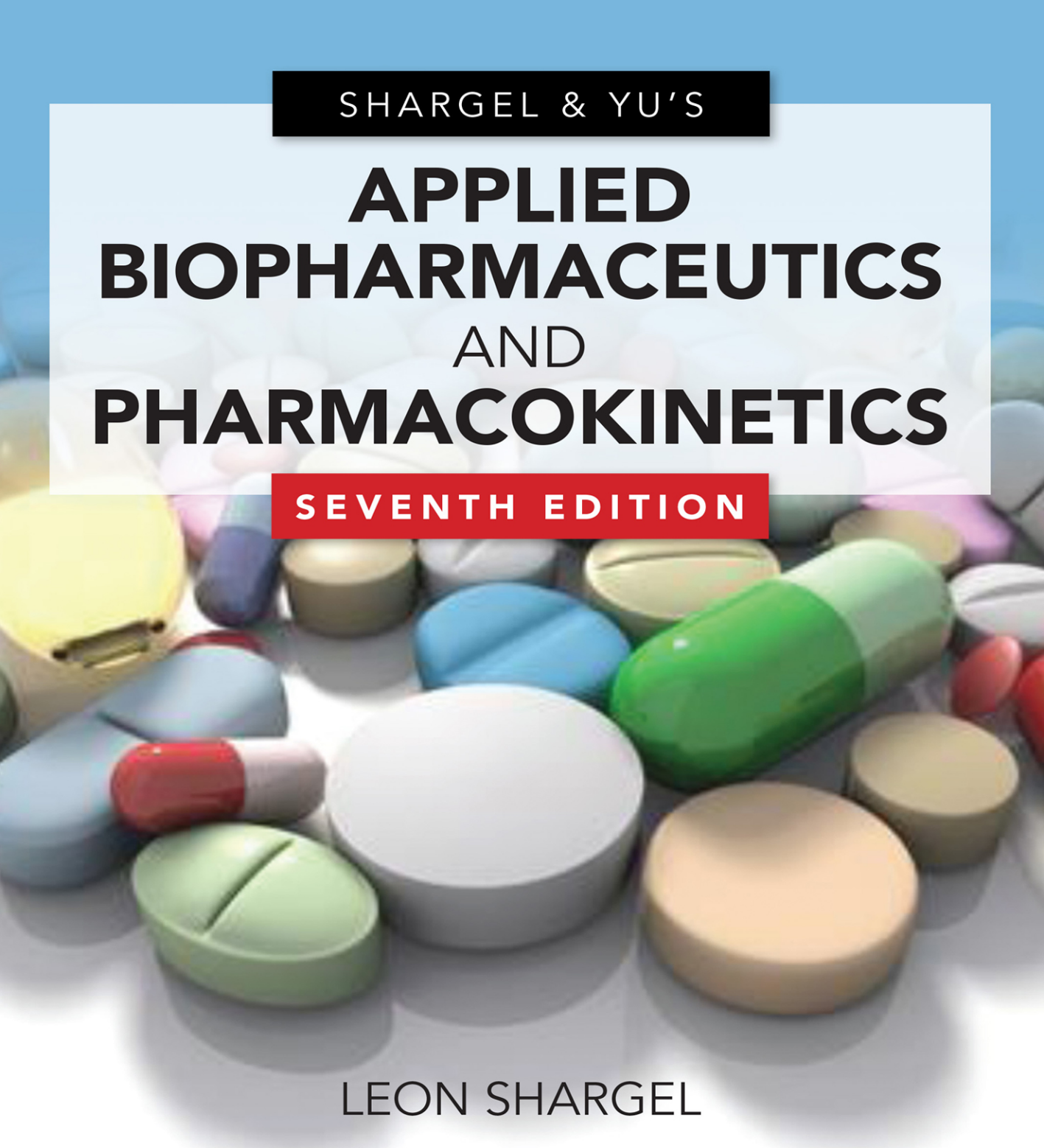
SHARGEL & YU'S

APPLIED BIOPHARMACEUTICS AND PHARMACOKINETICS

SEVENTH EDITION



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Applied Biopharmaceutics & Pharmacokinetics

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Applied Biopharmaceutics & Pharmacokinetics

Seventh Edition

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Preface

The publication of this seventh edition of *Applied Biopharmaceutics and Pharmacokinetics* represents over three decades in print. Since the introduction of classic pharmacokinetics in the first edition, the discipline has expanded and evolved greatly. The basic pharmacokinetic principles and biopharmaceutics now include pharmacogenetics, drug receptor theories, advances in membrane transports, and functional physiology. These advances are applied to the design of new active drug moieties, manufacture of novel drug products, and drug delivery systems. Biopharmaceutics and pharmacokinetics play a key role in the development of safer drug therapy in patients, allowing individualizing dosage regimens and improving therapeutic outcomes.

In planning for the seventh edition, we realized that we needed expertise for these areas. This seventh edition is our first edited textbook in which an expert with intimate knowledge and experience in the topic was selected as a contributor. We would like to acknowledge these experts for their precious time and effort. We are also grateful to our readers and colleagues for their helpful feedback and support throughout the years.

As editors of this edition, we kept the original objectives, starting with fundamentals followed by a holistic integrated approach that can be applied to practice (see scope and objectives in Preface to the first edition). This textbook provides the reader with a basic and practical understanding of the principles of biopharmaceutics and pharmacokinetics that can be applied to drug product development and drug therapy. Practice problems, clinical examples, frequently asked questions and learning questions are included in each chapter to demonstrate how these concepts relate to practical situations. This textbook remains unique in teaching basic concepts that may be applied to understanding complex issues associated with *in vivo* drug delivery that are essential for safe and efficacious drug therapy.

The primary audience is pharmacy students enrolled in pharmaceutical science courses in pharmacokinetics and biopharmaceutics. This text fulfills course work offered in separate or combined courses in these subjects. Secondary audiences for this textbook are research, technological and development scientists in pharmaceutics, biopharmaceutics, and pharmacokinetics.

This edition represents many significant changes from previous editions.

- The book is an edited textbook with the collaboration of many experts well known in biopharmaceutics, drug disposition, drug delivery systems, manufacturing, clinical pharmacology, clinical trials, and regulatory science.
- Many chapters have been expanded and updated to reflect current knowledge and application of biopharmaceutics and pharmacokinetics. Many new topics and updates are listed in Chapter 1.
- Practical examples and questions are included to encourage students to apply the principles in patient care and drug consultation situations.
- Learning questions and answers appear at the end of each chapter.
- Three new chapters have been added to this edition including, *Biostatistics* which provides introduction for popular topics such as risk concept, non-inferiority, and superiority concept in new drug evaluation, and *Application of Pharmacokinetics in Specific Populations* which discusses issues such as drug and patient related pharmacy

topics in during therapy in various patient populations, and *Biopharmaceutic Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence* which explains the synthesis, quality and physical/chemical properties of the active pharmaceutical ingredients affect the bioavailability of the drug from the drug product and clinical efficacy.

Leon Shargel
Andrew B.C. Yu

Preface to First Edition

The publication of the twelfth edition of this book is a testament to the vision and ideals of the original authors, Alfred Gilman and Louis Goodman, who, in 1941set forth the principles that have guided the book through eleven editions: to correlate pharmacology with related medical sciences, to reinterpret the actions and uses of drugs in light of advances in medicine and the basic biomedical sciences, to emphasize the applications of pharmacodynamics to therapeutics, and to create a book that will be useful to students of pharmacology and to physicians. These precepts continue to guide the current edition.

As with editions since the second, expert scholars have contributed individual chapters. A multiauthored book of this sort grows by accretion, posing challenges editors but also offering memorable pearls to the reader. Thus, portions of prior editions persist in the current edition, and I hasten to acknowledge the contributions of previous editors and authors, many of whom will see text that looks familiar. However, this edition differs noticeably from its immediate predecessors. Fifty new scientists, including a number from out-side. the U.S., have joined as contributors, and all chapters have been extensively updated. The focus on basic principles continues, with new chapters on drug invention, molecular mechanisms of drug action, drug toxicity and poisoning, principles of antimicrobial therapy and pharmacotherapy of obstetrical and gynecological disorders. Figures are in full color. The editors have continued to standardize the organization of chapters: thus, students should easily find the basic physiology, biochemistry, and pharmacology set forth in regular type; bullet points highlight important lists within the text; the clinician and expert will find details in extract type under clear headings.

Online features now supplement the printed edition. The entire text, updates, reviews of newly approved drugs, animations of drug action, and hyper links to relevant text in the prior edition are available on the Goodman & Gilman section of McGraw-Hill's websites, *AccessMedicine.com* and *AccessPharmacy.com*. An Image Bank CD accompanies the book and makes all tables and figures available for use in presentations.

The process of editing brings into view many remarkable facts, theories, and realizations. Three stand out: the invention of new classes of drugs has slowed to a trickle; therapeutics has barely begun to capitalize on the information from the human genome project; and, the development of resistance to antimicrobial agents, mainly through their overuse in medicine and agriculture, threatens to return us to the pre-antibiotic era. We have the capacity and ingenuity to correct these shortcomings.

Many, in addition to the contributors, deserve thanks for their work on this edition; they are acknowledged on an accompanying page. In addition, I am grateful to Professors Bruce Chabner (Harvard Medical School/Massachusetts General Hospital) and Björn Knollmann (Vanderbilt University Medical School) for agreeing to be associate editors of this edition at a late date, necessitated by the death of my colleague and friend Keith Parker in late 2008. Keith and I worked together on the eleventh edition and on planning this edition. In anticipation of the editorial work ahead, Keith submitted his chapters before anyone else and just a few weeks before his death; thus, he is well represented in this volume, which we dedicate to his memory.

Laurence L. Brunton

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Dr. Leon Shargel is a consultant for the pharmaceutical industry in biopharmaceutics and pharmacokinetics. Dr. Shargel has over 35 years experience in both academia and the pharmaceutical industry. He has been a member or chair of numerous national committees involved in state formulary issues, biopharmaceutics and bioequivalence issues, institutional review boards, and a member of the USP Biopharmaceutics Expert Committee. Dr. Shargel received a BS in pharmacy from the University of Maryland and a PhD in pharmacology from the George Washington University Medical Center. He is a registered pharmacist and has over 150 publications including several leading textbooks in pharmacy. He is a member of various professional societies, including the American Association Pharmaceutical Scientists (AAPS), American Pharmacists Association (APhA), and the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Dr. Andrew Yu has over 30 years of experience in academia, government, and the pharmaceutical industry. Dr. Yu received a BS in pharmacy from Albany College of Pharmacy and a PhD in pharmacokinetics from the University of Connecticut. He is a registered pharmacist and has over 30 publications and a patent in novel drug delivery. He had lectured internationally on pharmaceutics, drug disposition, and drug delivery.

1 Introduction to Biopharmaceutics and Pharmacokinetics

Leon Shargel and Andrew B.C. Yu

Chapter Objectives

- Define drug product performance and biopharmaceutics.
- Describe how biopharmaceutics affects drug product performance.
- Define pharmacokinetics and describe how pharmacokinetics is related to pharmacodynamics and drug toxicity.
- Define the term clinical pharmacokinetics and explain how clinical pharmacokinetics may be used to develop dosage regimens for drugs in patients.
- Define pharmacokinetic model and list the assumptions that are used in developing a pharmacokinetic model.
- Explain how the prescribing information or approved labeling for a drug helps the practitioner to recommend an appropriate dosage regimen for a patient.

DRUG PRODUCT PERFORMANCE

Drugs are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Drugs are given in a variety of dosage forms or *drug products* such as solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc, for systemic or local therapeutic activity. Drug products can be considered to be drug delivery systems that release and deliver drug to the site of action such that they produce the desired therapeutic effect. In addition, drug products are designed specifically to meet the patient's needs including palatability, convenience, and safety.

Drug product performance is defined as the release of the drug substance from the drug product either for local drug action or for drug absorption into the plasma for systemic therapeutic activity. Advances in pharmaceutical technology and manufacturing have focused on developing quality drug products that are safer, more effective, and more convenient for the patient.

BIOPHARMACEUTICS

Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. The importance of the drug substance and the drug formulation on absorption, and *in vivo* distribution of the drug to the site of action, is described as a sequence of events that precede elicitation of a drug's therapeutic effect. A general scheme describing this dynamic relationship is illustrated in Fig. 1-1.

First, the drug in its dosage form is taken by the patient 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 for local action or into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. A pharmacodynamic response results when the drug concentration at the site of

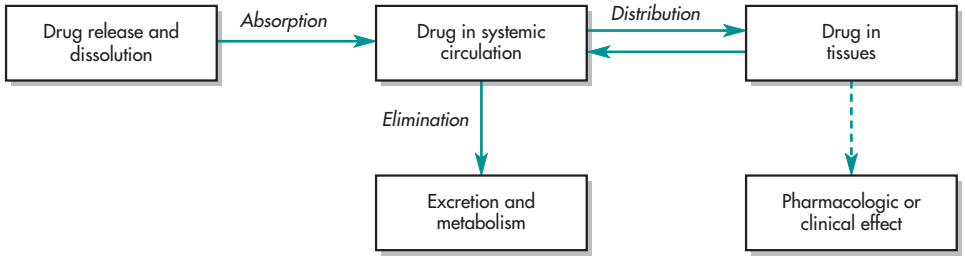

FIGURE 1-1 Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

action reaches or exceeds the *minimum effective concentration* (MEC). The suggested dosing regimen, including starting dose, maintenance dose, dosage form, and dosing interval, is determined in clinical trials to provide the drug concentrations that are therapeutically effective in most patients. This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form and the physicochemical properties of the drug.

Historically, pharmaceutical scientists have evaluated the relative drug availability to the body *in vivo* after giving a drug product by different routes 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. Thus, 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, is toxic, or has no apparent effect at all.

The US Food and Drug Administration (FDA) approves all drug products to be marketed in the United States. The pharmaceutical manufacturers must perform extensive research and development prior to approval. The manufacturer of a new drug product must submit a *New Drug Application* (NDA) to the FDA, whereas a generic drug pharmaceutical manufacturer must submit an *Abbreviated New Drug Application* (ANDA). Both the new and generic drug product manufacturers must characterize their drug and drug product and demonstrate that the drug product performs appropriately before the products can become available to consumers in the United States.

Biopharmaceutics provides the scientific basis for drug product design and drug product development. Each step in the manufacturing process of a finished dosage form may potentially affect the release of the drug from the drug product and the availability of the drug at the site of action. The most important steps in the manufacturing process are termed *critical manufacturing variables*. Examples of biopharmaceutic considerations in drug product design are listed in Table 1-1. A detailed discussion of drug product design is found in Chapter 15. Knowledge of physiologic factors necessary for designing oral products is discussed in Chapter 14. Finally, drug product quality of drug substance (Chapter 17) and drug product testing is discussed in later chapters (18, 19, 20, and 21). It is important for a pharmacist to know that drug product selection from multisources could be confusing and needs a deep understanding of the testing procedures and manufacturing technology which is included in the chemistry, manufacturing, and control (CMC) of the product involved. The starting material (SM) used to make the API (active pharmaceutical ingredient), the processing method used during chemical synthesis, extraction, and the purification method can result in differences in the API that can then affect drug product performance (Chapter 17). Sometimes a by-product of the synthetic process, residual solvents, or impurities that remain may be harmful or may affect the product's physical or chemical stability. Increasingly, many drug sources are imported and the manufacturing of these products is regulated by codes or pharmacopeia in other countries. For example, drugs in Europe may be meeting EP (European Pharmacopeia) and since 2006,

TABLE 1-1 Biopharmaceutic Considerations in Drug Product Design

Items	Considerations
Therapeutic objective	Drug may be intended for rapid relief of symptoms, slow extended action given once per day, or longer for chronic use; some drug may be intended for local action or systemic action
Drug (active pharmaceutical ingredient, API)	Physical and chemical properties of API, including solubility, polymorphic form, particle size; impurities
Route of administration	Oral, topical, parenteral, transdermal, inhalation, etc
Drug dosage and dosage regimen	Large or small drug dose, frequency of doses, patient acceptance of drug product, patient compliance
Type of drug product	Orally disintegrating tablets, immediate release tablets, extended release tablets, transdermal, topical, parenteral, implant, etc
Excipients	Although very little pharmacodynamic activity, excipients may affect drug product performance including release of drug from drug product
Method of manufacture	Variables in manufacturing processes, including weighing accuracy, blending uniformity, release tests, and product sterility for parenterals

agreed uniform standards are harmonized in ICH guidances for Europe, Japan, and the United States. In the US, the USP-NF is the official compendia for drug quality standards.

Finally, the equipment used during manufacturing, processing, and packaging may alter important product attribute. Despite compliance with testing and regulatory guidance involved, the issues involving pharmaceutical equivalence, bioavailability, bioequivalence, and therapeutic equivalence often evolved by necessity. The implications are important regarding availability of quality drug product, avoidance of shortages, and maintaining an affordable high-quality drug products. The principles and issues with regard to multisource drug products are discussed in subsequent chapters:

Chapter 14	Physiologic Factors Related to Drug Absorption	How stomach emptying, GI residence time, and gastric window affect drug absorption
Chapter 15	Biopharmaceutic Considerations in Drug Product Design	How particle size, crystal form, solubility, dissolution, and ionization affect *in vivo* dissolution and absorption. Modifications of a product with excipient with regard to immediate or delayed action are discussed. Dissolution test methods and relation to *in vivo* performance
Chapter 16	Drug Product Performance, *In Vivo*: Bioavailability and Bioequivalence	Bioavailability and bioequivalence terms and regulations, test methods, and analysis examples. Protocol design and statistical analysis. Reasons for poor bioavailability. Bioavailability reference, generic substitution. PE, PA, BA/BE, API, RLD, TE SUPAC (Scale-up postapproval changes) regarding drug products. What type of changes will result in changes in BA, TE, or performances of drug products from a scientific and regulatory viewpoint
Chapter 17	Biopharmaceutic Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence	Physicochemical differences of the drug, API due to manufacturing and synthetic pathway. How to select API from multiple sources while meeting PE (pharmaceutical equivalence) and TE (therapeutic equivalence) requirement as defined in CFR. Examples of some drug failing TE while apparently meeting API requirements. Formulation factors and manufacturing method affecting PE and TE. How particle size and crystal form affect solubility and dissolution. How pharmaceutical equivalence affects therapeutic equivalence. Pharmaceutical alternatives. How physicochemical characteristics of API lead to pharmaceutical inequivalency
Chapter 18	Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy	Drug product quality and drug product performance Pharmaceutical development. Excipient effect on drug product performance. Quality control and quality assurance. Risk management Scale-up and postapproval changes (SUPAC) Product quality problems. Postmarketing surveillance

Thus, biopharmaceutics involves factors that influence (1) the design of the drug product, (2) stability of the drug within the drug product, (3) the manufacture of the drug product, (4) the release of the drug from the drug product, (5) the rate of dissolution/release of the drug at the absorption site, and (6) delivery of drug to the site of action, which may involve targeting the drug to a localized area (eg, colon for Crohn disease) for action or for systemic absorption of the drug.

Both the pharmacist and the pharmaceutical scientist must understand these complex relationships to objectively choose the most appropriate drug product for therapeutic success.

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 15. 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.

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, metabolism and excretion). 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.

PHARMACODYNAMICS

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body; this includes the mechanisms of drug action and the relationship between drug concentration and effect. A typical example of pharmacodynamics is how a drug interacts quantitatively with a drug receptor to produce a response (effect). Receptors are the molecules that interact with specific drugs to produce a pharmacological effect in the body.

The pharmacodynamic effect, sometimes referred to as the pharmacologic effect, can be therapeutic and/or cause toxicity. Often drugs have multiple effects including the desired therapeutic response as well as unwanted side effects. For many drugs, the pharmacodynamic effect is dose/drug concentration related; the higher the dose, the higher drug concentrations in the body and the more intense the pharmacodynamic effect up to a maximum effect. It is desirable that side effects and/or toxicity of drugs occurs at higher drug concentrations than the drug concentrations needed for the therapeutic effect. Unfortunately, unwanted side effects often occur concurrently with the therapeutic doses. The relationship between pharmacodynamics and pharmacokinetics is discussed in Chapter 21.

CLINICAL PHARMACOKINETICS

During the drug development process, large numbers of patients are enrolled in clinical trials to determine efficacy and optimum dosing regimens. Along with safety and efficacy data and other patient information, the FDA approves a label that becomes the package insert discussed in more detail later in this chapter. The approved labeling recommends the proper starting dosage regimens for the general patient population and may have additional recommendations for special populations of patients that need an adjusted dosage regimen (see Chapter 23). These recommended dosage regimens 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 a 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 in patient care. 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 1-2 is a list of 10 age adjusted rates of death from 10 leading causes of death in the United States in 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 (see Chapter 23). The study of pharmacokinetic differences of drugs in various population groups is termed *population pharmacokinetics* (Sheiner and Ludden, 1992; see Chapter 22). Application of Pharmacokinetics to Specific Populations, Chapter 23, will discuss many of the important pharmacokinetic considerations for dosing subjects due to age, weight, gender, renal, and hepatic disease differences. Despite advances in modeling and genetics, sometimes it is necessary to monitor the plasma drug concentration precisely in a patient for safety and multidrug dosing consideration. Clinical 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).

TABLE 1-2 Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death* in the US, 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.

Labeling For Human Prescription Drug and Biological Products

In 2013, the FDA redesigned the format of the prescribing information necessary for safe and effective use of the drugs and biological products

(FDA Guidance for Industry, 2013). This design was developed to make information in prescription drug labeling easier for health care practitioners to access and read. The practitioner can use the prescribing information to make prescribing decisions. The labeling includes three sections:

- *Highlights of Prescribing Information (Highlights)*—contains selected information from the Full Prescribing Information (FPI) that health care practitioners most commonly reference and consider most important. In addition, highlights may contain any boxed warnings that give a concise summary of all of the risks described in the **Boxed Warning** section in the **FPI**.
- *Table of Contents (Contents)*—lists the sections and subsections of the FPI.
- *Full Prescribing Information (FPI*)—contains the detailed prescribing information necessary for safe and effective use of the drug.

An example of the Highlights of Prescribing Information and Table of Contents for Nexium (esomeprazole magnesium) delayed release capsules appears in Table 1-3B. The prescribing information sometimes referred to as the approved label or the package insert may be found at the FDA website, Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). Prescribing information is updated periodically as new information becomes available. The prescribing information contained in the label recommends dosage regimens for the average patient from data obtained from clinical trials. The indications and usage section are those indications that the FDA has approved and that have been shown to be effective in clinical trials. On occasion, a practitioner may want to prescribe the drug to a patient drug for a non-approved use or indication. The pharmacist must decide if there is sufficient evidence for dispensing the drug for a non-approved use (off-label indication). The decision to dispense a drug for a non-approved indication may be difficult and often made with consultation of other health professionals.

Clinical Pharmacology

Pharmacology is a science that generally deals with the study of drugs, including its mechanism, effects, and uses of drugs; broadly speaking, it includes pharmacognosy, pharmacokinetics, pharmacodynamics, pharmacotherapeutics, and toxicology. The application of pharmacology in clinical medicine including clinical trial is referred to as clinical pharmacology. For pharmacists and health professionals, it is important to know that NDA drug labels report many important study information under **Clinical Pharmacology** in Section 12 of the standard prescription label (Tables 1-3A and 1-3B).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Question

Where is toxicology information found in the prescription label for a new drug? Can I find out if a drug is mutagenic under side-effect sections?

Answer

Nonclinical toxicology information is usefully in Section 13 under **Nonclinical Toxicology** if available. Mutagenic potential of a drug is usually reported under animal studies. It is unlikely that a drug with known humanly mutagenicity will be marketed, if so, it will be labeled with special warning. Black box warnings are usually used to give warnings to prescribers in Section 5 under Warnings and Precautions.

Pharmacogenetics

Pharmacogenetics is the study of drug effect including distribution and disposition due to genetic differences, which can affect individual responses to drugs, both in terms of therapeutic effect and adverse effects. A related field is pharmacogenomics, which emphasizes different aspects of genetic effect on drug response. This important discipline is discussed in Chapter 13. Pharmacogenetics is the main reason why many new drugs still have to be further studied after regulatory approval, that is, postapproval phase 4 studies. The clinical trials prior to drug approval are generally limited such that some side effects and special responses due to genetic differences may not be adequately known and labeled.

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.
NEXIUM (esomeprazole magnesium) delayed-release capsules, for oral use
NEXIUM (esomeprazole magnesium) for delayed-release oral suspension
Initial U.S. Approval: 1989 (omeprazole)

RECENT MAJOR CHANGES

Warnings and Precautions. Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.8) 03/2014

INDICATIONS AND USAGE

NEXIUM is a proton pump inhibitor indicated for the following:
- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	20 mg or 40 mg	Once daily for 4 to 8 weeks
12 to 17 years	20 mg or 40 mg	Once daily for up to 8 weeks
1 to 11 years	10 mg or 20 mg	Once daily for up to 8 weeks
1 month to less than 1 year 2.5 mg, 5 mg or 10 mg (based on weight). Once daily, up to 6 weeks for erosive esophagitis (EE) due to acid-mediated GERD only.		
Risk Reduction of NSAID-Associated Gastric Ulcer		
	20 mg or 40 mg	Once daily for up to 6 months
***H. pylori* Eradication** (*Triple Therapy*):		
NEXIUM	40 mg	Once daily for 10 days
Amoxicillin	1000 mg	Twice daily for 10 days
Clarithromycin	500 mg	Twice daily for 10 days
Pathological Hypersecretory Conditions		
	40 mg	Twice daily
See full prescribing information for administration options (2)		
Patients with severe liver impairment do not exceed dose of 20 mg (2)		

DOSAGE FORMS AND STRENGTHS

- NEXIUM Delayed-Release Capsules: 20 mg and 40 mg (3)
- NEXIUM for Delayed-Release Oral Suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred) (4)

(*Continued*)

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules (Continued)

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- Symptomatic response does not preclude the presence of gastric malignancy (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy (5.2)
- PPI therapy may be associated with increased risk of *Clostriodium difficile*-associated diarrhea (5.3)
- Avoid concomitant use of NEXIUM with clopidogrel (5.4)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)
- Avoid concomitant use of NEXIUM with St John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7,7.3)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors (5.8,12.2)

ADVERSE REACTIONS

Most common adverse reactions (6.1):

- Adults (≥18 years) (incidence ≥1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth
- Pediatric (1 to 17 years) (incidence ≥2%) are headache, diarrhea, abdominal pain, nausea, and somnolence
- Pediatric (1 month to less than 1 year) (incidence 1%) are abdominal pain, regurgitation, tachypnea, and increased ALT

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended: if saquinavir is used with NEXIUM, monitor for toxicity and consider saquinavir dose reduction (7.1)
- May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, and digoxin) Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7.2)
- Combined inhibitor of CYP 2C19 and 3A4 may raise esomeprazole levels (7.3)
- Clopidogrel: NEXIUM decreases exposure to the active metabolite of clopidogrel (7.3)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction (7.3)
- Tacrolimus: NEXIUM may increase serum levels of tacrolimus (7.5)
- Methotrexate: NEXIUM may increase serum levels of methotrexate (7.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 03/2014

PRACTICAL FOCUS

Relationship of Drug Concentrations to Drug Response

The initiation of drug therapy starts with the manufacturer's recommended dosage regimen that includes the drug dose and frequency of doses (eg, 100 mg every 8 hours). Due to individual differences in the patient's genetic makeup (see Chapter 13 on pharmacogenetics) or pharmacokinetics, the recommended dosage regimen drug may not provide the desired therapeutic outcome. The measurement of plasma drug concentrations can confirm whether the drug dose was subtherapeutic due to the patient's individual pharmacokinetic profile (observed by low plasma drug concentrations) or was not responsive to drug therapy due to genetic difference in receptor response. In this case, the drug concentrations

TABLE 1-3B Contents for Full Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

FULL PRESCRIBING INFORMATION: CONTENTS*
1. INDICATIONS AND USAGE
1.1 Treatment of Gastroesophageal Reflux Disease (GERD)
1.2 Risk Reduction of NSAID-Associated Gastric Ulcer
1.3 *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
2. DOSAGE AND ADMINISTRATION
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 Concurrent Gastric Malignancy
5.2 Atrophic Gastritis
5.3 *Clostridium difficile* associated diarrhea
5.4 Interaction with Clopidogrel
5.5 Bone Fracture
5.6 Hypomagnesemia
5.7 Concomitant Use of NEXIUM with St John's Wort or rifampin
5.8 Interactions with Diagnostic Investigations for Neuroendocrine Tumors
5.9 Concomitant Use of NEXIUM with Methotrexate
6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7. DRUG INTERACTIONS
7.1 Interference with Antiretroviral Therapy
7.2 Drugs for Which Gastric pH Can Affect Bioavailability
7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways
7.4 Interactions with Investigations of Neuroendocrine Tumors
7.5 Tacrolimus
7.6 Combination Therapy with Clarithromycin
7.7 Methotrexate
8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14. CLINICAL STUDIES
14.1 Healing of Erosive Esophagitis
14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)
14.3 Pediatric Gastroesophageal Reflux Disease (GERD)
14.4 Risk Reduction of NSAID-Associated Gastric Ulcer
14.5 *Helicobacter pylori (H. Pylon)* Eradication in Patients with Duodenal Ulcer Disease
14.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
16. HOW SUPPLIED/STORAGE AND HANDLING
17. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Source: FDA Guidance for Industry (February 2013).

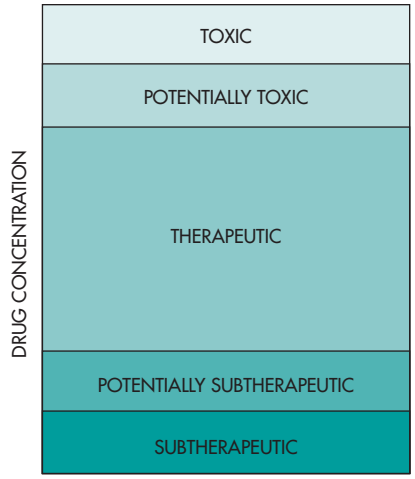

FIGURE 1-2 Relationship of drug concentrations to drug response.

are in the therapeutic range but the patient does not respond to drug treatment. Figure 1-2 shows that the concentration of drug in the body can range from subtherapeutic to toxic. In contrast, some patients respond to drug treatment at lower drug doses that result in lower drug concentrations. Other patients may need higher drug concentrations to obtain a therapeutic effect, which requires higher drug doses. It is desirable that adverse drug responses occur at drug concentrations higher relative to the therapeutic drug concentrations, but for many potent drugs, adverse effects can also occur close to the same drug concentrations as needed for the therapeutic effect.

Frequently Asked Questions

- *Which is more closely related to drug response, the total drug dose administered or the concentration of the drug in the body?*
- *Why do individualized dosing regimens need to be determined for some patients?*

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 at 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 21.

DRUG EXPOSURE AND DRUG RESPONSE

Drug exposure refers to the dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (eg, C_{max}, C_{min}, C_{ss}, AUC) (FDA Guidance for Industry, 2003). *Drug response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (eg, receptor occupancy) to a presumed mechanistic effect (eg, ACE inhibition), to a potential or accepted surrogate (eg, effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety.

Toxicologic and efficacy studies provide information on the safety and effectiveness of the drug during development and in special patient populations such as subjects with renal and hepatic insufficiencies. For many drugs, clinical use is based on weighing the risks of favorable and unfavorable outcomes at a particular dose. For some potent drugs, the doses and dosing rate may need to be titrated in order to obtain the desired effect and be tolerated.

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 aid in the interpretation

of toxicologic findings in animals and extrapolation of the resulting 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 10. Drugs frequently involved in toxicity cases include acetaminophen, salicylates, opiates (eg, 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 and mass spectrometric methods are most frequently employed for drug concentration measurement, because chromatography separates the drug from other related materials that may cause assay interference and mass spectrometry allows detection of molecules or molecule fragments based on their mass-to-charge ratio.

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. Analytical methods should be able to distinguish between protein-bound and unbound parent drug and each metabolite, and the pharmacologically active species should be identified. Such distinctions between metabolites in each tissue and fluid are especially important for initial pharmacokinetic modeling of a drug.

Drug Concentrations in Blood, Plasma, or Serum

Measurement of drug and metabolite concentrations (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 (Table 1-4). 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 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. Drugs in the plasma are often bound to plasma proteins, and often plasma proteins are filtered from the plasma before drug concentrations are measured. This is the unbound

TABLE 1-4 Blood Components

Blood Component	How Obtained	Components
Whole blood	Whole blood is generally obtained by venous puncture and contains an anticoagulant such as heparin or EDTA	Whole blood contains all the cellular and protein elements of blood
Serum	Serum is the liquid obtained from whole blood after the blood is allowed to clot and the clot is removed	Serum does not contain the cellular elements, fibrinogen, or the other clotting factors from the blood
Plasma	Plasma is the liquid supernatant obtained after centrifugation of non-clotted whole blood that contains an anticoagulant	Plasma is the noncellular liquid fraction of whole blood and contains all the proteins including albumin

drug concentration. Alternatively, drug concentration may be measured from unfiltered plasma; this is the total plasma drug concentration. When interpreting plasma concentrations, it is important to understand what type of plasma concentration the data reflect.

Frequently Asked Questions

- *Why are drug concentrations more often measured in plasma rather than whole blood or serum?*
- *What are the differences between bound drug, unbound drug, total drug, parent drug, and metabolite drug concentrations in the plasma?*

Plasma Drug Concentration–Time Curve

The plasma drug concentration (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 if the drug was given by an extravascular route. 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. Other elimination mechanisms may also be involved, such as elimination in the feces, sweat, or exhaled air.

The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in Fig. 1-3. 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

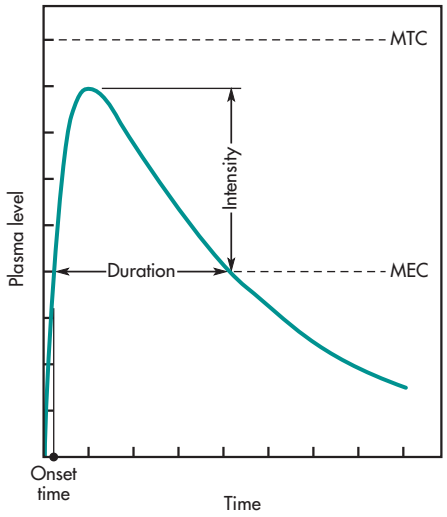

FIGURE 1-3 Generalized plasma level–time curve after oral administration of a drug.

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 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.

The *therapeutic window* is the concentrations between the MEC and the MTC. Drugs with a wide therapeutic window are generally considered safer than drugs with a narrow therapeutic window. Sometimes the term *therapeutic index* is used. This term refers to the ratio between the toxic and therapeutic doses.

In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as *peak plasma level* (C_{max}), *time for peak plasma level* (T_{max}), and *area under the curve,* or AUC (Fig. 1-4). The time for 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.

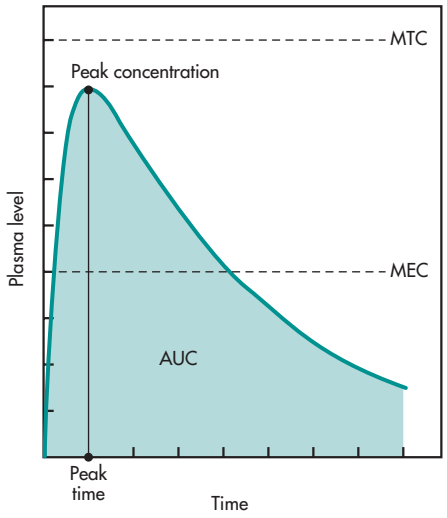

FIGURE 1-4 Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

Frequently Asked Questions

- *At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?*
- *What happens if plasma concentrations fall outside of the therapeutic window?*

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.

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 4.

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 heroin (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. 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 μg/mL. According to the literature, the maximum safe concentration of this drug is 15 μg/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 and be used to modify dosing for that specific patient.

Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order

to individualize and optimize therapeutic drug regimens. When alterations in physiologic functions occur, 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 happen simultaneously. Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events requires 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 parameterizes 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 the 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 25.

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 is the clinical implication of the liver drug concentration value? 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 25. 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 of 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. 1-5). 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

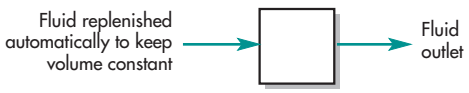

FIGURE 1-5 Tank with a constant volume of fluid equilibrated with drug. The volume of the fluid is 1.0 L. The fluid outlet is 10 mL/min. The fraction of drug removed per unit of time is 10/1000, or 0.01 min^{-1}.

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 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 to the 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 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 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-compartment or the 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 Fig. 1-6. 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.

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. 1-7). 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.

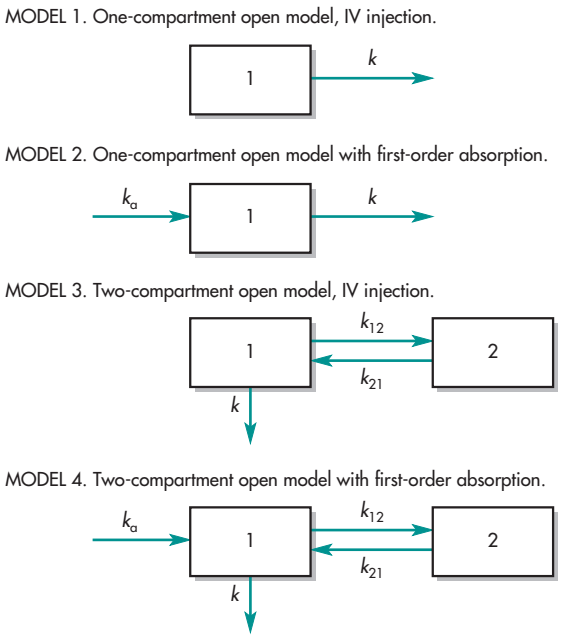

FIGURE 1-6 Various compartment models.

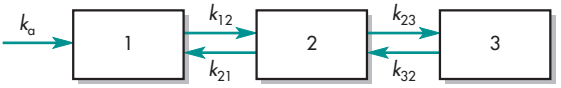

FIGURE 1-7 Example of caternary model.

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

EXAMPLE ▶▶▶

Two parameters are needed to describe model 1 (Fig. 1-6): 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. 1-6), 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 subsequent chapters.

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 is experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how 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 Fig. 1-8.

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.

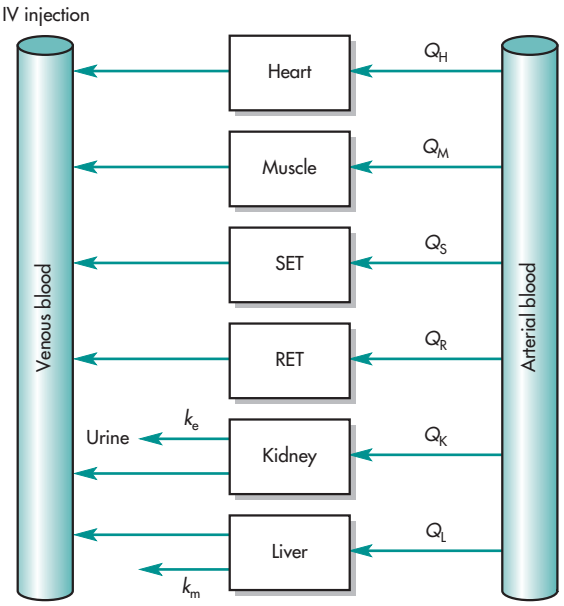

FIGURE 1-8 Pharmacokinetic model of drug perfusion. The *k*s represent kinetic constants: k_e is the first-order rate constant for urinary drug excretion and k_m is the rate constant for hepatic elimination. Each "box" represents a tissue compartment. Organs of major importance in drug absorption are 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*.

A physiologic based pharmacokinetic model (PBPK) using known blood flow was used to describe the distribution of lidocaine in blood and various organs (Benowitz et el 1974) and applied in anesthesiology in man (Tucker et el 1971). In PBKB models, organs such as lung, liver, brain, and muscle were individually described by differential equations as shown in Fig. 1-8, sometimes tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue) for simplicity to account for the mass balance of the drug. A general scheme showing blood flow for typical organs is shown in Fig. 1-8.

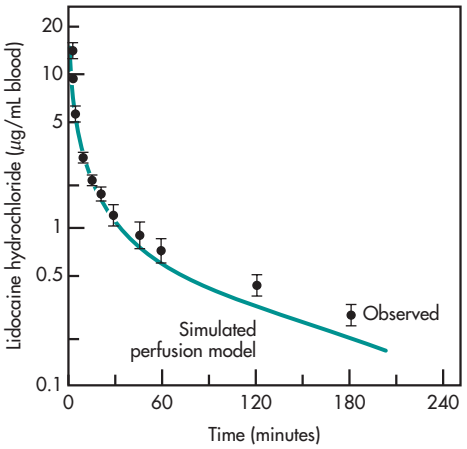

FIGURE 1-9 Observed mean (•) and simulated (—) arterial lidocaine blood concentrations in normal volunteers receiving 1 mg/kg/min constant infusion for 3 minutes. (From Tucker GT, Boas RA: Pharmacokinetic aspects of intravenous regional anesthesia. *Anesthesiology* **34**(6):538–549, 1971, with permission.)

The data showing blood concentration of lidocaine after an IV dose declining biexponentially (Fig. 1-9) was well predicted by the model. A later PBPK model was applied to model cyclosporine (Fig. 1-10). Drug level in various organs were well predicted and scaled to human based on this physiologic model (Kawai R et al, 1998). The tissue cyclosporine levels in the lung, muscle, and adipose and other organs are shown in Fig. 1-10. For lidocaine, the tissue such as adipose (fat) 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 resulting in curvature of plasma profile. The physiologic pharmacokinetic model provides a realistic means of modeling tissue drug levels. However, 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.

Frequently Asked Questions

▶ *What are the reasons to use a multicompartment model instead of a physiologic model?*

▶ *What do the boxes in the mammillary model mean?*

More sophisticated models are introduced as the understanding of human and animal physiology improves. For example, in Chapter 25, special compartment models that take into account transporter-mediated drug disposition are introduced for specific drugs. This approach is termed Physiologic Pharmacokinetic Model Incorporating Hepatic Transporter-Mediated Clearance. The differences between the physiologic pharmacokinetic model, the classical compartmental model, and the noncompartmental approach are discussed. It is important to note that mass transfer and balances of drug in and out of the body or body organs are fundamentally a kinetic process. Thus, the model may be named as physiologically based when all drug distributed to body organs are identified. For data analysis, parameters are obtained quantitatively with different assumptions. The model analysis may be compartmental or noncompartmental (Chapter 25). One approach is to classify models simply as empirically based models and mechanistic models. Although compartment models are critically referred to as a "black box" approach and not physiological. The versatility of compartment models and their easy application are based on simple mass transfer algorithms or a system of differential equations. This approach has allowed many body processes such as binding, transport, and metabolic clearance to be monitored. The advantage of a noncompartmental analysis is discussed in Chapter 25. In Appendix B, softwares used for various type of model analysis are discussed, for example, noncompartmental analysis is often used for pharmacokinetic and bioavailability data analysis for regulatory purpose.

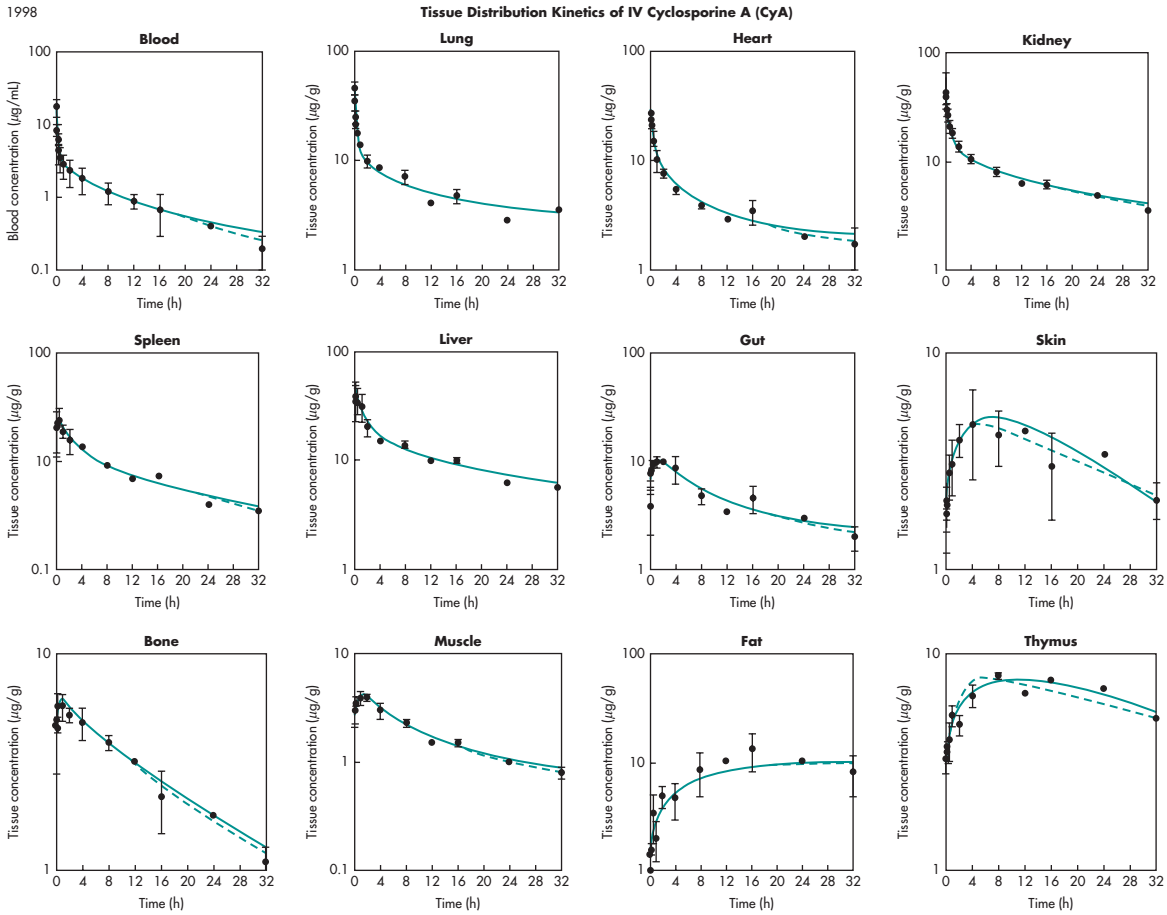

FIGURE 1-10 Measured and best fit predictions of CyA concentration in arterial blood and various organs/tissues in rat. Each plot and vertical bar represent the mean and standard deviation, respectively. Solid and dotted lines are the physiological-based pharmacokinetic (PBPK) best fit predictions based on the parameters associated with the linear or nonlinear model, respectively. (Reproduced with permission from Kawai R, Mathew D, Tanaka C, Rowland M: Physiologically based pharmacokinetics of cyclosporine A: Extension to tissue distribution kinetics in rats and scale-up to human. *JPET* **287:**457–468, 1998.)

CHAPTER SUMMARY

Drug product performance is the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable. *Biopharmaceutics* provides the scientific basis for drug product design and drug product performance by examining the interrelationship of the physical/chemical properties of the drug, the drug product in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. *Pharmacokinetics* is the science of the dynamics (kinetics) of drug absorption, distribution, and elimination (ie, excretion and metabolism), whereas *clinical pharmacokinetics* considers the applications of pharmacokinetics to drug therapy.

The quantitative measurement of drug concentrations in the plasma after dose administration is

important to obtain relevant data of systemic drug exposure. The plasma drug concentration-versus-time profile provides the basic data from which various pharmacokinetic models can be developed that predict the time course of drug action, relates the drug concentration to the pharmacodynamic effect or adverse response, and enables the development of individualized therapeutic dosage regimens and new and novel drug delivery systems.

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 Fig. 1-11 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 Fig. 1-11.
   - **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).
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.
7. Why is it important for a pharmacist to keep up with possible label revision in a drug newly approved? Which part of the label you expect to be mostly likely revised with more phase 4 information?
   - **a.** The chemical structure of the drug
   - **b.** The Description section
   - **c.** Adverse side effect in certain individuals

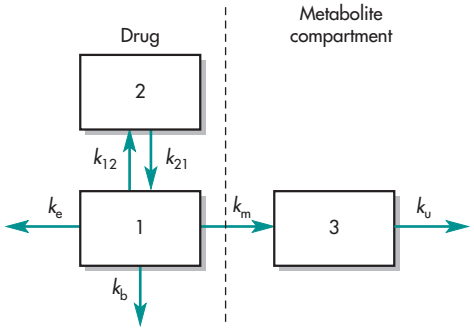

FIGURE 1-11 Pharmacokinetic model for a drug eliminated by renal and biliary excretion and drug metabolism. k_m = rate constant for metabolism of drug; k_u = rate constant for urinary excretion of metabolites; k_b = rate constant for biliary excretion of drug; and k_e = rate constant for urinary drug excretion.

8. A pharmacist wishing to find if an excipient such as aspartame in a product is mostly found under which section in the SPL drug label?
   a. How supplied
   b. Patient guide
   c. Description

9. A pregnant patient is prescribed pantoprazole sodium (Protonix) delayed release tablets for erosive gastroesophageal reflux disease (GERD). Where would you find information concerning the safety of this drug in pregnant women?

ANSWERS

Frequently Asked Questions

Why are drug concentrations more often measured in plasma rather than whole blood or serum?

- Blood is composed of plasma and red blood cells (RBCs). Serum is the fluid obtained from blood after it is allowed to clot. Serum and plasma do not contain identical proteins. RBCs may be considered a cellular component of the body in which the drug concentration in the serum or plasma is in equilibrium, in the same way as with the other tissues in the body. Whole blood samples are generally harder to process and assay than serum or plasma samples. Plasma may be considered a liquid tissue compartment in which the drug in the plasma fluid equilibrates with drug in the tissues and cellular components.

At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?

- The exact site of drug action is generally unknown for most drugs. The time needed for the drug to reach the site of action, produce a pharmacodynamic effect, and reach equilibrium are deduced from studies on the relationship of the time course for the drug concentration and the pharmacodynamic effect. Often, the drug concentration is sampled during the elimination phase after the drug has been distributed and reached equilibrium. For multiple-dose studies, both the peak and trough drug concentrations are frequently taken.

What are the reasons to use a multicompartment model instead of a physiologic model?

- Physiologic models are complex and require more information for accurate prediction compared to compartment models. Missing information in the physiologic model will lead to bias or error in the model. Compartment models are more simplistic in that they assume that both arterial and venous drug concentrations are similar. The compartment model accounts for a rapid distribution phase and a slower elimination phase. Physiologic clearance models postulate that arterial blood drug levels are higher than venous blood drug levels. In practice, only venous blood samples are usually sampled. Organ drug clearance is useful in the treatment of cancers and in the diagnosis of certain diseases involving arterial perfusion. Physiologic models are difficult to use for general application.

Learning Questions

1. The plasma drug level–time curve describes the pharmacokinetics of the systemically absorbed drug. Once a suitable pharmacokinetic model is obtained, plasma drug concentrations may be predicted following various dosage regimens such as single oral and IV bolus doses, multiple-dose regimens, IV infusion, etc. If the pharmacokinetics of the drug relates to its pharmacodynamic activity (or any adverse drug response or toxicity), then a drug regimen based on the drug's pharmacokinetics may be designed to provide optimum drug efficacy. In lieu of a direct

pharmacokinetic–pharmacodynamic relationship, the drug's pharmacokinetics describes the bioavailability of the drug including inter- and intrasubject variability; this information allows for the development of drug products that consistently deliver the drug in a predictable manner.

2. The purpose of pharmacokinetic models is to relate the time course of the drug in the body to its pharmacodynamic and/or toxic effects. The pharmacokinetic model also provides a basis for drug product design, the design of dosage regimens, and a better understanding of the action of the body on the drug.

3. (Figure A-1)

4. a. Nine parameters: V_1, V_2, V_3, k_{12}, k_{21}, k_e, k_b, k_m, k_u

b. Compartment 1 and compartment 3 may be sampled.

c. $k = k_b + k_m + k_e$

d. $\frac{dC_1}{dt} = k_{21}C_2 - (k_{12} + k_m + k_e + k_b)C_1$

6.

Compartment 1	Compartment 2
C_1	C_2

a. C_1 and C_2 are the *total* drug concentration in each compartment, respectively. $C_1 > C_2$ may occur if the drug concentrates in compartment 1 due to protein binding (compartment 1 contains a high amount of protein or special protein binding), due to partitioning (compartment 1 has a high lipid content and the drug is poorly water soluble), if the pH is different in each compartment and the drug is a weak electrolyte (the drug may be more ionized in compartment 1), or if there is an active transport mechanism for the drug to be taken up into the cell (eg, purine drug). Other explanations for $C_1 > C_2$ may be possible.

b. Several different experimental conditions are needed to prove which of the above hypotheses is the most likely cause for $C_1 > C_2$. These experiments may use *in vivo* or *in vitro* methods, including intracellular electrodes to measure pH *in vivo*, protein-binding studies *in vitro*, and partitioning of drug in chloroform/water *in vitro*, among others.

c. In the case of protein binding, the total concentration of drug in each compartment may be different (eg, $C_1 > C_2$) and, at the same time, the free (nonprotein-bound) drug concentration may be equal in each compartment—assuming that the free or unbound drug is easily diffusible. Similarly, if $C_1 > C_2$ is due to differences in pH and the nonionized drug is easily diffusible, then the nonionized drug concentration may be the same in each compartment. The total drug concentrations will be $C_1 = C_2$ when there is similar affinity for the drug and similar conditions in each compartment.

d. The total amount of drug, A, in each compartment depends on the volume, V, of the compartment and the concentration, C, of the drug in the compartment. Since the amount of drug (A) = concentration (C) times volume (V), any condition that causes the product, $C_1V_1 \neq C_2V_2$, will result in $A_1 \neq A_2$. Thus, if $C_1 = C_2$ and $V_1 \neq V_2$, then $A_1 \neq A_2$.

7. A newly approved NDA generally contains sufficient information for use labeled. However, as more information becomes available through postmarketing commitment studies, more information is added to the labeling, including Warnings and Precautions.

8. An excipient such as aspartame in a product is mostly found under the Description section, which describes the drug chemical structure and the ingredients in the drug product.

9. Section 8, Use in Specific Populations, reports information for geriatric, pediatric, renal, and hepatic subjects. This section will report dosing for pediatric subjects as well.

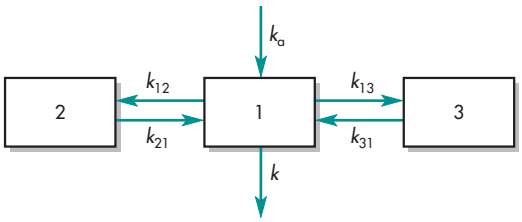

FIGURE A-1

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