before dosing. The meal is consumed over 30 minutes, with administration of the drug product immediately after the meal. The drug product is given with 240 mL (8 fluid ounces) of water. No food is allowed for at least 4 hours postdose. This study is required for all modified-release dosage forms and may be required for immediate-release dosage forms if the bioavailability of the active drug ingredient is known to be affected by food (eg, ibuprofen, naproxen). For certain extended-release capsules that contain coated beads, the capsule contents are sprinkled over soft foods such as apple sauce, which is taken by the fasted subject and the bioavailability of the drug is then measured. Bioavailability studies might also examine the affects of other foods and special vehicles such as apple juice.

Multiple-Dose (Steady-State) Study

In a few cases, a multiple-dose, steady-state, randomized, two-treatment, two-way crossover study comparing equal doses of the test and reference products may be performed in adult, healthy subjects. For these studies, three consecutive trough concentrations (C_{min}) on three consecutive days should be determined to ascertain that the subjects are at steady state. The last morning dose is given to the subject after an overnight fast, with continual fasting for at least 2 hours following dose administration. Blood sampling is performed similarly to the single-dose study.

Crossover Designs

Subjects who meet the inclusion and exclusion study criteria and have given informed consent are selected at random. A complete crossover design is usually employed, in which each subject receives the test drug product and the reference product. Examples of *Latin-square crossover designs* for a bioequivalence study in human

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TABLE 15.3 Latin-Square Crossover Design for a Bioequivalence Study of Three Drug Products in Six Human Volunteers

	DRUG PRODUCT		
SUBJECT	Study Period 1	Study Period 2	Study Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

volunteers, comparing three different drug formulations (A, B, C) or four different drug formulations (A, B, C, D), are described in Tables 10.3 and 10.4. The Latin-square design plans the clinical trial so that each subject receives each drug product only once, with adequate time between medications for the elimination of the drug from the body (Table 15.3). In this design, each subject is his own control, and subject-to-subject variation is reduced. Moreover, variation due to sequence, period, and treatment (formulation) are reduced, so that all patients do not receive the same drug product on the same day and in the same order. Possible carryover effects from any particular drug product are minimized by changing the sequence or order in which the drug products are given to the subject. Thus, drug product B may be followed by drug product A, D, or C (Table 15.4). After each subject receives a drug product, blood samples are collected at appropriate time intervals so that a valid blood drug level–time curve is obtained. The time intervals should be spaced so that the peak blood concentration, the total area under the curve, and the absorption and elimination phases of the curve may be well described.

TABLE 15.4 Latin-Square Crossover Design for a Bioequivalency Study of Four Drug Products in 16 Human Volunteers

	DRUG PRODUCT			
SUBJECT	Study Period 1	Study Period 2	Study Period 3	Study Period 4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C
5	A	B	D	C
6	B	D	C	A
7	D	C	A	B
8	C	A	B	D
9	A	C	B	D
10	C	B	D	A
11	B	D	A	C
12	D	A	C	B
13	A	C	D	B
14	C	D	B	A
15	D	B	A	C
16	B	A	C	D

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Period refers to the time period in which a study is performed. A two-period study is a study that is performed on two different days (time periods) separated by a *washout period* during which most of the drug is eliminated from the body—generally about 10 elimination half-lives. A *sequence* refers to the number of different orders in the treatment groups in a study. For example, a two-sequence, two-period study would be designed as follows:

	Period 1	Period 2
Sequence 1	T	R
Sequence 2	R	T

where R = reference and T = treatment.

Table 15.4 shows a design for three different drug treatment groups given in a three-period study with six different sequences. The order in which the drug treatments are given should not stay the same in order to prevent any bias in the data due to a residual effect from the previous treatment.

Replicated Crossover Design

Replicated crossover designs are used for the determination of individual bioequivalence, to estimate within-subject variance for both the Test and Reference drug products, and to provide an estimate of the subject-by-formulation interaction variance. Generally, a four-period, two-sequence, two-formulation design is recommended by the FDA.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

where R = reference and T = treatment.

The same reference and the same test are each given twice to the same subject. Other sequences are possible. In this design, Reference-to-Reference and Test-to-Test comparisons may also be made.

EVALUATION OF THE DATA

Analytical Method

The analytical method for measurement of the drug must be validated for accuracy, precision, sensitivity, and specificity. The use of more than one analytical method during a bioequivalence study may not be valid, because different methods may yield different values. Data should be presented in both tabulated and graphic form for evaluation. The plasma drug concentration–time curve for each drug product and each subject should be available.

Pharmacokinetic Evaluation of the Data

For single-dose studies, including a fasting study or a food intervention study, the pharmacokinetic analyses include calculation for each subject of the area under

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the curve to the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), T_{max}, and C_{max}. Additionally, the elimination rate constant, k, the elimination half-life, $t_{1/2}$, and other parameters may be estimated. For multiple-dose studies, pharmacokinetic analysis includes calculation for each subject of the steady-state area under the curve, (AUC_{0-t}), T_{max}, C_{min}, C_{max}, and the percent fluctuation [$100 \times (C_{max} - C_{min})/C_{min}$]. Proper statistical evaluation should be performed on the estimated pharmacokinetic parameters.

Statistical Evaluation of the Data

Bioequivalence is generally determined using a comparison of population averages of a bioequivalence metric, such as AUC and C_{max}. This approach, termed *average bioequivalence,* involves the calculation of a 90% confidence interval for the ratio of averages (population geometric means) of the bioequivalence metrics for the Test and Reference drug products. To establish bioequivalence, the calculated confidence interval should fall within a prescribed bioequivalence limit, usually, 80–125% for the ratio of the product averages. Standard crossover design studies are used to obtain the data. Another approach proposed by the FDA and others is termed *individual bioequivalence.* Individual bioequivalence requires a replicate crossover design, and estimates within-subject variability for the Test and Reference drug products, as well as subject-by-formulation interaction. Presently, only average bioequivalence estimates are used to establish bioequivalence of generic drug products.

To prove bioequivalence, there must be no statistical difference between the bioavailability of the Test product and the Reference product. Several statistical approaches are used to compare the bioavailability of drug from the test dosage form to the bioavailability of the drug from the reference dosage form. Many statistical approaches (parametric tests) assume that the data are distributed according to a normal distribution or "bell-shaped curve" (see Appendix A). The distribution of many biological parameters such as C_{max} and AUC have a longer right tail than would be observed in a normal distribution (Midha et al, 1993). Moreover, the true distribution of these biological parameters may be difficult to ascertain because of the small number of subjects used in a bioequivalence study. The distribution of data that has been transformed to log values resembles more closely a normal distribution compared to the distribution of non-log-transformed data. Therefore, log transformation of the bioavailability data (eg, C_{max}, AUC) is performed before statistical data evaluation for bioequivalence determination.

Analysis of Variance (ANOVA)

An analysis of variance (ANOVA) is a statistical procedure (Appendix A) used to test the data for differences within and between treatment and control groups. A bioequivalent product should produce no significant difference in all pharmacokinetic parameters tested. The parameters tested usually include AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, and C_{max} obtained for each treatment or dosage form. Other metrics of bioavailability have also been used to compare the bioequivalence of two or more formulations. The ANOVA may evaluate variability in subjects, treatment groups, study period, formulation, and other variables, depending on the study design. If the variability in the data is large, the difference in means for each pharmacokinetic

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parameter, such as AUC, may be masked, and the investigator might erroneously conclude that the two drug products are bioequivalent.

A statistical difference between the pharmacokinetic parameters obtained from two or more drug products is considered statistically significant if there is a probability of less than 1 in 20 times or 0.05 probability ($p \leq 0.05$) that these results would have happened on the basis of chance alone. The probability, p, is used to indicate the level of statistical significance. If $p < 0.05$, the differences between the two drug products are not considered statistically significant.

To reduce the possibility of failing to detect small differences between the test products, a *power test* is performed to calculate the probability that the conclusion of the ANOVA is valid. The power of the test will depend on the sample size, variability of the data, and desired level of significance. Usually the power is set at 0.80 with a $\beta = 0.2$ and a level of significance of 0.05. The higher the power, the more sensitive the test and the greater the probability that the conclusion of the ANOVA is valid.

Two One-Sided Tests Procedure

The two one-sided tests procedure is also referred to as the *confidence interval approach* (Schuirmann, 1987). This statistical method is used to demonstrate if the bioavailability of the drug from the Test formulation is too low or high in comparison to that of the Reference product. The objective of the approach is to determine if there are large differences (ie, greater than 20%) between the mean parameters.

The 90% confidence limits are estimated for the sample means. The interval estimate is based on a Student's t distribution of the data. In this test, presently required by the FDA, a 90% confidence interval about the ratio of means of the two drug products must be within ±20% for measurement of the rate and extent of drug bioavailability. For most drugs, up to a 20% difference in AUC or C_{max} between two formulations would have no clinical significance. The lower 90% confidence interval for the ratio of means cannot be less than 0.80, and the upper 90% confidence interval for the ratio of the means cannot be greater than 1.20. When log-transformed data are used, the 90% confidence interval is set at 80–125%. These confidence limits have also been termed the *bioequivalence interval* (Midha et al, 1993). The 90% confidence interval is a function of sample size and study variability, including inter- and intrasubject variability.

For a single-dose, fasting study, an analysis of variance (ANOVA) is usually performed on the log-transformed AUC and C_{max} values. There should be no statistical differences between the mean AUC and C_{max} parameters for the Test (generic) and Reference drug products. In addition, the 90% confidence intervals about the ratio of the means for AUC and C_{max} values of the Test drug product should not be less than 0.80 (80%) nor greater than 1.25 (125%) of that of the Reference product based on log-transformed data.

BIOEQUIVALENCE EXAMPLE

A simulated example of the results for a single-dose, fasting study is shown in Table 15.5 and in Figure 15-8. As shown by the ANOVA, no statistical differences

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TABLE 15.5 Bioavailability Comparison of a Generic (Test) and Brand-Name (Reference) Drug Products (Log-Normal Transformed Data)

VARIABLE	UNITS	GEOMETRIC MEAN		% RATIO	90% CONFIDENCE INTERVAL (LOWER LIMIT, UPPER LIMIT)	*p* VALUES FOR PRODUCT EFFECTS	POWER OF ANOVA	ANOVA % CV
		Test	Reference					
C_{max}	ng/mL	344.79	356.81	96.6	(89.5,112)	0.3586	0.8791	17.90%
AUC_{0-t}	ng hr/mL	2659.12	2674.92	99.4	(95.1,104)	0.8172	1.0000	12.60%
AUC_{∞}		2708.63	2718.52	99.6	(95.4,103)	0.8865	1.0000	12.20%
T_{max}	hr	4.29	4.24	101				
K_{elim}	1/hr	0.0961	0.0980	98.1				
$t_{1/2}$	hr	8.47	8.33	101.7				

The results were obtained from a two-way, crossover, single-dose study in 36 fasted, healthy, adult male and female volunteers. No statistical differences were observed for the mean values between Test and Reference products.

for the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were observed between the Test product and the brand-name product. The 90% confidence limits for the mean pharmacokinetic parameters of the Test product were within 0.80–1.25 (80–125%) of the reference product means based on log transformation of the data. The power test for the AUC measures were above 99%, showing good precision of the data. The power test for the C_{max} values was 87.9%, showing that this parameter was more variable.

Table 15.6 shows the results for a hypothetical bioavailability study in which three different tablet formulations were compared to a solution of the drug given in the same dose. As shown in the table, the bioavailability from all three tablet formulations was greater than 80% of that of the solution. According to the ANOVA, the

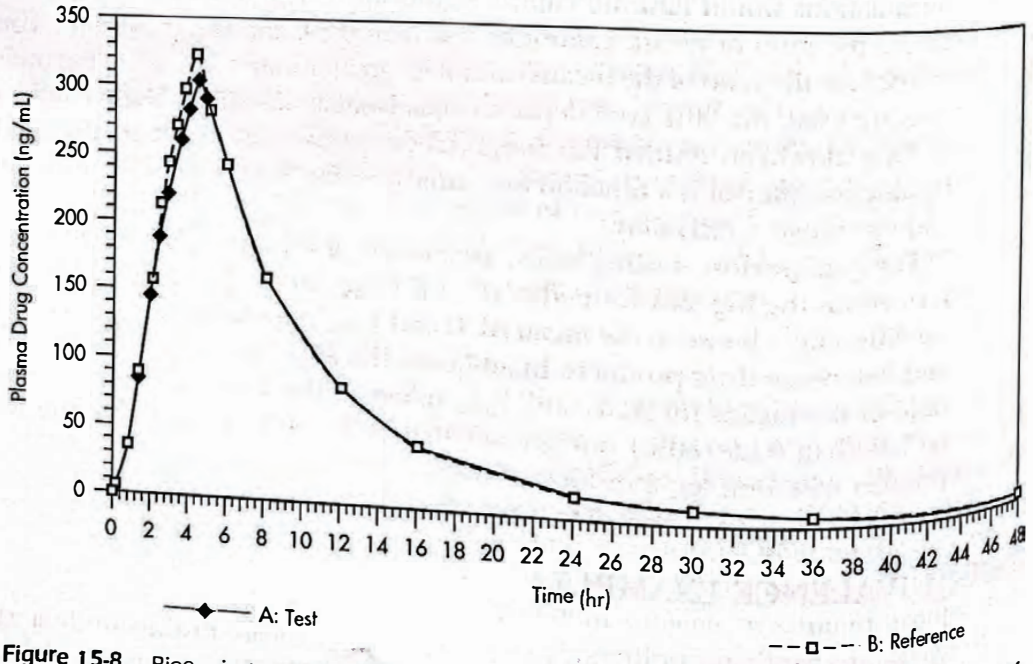


Figure 15-8. Bioequivalence of Test and Reference drug products: mean plasma drug concentrations.

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TABLE 15.6 Summary of the Results of a Bioavailability Study[a]

DOSAGE FORM	C_{max} (μg/mL)	t_{max} (hr)	AUC_{0-24} (μg hr/mL)	F[b]	90% CONFIDENCE INTERVAL FOR AUC
Solution	16.1 ± 2.5	1.5 ± 0.85	1835 ± 235		
Tablet A	10.5 ± 3.2[c]	2.5 ± 1.0[c]	1523 ± 381	81	74–90%
Tablet B	13.7 ± 4.1	2.1 ± 0.98	1707 ± 317	93	88–98%
Tablet C	14.8 ± 3.6	1.8 ± 0.95	1762 ± 295	96	91–103%

[a] The bioavailability of a drug from four different formulations was studied in 24 healthy, adult male subjects using a four-way Latin-square crossover design. The results represent the mean ± standard deviation.
[b] Oral bioavailability relative to the solution.
[c] $p \leq 0.05$.

mean AUC values were not statistically different from each other nor different from that of the solution. However, the 90% confidence interval for the AUC showed that for tablet A, the bioavailability was less than 80% (ie, 74%), compared to the solution at the low-range estimate and would not be considered bioequivalent based on AUC.

For illustrative purposes, consider a drug that has been prepared at the same dosage level in three formulations, A, B, and C. These formulations are given to a group of volunteers using a three-way, randomized crossover design. In this experimental design, all subjects receive each formulation once. From each subject, plasma drug level and urinary drug excretion data are obtained. With these data we can observe the relationship between plasma and urinary excretion parameters and drug bioavailability (Fig. 15-9). The rate of drug absorption from formulation A is more rapid than that from formulation B, because the t_{max} for formulation A is shorter. Because the AUC for formulation A is identical to the AUC for formulation B, the extent of bioavailability from both of these formulations is the same. Note, however,

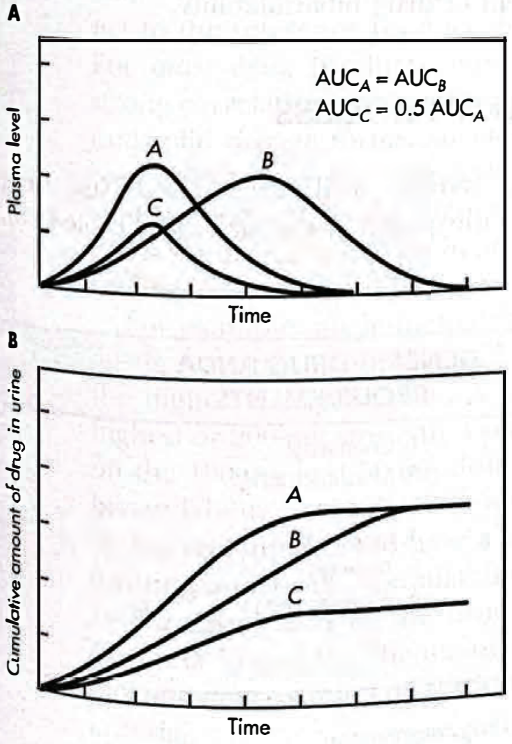


Figure 15-9. Corresponding plots relating plasma concentration and urinary excretion data.

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TABLE 15.7 Relationship of Plasma Level and Urinary Excretion Parameters to Drug Bioavailability

EXTENT OF DRUG BIOAVAILABILITY DECREASES		RATE OF DRUG BIOAVAILABILITY DECREASES	
Parameter	**Change**	**Parameter**	**Change**
Plasma data			
t_{max}	Same	t_{max}	Increase
C_{max}	Decrease	C_{max}	Decrease
AUC	Decrease	AUC	Same
Urine data			
t^{∞}	Same	t^{∞}	Increase
$[dD_u/dt]_{max}$[a]	Decrease	$[dD_u/dt]_{max}$[a]	Decrease
D_u^{∞}	Decrease	D_u^{∞}	Same

[a] Maximum rate of urinary drug excretion.

the C_{max} for A is higher than that for B, because the rate of drug absorption is more rapid.

The C_{max} is generally higher when the extent of drug bioavailability is greater. The rate of drug absorption from formulation C is the same as that from formulation A, but the extent of drug available is less. The C_{max} for formulation C is less than that for formulation A. The decrease in C_{max} for formulation C is proportional to the decrease in AUC in comparison to the drug plasma level data for formulation A. The corresponding urinary excretion data confirm these observations. These relationships are summarized in Table 15.7. The table illustrates how bioavailability parameters for plasma and urine change when only the extent and rate of bioavailability are changed, respectively. Formulation changes in a drug product may affect both the rate and extent of drug bioavailability.

STUDY SUBMISSION AND DRUG REVIEW PROCESS

The contents of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) are similar in terms of the quality of manufacture (Table 15.8).

TABLE 15.8 NDA Versus ANDA Review Process

BRAND-NAME DRUG NDA REQUIREMENTS	GENERIC DRUG ANDA REQUIREMENTS
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal studies	6. Bioequivalence
7. Clinical studies	
8. Bioavailability	

Source: Center for Drug Evaluation & Research, U.S. Food & Drug Administration.

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The submission for a NDA must contain safety and efficacy study as provided by animal toxicology studies, clinical efficacy studies, and pharmacokinetic/bioavailability studies. For the generic drug manufacturer, the bioequivalence study is the pivotal study in the ANDA that replaces the animal, clinical, and pharmacokinetic studies.

An outline for the submission of a completed bioavailability study for submission to the FDA is shown in Table 15.9. The investigator should be sure that the study has been properly designed, the objectives are clearly defined, and the method of analysis has been validated (ie, shown to measure precisely and accurately the plasma drug concentration). The results are analyzed both statistically and pharmacokinetically. These results, along with case reports and various data supporting the validity of the analytical method, are included in the submission. The FDA reviews the study in detail according to the outline presented in Table 15.10. If necessary, an FDA investigator may inspect both the clinical and analytical facilities used in the study and audit the raw data used in support of the bioavailability study. For ANDA applications, the FDA Office of Generic Drugs reviews the entire ANDA as shown in Figure 15-10. If the application is incomplete, the FDA will not review the submission and the sponsor will receive a Refusal to File letter.

Waivers of *In-Vivo* Bioequivalence Studies (Biowaivers)

In some cases, *in-vitro* dissolution testing may be used in lieu of *in-vivo* bioequivalence studies. When the drug product is in the same dosage form but in different strengths, and is proportionally similar in active and inactive ingredients, an *in-vivo* bioequivalence study of one or more lower strengths can be waived based on the dissolution tests and an *in-vivo* bioequivalence study on the highest strength. Ideally, if there is a strong correlation between dissolution of the drug and the bioavailability of the drug, then the comparative dissolution tests comparing the test product to the reference product should be sufficient to demonstrate bioequivalence. For most drug products, especially immediate-release tablets and capsules, no strong correlation exists, and the FDA requires an *in-vivo* bioequivalence study. For oral solid dosage forms, an *in-vivo* bioequivalence study may be required to support at least one dose strength of the product. Usually, an *in-vivo* bioequivalence study is required for the highest dose strength. If the lower-dose-strength test product is substantially similar in active and inactive ingredients, then only a comparison *in-vitro* dissolution between the test and brand-name formulations may be used.

For example, an immediate-release tablet is available in 200-mg, 100-mg, and 50-mg strengths. The 100- and 50-mg-strength tablets are made the same way as the highest-strength tablet. A human bioequivalence study is performed on the highest or 200-mg strength. Comparative *in-vitro* dissolution studies are performed on the 100-mg and 50-mg dose strengths. If these drug products have no known bioavailability problems, are well absorbed systemically, are well correlated with *in-vitro* dissolution, and have a large margin of safety, then arguments for not performing an *in-vivo* bioavailability study may be valid. Methods for correlation of *in-vitro* dissolution of the drug with *in-vivo* drug bioavailability are discussed in Chapters 14 and 17. The manufacturer does not need to perform additional *in-vivo* bioequivalence studies on the lower-strength products if the products meet all *in-vitro* criteria.

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TABLE 15.9 Proposed Format and Contents of an *in-Vivo* Bioequivalence Study Submission and Accompanying *in-Vitro* Data

Title page
- Study title
- Name of sponsor
- Name and address of clinical laboratory
- Name of principal investigator(s)
- Name of clinical investigator
- Name of analytical laboratory
- Dates of clinical study (start, completion)
- Signature of principal investigator (and date)
- Signature of clinical investigator (and date)

Table of contents

I. Study Résumé
- Product information
- Summary of bioequivalence study
- Summary of bioequivalence data
  - Plasma
  - Urinary excretion
- Figure of mean plasma concentration–time profile
- Figure of mean cumulative urinary excretion
- Figure of mean urinary excretion rates

II. Protocol and Approvals
- Protocol
- Letter of acceptance of protocol from FDA
- Informed consent form
- Letter of approval of Institutional Review Board
- List of members of Institutional Review Board

III. Clinical Study
- Summary of the study
- Details of the study
- Demographic characteristics of the subjects
- Subject assignment in the study
- Mean physical characteristics of subjects arranged by sequence
- Details of clinical activity
- Deviations from protocol
- Vital signs of subjects
- Adverse reactions report

IV. Assay Methodology and Validation
- Assay method description
- Validation procedure
- Summary of validation
- Data on linearity of standard samples
- Data on interday precision and accuracy
- Data on intraday precision and accuracy
- Figure for standard curve(s) for low/high ranges
- Chromatograms of standard and quality control samples
- Sample calculation

V. Pharmacokinetic Parameters and Tests
- Definition and calculations
- Statistical tests
- Drug levels at each sampling time and pharmacokinetic parameters
- Figure of mean plasma concentration–time profile
- Figures of individual subject plasma concentration–time profiles
- Figure of mean cumulative urinary excretion
- Figures of individual subject cumulative urinary excretion
- Figure of mean urinary excretion rates
- Figures of individual subject urinary excretion rates
- Tables of individual subject data arranged by drug, drug/period, drug/sequence

VI. Statistical Analyses
- Statistical considerations
- Summary of statistical significance
- Summary of statistical parameters
- Analysis of variance, least squares estimates and least-squares means
- Assessment of sequence, period, and treatment effects
- 90% Confidence intervals for the difference between Test and Reference products for the log-normal-transformed parameters of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} should be within 80% and 125%

VII. Appendices
- Randomization schedule
- Sample identification codes
- Analytical raw data
- Chromatograms of at least 20% of subjects
- Medical record and clinical reports
- Clinical facilities description
- Analytical facilities description
- *Curricula vitae* of the investigators

VIII. *In-Vitro* Testing
- Dissolution testing
- Dissolution assay methodology
- Content uniformity testing
- Potency determination

IX. Batch Size and Formulation
- Batch record
- Quantitative formulation

Modified from Dighe and Adams (1991), with permission.

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TABLE 15.10 General Elements of a Biopharmaceutics Review

Introduction	Summary and analysis of data
Study design	Comments
Study objective(s)	Deficiencies
Assay description and validation	Recommendation
Assay for individual samples checked	

Dissolution Profile Comparison

Comparative dissolution profiles are used as (1) the basis for formulation development of bioequivalent drug products and proceeding to the pivotal *in-vivo* bioequivalence study; (2) comparative dissolution profiles are used for demonstrating the equivalence of a change in the formulation of a drug product after the drug product has been approved for marketing (see SUPAC in Chapter 16); and (3) the basis of a biowaiver of a lower-strength drug product that is dose proportional in active and inactive ingredients to the higher-strength drug product.

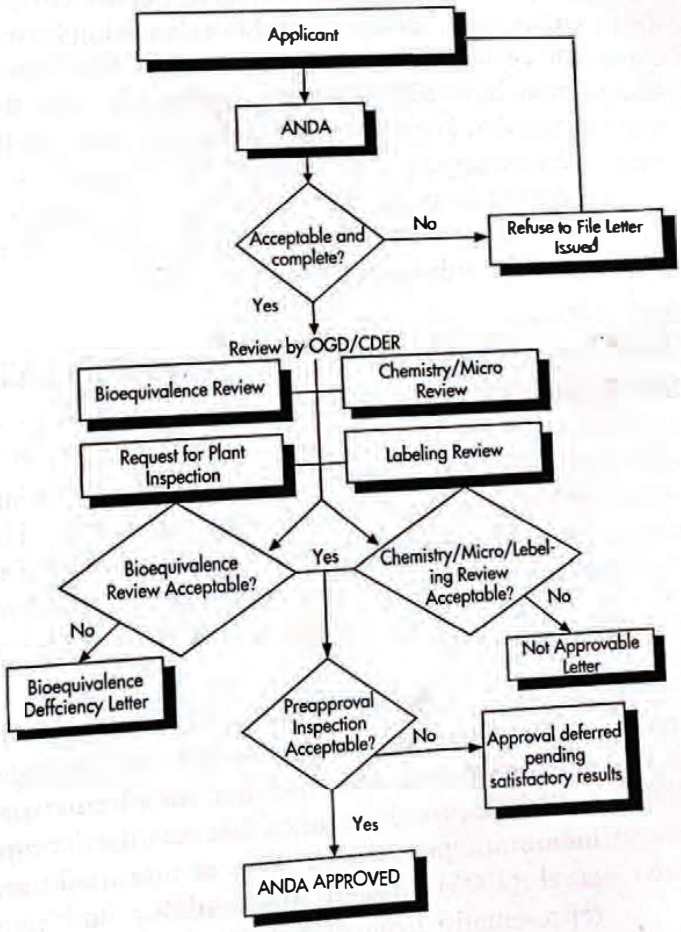


Figure 15-10. Generic drug review process.
Source: Office of Generic Drugs, Center for Drug Evaluation & Research, U.S. Food & Drug Administration.

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A model-independent mathematical method was developed by Moore and Flanner (1996) to compare dissolution profiles using two factors, f_1 and f_2. The factor f_2, known as the *similarity factor*, measures the closeness between the two profiles:

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_1 - T_1)^2 \right]^{-5} \times 100 \right\}$$

where n is the number of time points, R_1 is the dissolution value of the Reference product at time t, and T_1 is the dissolution value of the Test product batch at time t.

The Reference may be the original drug product before a formulation change (prechange) and the Test may be the drug product after the formulation was changed (postchange). Alternatively, the Reference may be the higher-strength drug product and the Test may be the lower-strength drug product. The f_2 comparison is the focus of several FDA guidances and is of regulatory interest in knowing the similarity of the two dissolution curves. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time points results in a f_2 value of 50. The FDA has set a public standard for f_2 value between 50 and 100 to indicate similarity between two dissolution profiles.

In some cases, two generic drug products may have dissimilar dissolution profiles and still be bioequivalent *in-vivo*. For example, Polli et al (1997) have shown that slow-, medium-, and fast-dissolving formulations of metoprolol tartrate tablets were bioequivalent. Furthermore, bioequivalent modified-release drug products may have different drug release mechanisms and therefore different dissolution profiles. For example, for theophylline extended-release capsules, the *United States Pharmacopeia* (USP) lists 10 individual drug release tests for products labeled for dosing every 12 hours. However, only generic drug products that are FDA approved as bioequivalent drug products and listed in the current edition of the *Orange Book* may be substituted for each other.

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

A theoretical basis for correlating *in-vitro* drug dissolution with *in-vivo* bioavailability was developed by Amidon et al (1995). This approach is based on the aqueous solubility of the drug and the permeation of the drug through the gastrointestinal tract. The classification system is based on Fick's first law applied to a membrane:

$$J_w = P_w C_w$$

where J_w is the drug flux (mass/area/time) through the intestinal wall at any position and time, P_w is the permeability of the membrane, and C_w is the drug concentration at the intestinal membrane surface.

This approach assumes that no other components in the formulation affect the membrane permeability and/or intestinal transport. Using this approach, Amidon et al (1995) studied the solubility and permeability characteristics of various representative drugs and obtained a biopharmaceutic drug classification (Table 15.11) for predicting the *in-vitro* drug dissolution of immediate-release solid oral drug products with *in-vivo* absorption.

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TABLE 15.11 Biopharmaceutics Classification System

CLASS	SOLUBILITY	PERMEABILITY	COMMENTS
Class 1	High	High	Drug dissolves rapidly and is well absorbed. Bioavailability problem is not expected for immediate release drug products.
Class 2	Low	High	Drug is dissolution limited and well absorbed. Bioavailability is controlled by the dosage form and rate of release of the drug substance.
Class 3	High	Low	Drug is permeability limited. Bioavailability may be incomplete if drug is not released and dissolved within absorption window.
Class 4	Low	Low	Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed.

From *FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System* (2000), and Amidon et al (1995).

The FDA may waive the requirement for performing an *in-vivo* bioavailability or bioequivalence study for certain immediate-release solid oral drug products that meet very specific criteria, namely, the permeability, solubility, and dissolution of the drug. These characteristics include the *in-vitro* dissolution, of the drug product in various media, drug permeability information, and assuming ideal behavior of the drug product, drug dissolution, and absorption in the GI tract. For regulatory purpose, drugs are classified according to the Biopharmaceutics Classification System (BCS) in accordance the solubility, permeability, and dissolution characteristics of the drug (*FDA Guidance for Industry*, 2000; Amidon et al, 1995).

Solubility

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate physiologic conditions. For this purpose, determination of pH–solubility profiles over a pH range of 1–8 is suggested. The solubility class is determined by calculating what volume of an aqueous medium is sufficient to dissolve the highest anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous medium over the pH range 1–8. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water.

Permeability

Studies of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption > 90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical-chemical properties (eg, octanol: water partition coefficient).

Some methods to determine the permeability of a drug from the gastrointestinal tract include: (1) *in-vivo* intestinal perfusion studies in humans; (2) *in-vivo* or

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in-situ intestinal perfusion studies in animals; (3) *in-vitro* permeation experiments using excised human or animal intestinal tissues; and (4) *in-vitro* permeation experiments across a monolayer of cultured human intestinal cells. When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.

Dissolution

The dissolution class is based on the *in-vitro* dissolution rate of an immediate-release drug product under specified test conditions and is intended to indicate rapid *in-vivo* dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate-release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 minutes using USP Apparatus I (see Chapter 14) at 100 rpm or Apparatus II at 50 rpm in a volume of 900 mL or less in each of the following media: (1) acidic media such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Drug Products for Which Bioavailability or Bioequivalence May Be Self-Evident

The best measure of a drug product's performance is to determine the *in-vivo* bioavailability of the drug. For some well-characterized drug products and for certain drug products in which bioavailability is self-evident (eg, sterile solutions for injection), *in-vivo* bioavailability studies may be unnecessary or unimportant to the achievement of the product's intended purposes. The FDA will waive the requirement for submission of *in-vivo* evidence demonstrating the bioavailability of the drug product if the product meets one of the following criteria (U.S. Code of Federal Regulations, 21 CFR 320.22). However, there may be specific requirements for certain drug products, and the appropriate FDA division should be consulted.

1. The drug product (a) is a solution intended solely for intravenous administration and (b) contains an active drug ingredient or therapeutic moiety combined with the same solvent and in the same concentration as in an intravenous solution that is the subject of an approved, full, New Drug Application.
2. The drug product is a topically applied preparation (eg, a cream, ointment, or gel intended for local therapeutic effect). The FDA has released guidances for the performance of bioequivalence studies on topical corticosteroids and antifungal agents. The FDA is also considering performing dermatopharmacokinetic (DPK) studies on other topical drug products. In addition, *in-vitro* drug release and diffusion studies may be required.
3. The drug product is in an oral dosage form that is not intended to be absorbed (eg, an antacid or a radiopaque medium). Specific *in-vitro* bioequivalence studies may be required by the FDA. For example, the bioequivalence of cholestyramine resin is demonstrated *in-vitro* by the binding of bile acids to the resin.

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4. The drug product meets both of the following conditions:
   a. It is administered by inhalation as a gas or vapor (eg, as a medicinal or as an inhalation anesthetic).
   b. It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved, full, New Drug Application (NDA).
5. The drug product meets all of the following conditions:
   a. It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.
   b. It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved, full, New Drug Application.
   c. It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

GENERIC BIOLOGICS

Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources such as human, animal, or microorganisms. Many biologics are complex mixtures that are not easily identified or characterized and are manufactured by biotechnology. Other biological drugs, such as insulin and growth hormone, are proteins derived by biotechnology and have been well characterized.

Presently, there is no FDA regulatory pathway to establish the bioequivalence of a biotechnology-derived drug product. Scientifically, there are advocates for and against the feasibility for the manufacture of generic biotechnology-derived drug products (generic biologics) that are bioequivalent to the innovator or brand-drug product.

Those opposed to the development of generic biologics have claimed that generic manufacturers do not have the ability to fully characterize the active ingredient(s), that immunogenicity-related impurities may be present in the product, and that the manufacture of a biologic drug product is process dependent.

Many biologic drug products are given parenterally. The efficacy of the biologic may be affected by the development of antibodies to the active ingredient or to product-related impurities. The degree of immunogenicity and subsequent antibody formation to a foreign peptide or protein will alter the efficacy of the drug. Antibodies can increase bioavailability if they are not neutralizing, which would result in higher drug levels in the body. In contrast, antibodies can decrease bioavailability of the biologic drug by forming an antibody–protein complex that results in a change in drug distribution and a change in clearance.

Advocates for the manufacture of generic biologics argue that bioequivalent biotechnology-derived drug products can be made on a case-by-case basis. Currently, manufacturers of marketed biotechnology drugs may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. These manufacturers have developed improvements in production methods, process and control test methods, and test methods for product characterization.

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For example, a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study. The FDA may not require the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. Such manufacturing process changes, implemented before or after product approval, have included changes implemented during expansion from pilot-scale to full-scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the manufacturing process such as fermentation, purification, and formulation. The manufacturer may be able to demonstrate product comparability between a biological product made after a manufacturing change ("new" product) and a product made before implementation of the change ("old" product) through different types of analytical and functional testing, with or without preclinical animal testing. The FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency (*FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products*, 1996). The FDA currently requires that manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the preexisting product. Determinations of product comparability may be based on chemical, physical, and biological assays and, in some cases, other nonclinical data.

It is important to note that the FDA uses such terms as *comparable* and *similar* for approval of manufacturing changes of biologic drug products (*FDA Guidance*, 1996). In contrast, the FDA uses the term *bioequivalence* for approval of manufacturing changes of drug products that contain chemically derived active ingredients. Advocates for the manufacturer of generic biologics feel that the science and technology for the manufacture of certain bioequivalent biologic drug products are already available. Moreover, if the innovator manufacturer of a marketed biologic drug product can perform a manufacturing change and demonstrate the comparability of the "new" to the "old" marketed biologic drug product, then a generic manufacturer should be able to use similar techniques to demonstrate bioequivalence of the generic drug product.

CLINICAL SIGNIFICANCE OF BIOEQUIVALENCE STUDIES

Bioequivalence of different formulations of the same drug substance involves equivalence with respect to rate and extent of systemic drug absorption. Clinical interpretation is important in evaluating the results of a bioequivalence study. A small difference between drug products, even if statistically significant, may produce very little difference in therapeutic response. Generally, two formulations whose rate and extent of absorption differ by 20% or less are considered bioequivalent. The Report by the Bioequivalence Task Force (1988) considered that differences of less than 20% in AUC and C_{max} between drug products are "unlikely to be clinically significant in patients." The Task Force further stated that "clinical studies of effectiveness have difficulty detecting differences in doses of even 50–100%."

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Therefore, normal variation is observed in medical practice and plasma drug levels may vary among individuals greater than 20%.

According to Westlake (1972), a small, statistically significant difference in drug bioavailability from two or more dosage forms may be detected if the study is well controlled and the number of subjects is sufficiently large. When the therapeutic objectives of the drug are considered, an equivalent clinical response should be obtained from the comparison dosage forms if the plasma drug concentrations remain above the minimum effective concentration (MEC) for an appropriate interval and do not reach the minimum toxic concentration (MTC). Therefore, the investigator must consider whether any statistical difference in bioavailability would alter clinical efficiency.

Special populations, such as the elderly or patients on drug therapy, are generally not used for bioequivalence studies. Normal, healthy volunteers are preferred for bioequivalence studies, because these subjects are less at risk and may more easily endure the discomforts of the study, such as blood sampling. Furthermore, the objective of these studies is to evaluate the bioavailability of the drug from the dosage form, and use of healthy subjects should minimize both inter- and intrasubject variability. It is theoretically possible that the excipients in one of the dosage forms tested may pose a problem in a patient who uses the generic dosage form.

For the manufacture of a dosage form, specifications are set to provide uniformity of dosage forms. With proper specifications, quality control procedures should minimize product-to-product variability by different manufacturers and lot-to-lot variability with a single manufacturer (see Chapter 16).

SPECIAL CONCERNS IN BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

The general bioequivalence study designs and evaluation, such as the comparison of AUC, C_{max}, and t_{max}, may be used for systemically absorbed drugs and conventional oral dosage forms. However, for certain drugs and dosage forms, systemic bioavailability and bioequivalence are difficult to ascertain (Table 15.12).

TABLE 15.12 Problems in Bioavailability and Bioequivalence

- Drugs with high intrasubject variability
- Drugs with long elimination half-life
- Biotransformation of drugs
  - Stereoselective drug metabolism
  - Drugs with active metabolites
  - Drugs with polymorphic metabolism
- Nonbioavailable drugs (drugs intended for local effect)
  - Antacids
  - Local anesthetics
  - Anti-infectives
  - Anti-inflammatory steroids
- Dosage forms for nonoral administration
  - Transdermal
  - Inhalation
  - Ophthalmic
  - Intranasal
- Bioavailable drugs that should not produce peak drug levels
  - Potassium supplements
- Endogeneous drug levels
  - Hormone replacement therapy
- Biotechnology-derived drugs
  - Erythropoietin interferon
  - Protease inhibitors
- Complex drug substances
  - Conjugated estrogens

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Drugs and drug products (eg, cyclosporine, chlorpromazine, verapamil, isosorbide dinitrate, sulindac) are considered to be highly variable if the intrasubject variability in bioavailability parameters is greater than 30% by analysis of variance coefficient of variation (Shah et al, 1996). The number of subjects required to demonstrate bioequivalence for these drug products may be excessive, requiring more than 60 subjects to meet current FDA bioequivalence criteria. The intrasubject variability may be due to the drug itself or to the drug formulation or to both. The FDA has held public forums to determine whether the current bioequivalence guidelines need to be changed for these highly variable drugs (Shah et al, 1996).

For drugs with very long elimination half-lives or a complex elimination phase, a complete plasma drug concentration–time curve (ie, three elimination half-lives or an AUC representing 90% of the total AUC) may be difficult to obtain for a bioequivalence study using a crossover design. For these drugs, a truncated (shortened) plasma drug concentration–time curve (0–72 hr) may be more practical. The use of a truncated plasma drug concentration-time curve allows for the measurement of peak absorption and decreases the time and cost for performing the bioequivalence study.

Many drugs are stereoisomers, and each isomer may give a different pharmacodynamic response and may have a different rate of biotransformation. The bioavailability of the individual isomers may be difficult to measure because of problems in analysis. Some drugs have active metabolites, which should be quantitated as well as the parent drug. Drugs such as thioridazine and selegilene have two active metabolites. The question for such drugs is whether bioequivalence should be proven by matching the bioavailability of both metabolites and the parent drug. Assuming both biotransformation pathways follow first-order reaction kinetics, then the metabolites should be in constant ratio to the parent drug. Genetic variation in metabolism may present a bioequivalence problem. For example, the acetylation of procainamide to N-acetylprocainamide demonstrates genetic polymorphism, with two groups of subjects consisting of rapid acetylators and slow acetylators. To decrease intersubject variability, a bioequivalence study may be performed on only one phenotype, such as the rapid acetylators.

Some drugs (eg, benzocaine, hydrocortisone, anti-infectives, antacids) are intended for local effect and formulated as topical ointments, oral suspensions, or rectal suppositories. These drugs should not have significant systemic bioavailability from the site of administration. The bioequivalence determination for drugs that are not absorbed systemically from the site of application can be difficult to assess. For these nonsystemic-absorbable drugs, a "surrogate" marker is needed for bioequivalence determination (Table 15.13). For example, the acid-neutralizing capacity of an oral antacid and the binding of bile acids to cholestyramine resin have been used as surrogate markers in lieu of *in-vivo* bioequivalence studies.

Various drug delivery systems and newer dosage forms are designed to deliver the drug by a nonoral route, which may produce only partial systemic bioavailability. For the treatment of asthma, inhalation of the drug (eg, albuterol, beclomethasone dipropionate) has been used to maximize drug in the respiratory passages and to decrease systemic side effects. Drugs such as nitroglycerin given transdermally may differ in release rates, in the amount of drug in the transdermal delivery system,

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TABLE 15.13 Possible Surrogate Markers for Bioequivalence Studies

DRUG PRODUCT	DRUG	POSSIBLE SURROGATE MARKER FOR BIOEQUIVALENCE
Metered-dose inhaler	Albuterol	Forced expiratory volume (FEV_1)
Topical steroid	Hydrocortisone	Skin blanching
Anion-exchange resin	Cholestyramine	Binding to bile acids
Antacid	Magnesium and aluminum hydroxide gel	Neutralization of acid
Topical antifungal	Ketoconazole	Drug uptake into stratum corneum

and in the surface area of the skin to which the transdermal delivery system is applied. Thus, the determination of bioequivalence among different manufacturers of transdermal delivery systems for the same active drug is difficult. Dermatokinetics are pharmacokinetic studies that investigate drug uptake into skin layers after topical drug administration. The drug is applied topically, the skin is peeled at various time periods after the dose, using transparent tape, and the drug concentrations are measured in the skin.

Drugs such as potassium supplements are given orally and may not produce the usual bioavailability parameters of AUC, C_{max}, and t_{max}. For these drugs, more indirect methods must be used to ascertain bioequivalence. For example, urinary potassium excretion parameters are more appropriate for the measurement of bioavailability of potassium supplements. However, for certain hormonal replacement drugs (eg, levothyroxine), the steady-state hormone concentration in hypothyroid individuals, the thyroidal-stimulating hormone level, and pharmacodynamic endpoints may also be appropriate to measure.

GENERIC SUBSTITUTION

To contain drug costs, most states have adopted generic substitution laws to allow pharmacists to dispense a generic drug product for a brand-name drug product that has been prescribed. Some states have adopted a *positive formulary*, which lists therapeutically equivalent or interchangeable drug products that pharmacists may dispense. Other states use a *negative formulary*, which lists drug products that are not therapeutically equivalent, and/or the interchange of which is prohibited. If the drug is not in the negative formulary, the unlisted generic drug products are assumed to be therapeutically equivalent and may be interchanged.

Approved Drug Products with Therapeutic Equivalence Evaluations (*Orange Book*)

Due to public demand, the FDA Center for Drug Evaluation and Research publishes annually a listing of approved drug products, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the *Orange Book*). The Orange Book is available on the Internet at www.fda.gov/cder/ob/default.htm.

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TABLE 15.14 Therapeutic Equivalence Evaluation Codes

A Codes

Drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products

- AA Products in conventional dosage forms not presenting bioequivalence problems
- AB Products meeting bioequivalence requirements
- AN Solutions and powders for aerosolization
- AO Injectable oil solutions
- AP Injectable aqueous solutions
- AT Topical products

B Codes

Drug products that the FDA does not consider to be therapeutically equivalent to other pharmaceutically equivalent products

- B* Drug products requiring further FDA investigation and review to determine therapeutic equivalence
- BC Extended-release tablets, extended-release capsules, and extended-release injectables
- BD Active ingredients and dosage forms with documented bioequivalence problems
- BE Delayed-release oral dosage forms
- BN Products in aerosol–nebulizer drug delivery systems
- BP Active ingredients and dosage forms with potential bioequivalence problems
- BR Suppositories or enemas for systemic use
- BS Products having drug standard deficiencies
- BT Topical products with bioequivalence issues
- BX Insufficient data

Adopted from: *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) (www.fda.cder/ob/default.htm) 2003.

The Orange Book contains therapeutic equivalence evaluations for approved drug products made by various manufacturers. These marketed drug products are evaluated according to specific criteria. The evaluation codes used for these drugs are listed in Table 15.14. The drug products are divided into two major categories: "A" codes apply to drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products, and "B" codes apply to drug products that the FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products. A list of therapeutic-equivalence-related terms and their definitions is also given in the monograph. According to the FDA, evaluations do not mandate that drugs be purchased, prescribed, or dispensed, but provide public information and advice. The FDA evaluation of the drug products should be used as a guide only, with the practitioner exercising professional care and judgment.

The concept of therapeutic equivalence as used to develop the Orange Book applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (eg, propoxyphene hydrochloride versus pentazocine hydrochloride for the treatment of pain). Any drug product in the Orange Book that is repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as nonequivalent

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(eg, BN). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications. With this limitation, however, the FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product (www.fda.gov/cder/ob/default.htm).

Professional care and judgment should be exercised in using the Orange Book. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by the FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of the FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.



FREQUENTLY ASKED QUESTIONS

1. Why are preclinical animal toxicology studies and clinical efficacy drug studies in human subjects not required by the FDA to approve a generic drug product as a therapeutic equivalent to the brand-name drug product?
2. What do sequence, washout period, and period mean in a crossover bioavailability study?
3. Why does the FDA require a food intervention (food effect) study for some generic drug products before granting approval? For which drug products are food effect studies required?

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4. What type of bioequivalence studies are required for drugs that are not systemically absorbed or for those drugs in which the C_{max} and AUC cannot be measured in the plasma?
5. How does inter- and intrasubject variability affect the statistical demonstration of bioequivalence for a drug product?
6. Can chemically equivalent drug products that are not bioequivalent (ie, bioinequivalent) to each other have similar clinical efficacy?



LEARNING QUESTIONS

1. An antibiotic was formulated into two different oral dosage forms, A and B. Biopharmaceutic studies revealed different antibiotic blood level curves for each drug product (Fig. 15-11). Each drug product was given in the same dose as the other. Explain how the various possible formulation factors could have caused the differences in blood levels. Give examples where possible. How would the corresponding urinary drug excretion curves relate to the plasma level–time curves?
2. Assume that you have just made a new formulation of acetaminophen. Design a protocol to compare your drug product against the acetaminophen drug products on the market. What criteria would you use for proof of bioequivalence for your new formulation? How would you determine if the acetaminophen was completely (100%) systemically absorbed?
3. The data in Table 15.15 represent the average findings in antibiotic plasma samples taken from 10 humans (average weight 70 kg), tabulated in a four-way crossover design.
   a. Which of the four drug products in Table 15.15 would be preferred as a reference standard for the determination of relative bioavailability? Why?

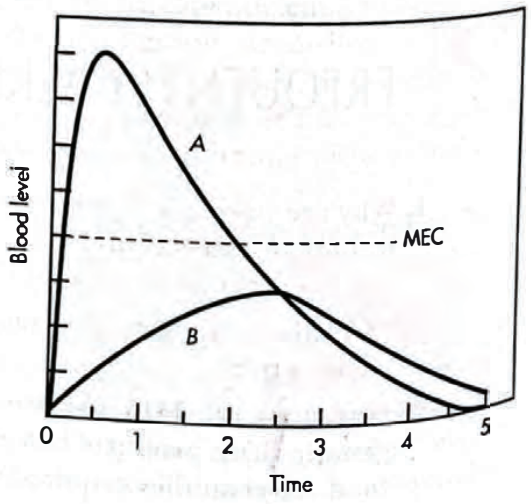


Figure 15-11. Blood-level curves for two different oral dosage forms of a hypothetical antibiotic.

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TABLE 15.15 Comparison of Plasma Concentrations of Antibiotic, as Related to Dosage Form and Time

TIME AFTER DOSE (hr)	PLASMA CONCENTRATION (μg/ml)			
	IV Solution (2 mg/kg)	Oral Solution (10 mg/kg)	Oral Tablet (10 mg/kg)	Oral Capsule (10 mg/kg)
0.5	5.94	23.4	13.2	18.7
1.0	5.30	26.6	18.0	21.3
1.5	4.72	25.2	19.0	20.1
2.0	4.21	22.8	18.3	18.2
3.0	3.34	18.2	15.4	14.6
4.0	2.66	14.5	12.5	11.6
6.0	1.68	9.14	7.92	7.31
8.0	1.06	5.77	5.00	4.61
10.0	0.67	3.64	3.16	2.91
12.0	0.42	2.30	1.99	1.83
$AUC\left(\frac{\mu g}{mL} \times hr\right)$	29.0	145.0	116.0	116.0

b. From which oral drug product is the drug absorbed more rapidly?

c. What is the absolute bioavailability of the drug from the oral solution?

d. What is the relative bioavailability of the drug from the oral tablet compared to the reference standard?

e. From the data in Table 15.15, determine:

(1) Apparent V_D

(2) Elimination $t_{1/2}$

(3) First-order elimination rate constant k

(4) Total body clearance

f. From the data above, graph the cumulative urinary excretion curves that would correspond to the plasma concentration time curves.

4. Aphrodisia is a new drug manufactured by the Venus Drug Company. When tested in humans, the pharmacokinetics of the drug assume a one-compartment open model with first-order absorption and first-order elimination:

$$D_{GI} \xrightarrow{k_a} D_B V_D \xrightarrow{k}$$

The drug was given in a single oral dose of 250 mg to a group of college students 21–29 years of age. Mean body weight was 60 kg. Samples of blood were obtained at various time intervals after the administration of the drug, and the plasma fractions were analyzed for active drug. The data are summarized in Table 15.16.

a. The minimum effective concentration of Aphrodisia in plasma is 2.3 μg/mL. What is the onset time of this drug?

b. The minimum effective concentration of Aphrodisia in plasma is 2.3 μg/mL. What is the duration of activity of this drug?

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TABLE 15.16 Data Summary of Active Drug Concentration in Plasma Fractions

TIME (hr)	C_p (μg/mL)	TIME (hr)	C_p (μg/mL)
0	0	12	3.02
1	1.88	18	1.86
2	3.05	24	1.12
3	3.74	36	0.40
5	4.21	48	0.14
7	4.08	60	0.05
9	3.70	72	0.02

c. What is the elimination half-life of Aphrodisia in college students?

d. What is the time for peak drug concentration (t_{max}) of Aphrodisia?

e. What is the peak drug concentration (C_{max})?

f. Assuming that the drug is 100% systemically available (ie, fraction of drug absorbed equals unity), what is the AUC for Aphrodisia?

5. You wish to do a bioequivalence study on three different formulations of the same active drug. Lay out a Latin-square design for the proper sequencing of these drug products in six normal, healthy volunteers. What is the main reason for using a crossover design in a bioequivalence study? What is meant by a "random" population?

6. Four different drug products containing the same antibiotic were given to 12 volunteer adult males (age 19–28 years, average weight 73 kg) in a four-way crossover design. The volunteers were fasted for 12 hours prior to taking the drug product. Urine samples were collected up to 72 hours after the administration of the drug to obtain the maximum urinary drug excretion, D_u^∞. The data are presented in Table 15.17.

a. What is the absolute bioavailability of the drug from the tablet?

b. What is the relative bioavailability of the capsule compared to the oral solution?

7. According to the prescribing information for cimetidine (Tagamet), following IV or IM administration, 75% of the drug is recovered from the urine after 24 hours as the parent compound. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. From this information, determine what fraction of the drug is absorbed systemically from an oral dose after 24 hours.

TABLE 15.17 Urinary Drug Excretion Data Summary

DRUG PRODUCT	DOSE (mg/kg)	CUMULATIVE URINARY DRUG EXCRETION (D_u^∞), 0–72 hr (mg)
IV solution	0.2	20
Oral solution	4	380
Oral tablet	4	340
Oral capsule	4	360

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TABLE 15.18 Blood Level Data Summary for Two Drug Products

KINETIC VARIABLE	UNIT	DRUG PRODUCT A 4 × 250-mg Tablet	DRUG PRODUCT B 1000-mg Tablet	STATISTIC
Time for peak drug concentration (range)	hr	1.3 (0.7–1.5)	1.8 (1.5–2.2)	$p < 0.05$
Peak concentration (range)	μg/mL	53 (46–58)	47 (42–51)	$p < 0.05$
AUC (range)	μg hr/mL	118 (98–125)	103 (90–120)	NS
$t_{1/2}$	hr	3.2 (2.5–3.8)	3.8 (2.9–4.3)	NS

8. Define *bioequivalence requirement.* Why does the FDA require a bioequivalence requirement for the manufacture of a generic drug product?
9. Why can we use the time for peak drug concentration (t_{max}) in a bioequivalence study for an estimate of the rate of drug absorption, rather than calculating the k_a?
10. Ten male volunteers (18–26 years of age) weighing an average of 73 kg were given either 4 tablets each containing 250 mg of drug (drug product A) or 1 tablet containing 1000 mg of drug (drug product B). Blood levels of the drug were obtained and the data are summarized in Table 15.18.
    a. State a possible reason for the difference in the time for peak drug concentration ($t_{max,A}$) after drug product A compared to the $t_{max,B}$ after drug product B. (Assume that all the tablets were made from the same formulation—that is, the drug is in the same particle size, same salt form, same excipients, and same ratio of excipients to active drug.)
    b. Draw a graph relating the cumulative amount of drug excreted in urine of patients given drug product A compared to the cumulative drug excreted in urine after drug product B. Label axes!
    c. In a second study using the same 10 male volunteers, a 125-mg dose of the drug was given by IV bolus and the AUC was computed as 20 μg hr/mL. Calculate the fraction of drug systemically absorbed from drug product B (1 × 1000 mg) tablet using the data in Table 15.19.
11. After performing a bioequivalence test comparing a generic drug product to a brand-name drug product, it was observed that the generic drug product had greater bioavailability than the brand-name drug product.
    a. Would you approve marketing the generic drug product, claiming it was superior to the brand-name drug product?
    b. Would you expect identical pharmacodynamic responses to both drug products?
    c. What therapeutic problem might arise in using the generic drug product that might not occur when using the brand-name drug product?

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TABLE 15.19 Disintegration Times and Dissolution Rates of Tolazamide Tablets[a]

TABLET	MEAN DISINTEGRATION TIME[b] MIN (RANGE)	PERCENT DISSOLVED IN 30 MIN[c] (RANGE)
A	3.8 (3.0–4.0)	103.9 (100.5–106.3)
B	2.2 (1.8–2.5)	10.9 (9.3–13.5)
C	2.3 (2.0–2.5)	31.6 (26.4–37.2)
D	26.5 (22.5–30.5)	29.7 (20.8–38.4)

[a] $N = 6$.
[b] By the method of USP-23.
[c] Dissolution rates in pH 7.6 buffer.

From Welling et al (1982), with permission.

12. The following study is from Welling and associates (1982):

Tolazamide Formulations. Four tolazamide tablet formulations were selected for this study. The tablet formulations were labeled A, B, C, and D. Disintegration and dissolution tests were performed by standard USP-23 procedures.

Subjects. Twenty healthy adult male volunteers between the ages of 18 and 38 (mean, 26 years) and weighing between 61.4 and 95.5 kg (mean, 74.5 kg) were selected for the study. The subjects were randomly assigned to 4 groups of 5 each. The four treatments were administered according to 4×4 Latin-square design. Each treatment was separated by 1-week intervals. All subjects fasted overnight before receiving the tolazamide tablet the following morning. The tablet was given with 180 mL of water. Food intake was allowed at 5 hours postdose. Blood samples (10 mL) were taken just before the dose and periodically after dosing. The serum fraction was separated from the blood and analyzed for tolazamide by high-pressure liquid chromatography.

Data Analysis. Serum data were analyzed by a digital computer program using a regression analysis and by the percent of drug unabsorbed by the method of Wagner and Nelson, 1963 (see Chapter 7). AUC was determined by the trapezoidal rule and an analysis of variance was determined by Tukey's method.

a. Why was a Latin-square crossover design used in this study?

b. Why were the subjects fasted before being given the tolazamide tablets?

c. Why did the authors use the Wagner–Nelson method rather than the Loo–Riegelman method for measuring the amount of drug absorbed?

d. From the data in Table 15.20 only, from which tablet formulation would you expect the highest bioavailability? Why?

e. From the data in Table 15.20, did the disintegration times correlate with the dissolution times? Why?

f. Do the data in Table 15.20 appear to correlate with the data in Table 15.19? Why?

g. Draw the expected cumulative urinary excretion–time curve for formulations A and B. Label axes and identify each curve.

h. Assuming formulation A is the reference formulation, what is the relative bioavailability of formulation D?

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TABLE 15.20 Mean Tolazamide Concentrations[a] in Serum

TIME (hr)	TREATMENT (μg/mL) A	B	C	D	STATISTIC[b]
0	10.8 ± 7.4	1.3 ± 1.4	1.8 ± 1.9	3.5 ± 2.6	ADCB
1	20.5 ± 7.3	2.8 ± 2.8	5.4 ± 4.8	13.5 ± 6.6	ADCB
3	23.9 ± 5.3	4.4 ± 4.3	9.8 ± 5.6	20.0 ± 6.4	ADCB
4	25.4 ± 5.2	5.7 ± 4.1	13.6 ± 5.3	22.0 ± 5.4	ADCB
5	24.1 ± 6.3	6.6 ± 4.0	15.1 ± 4.7	22.6 ± 5.0	ADCB
6	19.9 ± 5.9	6.8 ± 3.4	14.3 ± 3.9	19.7 ± 4.7	ADCB
8	15.2 ± 5.5	6.6 ± 3.2	12.8 ± 4.1	14.6 ± 4.2	ADCB
12	8.8 ± 4.8	5.5 ± 3.2	9.1 ± 4.0	8.5 ± 4.1	CADB
16	5.6 ± 3.8	4.6 ± 3.3	6.4 ± 3.9	5.4 ± 3.1	CADB
24	2.7 ± 2.4	3.1 ± 2.6	3.1 ± 3.3	2.4 ± 1.8	CBAD
C_{max}, μg/mL[c]	27.8 ± 5.3	7.7 ± 4.1	16.4 ± 4.4	24.0 ± 4.5	ADCB
t_{max}, hr[d]	3.3 ± 0.9	7.0 ± 2.2	5.4 ± 2.0	4.0 ± 0.9	BCDA
$AUC_{0\text{-}24}$, μg hr/mL[e]	260 ± 81	112 ± 63	193 ± 70	231 ± 67	ADCB

[a]Concentrations ± 1 SD, $n = 20$.
[b]For explanation see text.
[c]Maximum concentration of tolazamide in serum.
[d]Time of maximum concentration.
[e]Area under the 0–24-hr serum tolazamide concentration curve calculated by trapezoidal rule.

From Welling et al (1982), with permission.

i. Using the data in Table 15.20 for formulation A, calculate the elimination half-life ($t_{1/2}$) for tolazamide.

13. If *in-vitro* drug dissolution and/or release studies for an oral solid dosage form (eg, tablet) does not correlate with the bioavailability of the drug *in-vivo*, why should the pharmaceutical manufacturer continue to perform *in-vitro* release studies for each production batch of the solid dosage form?

14. Is it possible for two pharmaceutically equivalent solid dosage forms containing different inactive ingredients (ie, excipients) to demonstrate bioequivalence *in-vivo* even though these drug products demonstrate differences in drug dissolution tests *in-vitro*?

15. For bioequivalence studies, t_{max}, C_{max}, and AUC, along with an appropriate statistical analyses, are the parameters generally used to demonstrate the bioequivalence of two similar drug products containing the same active drug.

a. Why are the parameters t_{max}, C_{max}, and AUC acceptable for proving that two drug products are bioequivalent?

b. Are pharmacokinetic models needed in the evaluation of bioequivalence?

c. Is it necessary to use a pharmacokinetic model to completely describe the plasma drug concentration–time curve for the determination of t_{max}, C_{max}, and AUC?

d. Why are log-transformed data used for the statistical evaluation of bioequivalence?

e. What is an add-on study?

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REFERENCES

Amidon, GL, Lennernas H, Shah VP, Crison JR: A theoretical basis for a biopharmaceutic drug classification: The correlation of *in-vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res* 12:413–420, 1995

Dighe SV, Adams WP: Bioequivalence: A United States regulatory perspective. In Welling PG, Tse FLS, Dighe SV (eds), *Pharmaceutical Bioequivalence.* New York, Marcel Dekker, 1991, chap 12

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996

FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations, March 2003

FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997

FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001

FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System, August 2000

Feldman CH, Hutchinson VE, Sher TH, et al: Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* 4:69–76, 1982

Gardner S: Bioequivalence requirements and *in vivo* bioavailability procedures. *Fed Reg* 42:1651, 1977

Hendles L, Iafrate RP, Weinberger M: A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. *Clin Pharmacokinet* 9:95–135, 1984

Midha KA, Ormsby ED, Hubbard JW, McKay G, Hawes EM, Gavalas, McGilvery IJ: Logarithmic transformation in bioequivalence: Application with two formulations of perphenazine. *J Pharm Sci* 82:138–144, 1993

Moore JW, Flanner HH: Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. *Pharm Tech* 20(6):64–74, 1996

Mordenti J, Cavagnaro JA, Green JD: Design of biological equivalence programs for therapeutic biotechnology products in clinical development: A perspective. *Pharm Res* 13:1427–1437, 1996

Polli JE, Rekhi GS, Augsburger LL, Shah VP: Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. *J Pharm Sci* 86(6):690–700, 1997

Purich E: Bioavailability/bioequivalence regulations: An FDA perspective. In Albert KS (ed), *Drug Absorption and Disposition, Statistical Considerations.* Washington, DC, American Pharmaceutical Association, 1980

Report by the Bioequivalence Task Force 1988 on Recommendations from the Bioequivalence Hearings Conducted by the Food and Drug Administration, Sept 29–Oct 1, 1986. Rockville, MD, FDA, 1988

Schuirmann DJ: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharmaceut* 15:657–680, 1987

Shah P, Yacobi A, Barr WH, Benet LZ, Breimer D, et al: Evaluation of orally administered highly variable drugs and drug formulations. *Pharm Res* 13:1590–1595, 1996

Wagner JG, Nelson E: Percent absorbed time plots from blood level and for urinary excretion data. *J Pharm Sci* 52:610–61, 1963

Welling PG, Patel RB, Patel UR, et al: Bioavailability of tolazamide from tablets: Comparison of *in vitro* and *in vivo* results. *J Pharm Sci* 71:1259–1263, 1982

Westlake WJ: Use of confidence intervals in analysis of comparative bioavailability trials. *J Pharm Sci* 61:1340–1341, 1972

Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS: Biopharmaceutics classification system: The scientific basis for biowaiver extensions. *Pharm Res* 19(7):921–925, 2002

BIBLIOGRAPHY

Abdou HM: *Dissolution, Bioavailability and Bioequivalence.* Easton, PA, Mack, 1989

Bennett RW, Popovitch NG: Statistical inferences as applied to bioavailability data: A guide for the practicing pharmacist. *Am J Hosp Pharm* 34:712–723, 1977

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Chodes DJ, DiSanto AR: *Basics of Bioavailability.* Kalamazoo, MI, Upjohn, 1974
Dighe SV: Biopharmaceutics program. *Clin Res Pract Drug Res Aff* 1:61–76, 1983
DiSanto AR, Desante KA: Bioavailability and pharmacokinetics of prednisone in humans. *J Pharm Sci* 64:109–112, 1975
Hendeles L, Wienberger M, Bighley L: Absolute bioavailability of oral theophylline. *Am J Hosp Pharm* 34:525–527, 1977
Kennedy D: Therapeutically equivalent drugs. *Fed Reg* 44:2932–2952, 1979
Martin A, Dolusio JT (eds): *Industrial Bioavailability and Pharmacokinetics: Guidelines, Regulations and Controls.* Austin, TX, Austin Drug Dynamics Institute, University of Texas, 1977
Metzler CM: Bioavailability: A problem in equivalence. *Biometrics* 30:309–317, 1974
Report of the Blue Ribbon Committee on Generic Medicines. Generic Medicines: Restoring Public Confidence. Rockville, MD, FDA, 1990
Schumacher GE: Use of bioavailability data by practitioners, I. Pitfalls in interpreting the data. *Am J Hosp Pharm* 32:839–842, 1975
Schumacher GE: Interpretation of bioavailability data by practitioners. *J Clin Pharmacol* 16:554–559, 1976
Wagner JG: An overview of the analysis and interpretation of bioavailability studies in man. *Pharmacology* 8:102–117, 1972
Welling PG, Tse FLS, Dighe SV (eds): *Pharmaceutical Bioequivalence.* New York, Marcel Dekker, 1991
Westlake WJ: The design and analysis of comparative blood level trials. In Swarbrick J (ed), *Current Concepts in Pharmaceutical Sciences: Dosage Form Design and Bioavailability.* Philadelphia, Lea & Febiger, 1973, chap 5
Westlake WJ: Use of statistical methods in evaluation of *in vivo* performance of dosage forms. *J Pharm Sci* 62:1579–1589, 1973

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19

RELATIONSHIP BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS

PHARMACODYNAMICS AND PHARMACOKINETICS

Previous chapters in this book have discussed the importance of using pharmacokinetics to develop dosing regimens that will result in plasma concentrations in the therapeutic window and yield the desired therapeutic or pharmacologic response. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacodynamic or pharmacologic response. The term *pharmacodynamics* refers to the relationship between drug concentrations at the site of action (receptor) and pharmacologic response, including the biochemical and physiologic effects that influence the interaction of drug with the receptor. Early pharmacologic research demonstrated that the pharmacodynamic response produced by the drug depends on the chemical structure of the drug molecule. Drug receptors interact only with drugs of specific chemical structure, and the receptors were classified according to the type of pharmacodynamic response induced.

Since most pharmacologic responses are due to noncovalent interaction between the drug and the receptor, the nature of the interaction is generally assumed to be reversible and conforms to the *Law of Mass Action*. One or several drug molecules may interact simultaneously with the receptor to produce a pharmacologic response. Typically, a single drug molecule interacts with a receptor with a single binding site to produce a pharmacologic response, as illustrated below.

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$$[\text{Drug}] + [\text{receptor}] \Leftrightarrow [\text{drug–receptor complex}] \rightarrow \text{response}$$

where the brackets [ ] denote molar concentrations. This scheme illustrates the *occupation theory* and the interaction of a drug molecule with a receptor molecule. The following assumptions are made in this model.

1. The drug molecule combines with the receptor molecule as a bimolecular association, and the resulting drug–receptor complex disassociates as a unimolecular entity.
2. The binding of drug with the receptor is fully reversible.
3. The basic model assumes a single type of receptor binding site, with one binding site per receptor molecule. It is also assumed that a receptor with multiple sites may be modeled after this (Taylor and Insel, 1990).

It is assumed that the occupancy of the drug molecule at one receptor site does not change the affinity of more drug molecules to complex at additional receptor sites. However, the model is not suitable for drugs with *allosteric* binding to receptors, in which the binding of one drug molecule to the receptor affects the binding of subsequent drug molecules, as in the case of oxygen molecules binding to iron in hemoglobin. As more receptors are occupied by drug molecules, a greater pharmacodynamic response is obtained until a maximum response is reached.

The receptor occupancy concept was extended to show how drugs elicit a pharmacologic response as an *agonist,* or produce an opposing pharmacologic response as an *antagonist* through drug–receptor interactions. Basically, three types of related responses may occur at the receptor: (1) a drug molecule that interacts with the receptor and elicits a maximal pharmacologic response is referred to as an *agonist;* (2) a drug that elicits a partial (below maximal) response is termed a *partial agonist;* and (3) an agent that elicits no response from the receptor, but inhibits the receptor interaction of a second agent, is termed an *antagonist.* An antagonist may prevent the action of an agonist by competitive (reversible) or noncompetitive (irreversible) inhibition.

Spare, unoccupied receptors are assumed to be present at the site of action, because a maximal pharmacologic response may be obtained when only a small fraction of the receptors are occupied by drug molecules. Equimolar concentrations of different drug molecules that normally bind to the same receptor may give different degrees of pharmacologic response. The term *intrinsic activity* is used to distinguish the relative extent of pharmacologic response between different drug molecules that bind to the same receptor. The *potency* of a drug is the concentration of drug needed to obtain a specific pharmacologic effect, such as the EC_{50} (see E_{max} model, below).

The receptor occupation theory, however, was not consistent with all kinetic observations. An alternative theory, known as the *rate theory,* essentially states that the pharmacologic response is not dependent on drug–receptor complex concentration but rather depends on the rate of association of the drug and the receptor. Each time a drug molecule "hits" a receptor, a response is produced, similar to a ball bouncing back and forth from the receptor site. The rate theory predicts that an agonist will associate rapidly to form a receptor complex, which dissociates rapidly to produce a response. An antagonist associates rapidly to form a receptor–drug complex and dissociates slowly to maintain the antagonist response.

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Both theories are consistent with the observed saturation *(sigmoidal)* drug–dose response relationships, but neither theory is sufficiently advanced to give a detailed description of the "lock-and-key" or the more recent "induced-fit" type of drug interactions with enzymatic receptors. Newer theories of drug action are based on *in-vitro* studies on isolated tissue receptors and on observation of the conformational and binding changes with different drug substrates. These *in-vitro* studies show that other types of interactions between the drug molecule and the receptor are possible. However, the results from the *in-vitro* studies are difficult to extrapolate to *in-vivo* conditions. The pharmacologic response in drug therapy is often a product of physiologic adaptation to a drug response. Many drugs trigger the pharmacologic response through a cascade of enzymatic events highly regulated by the body.

Unlike pharmacokinetic modeling, pharmacodynamic modeling can be more complex because the clinical measure (change in blood pressure or clotting time) is often a surrogate for the drug's actual pharmacologic action. For example, after the drug is systemically absorbed, it is then transported to site of action where the pharmacologic receptor resides. Drug–receptor binding may then cause a secondary response, such as signal transduction, which then produces the desired effect. Clinical measurement of drug response may only occur after many such biologic events, such as transport or signal transduction (an *indirect effect*), so pharmacodynamic modeling must account for biologic processes involved in eliciting drug-induced responses.

The complexity of the molecular events triggering a pharmacologic response is less difficult to describe using a pharmacokinetic approach. Pharmacokinetic models allow very complex processes to be simplified. The process of pharmacokinetic modeling continues until a model is found that describes the real process quantitatively. The understanding of drug response is greatly enhanced when pharmacokinetic modeling techniques are combined with clinical pharmacology, resulting in the development of *pharmacokinetic–pharmacodynamic models.* Pharmacokinetic–pharmacodynamic models use data derived from the plasma drug concentration-versus-time profile and from the time course of the pharmacologic effect to predict the pharmacodynamics of the drug. Pharmacokinetic–pharmacodynamic models have been reported for antipsychotic medications, anticoagulants, neuromuscular blockers, antihypertensives, anesthetics, and many antiarrhythmic drugs (the pharmacologic responses of these drugs are well studied because of easy monitoring).

RELATION OF DOSE TO PHARMACOLOGIC EFFECT

The onset, intensity, and duration of the pharmacologic effect depend on the dose and the pharmacokinetics of the drug. As the dose increases, the drug concentration at the receptor site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum effect at the plateau (Fig. 19-1). The same data may be compressed and plotted on a log–linear scale and results in a sigmoid curve (Fig. 19-2).

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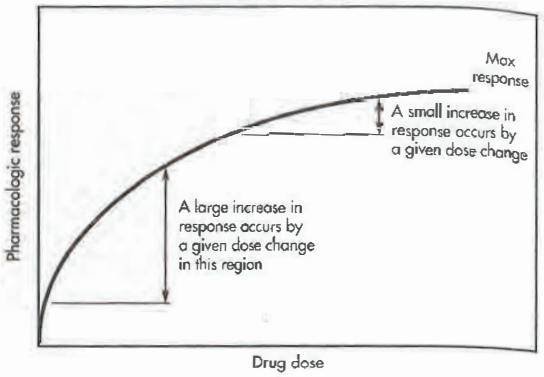


Figure 19-1. Plot of pharmacologic response versus dose on a linear scale.

For many drugs, the graph of log dose–response curve shows a linear relationship at a dose range between 20% and 80% of the maximum response, which typically includes the therapeutic dose range for many drugs. For a drug that follows one-compartment pharmacokinetics, the volume of distribution is constant; therefore, the pharmacologic response is also proportional to the log plasma drug concentration within a therapeutic range, as shown in Figure 19-3.

Mathematically, the relationship in Figure 19-3 may be expressed by the following equation, where m is the slope, e is an extrapolated intercept, and E is the drug effect at drug concentration C:

$$E = m \log C + e \tag{19.1}$$

Solving for log C yields

$$\log C = \frac{E - e}{m} \tag{19.2}$$

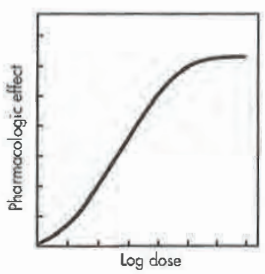


Figure 19-2. Typical log dose versus pharmacologic response curve.

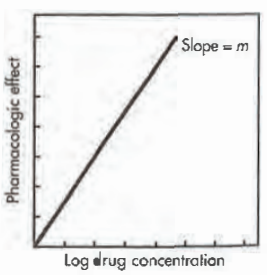


Figure 19-3. Graph of log drug concentration versus pharmacologic effect. Only the linear portion of the curve is shown.

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However, after an intravenous dose, the concentration of a drug in the body in a one-compartment open model is described as follows:

$$\log C = \log C_0 - \frac{kt}{2.3} \tag{19.3}$$

By substituting Equation 19.2 into Equation 19.3, we get Equation 19.4, where E_0 = effect at concentration C_0:

$$\frac{E - e}{m} = \frac{E_0 - e}{m} - \frac{kt}{2.3}$$

$$E = E_0 - \frac{kmt}{2.3} \tag{19.4}$$

The theoretical pharmacologic response at any time after an intravenous dose of a drug may be calculated using Equation 19.4. Equation 19.4 predicts that the pharmacologic effect will decline linearly with time for a drug that follows a one-compartment model, with a linear log dose–pharmacologic response. From this equation, the pharmacologic effect declines with a slope of $km/2.3$. The decrease in pharmacologic effect is affected by both the elimination constant k and the slope m. For a drug with a large m, the pharmacologic response declines rapidly and multiple doses must be given at short intervals to maintain the pharmacologic effect.

The relationship between pharmacokinetics and pharmacologic response can be demonstrated by observing the percent depression of muscular activity after an IV dose of (+)-tubocurarine. The decline of pharmacologic effect is linear as a function of time (Fig. 19-4). For each dose and resulting pharmacologic response, the slope of each curve is the same. Because the values for each slope, which include km (Eq. 19.4), are the same, the sensitivity of the receptors for (+)-tubocurarine is assumed to be the same at each site of action. Note that a plot of the log concentration of drug versus time yields a straight line.

A second example of the pharmacologic effect declining linearly with time was observed with lysergic acid diethylamide, or LSD (Fig. 19-5). After an IV dose of the drug, log concentrations of drug decreased linearly with time except for a brief distribution period. Furthermore, the pharmacologic effect, as measured by the performance score of each subject, also declined linearly with time. Because the

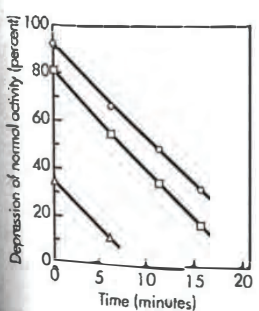


Figure 19-4. Depression of normal muscle activity as a function of time after IV administration of 0.1–0.2 mg (+)-tubocurarine per kilogram to unanesthetized volunteers, presenting mean values of 6 experiments on 5 subjects. Circles represent head lift; squares, hand grip; and triangles, inspiratory flow. (Adapted from Johansen et al, 1964, with permission.)

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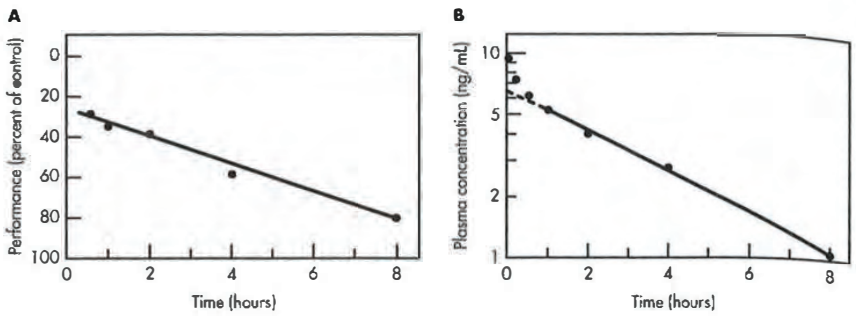


Figure 19-5. Mean plasma concentrations of LSD and performance test scores as a function of time after IV administration of 2 μg LSD per kilogram to 5 normal human subjects. (Adapted from Aghajanian and Bing, 1964, with permission.)

slope is governed in part by the elimination rate constant, the pharmacologic effect declines much more rapidly when the elimination rate constant is increased as a result of increased metabolism or renal excretion. Conversely, a longer pharmacologic response is experienced in patients when the drug has a longer half-life.

RELATIONSHIP BETWEEN DOSE AND DURATION OF ACTIVITY (t_{eff}), SINGLE IV BOLUS INJECTION

The relationship between the duration of the pharmacologic effect and the dose can be inferred from Equation 19.3. After an intravenous dose, assuming a one-compartment model, the time needed for any drug to decline to a concentration C is given by the following equation, assuming the drug takes effect immediately:

$$t = \frac{2.3\,(\log C_0 - \log C)}{k} \tag{19.5}$$

Using C_{eff} to represent the minimum effective drug concentration, the duration of drug action can be obtained as follows:

$$t_{eff} = \frac{2.3[\log\,(D_0/V_D) - \log\,C_{eff}]}{k} \tag{19.6}$$

Some practical applications are suggested by this equation. For example, a doubling of the dose will not result in a doubling of the effective duration of pharmacologic action. On the other hand, a doubling of $t_{1/2}$ or a corresponding decrease in k will result in a proportional increase in duration of action. A clinical situation is often encountered in the treatment of infections in which C_{eff} is the bacteriocidal concentration of the drug, and, in order to double the duration of the antibiotic, a considerably greater increase than simply doubling the dose is necessary.

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PRACTICE PROBLEM

The minimum effective concentration (MEC) in plasma for a certain antibiotic is 0.1 μg/mL. The drug follows a one-compartment open model and has an apparent volume of distribution, V_D, of 10 L and a first-order elimination rate constant of 1.0 hr^{-1}.

a. What is the t_{eff} for a single 100-mg IV dose of this antibiotic?

b. What is the new t_{eff} or t'_{eff} for this drug if the dose were increased 10-fold, to 1000 mg?

Solution

a. The t_{eff} for a 100-mg dose is calculated as follows. Because V_D = 10,000 mL,

$$C_0 = \frac{100 \text{ mg}}{10{,}000 \text{ mL}} = 10 \ \mu\text{g/mL}$$

For a one-compartment-model IV dose, $C = C_0 e^{-kt}$. Then

$$0.1 = 10e^{-(1.0)t_{eff}}$$

$$t_{eff} = 4.61 \text{ hr}$$

b. The t'_{eff} for a 1000-mg dose is calculated as follows (prime refers to a new dose). Because V_D = 10,000 mL,

$$C'_0 = \frac{1000 \text{ mg}}{10{,}000 \text{ mL}} = 100 \ \mu\text{g/mL}$$

and

$$C'_{eff} = C'_0 e^{-kt'_{eff}}$$

$$0.1 = 100e^{-(1.0)t'_{eff}}$$

$$t'_{eff} = 6.91 \text{ hr}$$

The percent increase in t_{eff} is therefore found as

$$\text{Percent increase in } t_{eff} = \frac{t'_{eff} - t_{eff}}{t_{eff}} \times 100$$

$$\text{Precent increase in } t_{eff} = \frac{6.91 - 4.61}{4.61} \times 100$$

$$\text{Percent increase in } t_{eff} = 50\%$$

This example shows that a 10-fold increase in the dose increases the duration of action of a drug (t_{eff}) by only 50%.

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EFFECT OF BOTH DOSE AND ELIMINATION HALF-LIFE ON THE DURATION OF ACTIVITY

A single equation can be derived to describe the relationship of dose (D_0) and the elimination half-life ($t_{1/2}$) on the effective time for therapeutic activity (t_{eff}). This expression is derived below.

$$\ln C_{eff} - \ln C_0 - kt_{eff}$$

Because $C_0 = D_0/V_D$,

$$\ln C_{eff} = \ln\left(\frac{D_0}{V_D}\right) - kt_{eff}$$

$$kt_{eff} = \ln\left(\frac{D_0}{V_D}\right) - \ln C_{eff} \tag{19.7}$$

$$t_{eff} = \frac{1}{k}\ln\left(\frac{D_0/V_D}{C_{eff}}\right)$$

Substituting $0.693/t_{1/2}$ for k,

$$t_{eff} = 1.44t_{1/2}\ln\left(\frac{D_0}{V_D C_{eff}}\right) \tag{19.8}$$

From Equation 19.8, an increase in $t_{1/2}$ will increase the t_{eff} in direct proportion. However, an increase in the dose, D_0, does not increase the t_{eff} in direct proportion. The effect of an increase in V_D or C_{eff} can be seen by using generated data. Only the positive solutions for Equation 19.8 are valid, although mathematically a negative t_{eff} can be obtained by increasing C_{eff} or V_D. The effect of changing dose on t_{eff} is shown in Figure 19-6 using data generated with Equation 19.8. A nonlinear increase in t_{eff} is observed as dose increases.

EFFECT OF ELIMINATION HALF-LIFE ON DURATION OF ACTIVITY

Because elimination of drugs is due to the processes of excretion and metabolism, an alteration of any of these elimination processes will effect the $t_{1/2}$ of the drug. In certain disease states, pathophysiologic changes in hepatic or renal function will

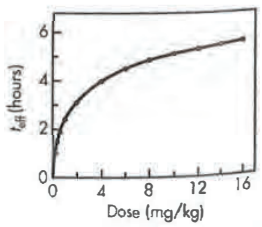


Figure 19-6. Plot of t_{eff} versus dose.

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decrease the elimination of a drug, as observed by a prolonged $t_{1/2}$. This prolonged $t_{1/2}$ will lead to retention of the drug in the body, thereby increasing the duration of activity of the drug (t_{eff}) as well as increasing the possibility of drug toxicity.

To improve antibiotic therapy with the penicillin and cephalosporin antibiotics, clinicians have intentionally prolonged the elimination of these drugs by giving a second drug, probenecid, which competitively inhibits renal excretion of the antibiotic. This approach to prolonging the duration of activity of antibiotics that are rapidly excreted through the kidney has been used successfully for a number of years. Similarly, Augmentin is a combination of amoxicillin and clavulanic acid; the latter is an inhibitor of β-lactamase. This β-lactamase is a bacterial enzyme that degrades penicillin-like drugs. The data in Table 19.1 illustrate how a change in the elimination $t_{1/2}$ will affect the t_{eff} for a drug. For all doses, a 100% increase in the $t_{1/2}$ will result in a 100% increase in the t_{eff}. For example, for a drug whose $t_{1/2}$ is 0.75 hour and that is given at a dose of 2 mg/kg, the t_{eff} is 3.24 hours. If the $t_{1/2}$ is increased to 1.5 hours, the t_{eff} is increased to 6.48 hours, an increase of 100%. However, the effect of doubling the dose from 2 to 4 mg/kg (no change in elimination processes) will only increase the t_{eff} to 3.98 hours, an increase of 22.8%. The effect of prolonging the elimination half-life has an extremely important effect on the treatment of infections, particularly in patients with high metabolism, or clearance, of the antibiotic. Therefore, antibiotics must be dosed with full consideration of the effect of alteration of the $t_{1/2}$ on the t_{eff}. Consequently, a simple proportional increase in dose will leave the patient's blood concentration below the effective antibiotic level most of the time during drug therapy. The effect of a prolonged t_{eff} is shown in lines *a* and *c* in Figure 19-7, and the disproportionate increase in t_{eff} as the dose is increased 10-fold is shown in lines *a* and *b*.

TABLE 19.1 Relationship between Elimination Half-Life and Duration of Activity

DOSE (mg/kg)	$t_{1/2}$ = 0.75 hr t_{eff} (hr)	$t_{1/2}$ = 1.5 hr t_{eff} (hr)
2.0	3.24	6.48
3.0	3.67	7.35
4.0	3.98	7.97
5.0	4.22	8.45
6.0	4.42	8.84
7.0	4.59	9.18
8.0	4.73	9.47
9.0	4.86	9.72
10	4.97	9.95
11	5.08	10.2
12	5.17	10.3
13	5.26	10.5
14	5.34	10.7
15	5.41	10.8
16	5.48	11.0
17	5.55	11.1
18	5.61	11.2
19	5.67	11.3
20	5.72	11.4

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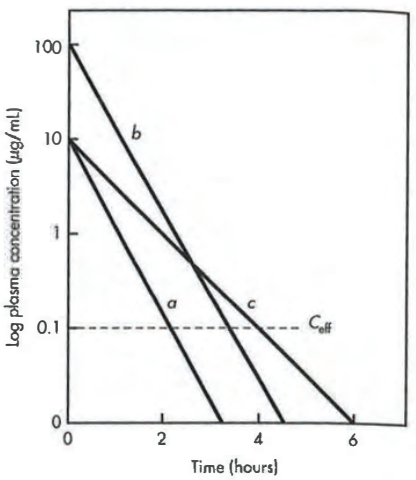


Figure 19-7. Plasma level–time curves describing the relationship of both dose and elimination half-life on duration of drug action. C_{eff} = effective concentration. Curve *a* = single 100-mg IV injection of drug; $k = 1.0\ hr^{-1}$. Curve *b* = single 1000-mg IV injection; $k = 1.0\ hr^{-1}$. Curve *c* = single 100-mg IV injection; $k = 0.5\ hr^{-1}$. V_D is 10 L.



CLINICAL EXAMPLES

Pharmacokinetic/Pharmacodynamic Relationships and Efficacy of Antibiotics

In the previous section, the time above the effective concentration, t_{eff}, was shown to be important in optimizing the therapeutic response of many drugs. This concept has been applied to antibiotic drugs (Drusano, 1988; Craig, 1995; Craig and Andes, 1996; Scaglione, 1997). For example, Craig and Andes (1996) discussed the antibacterial treatment of otitis media. Using the minimum inhibitory antibiotic concentration (MIC) for the microorganism in serum, the percent time for the antibiotic drug concentration to be above the MIC was calculated for several antibacterial classes, including cephalosporins, macrolides, and trimethoprim-sulfamethoxazole (TMP/SMX) combination (Table 19.2). Although the drug concentration in the

TABLE 19.2 Middle Ear Fluid-to-Serum Ratios for Common Antibiotics

ANTIBIOTIC	MIDDLE EAR FLUID (MEF)/SERUM RATIO
Cephalosporins	
Cefaclor	0.18–0.28
Cefuroxime	0.22
Macrolide antibiotic	
Erythromycin	0.49
Sulfa drug	
Sulfisoxazole	0.20

From Craig and Andes (1996).

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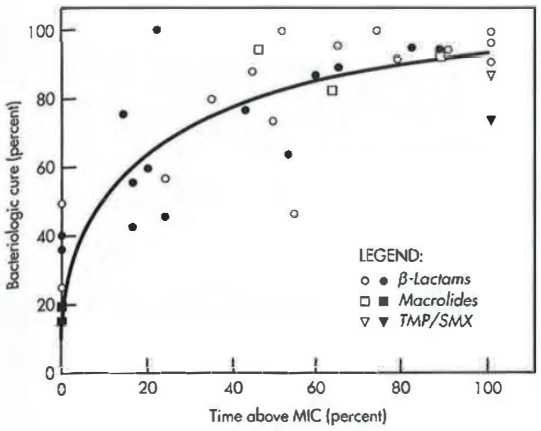


Figure 19-8. Relationship between the percent time above MIC_{90} of the dosing interval during therapy and percent of bacteriologic cure in otitis media caused by *S. pneumoniae* (open symbols) and β-lactamase-positive and -negative *H. influenzae* (closed symbols). (Circles, closed and open = β-lactams; squares, closed and open = macrolides; triangles, closed and open = TMP/SMX.)
(From Craig and Andres, 1996, with permission.)

middle ear fluid (MEF) is important, once the ratio (MEF/serum) is known, the serum drug level may be used to project MEF drug levels. The percent time above MIC of the dosing interval during therapy correlated well to the percent of bacteriologic cure (Figure 19-8). An almost 100% cure was attained by maintaining the drug concentration above the MIC for 60–70% of the dosing interval; an 80–85% cure was achieved with 40–50% of the dosing interval above MIC. When the percent of time above MIC falls below a critical value, bacteria will regrow, thereby prolonging the time for eradication of the infection. The pharmacokinetic model was further supported by experiments from a mouse infection model in which an infection in the thigh due to *Pseudomonas aeruginosa* was treated with ticarcillin and tobramycin.

In another study, Craig (1995) compared the AUC/MIC, the time above MIC, and drug peak concentration over MIC and found that the best fit was obtained when colony-forming units (CFUs) were plotted versus time above MIC for cefotaxime in a mouse infection model (Fig. 19-9).

Both Drusano (1988) and Craig (1995) reviewed the relationship of pharmacokinetics and pharmacodynamics in the therapeutic efficacy of antibiotics. For some antibiotics, such as the aminoglycosides and fluoroquinolones, both the drug concentration and the dosing interval have an influence on the antibacterial effect. For some antibiotics, such as the β-lactams, vancomycin, and the macrolides, the duration of exposure (time-dependent killing) or the time the drug levels are maintained above the MIC (t_{eff}) is most important for efficacy. For many antibiotics (eg, fluoroquinolones), there is a defined period of bacterial growth suppression after short exposures to the antibiotic. This phenomenon is known as the *postantibiotic effect* (PAE). Other influences on antibiotic activity include the presence of active metabolite(s), plasma drug protein binding, and the penetration of the antibiotic into the tissues. In addition, the MIC for the antibiotic depends on the infectious microorganism and the resistance of the microorganism to the antibiotic. In the case of ciprofloxacin, a quinolone, the percent of cure of infection at various doses was better related to AUIC, which is the product of area under the curve and the

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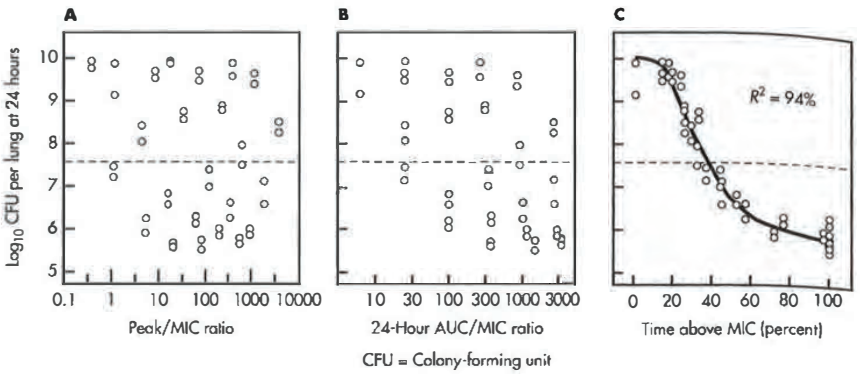


Figure 19-9. Relationship among three pharmacodynamic parameters and the number of *Klebsiella pneumoniae* in the lungs of neurotroponic mice after 24-hour therapy with cefotaxime. Each point represents one mouse.
(From Craig WA, 1995, with permission.)

reciprocal of minimum inhibition concentration, MIC (Forrest et al, 1993). Interestingly, quinolones inhibit bacterial DNA gyrase, quite different from the β-lactam antibiotics, which involve damage to bacterial cell walls.

Relationship between Systemic Exposure and Response—Anticancer Drugs

Plasma drug concentrations for drugs that have highly variable drug clearance in patients fluctuate widely even after intravenous infusion (Rodman and Evans, 1991). For highly variable drugs, there is no apparent relationship between the therapeutic response and the drug dose. For example, the anticancer drug teniposide at three different doses give highly variable steady-state drug concentrations and therapeutic response (Fig. 19-10). In some patients, single-point drug concentrations were variable and even higher with lower doses. Careful pharmacokinetic–pharmacodynamic analysis showed that a graded response curve may be obtained when responses are plotted versus systemic exposure as

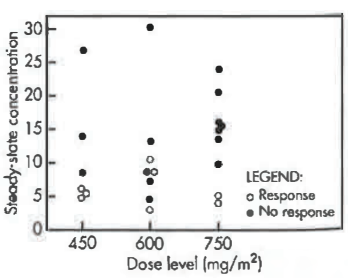


Figure 19-10. Steady-state concentration and response after three levels of teniposide administered by intravenous infusion.
(From Rodman and Evans, 1991, with permission.)

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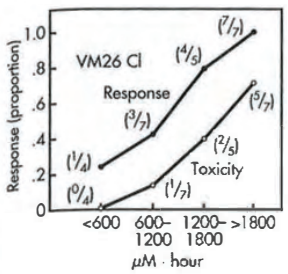


Figure 19-11. *Relationship between systemic exposure for teniposide and toxicity and efficacy, shown as proportions of patients.*
(From Rodman and Evans, 1991, with permission.)

measured by "concentration × time" (Fig. 19-11). This is one example showing that anticancer response may be better correlated to total area under the drug concentration curve (AUC), even when no apparent dose–response relationship is observed. Undoubtedly, the cytotoxic effect of the drug involves killing cancer cells with multiple-resistance thresholds that require different time exposures to the drug. The objective of applying pharmacokinetic–pharmacodynamic principles is to achieve therapeutic efficacy without triggering drug toxicity. This relationship is illustrated by the sigmoid curves for response and toxicity (Fig. 19-11), both of which lie close to each other and intensify as concentration increases.

RATE OF DRUG ABSORPTION AND PHARMACODYNAMIC RESPONSE

The rate of drug absorption influences the rate in which the drug gets to the receptor and the subsequent pharmacologic effect. For drugs that exert an acute pharmacologic effect, usually a direct-acting drug agonist, extremely rapid drug absorption may have an intense and possibly detrimental effect. For example, niacin (nicotinic acid) is a vitamin given in large doses to decrease elevated plasma cholesterol and triglycerides. Rapid systemic absorption of niacin when given in an immediate-release tablet will cause vasodilation, leading to flushing and postural hypertension. Extended-release niacin products are preferred because the more slowly absorbed niacin allows the baroreceptors to adjust to the vasodilation and hypotensive effects of the drug. Phenylpropanolamine was commonly used as a nasal decongestant in cough and cold products or as an anorectant in weight-loss products. Phenylpropanolamine acts as a pressor, increasing the blood pressure much more intensely when given as an immediate-release product compared to an extended-release product.

Equilibration Pharmacodynamic Half-Life

For some drugs, the half-time for drug equilibration has been estimated by observing the onset of response. A list of drug half-times reported by Lalonde (1992) is shown in Table 19.3. The factors that affect this parameter include perfusion of

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TABLE 19.3 Equilibration Half-Times Determined Using the Effect Compartment Method

DRUG	EQUILIBRATION $t_{1/2}$ (min)	PHARMACOLOGIC RESPONSE
d-Tubocurarine	4	Muscle paralysis
Disopyramide	2	QT prolongation
Quinidine	8	QT prolongation
Digoxin	214	LVET shortening
Terbutaline	7.5	FEV_1
Terbutaline	11.5	Hypokalemia
Theophylline	11	FEV_1
Verapamil	2	PR prolongation
Nizatidine	83	Gastric pH
Thiopental	1.2	Spectral edge
Fentanyl	6.4	Spectral edge
Alfentanil	1.1	Spectral edge
Ergotamine	595	Vasoconstriction
Vercuronium	4	Muscle paralysis
N-Acetylprocainamide	6.4	QT prolongation

From Lalonde (1992), with permission.

the effect compartment, blood–tissue partitioning, drug diffusion from capillaries to the effect compartment, protein binding, and elimination of the drug from the effect compartment.

Substance Abuse Potential

The rate of drug absorption has been associated with the potential for substance abuse. Drugs taken by the oral route have the lowest abuse potential. For example, cocoa leaves containing cocaine alkaloid have been chewed by South American Indians for centuries (Johanson and Fischman, 1989). Cocaine abuse has become a problem as a result of the availability of cocaine alkaloid ("crack" cocaine) and because of the use of other routes of drug administration (intravenous, intranasal, or smoking) that allow a very rapid rate of drug absorption and onset of action (Cone, 1995). Studies on diazepam (deWit et al, 1993) and nicotine (Henningfield and Keenan, 1993) have shown that the rate of drug delivery correlates with the abuse liability of such drugs. Thus, the rate of drug absorption influences the abuse potential of these drugs, and the route of drug administration that provides faster absorption and more rapid onset leads to greater abuse.

DRUG TOLERANCE AND PHYSICAL DEPENDENCY

The study of drug tolerance and physical dependency is of particular interest in understanding the actions of abused drug substances, such as opiates and cocaine. Drug *tolerance* is a quantitative change in the sensitivity of the drug and is demonstrated by a decrease in pharmacodynamic effect after repeated exposure to the same drug. The degree of tolerance may vary greatly (Cox, 1990). Drug tolerance has been well described for organic nitrates, opioids, and other drugs. For example,

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the nitrates relax vascular smooth muscle and have been used for both acute angina (eg, nitroglycerin sublingual spray or transmucosal tablet) or angina prophylaxis (eg, nitroglycerin transdermal, oral controlled-release isosorbide dinitrate). Well-controlled clinical studies have shown that tolerance to the vascular and antianginal effects of nitrates may develop. For nitrate therapy, the use of a low nitrate or nitrate-free periods has been advocated as part of the therapeutic approach. The magnitude of drug tolerance is a function of both the dosage and the frequency of drug administration. *Cross tolerance* can occur for similar drugs that act on the same receptors. Tolerance does not develop uniformly to all the pharmacologic or toxic actions of the drug. For example, patients who show tolerance to the depressant activity of high doses of opiates will still exhibit "pinpoint" pupils and constipation.

The mechanism of drug tolerance may be due to (1) disposition or pharmacokinetic tolerance or (2) pharmacodynamic tolerance. *Pharmacokinetic tolerance* is often due to enzyme induction (discussed in earlier chapters), in which the hepatic drug clearance increases with repeated drug exposure. *Pharmacodynamic tolerance* is due to a cellular or receptor alteration in which the drug response is less than what is predicted in the patient given subsequent drug doses. Measurement of serum drug concentrations may differentiate between pharmacokinetic tolerance and pharmacodynamic tolerance. Acute tolerance, or *tachyphylaxis,* which is the rapid development of tolerance, may occur due to a change in the sensitivity of the receptor or depletion of a cofactor after only a single or a few doses of the drug. Drugs that work indirectly by releasing norepinephrine may show tachyphylaxis. Drug tolerance should be differentiated from genetic factors which account for normal variability in the drug response.

Physical dependency is demonstrated by the appearance of withdrawal symptoms after cessation of the drug. Workers exposed to volatile organic nitrates in the workplace may initially develop headaches and dizziness followed by tolerance with continuous exposure. However, after leaving the workplace for a few days, the workers may demonstrate nitrate withdrawal symptoms. Factors that may affect drug dependency may include the dose or amount of drug used (intensity of drug effect), the duration of drug use (months, years, and peak use) and the total dose (amount of drug × duration). The appearance of withdrawal symptoms may be abruptly precipitated in opiate-dependent subjects by the administration of naloxone (Narcan), an opioid antagonist that has no agonist properties.

HYPERSENSITIVITY AND ADVERSE RESPONSE

Many drug responses, such as hypersensitivity and allergic responses, are not fully explained by pharmacodynamics and pharmacokinetics. Allergic responses generally are not dose related, although some penicillin-sensitive patients may respond to threshold skin concentrations, but, otherwise, no dose–response relationship has been established. Skin eruption is a common symptom of drug allergy. Allergic reactions can occur at extremely low drug concentrations. Some urticaria episodes in patients have been traced to penicillin contamination in food or to penicillin contamination during dispensing or manufacturing of other drugs. Allergic reactions are important data that must be recorded in the patient's profile along with other

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adverse reactions. Penicillin allergic reaction in the population is often detected by skin test with benzylpenicilloyl polylysine (PPL). The incidence of penicillin allergic reaction occurs in about 1–10% of patients. The majority of these reactions are minor cutaneous reactions such as urticaria, angioedema, and pruritus. Serious allergic reactions, such as anaphylaxis, are rare, with an incidence of 0.021–0.106% for penicillins (Lin, 1992). For cephalosporins, the incidence of anaphylactic reaction is less than 0.02%. Anaphylactic reaction for cefaclor was reported to be 0.001% in a postmarketing survey. There are emerging trends showing that there may be a difference between the original and the new generations of cephalosporins (Reisman and Reisman, 1995). Cross sensitivity to similar chemical classes of drugs can occur.

Allergic reactions may be immediate or delayed and have been related to IgE mechanisms. In β-lactam (penicillin) drug allergy, immediate reactions occur in about 30 to 60 minutes, but delayed reaction, or accelerated reaction, may occur from 1 to 72 hours after administration. Anaphylactic reaction may occur in both groups. Although some early evidence of cross hypersensitivity between penicillin and cephalosporin was observed, the incidence in patients sensitive to penicillin show only a twofold increase in sensitivity to cephalosporin compared with that of the general population. The report rationalized that it is safe to administer cephalosporin to penicillin-sensitive patients and that the penicillin skin test is not useful in identifying patients who are allergic to cephalosporin, because of the low incidence of cross reactivity (Reisman and Reisman, 1995). In practice, the clinician should evaluate the risk of drug allergy against the choice of alternative medication. Some earlier reports showed that cross sensitivity between penicillin and cephalosporin was due to the presence of trace penicillin present in cephalosporin products.

DRUG DISTRIBUTION AND PHARMACOLOGIC RESPONSE

After systemic absorption, the drug is carried throughout the body by the general circulation. Most of the drug dose will reach unintended target tissues, in which the drug may be passively stored, produce an adverse effect, or be eliminated. A fraction of the dose will reach the target site and establish an equilibrium. The receptor site is unknown most of the time, but, kinetically, it is known as the *effect compartment.* The time course of drug delivery to the effect compartment will determine whether the onset of pharmacologic response is immediate or delayed. The delivery of drug to the effect compartment is affected by the rate of blood flow, diffusion, and partition properties of the drug and the receptor molecules.

At the receptor site, the onset, duration, and intensity of the pharmacologic response are controlled by receptor concentration and the concentration of the drug and/or its active metabolites. The ultimate pharmacologic response (*effect*) may depend largely on the stereospecific nature of the interaction of the drug with the receptor and the rates of association and dissociation of the drug–receptor complex. Depending on their location and topography, not all receptor molecules are occupied by drug molecules when a maximum pharmacologic response

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is produced. Other variables, such as age, sex, genetics, nutrition, and tolerance, may also modify the pharmacologic response, making it difficult to relate the pharmacologic response to plasma drug concentration. To control data fluctuation and simplify pharmacodynamic fitting, the pharmacologic response is often expressed as a percent of response above a baseline or percent of maximum response. By combining pharmacokinetics and pharmacodynamics, some drugs with relatively complex pharmacologic responses have been described by pharmacodynamic models that account for their onset, intensity, and duration of action.

After the pharmacodynamics of a drug are characterized, the time course of pharmacologic response may be predicted after drug administration. Also, from these data, it is possible to determine from the pharmacokinetic parameters whether an observed change in pharmacologic response is due to pharmacodynamic factors, such as tachyphylaxis or tolerance, or to pharmacokinetic factors, such as a change in drug absorption, elimination, or distribution.

Drug–Receptor Theory Relating Pharmacologic Effect and Dose

The relationship between pharmacologic effect and dose was advanced by Wagner (1968), who derived a kinetic expression that relates drug concentration to pharmacologic effect. This theoretical development transformed the semiempirical dose–effect relationship (the hyperbolic or log sigmoid profile) into a theoretical equation that relates pharmacologic effect to pharmacokinetics (ie, a pharmacokinetics/pharmacodynamic, PK/PD model). Because the equation was developed for a drug receptor with either single or multiple drug binding, many drugs with a sigmoid concentration effect profile may be described by this model. The slope of the profile also provides some insight into the drug–receptor interaction.

The basic equation mimics somewhat the kinetic equation for protein drug binding (Chapter 10). One or more drug molecules may interact with a receptor to form a complex that in turn elicits a pharmacodynamic response, as illustrated in Figure 19-12. The rate of change in the number of drug–receptor complexes is expressed as db/dt. From Figure 19-12, a differential equation is obtained as shown:

$$\frac{db}{dt} = k_1 c^S (a - b) - bk_2 \qquad (19.9)$$

where $k_1 c^S (a - b)$ = rate of receptor complex formation and bk_2 = rate of dissociation of the receptor complex.

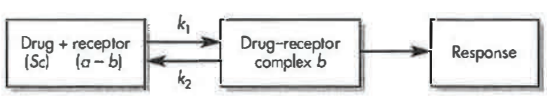


Figure 19-12. Model of the drug–receptor theory: a = total number of drug receptors, c = concentration of drug, S = number of moles of drug that combine with one receptor (constant for each drug), and b = number of drug–receptor complexes.

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At steady state, $db/dt = 0$ and Equation 19.9 reduces to

$$k_1 c^s a - k_1 c^s b - b k_2 = 0$$

$$\frac{b}{a} = \frac{k_1 c^s}{k_1 c^s + k_2} = \frac{1}{1 + (k_2/k_1 c^s)} \tag{19.10}$$

For many drugs, the pharmacologic response (R) is proportional to the number of receptors occupied:

$$R \propto \frac{b}{a} \tag{19.11}$$

The pharmacologic response (R) is related to the maximum pharmacologic response (R_{max}), concentration of drug, and rate of change in the number of drug receptor complexes occupied:

$$R = \frac{R_{max}}{1 + (k_2/k_1 c^s)} \tag{19.12}$$

A graph of Equation 19.12 constructed from the percent pharmacologic response, $(R/R_{max}) \times 100$, versus the concentration of drug gives the response–concentration curve (Fig. 19-13). This type of theoretical development explains that the pharmacologic response–dose curve is not completely linear over the entire dosage range, as is frequently observed.

The total pharmacologic response elicited by a drug is difficult to quantitate in terms of the intensity and the duration of the drug response. The *integrated pharmacologic response* is a measure of the total pharmacologic response and is expressed mathematically as the product of these two factors (ie, duration and intensity of drug action) summed up over a period of time. Using Equation 19.12, an integrated pharmacologic response is generated if the drug plasma concentration–time curve can be adequately described by a pharmacokinetic model.

Table 19.4 is based on a hypothetical drug that follows a one-compartment open model. The drug is given intravenously in divided doses. With this drug, the total integrated response increases considerably when the total dose is given in a greater number of divided doses. By giving the drug in a single dose, two doses, four doses, and eight doses, an integrated response was obtained that ranged from 100% to 138.9%, using the single-dose response as a 100% reference. It should be noted that when the bolus dose is broken into a smaller number of doses, the largest percent increase in the integrated response occurs when the bolus dose is divided into two doses. Further division will cause less of an increase, proportionally. The

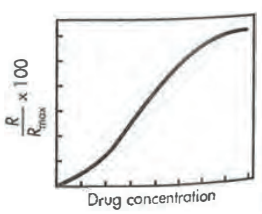


Figure 19-13. Graph of drug concentration versus pharmacologic response.

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TABLE 19.4 Hypothetical Drug Given Intravenously in Single and Divided Doses[a]

DOSE NUMBER	SINGLE DOSE	DOSE GIVEN INITIALLY AND AT 12th hr	DOSE GIVEN AT 0, 6, 12, 18 hr	DOSE GIVEN AT 0, 3, 6, 9, 12, 15, 18, 21 hr
1	422	272	139.4	62.53
2		276	148.2	71.46
3			148.5	74.41
4			149.0	75.61
5				76.27
6				76.44
7				76.71
8				76.81
Total response	422	548	585.1	590.2
Percent response	100	130	138.7	138.9

[a]The drug follows a one-compartment open model. Each value represents a unit of integrated pharmacologic response.

Adapted with permission from Wagner (1968).

actual percent increase in integrated response depends on the $t_{1/2}$ of the drug as well as the dosing interval.

The values in Table 19.4 were generated from theory. However, these data illustrate that the pharmacologic response depends on the dosing schedule. A large total dose given in divided doses may produce a pharmacologic response quite different from that obtained by administering the drug in a single dose.

Correlation of pharmacologic response to pharmacokinetics is not always possible with all drugs. Sometimes intermediate steps are involved in the mechanism of drug action that are more complex than is assumed in the model. For example, warfarin (an anticoagulant) produces a delayed response, and there is no direct correlation of the anticoagulant activity to the plasma drug concentration. The plasma warfarin level is correlated with the inhibition of the prothrombin complex production rate. However, many correlations between pharmacologic effect and plasma drug concentration are performed by proposing models that may be discarded after more data are collected. The process of pharmacokinetic modeling can greatly enhance our understanding of the way drugs act in a quantitative manner.

PHARMACODYNAMIC MODELS

No unified general pharmacodynamic model based on detailed drug–receptor theory that relates pharmacologic response to pharmacokinetics is available. Most of the drug–receptor-based models are descriptive and lack quantitative details. Successful modeling of pharmacologic response has been achieved with semiempirically based assumptions and usually with some oversimplification of the real process. Many of the classic pharmacodynamic models were developed without detailed knowledge of the drug–receptor interaction. The successful modeling of the degree of muscle paralysis of *d*-tubocurarine to plasma concentrations is an

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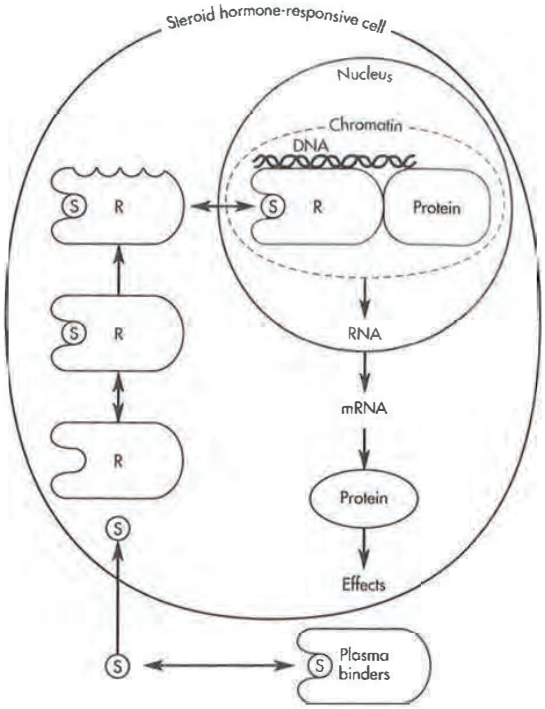


Figure 19-14. Receptor-mediated (R) mechanism of action of corticosteroid (S) hormones.
(From Baxter and Funder, 1979, with permission. Cited by Boudinot et al, 1986.)

interesting example in which the exact mechanism of the drug–receptor interaction was not considered. One of the few pharmacodynamic models that takes into account the interaction between the receptor and the drug molecule leading to a pharmacologic effect was described by Boudinot et al (1986) using the drug prednisolone as an example. Prednisolone is a corticosteroid that binds to cytosolic receptors within the cell (Fig. 19-14). The bound steroid receptor complex is activated and translocated into the nucleus of the cell. Within the cell, the drug–receptor complex associates with specific DNA sequences and modulates the transcription of RNA, which ultimately initiates protein synthesis (Boudinot et al, 1986). Tyrosine aminotransferase (TAT) is an enzyme protein that is increased (induced) by the action of prednisolone. In the liver cell, the prednisolone concentration, drug–receptor concentration, and TAT enzyme were measured with respect to time.

The pharmacodynamic model accounted for the delayed response of prednisolone, a characteristic of corticosteroid response. In this model, prednisolone is first bound to plasma protein, and free drug must leave the plasma compartment and enter the cell to form a drug–receptor complex; creation of this complex then triggers the pharmacologic events leading to an increase in intracellular TAT concentration. A decrease in free receptor or an increase in bound receptor complexes after drug administration was observed. Plasma prednisolone concentrations were

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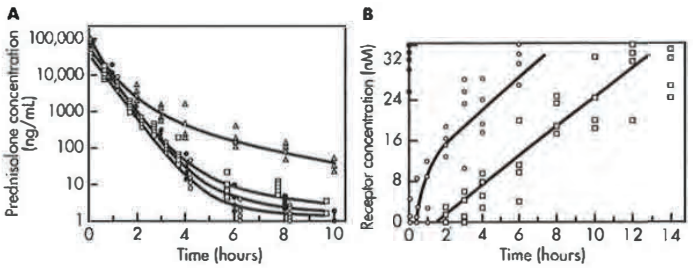


Figure 19-15. **A.** Prednisolone levels in plasma (□) and liver (Δ) fall exponentially after 50 mg/kg of drug IV during the first 10 hours, as described by a pharmacokinetic model. **B.** Free cytosolic glucocorticoid receptor (CGR) concentration fell from control level (●) after 5- (○) and 50-mg/kg (□) IV doses of prednisolone. Free CGR fell as prednisolone interacted with receptor to form receptor complex. The free CGR returned to baseline level after about 10 hours.
(From Boudinot et al, 1986, with permission.)

described by a triexponential equation, and a time lag was built into the model to account for the delay between TAT increase and the drug–receptor–DNA complex formation (Figs. 19-15 and 19-16). A review on PK/PD modelling has been published by Meibohm and Derendorf, 1997.

Maximum Effect (E_{max}) Model

The *maximum effect model* (E_{max}) is an empirical model that relates pharmacologic response to drug concentrations. This model incorporates the observation known as the *law of diminishing return,* which shows that an increase in drug concentration near the maximum pharmacologic response produces a disproportionately smaller increase in the pharmacologic ressponse (Fig. 19-17). The E_{max} model describes drug action in terms of maximum effect (E_{max}) and EC_{50}, the drug concentration that produces 50% maximum pharmacologic effect.

$$E = \frac{E_{max} C}{EC_{50} + C} \qquad (19.13)$$

where C is the plasma drug concentration and E is the pharmacologic effect.

Equation 19.13 is a saturable process resembling Michaelis–Menton enzyme kinetics. As the plasma drug concentration C increases, the pharmacologic effect

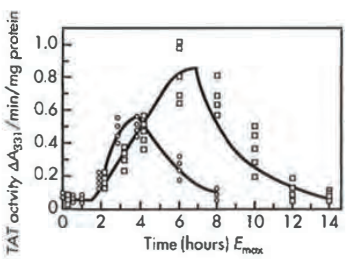


Figure 19-16. Tyrosine aminotransferase (TAT) activity in liver was described by a pharmacodynamic model (solid line) after 5 (○) and 50 mg/kg (□) IV prednisolone. The pharmacodynamic model accounts for the delay of TAT activity.
(From Boudinot et al, 1986, with permission.)

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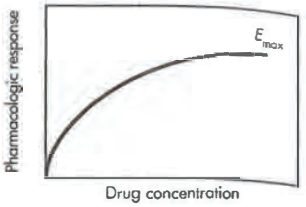


Figure 19-17. Plot of pharmacologic response versus plasma drug concentration in a hyperbolic model.

E approaches E_{max} asymptotically. A double-reciprocal plot of Equation 19.13 may be used to linearize the relationship, similar to a Lineweaver–Burke equation.

E_{max} is the maximum pharmacologic effect that may be obtained by the drug. EC_{50} is the drug concentration that produces one-half (50%) of the maximum pharmacologic response. In this model, both E_{max} and EC_{50} can be measured. For example, the bronchodilator activity of theophylline may be monitored by measuring FEV_1 (forced expiratory volume) at various plasma drug concentrations (Fig. 19-18). For theophylline, a small gradual increase in FEV_1 is obtained as the plasma drug concentrations are increased higher than 10 mg/L. Only a 17% increase in FEV_1 is observed when the plasma theophylline concentration is doubled from 10 to 20 mg/L. The EC_{50} for theophylline is 10 mg/L. The E_{max} is equivalent to 63% of normal FEV_1. A further increase in the plasma theophylline concentration will not yield an improvement in the FEV_1 beyond E_{max}. Either drug saturation of the receptors or other limiting factors prevent further improvement in the pharmacologic response.

The E_{max} model describes two key features of the pharmacologic response: (1) the model mimics the hyperbolic shape of the pharmacologic response–drug concentration curve, and (2) a maximum pharmacologic response (E_{max}) may be induced by a certain drug concentration, beyond which no further increase

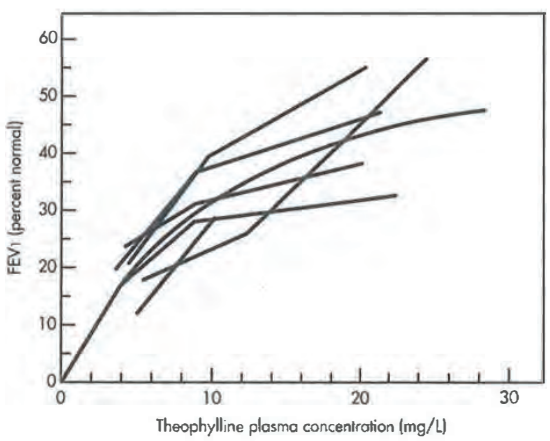


Figure 19-18. Use of E_{max} model to describe the effects of theophylline on change in normalized forced expiratory volume (FEV_1); E_{max} = 63%, EC_{50} = 10 mg/L.
(From Mitenko and Ogilvie, 1973, and Holford and Sheiner, 1981, with permission.)

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in pharmacologic response is obtained (Fig. 19-17). The drug concentration that produces a 50% maximum pharmacologic response (EC_{50}) is useful as a guide for achieving drug concentration that lies within the therapeutic range.

In many cases, the measured pharmacologic effect has some value when drug is absent (eg, blood pressure, heart rate, respiration rate). E_0 is the measured pharmacologic effect (baseline activity) at zero drug concentration in the body. The measurement for E_0 may be variable due to intra- and intersubject differences. Using E_0 as a baseline constant-effect term, Equation 19.13 may be modified as follows:

$$E = E_0 + \frac{E_{max} C}{EC_{50} + C} \tag{19.14}$$

Sigmoid E_{max} Model

The *sigmoid E_{max} model* describes the pharmacologic response–drug concentration curve for many drugs that appear to be S-shaped (ie, sigmoidal) rather than hyperbolic as described by the simpler E_{max} model. The model was first used by Hill (1910) to describe the association of oxygen with hemoglobin, in which the association with one oxygen molecule influences the association of the hemoglobin with the next oxygen molecule. The equation for the sigmoid E_{max} model is an extension of the E_{max} model:

$$E = \frac{E_{max} C^n}{EC_{50} + C^n} \tag{19.15}$$

where n is an exponent describing the number of drug molecules that combine with each receptor molecule. When n is equal to unity ($n = 1$), the sigmoidal E_{max} model reduces to the E_{max} model. A value of $n > 1$ influences the slope of the curve and the model fit.

The sigmoidal E_{max} model has been used to describe the effect of tocainamide on the suppression of ventricular extrasystoles (Winkle et al, 1976). As shown in Figure 19-19, the very steep slope of the tocainamide concentration–response curve

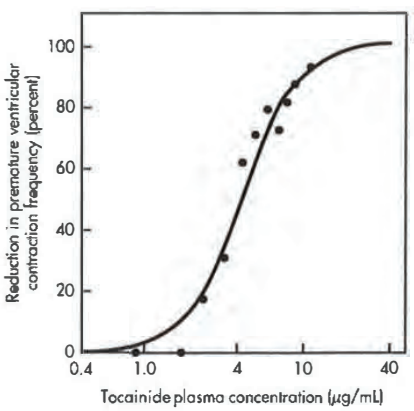


Figure 19-19. Steep concentration response curve for tocainide requiring use of the sigmoid E_{max} model. (From Winkle et al, 1976, with permission.)

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required that $n = 20$ in order to fit the model. Although this model was developed empirically, the mathematical equation describing the model is similar to the one elaborated by Wagner (1968) and discussed earlier in this chapter.

In the sigmoid E_{max} model, the slope is influenced by the number of drug molecules bound to the receptor. Moreover, a very large n value may indicate *allosteric* or *cooperative effects* in the interaction of the drug molecules with the receptor.

Pharmacokinetic Pharmacodynamic Models with an Effect Compartment

Many pharmacokinetic models describe the time course for drug and metabolite concentrations in the body. Using either the sigmoid E_{max} or one of the other pharmacodynamic models described earlier, the pharmacologic response may be obtained at various time periods. This simple approach has worked for some neuromuscular blockers and anesthetic agents, whose activities are related to plasma drug concentrations.

For some drugs, the time course for the pharmacologic response may not directly parallel the time course of the plasma drug concentration. The maximum pharmacologic response produced by the drug may be observed before or after the plasma drug concentration has peaked. Moreover, other drugs may produce a delayed pharmacologic response unrelated to the plasma drug concentration.

A pharmacokinetic/pharmacodynamic model with an effect compartment is used to describe the pharmacokinetics of the drug in the plasma and the time course of a pharmacologic effect of a drug in the site of action. To account for the pharmacodynamics of an indirect or delayed drug response, a hypothetical *effect compartment* has been postulated (Fig. 19-20). This effect compartment is not part of the pharmacokinetic model but is a hypothetical pharmacodynamic compartment that links to the plasma compartment containing drug. Drug transfers from the plasma compartment to the effect compartment, but no significant amount of drug moves from the effect compartment to the plasma compartment. Only free drug will diffuse into the effect compartment, and the transfer rate constants are usually first order. The pharmacologic response is determined from the rate constant, k_{e0}, and the drug concentration in the effect compartment (Fig. 19-20).

The amount of drug in the hypothetical effect compartment after a bolus IV dose may be obtained by writing a differential describing the rate of change in drug amounts in each compartment:

$$\frac{dD_e}{dt} = k_{1e}D_1 - k_{e0}D_e \qquad \textbf{(19.16)}$$

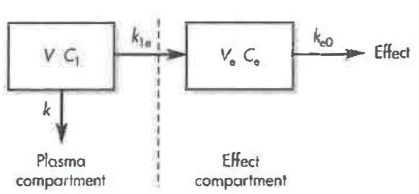


Figure 19-20. Pharmacokinetic–pharmacodynamic model with an effect compartment.

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where D_e is the amount of drug in the effect compartment, D_1 is the amount of drug in the central compartment, k_{1e} is the transfer rate constant for drug movement from the central compartment into the effect compartment, and k_{e0} is the transfer rate constant out of the effect compartment.

Integrating Equation 19.16 yields the amount of drug in the effect compartment D_e:

$$D_e = \frac{D_0 k_{1e}}{(k_{e0} - k)}(e^{-kt} - e^{-k_{e0}t}) \tag{19.17}$$

Dividing Equation 19.17 by V_e, the volume of the effect compartment, yields the concentration C_e of the effect compartment:

$$C_e = \frac{D_0 k_{1e}}{V_e(k_{e0} - k)}(e^{-kt} - e^{-k_{e0}t}) \tag{19.18}$$

where D_0 is the dose, V_e is the volume of the effect compartment, and k is the elimination rate constant from the central compartment. Equation 19.18 is not very useful because the parameters V_e and k_{1e} are both unknown and cannot be obtained from plasma drug concentration data. Several assumptions were made to simplify this equation.

The pharmacodynamic model assumes that even though an effect compartment is present in addition to the plasma compartment, this hypothetical effect compartment takes up only a negligible amount of the drug dose, so that plasma drug level still follows a one-compartment equation. After an IV bolus dose, the rate of drug entering and leaving the effect compartment is controlled by the incoming rate constant k_{1e} and the elimination rate constant k_{e0}. (There is no diffusion of drug from the effect compartment into the plasma compartment.) At steady state, both the input and output rates from the effect compartment are equal,

$$k_{1e}D_1 = D_e k_{e0} \tag{19.19}$$

Rearranging,

$$D_1 = \frac{k_{e0}D_e}{k_{1e}} \tag{19.20}$$

Dividing by V_D yields the steady-state plasma drug concentration C_1:

$$C_1 = \frac{k_{e0}D_e}{k_{1e}V_D} \tag{19.21}$$

$$D_e = \frac{D_0 k_{1e}}{(k_{e0} - k)}(e^{-kt} - e^{-k_{e0}t}) \tag{19.22}$$

Substituting for D_e into Equation 19.21 yields

$$C_1 = \frac{k_{e0}D_0 k_{1e}}{k_{1e}V_D(k_{e0} - k)}(e^{-kt} - e^{-k_{e0}t}) \tag{19.23}$$

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Cancelling the common term k_{1e},

$$C_1 = \frac{k_{e0} D_0}{V_D (k_{e0} - k)} (e^{-kt} - e^{-k_{e0} t}) \tag{19.24}$$

At steady state, C_1 is unaffected by k_{1e} and is controlled only by the elimination constant k and k_{e0}. C_1 is called $C_{p_{ss}}$, or steady-state drug concentration, and has been used successfully to relate the pharmacodynamics of many drugs, including some with delayed equilibration between the plasma and the effect compartment. Thus, k and k_{e0} jointly determine the pharmacodynamic profile of a drug. In fitting the pharmacokinetic–pharmacodynamic model, the IV bolus equation is fitted to the plasma drug concentration–time data to obtain k and V_D, while $C_{p_{ss}}$, or C_1 from Equation 19.24, is used to substitute into the concentration in Equation 19.15 to fit the pharmacologic response.

Many drug examples have been described by this type of pharmacokinetic–pharmacodynamic model. The key feature of this model is its dynamic flexibility and adaptability to pharmacokinetic models that account for drug distribution and pharmacologic response. The aggregate effects of drug elimination, binding, partitioning, and distribution in the body are accommodated by the model. The basic assumptions are practical and pragmatic, although some critics of the model (Colburn, 1987) believe the hypothetical effect compartment may oversimplify more complex drug–receptor events. On the positive side, the model represents elegantly an *in-vivo* pharmacologic event relating to the plasma drug concentrations that a clinician can monitor and adjust.

Until more information is known about the effect compartment, a pharmacokinetic–pharmacodynamic model is proposed to describe these kinetic processes combining some of the variables. A good fit of the data to the model is useful but does not necessarily describe the actual pharmacodynamic process. The process of model development evolves until a better model replaces an inadequate one. Several examples of drugs incorporating the effect compartment concept cited in the next section support the versatility of this model. The model accommodates some difficult drug response–concentration profiles, such as the puzzling hysteresis profile of some drug responses (eg, responses to cocaine and ajmaline).

Pharmacodynamic Models Using an Effect Compartment

The antiarrhythmic drug ajmaline slows the heart rate by delaying the depolarization of the heart muscle in the atrium and the ventricle. The pharmacologic effect of the drug is observed in the ECG by measuring the prolongation of the PQ and QRS interval after an IV infusion of ajmaline. A two-compartment model with binding described the pharmacokinetics of the drug and a pharmacodynamic model with an effect compartment was linked to the central compartment in which free drug may diffuse into the effect compartment. The effect compartment was necessary because the plasma ajmaline concentration did not correlate well with changes in recorded ECG events. When the effect-compartment drug concentration was used instead, drug activity was well described by the model (Figs. 19-21 and 19-22).

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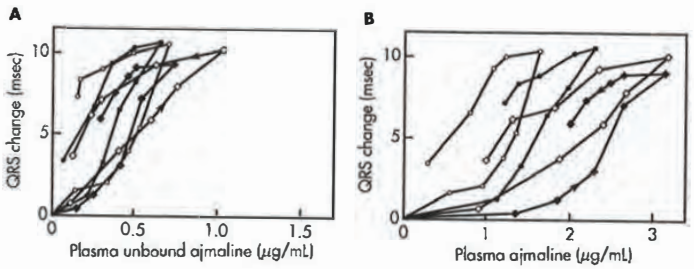


Figure 19-21. Plot of ajmaline concentration versus change in QRS interval for four dogs: (◆) 1, (◇) 2, (●) 3, (○) 4. **A.** Unbound plasma ajmaline versus response. **B.** Plasma ajmaline versus response. (From Yasuhara et al, 1987, with permission.)

Hysteresis of Pharmacologic Response

Many pharmacologic responses are complex and do not show a direct relationship between pharmacologic effect and plasma drug concentration. Some drugs have a plasma drug concentration–pharmacologic response that resembles a *hysteresis loop* (Fig. 19-23). For these drugs, an identical plasma concentration can result in significantly different pharmacologic responses, depending on whether the plasma drug concentration is on the ascending or descending phase of the loop. The time-dependent nature of a pharmacologic response may be due to tolerance, induced metabolite deactivation, reduced response, or translocation of receptors at the site of action. This type of time-dependent pharmacologic response is characterized by a clockwise profile when pharmacologic response is plotted versus plasma drug concentrations over time (Fig. 19-23).

For example, fentanyl (a lipid-soluble, opioid anesthetic) and alfentanil (a closely related drug) display *clockwise* hysteresis, apparently due to rapid lipid partition. β-Adrenoreceptors, such as isoproterenol, apparently have no direct relationship between response and plasma drug concentration and show hysteresis features. The diminished pharmacologic response was speculated to be a result of cellular response and physiologic adaptation to intense stimulation of the drug. A decrease in the number of receptors as well as translocation of receptors was proposed as the explanation for the observation. The euphoria produced by cocaine also displayed a clockwise profile when responses were plotted versus plasma cocaine concentration (Fig. 19-24).

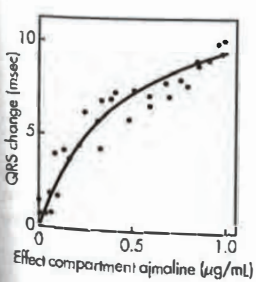


Figure 19-22. Plot of change in QRS interval versus ajmaline concentration in the effect compartment in dog 2. The lines were generated based on the effect compartment model.
(From Yasuhara et al, 1987, with permission.)

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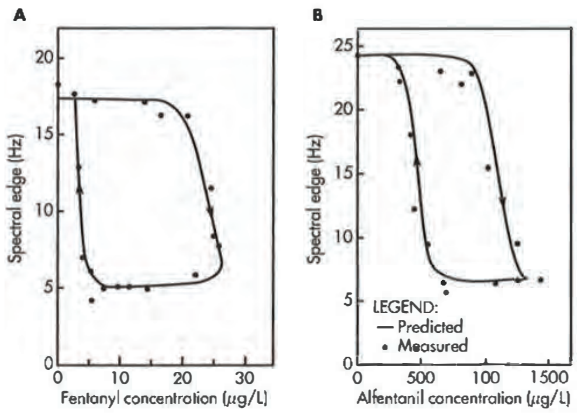


Figure 19-23. Response of the EEG spectral edge to changing fentanyl **(A)** and alfentanil **(B)** serum concentrations. Plots are data from single patients after rapid drug infusion. Time is indicated by arrows. The clockwise hysteresis indicates a significant time lag between blood and effect site. (From Scott and Stanski, 1985, with permission.)

A second type of pharmacologic response shows a *counterclockwise* hysteresis profile (Fig. 19-25). The pharmacologic response increases with time as the pharmacologic response is plotted versus plasma drug concentrations. An example of a counterclockwise hysteresis loop is the antiarrhythmic drug ajmaline. When the QRS interval changes in dogs were plotted versus plasma ajmaline concentration in each dog, an interesting counterclockwise hysteresis loop was seen (Fig. 19-21). Yasuhara and co-workers (1987) developed a pharmacodynamic model to analyze the molecular events between drug concentration and change in ECG parameters such as QRS. A relationship was established between pharmacologic response and drug concentration in the effect-compartment drug level (Fig. 19-22). The hysteresis profile (Fig. 19-21) is the result of the drug being highly bound to the plasma protein (α_1-acid glycoprotein), and of a slow initial diffusion of drug into the effect compartment.

Counterclockwise hysteresis curves may also result when the measured pharmacodynamic response is not the primary effect of the drug, ie, there is an *indirect*

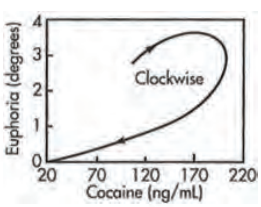


Figure 19-24. Clockwise hysteresis loop typical of tolerance is seen after intranasal administration of cocaine when related to degree of euphoria experienced in volunteers. (From van Dyke et al, 1978.)

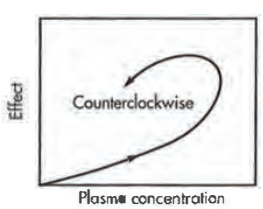


Figure 19-25. Counterclockwise hysteresis loop indicating equilibration delay between plasma concentration and the effect site producing the effect. (From Holford and Sheiner, 1981.)

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effect. For example, warfarin inhibits hepatic synthesis of clotting factors II, VII, IX, and X, but prothrombin time is measured as a surrogate for warfarin activity and clotting factor concentration.

To predict the time course of drug response using a pharmacodynamic model, a mathematical expression is developed to describe the drug concentration–time profile of the drug at the receptor site. This equation is then used to relate drug concentrations to the time course and intensity of the pharmacologic response. Most pharmacodynamic models assume that pharmacologic action is due to a drug–receptor interaction, and the magnitude of the response is related quantitatively to the drug concentration in the receptor compartment. In the simplest case, the drug receptor lies in the plasma compartment and pharmacologic response is established through a one-compartment model with drug response proportional to log drug concentration (Eq. 19.1). A more complicated model involving a receptor compartment that lies outside the central compartment was proposed by Sheiner and associates (1979). This model locates the receptor in an effect compartment in which a drug equilibrates from the central compartment by a first-order rate constant k_{1e}. There is no back diffusion of drug away from the effect compartment, thereby simplifying the complexity of the equations. This model was applied successfully to monitor the pharmacologic effects of the drug trimazosin (Meredith et al, 1983).

The pharmacokinetics of trimazosin are described as a two-compartment open model with conversion to a metabolite by a first-order rate constant k_{1m}. The pharmacokinetics of the metabolite are described by a one compartment model with a first-order elimination constant k_{m0}. The drug effect may be described by two pharmacodynamic models, either model A or B. Model A assumes that the drug effect in the effect compartment is produced by the drug only. Model B assumes that both the drug and a metabolite produce drug effect (Fig. 19-26).

The following equation describes the pharmacokinetics and pharmacodynamics of the drug:

$$C_p = Ae^{-at} - Be^{-bt} \tag{19.25}$$

where C_p is the concentration of the drug in the central compartment.

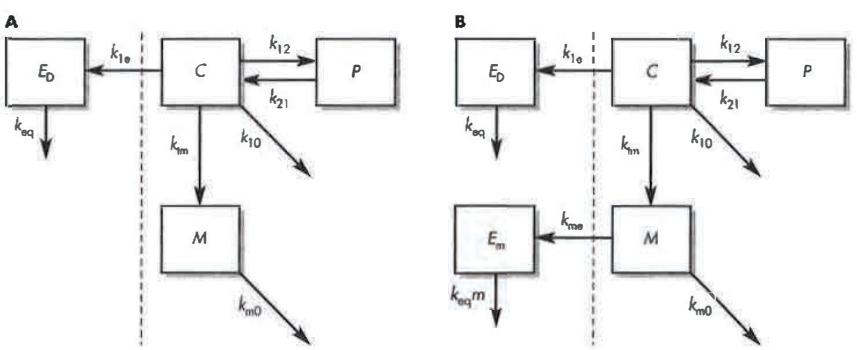


Figure 19-26. Two proposed pharmacodynamic models for describing the hypotensive effect of trimazosin. **A** assumes an effect compartment (left of dashed line) for the drug. **B** assumes an effect compartment for the drug as well as the metabolite.
(From Meredith et al, 1983, with permission.)

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$$C_m = \frac{V_1 k_{1m}}{V_m}\left[\frac{A}{(k_{m0} - a)}(e^{-at} - e^{-k_{m0}t}) + \frac{B}{(k_{m0} - b)}(e^{-bt} - e^{-k_{m0}t})\right] \quad (19.26)$$

where C_m is the concentration of the metabolite in the body, V_m is the volume of distribution of the metabolite, V_1 is the volume of the central compartment of the body, k_{1m} is the first-order constant for converting drug to metabolite, k_{m0} is the elimination rate constant of the metabolite, A and B are two-compartment model coefficients for the drug (see Chapter 4), and k_{10} is the elimination rate constant of the drug.

The drug concentration in the effect compartment is calculated by assuming that at equilibrium the concentration of the drug in the effect compartment and the central compartment are equal,

$$k_{1e}V_1 = k_{eq}V_e \quad (19.27)$$

where V_e is volume of the effect compartment and k_{eq} is the elimination rate constant of the drug from the effect compartment. Therefore, the drug concentration in the effect compartment $C(e, d)$ is calculated as

$$C(e, d) = \frac{AK_{eq}}{(k_{eq} - a)}(e^{-at} - e^{-k_{eq}t}) + \frac{Bk_{eq}}{(k_{eq} - b)}(e^{-bt} - e^{-k_{eq}t}) \quad (19.28)$$

The effect due to drug is assumed to be linear,

$$E = M_d C(e, d) + i \quad (19.29)$$

where M_d is the *sensitivity slope* to the drug (ie, the effect per unit of drug concentration in the effect compartment). The parameters M_d, i, and k_{eq} are determined by least-squares fitting of the data. For the metabolite, the concentration of metabolite in the effect compartment is $C(e, m)$.

$$C(e, m) = \frac{AV_1 k_{1m} k_{eq} m}{V_m} \quad (19.30)$$

$$\times\left[\frac{e^{-at}}{(a - k_{m0})(a - k_{eq}m)} + \frac{e^{-k_{m0}t}}{(a - k_{m0})(k_{eq}m - k_{m0})}\right.$$

$$-\frac{e^{-k_{eq}mt}}{(a - k_{eq}m)(k_{eq}m - k_{m0})}$$

$$+\frac{BV_1 k_{1m} k_{eq} m}{V_m}\frac{e^{-bt}}{(b - k_{m0})(b - k_{eq}m)}$$

$$\left.+\frac{e^{-k_{m0}t}}{(b - k_{m0})(k_{eq}m - k_{m0})} - \frac{e^{-k_{eq}mt}}{(b - k_{eq}m)(k_{eq}m - k_{m0})}\right]$$

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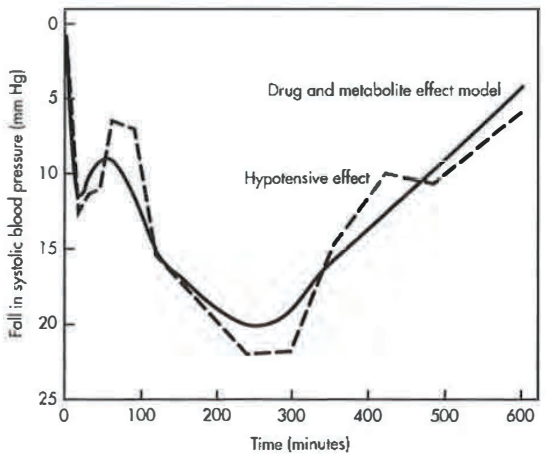


Figure 19-27. Diagram showing the agreement between recorded hypotensive effect (solid line) and hypotensive effect as projected by model B (broken line). (From Meredith et al, 1983, with permission.)

The concentration of the metabolite in the effect compartment is in turn related to drug effect as for the parent drug. The total effect produced is

$$E = M_d C(e,d) + M_m C(e,m) + i \qquad (19.31)$$

The five parameters M_d, M_m, i, k_{eq}, k_{eqm} may be estimated from Equation 19.31 by fitting the data to an appropriate model. Figure 19-27 shows the observed decline in systolic blood pressure compared with the theoretical decline in blood pressure predicted by the model. An excellent fit of the data was obtained by assuming that both drug and metabolite are active. This example illustrates that, for a dose of a drug, the drug concentration in the effect compartment and others may be described by a mathematical model. These equations were further developed to describe the time course of a pharmacologic event. In this case, Meredith and associates (1983) demonstrated that both the drug and the metabolite formed in the body may affect the time course of the pharmacologic action of the drug in the body.

Simulation of *In-Vitro* Pharmacodynamic Effect Involving Hysteresis

An *in-vitro* model simulation of the sum of pharmacologic effect contributed by a drug and its active metabolite may explain the observation of the hysteresis response curve *in vivo*. Gupta et al (1993) discussed the factors that affect the shape of the response curve. In the simplest case, pharmacokinetic equations are developed to calculate C_p, the drug concentration, and C_m, the metabolite concentration. To estimate the pharmacologic effect due to both the drug and active metabolite, the potency of the drug is defined as P, the potency of the metabolite is P_m, and

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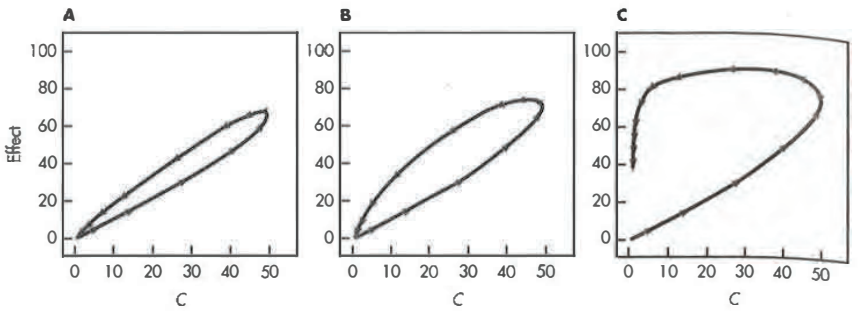


Figure 19-28. Simulated *in-vitro* pharmacodynamic response versus concentration (C) contributed by a drug and a metabolite. Potency of parent drug and metabolite are equal, but **(A)** k_{m0} = large, **(B)** k_{m0} = medium, and **(C)** k_{m0} = small.
(From Gupta et al, 1993, with permission.)

the sum of the pharmacologic effect is as shown below. (In their first simulation, Gupta et al assumed that the effect is linearly related to drug and metabolite concentrations.)

$$E = PC_p + P_m C_m \tag{19.32}$$

The shape of hysteresis simulated is very dependent on P_m and k_{m0}, the rate constant of metabolite elimination. If k_{m0} is given a high, medium, or low value, the effect on the shape of the hysteresis loop is changed dramatically, as shown in Figure 19-28. A temporal effect causes a counterclockwise loop. In the case of a metabolite that acts as an antagonist, the hysteresis loop is clockwise. The more elaborate features of an E_{max} model were simulated by Gupta et al (1993) in their paper.



CLINICAL EXAMPLE

Lorazepam Pharmacodynamics—Example of an In-Vivo Hysteresis Loop

Many drugs that act on the central nervous systems (CNS) have a lag time before the tissues and the plasma are equilibrated with drug. The pharmacokinetics of lorazepam after oral absorption were fitted to a two-compartment model with lag time. Lorazepam was studied because the drug accounts for all the activity, such that the counterclockwise response profile may be attributed to equilibration rather than to metabolism (Gupta et al, 1990).

The description of the plasma drug concentrations, C_p, is obtained by conventional pharmacokinetic equations, whereas the pharmacodynamic effect, E, is

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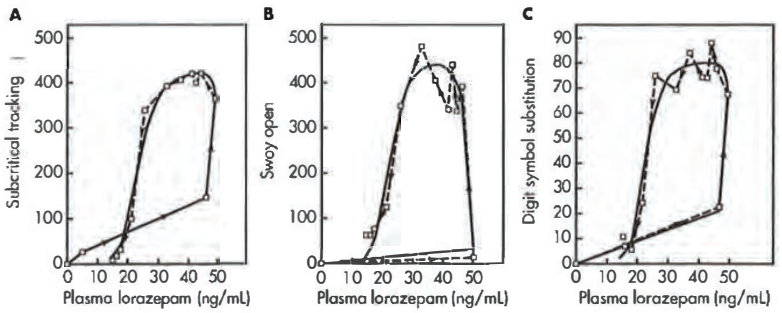


Figure 19-29. Plot of responses of lorazepam versus plasma drug concentration showing counterclockwise hysteresis.
(From Gupta et al, 1990, with permission.)

described by a sigmoid E_{max} model similar to Equation 19.15, except that the baseline effect is also included. Gupta et al (1990) monitored three pharmacodynamic effects due to lorazepam. The monitored pharmacodynamic effects were mental impairment processes evaluated by the cognitive and psychomotor performance of the subjects, including (A) subcritical tracking, (B) sway open (a measurement of gross body movements), and (C) digital symbol substitution. When the time course of each effect was plotted versus plasma drug concentration, a counterclockwise loop was observed (Fig. 19-29). When the same pharmacodynamic responses were plotted versus lorazepam concentration in the effect compartment accounting for the equilibration lag, a classical sigmoid relation was observed (Fig. 19-30). The observations showed that the temporal response of many drugs may be the result of pharmacodynamic and distributional factors interacting with each other. Thus, a model with an effect compartment can more fully help to understand the time course of the drug response.

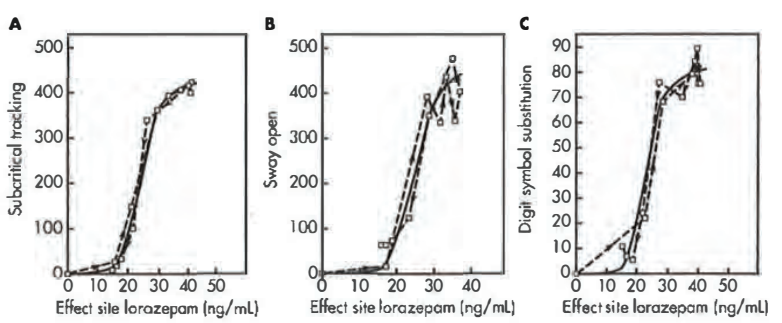


Figure 19-30. Plot of responses to lorazepam versus effect compartment concentration showing sigmoid relationship between effect and concentration without hysteresis.
(From Gupta et al, 1990, with permission.)

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FREQUENTLY ASKED QUESTIONS

1. Explain why doubling the dose of a drug does not double the pharmacodynamic effect of the drug.
2. What is meant by a hysteresis loop? Why do some drugs follow a clockwise hysteresis loop and other drugs follow a counterclockwise hysteresis loop?
3. What is meant by an effect compartment? How does the effect compartment differ from pharmacokinetic compartments, such as the central compartment and the tissue compartment?

LEARNING QUESTIONS

1. On the basis of the graph in Figure 19-31, answer "true" or "false" to statements (a)–(e) and state the reason for each answer.
   a. The plasma drug concentration is more related to the pharmacodynamic effect of the drug compared to the dose of the drug.
   b. The pharmacologic response is directly proportional to the log plasma drug concentration.
   c. The volume of distribution is not changed by uremia.
   d. The drug is exclusively eliminated by hepatic biotransformation.
   e. The receptor sensitivity is unchanged in the uremic patient.
2. What do clavulanate, sulbactam, and tazobactam have in common? Why are they used together with antibiotics?
3. Explain why subsequent equal doses of a drug do not produce the same pharmacodynamic effect as the first dose of a drug.
   a. Provide an explanation based on pharmacokinetic considerations.
   b. Provide an explanation based on pharmacodynamic considerations.

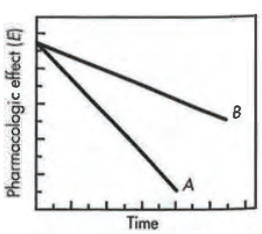


Figure 19-31. Graph of pharmacologic response *E* as a function of time for the same drug in patients with normal **(A)** and uremic **(B)** kidney function, respectively.

4. How are the parameters AUC and t_{eff} used in pharmacodynamic models?
5. What class of drug tends to have a lag time between the plasma and the effect compartment?
6. Name an example of a pharmacodynamic response that does not follow a drug dose–response profile?
7. When an antibiotic concentration falls below the MIC, there is a short time period in which bacteria fail to regrow because of postantibiotic effect (PAE). This time period is referred to as PAT. What is PAT?
8. What is AUIC with regard to an antibiotic?

REFERENCES

Aghajanian OK, Bing OHL: Persistence of lysergic acid diethylamide in the plasma of human subjects. *Clin Pharmacol Ther* 5:611–614, 1964

Baxter JD, Funder JW: Hormone receptors. *N Engl J Med* 301:1149–1161, 1979

Boudinot FD, D'Ambrosio R, Jusko WJ: Receptor-mediated pharmacodynamics of prednisolone in the rat. *J Pharmacokinet Biopharm* 14:469–493, 1986

Colburn WA: Perspectives in pharmacokinetics: Pharmacokinetic/pharmacodynamic modeling: What is it? *J Pharmacokinet Biopharm* 15:545–553, 1987

Cone EJ: Pharmacokinetics and pharmacodynamics of cocaine. *J Anal Toxicol* 19:459–478, 1995

Cox, BM: Drug tolerance and physical dependence. In WB Pratt, P Taylor (eds): *Principles of Drug Action. The Basis of Pharmacology.* New York, Churchill Livingstone, 1990, chap 10

Craig, WA: Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diag Microbiol Infect Dis* 22:89–96, 1995

Craig WA, Andes D: Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *J Pediatr Infect Dis* 15:255–259, 1996

deWit H, Dudish S, Ambre J: Subjective behavioral effects of diazepam depend upon its rate of onset. *Psychopharmacology* 112:324–330, 1993

Drusano GL: Minireview: Role of pharmacokinetics in the outcome of infections. *Antimicrob Agents Chemother* 32(3):289–297, 1988

Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ: Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 37(5):1073–1081, 1993

Gupta SK, Ellinwood EH, Nikaido AM, Heatherly DG: Simultaneous modeling of the pharmacokinetic and pharmacodynamic properties of benzodiazepines I: Lorazepam. *J Pharmacokinet Biopharm* 18:89–102, 1990

Gupta SK, Hwang SS, Benet LZ, Gumbleton M: Interpretation and utilization of effect and concentration data collected in an *in vivo* pharmacokinetic and in vitro pharmacodynamic study. *Pharm Res* 10:889–894, 1993

Henningfield JE, Keenan RM: Nicotine delivery kinetics and abuse liability. *J Consult Clin Pharmacol* 61:743–750, 1993

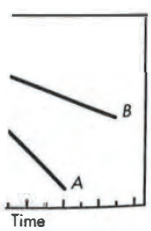
Hill AV: The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *J Physiol* 40:4–7, 1910

Holford NHG, Sheiner LB: Understanding the dose–effect relationship. Clinical application of pharmacokinetic–pharmacodynamic models. *Clin Pharmacokinet* 6:429–453, 1981

Holford NHG, Sheiner LB: Kinetics of pharmacologic response. *Pharm Ther* 16:143–166, 1982

Johanson C-E, Fischman MW: The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 41:3–52, 1989

Johansen SH, Jorgensen M, Molbech S: Effect of tubocurarine on respiratory and nonrespiratory muscle power in man. *J Appl Physiol* 19:990–991, 1964



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DR. REDDY'S LABORATORIES, INC.
IPR2024-00009
Ex. 1045, p. 113 of 115

Lalonde RL: Pharmacodynamics. In Evans WE et al. (eds): *Applied Pharmacokinetics*, 3rd ed. Vancouver, WA, Applied Therapeutics, 1992, chap 4

Lin RY: A perspective on penicillin allergy. *Arch Intern Med* **152**:930–937, 1992

Meredith PA, Kelman AW, Eliott HL, Reid JL: Pharmacokinetic and pharmacodynamic modeling of trimazosin and its major metabolite. *J Pharmacokinet Biopharm* **11**:323–334, 1983

Meibohm B, Derendorf H: Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *Int J Clin Pharmacol* **35**(10):401–413, 1997

Mitenko PA, Ogilvie RI: Rational intravenous doses of theophylline. *N Engl J Med* **289**:600–603, 1973

Reisman AS, Reisman RE: Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Aller Asthma Immunol* **74**:167–170, 1995

Rodman JH, Evans WE: Targeted systemic exposure for pediatric cancer therapy. In D'Argenio (ed): *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*. New York, Plenum Press, 1991, pp 177–183

Scaglione F: Predicting the clinical efficacy of antibiotics: Toward definitive criteria. *Pediatr Infect Dis J* **3**:S56–S59, 1997

Scott JC, Stanski DR: Decreased fentanyl/alfentanil dose requirement with increasing age: A pharmacodynamic basis. *Anesthesiology* **63**:A374, 1985

Sheiner LB, Stanski DR, Vozeh S, et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. *Clin Pharmacol Ther* **25**:358–370, 1979

Taylor P, Insel PA: Molecular basis of pharmacologic selectivity. In Pratt WB, Taylor P (eds): *Principles of Drug Action. The Basis of Pharmacology*, 3rd ed. New York, Churchill Livingstone, 1990

van Dyke C, Jatlow P, Ungerer J, et al: Oral cocaine: Plasma concentration and central effects. *Science* **200**:211–213, 1978

Wagner JG: Kinetics of pharmacologic response: I. Proposed relationship between response and drug concentration in the intact animal and man. *J Theor Biol* **20**:173–201, 1968

Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC: Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide. *Circulation* **54**:884–889, 1976

Yasuhara M, Hashimoto Y, Okumura K, et al: Kinetics of ajmaline disposition and pharmacologic response in beagle dogs. *J Pharmacokinet Biopharm* **15**:39–56, 1987

BIBLIOGRAPHY

Derendorf H, Meibohm B: Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: Concepts and perspectives. *Pharm Res* **6**:176–185, 1999

Drusano GL: Human pharmacodynamics of beta-lactams, aminoglycosides and their combination. *Scand J Infect Dis* **74**(suppl):235–248, 1991

Drusano GL, Craig WA: Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J Chemother* **9**(suppl 3):38–44, 1997

Galeazzi RL, Benet LZ, Sheiner LB: Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clin Pharmacol Ther* **20**:278–289, 1976

Gibaldi M, Levy G, Weintraub H: Drug distribution and pharmacologic effects. *Clin Pharmacol Ther* **12**:734, 1971

Gunderson BW, Ross GH, Ibrahim KH, Rotschafer JC: What do we really know about antibiotic pharmacodynamics? *Pharmacotherapy* **21**(11s):302s–318s, 2001

Harron DWG: Digoxin pharmacokinetic modeling—10 years later. *Int J Pharm* **53**:181–188, 1989

Hochhaus G, Barrett JS, Derendorf H: Evolution of pharmacokinetics and pharmacokinetic/dynamic correlations during the 20th century. *J Clin Pharmacol* **40**(9):908–917, 2000

Holford NHG: Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose–effect relationship. *Clin Pharmacokinet* **11**:583–604, 1986

Jusko WJ: Pharmacodynamics of chemotherapeutic effects: Dose–time–response relationship for phase-nonspecific agents. *J Pharm Sci* **60**:892, 1971

Levy G: Kinetics of pharmacologic effects. *Clin Pharmacol Ther* **1**:362, 1966

Meffin PJ, Winkle RA, Blaschke RF, et al: Response optimization of drug dosage: Antiarrhythmic studies with tocainide. *Clin Pharmacol Ther* **22**:42–57, 1977

MPI EXHIBIT 1045 PAGE 114

DR. REDDY'S LABORATORIES, INC.
IPR2024-00009
Ex. 1045, p. 114 of 115

Meibohm B, Derendorf H: Pharmacokinetic/pharmacodynamic studies in drug product development. *J Pharm Sci* **91**:18–31, 2002

Mueller M, de la Pena A, Derendorf H: Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: Kill curves versus MIC. *Antimicrob Agents Chemother* **48**(2):369–377, 2004

Packer M, Carver JR, Rodeheffer RJ, et al: Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* **21**:1468, 1991

Schwinghammer TL, Kroboth PD: Basic concepts in pharmacodynamic modeling. *J Clin Pharmacol* **28**:388–394, 1988

Seeman P, Lee T, Chau-Wong M, Wong K: Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **261**:717–719, 1976

Sheiner LB: Commentary to pharmacokinetic/pharmacodynamic modeling: What it is! *J Pharmacokinet Biopharm* **15**:553–555, 1987

Suresh A, Reisman RE: Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* **74**:167–170, 1995

Swerdlow BN, Holley FO: Intravenous anaesthetic agents. Pharmacokinetic/pharmacodynamic relationships. *Clin Pharmacokinet* **12**:79–110, 1987

Verrijk R, Vleeming W, Hans H, et al: Plasma elimination of milrinone in rats in relation to its hemodynamic effects. *J Pharm Sci* **79**:236–239, 1990

Whiting B, Holford NHG, Sheiner LB: Quantitative analysis of the disopyramide concentration–effect relationship. *Br J Clin Pharmacol* **9**:67–75, 1980

MPI EXHIBIT 1045 PAGE 115

DR. REDDY'S LABORATORIES, INC.
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