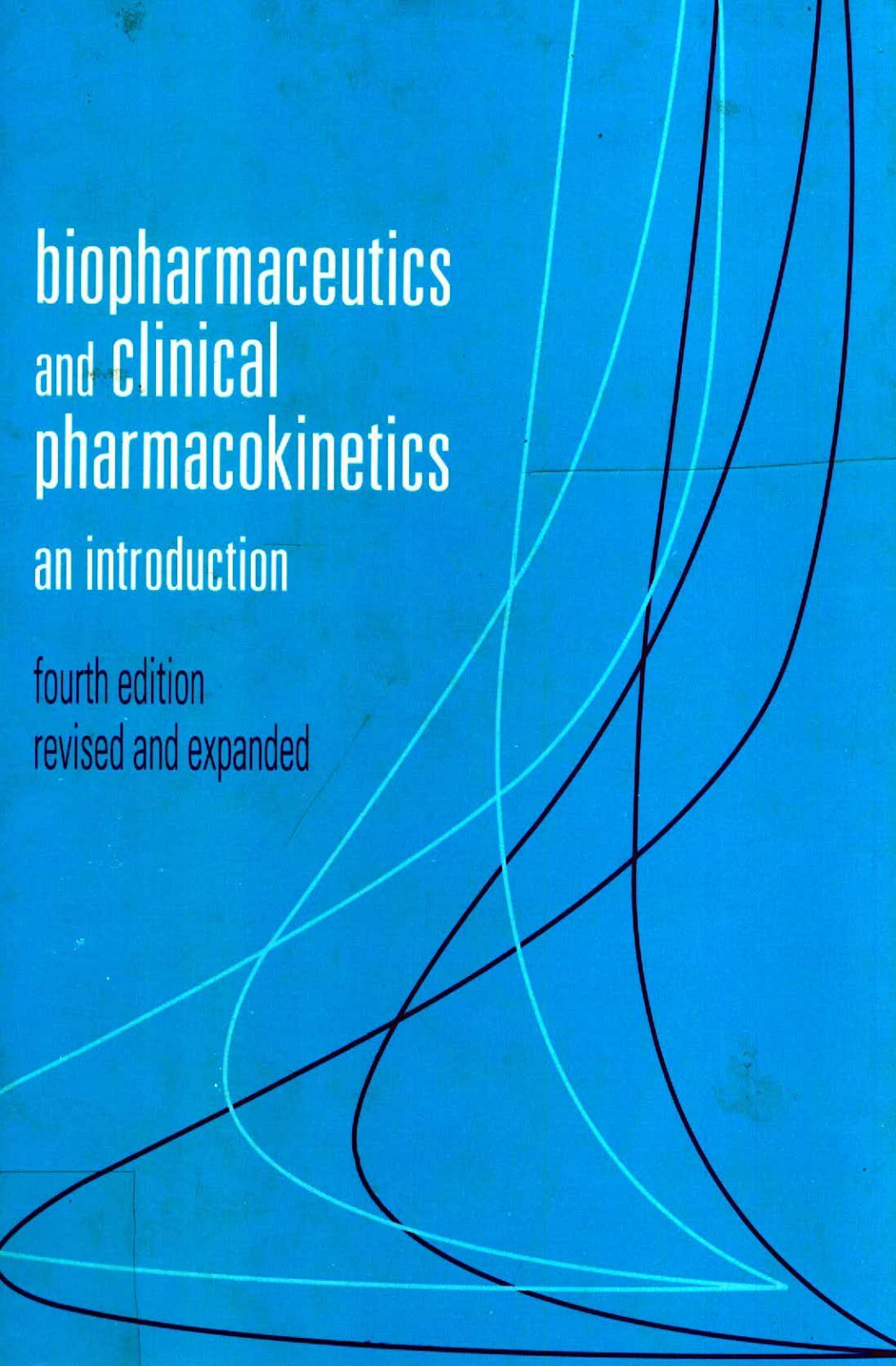
biopharmaceutics and clinical pharmacokinetics

an introduction

fourth edition
revised and expanded



Robert E. Notari

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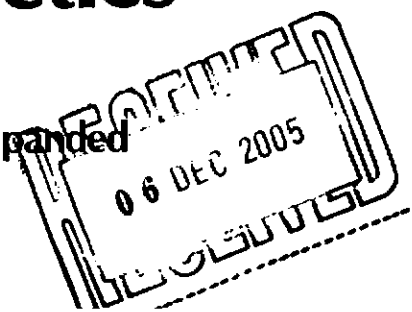
AN INTRODUCTION

Fourth Edition, Revised and Expanded



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To my parents

Contents

Preface to the Fourth Edition

Biopharmaceutics and pharmacokinetics are quantitative subjects. One cannot appreciate their meaning simply by reading about them any more than one could learn mathematics by reading descriptions of it. This text is designed to help the reader to discover their meaning through experience in the manner that a researcher would gain such insight. The experience is provided by analyzing data presented in problems. These problems are strategically placed to complement the descriptions of each concept, thus making this text a workbook. The format can best be regarded as a complete course, wherein the subjects are presented in sequence. The student is expected to interact by solving problems, but may, depending upon the level of past experiences, omit material. Based on this text a typical course outline might be:

I. Introduction and Overview
II. Kinetic Analysis of Data: Order and Rate Constants
III. Kinetics of Drug Transport Through Membranes
IV. Model-Independent versus Compartmental Model Pharmacokinetic Analyses
V. Biopharmaceutics in the Evaluation and Design of Drug Delivery Systems
VI. Dosage Regimen Design and Adjustment in Renal Failure
VII. Pharmacokinetic Evaluation and Design in Molecular Modification
VIII. Application of Pharmacokinetics to Drug Therapy

Presentation of these subjects is meant to form a logical chain. Chapter 1 gives an historical perspective, emphasizing the half-century lag period between the awareness of drug product quality and the concern for bioavailability. The kinetic analysis of data comprises Chapter 2, which teaches how to plot

data to treat first-order, zero-order, or Michaelis-Menten kinetics. Drug transport is addressed in Chapter 3, which extends kinetic analyses to active and passive transport, the influence of protein binding and pH, and data treatment involving asymptotic values. The calculation of pharmacokinetic parameters based on model-independent analyses is presented in Chapter 4. Because of widespread use of modeling in the literature, one-, two-, and three-compartment open-model methods, together with their limitations, are also presented. Biopharmaceutics is treated in Chapter 5, which stresses how the formulation can influence the drug plasma concentration time-course. It includes factors influencing absorption, clinical assessment of bioavailability, design of controlled-release devices, and clinical evaluations. Since these subjects entail analyses of drug plasma concentration time-courses, biopharmaceutics is intentionally placed after the pharmacokinetic chapter, which deals with the fate of a drug introduced into the blood. Dosage regimens are covered in Chapter 6, which presents the kinetic determination of size and frequency of dosing to achieve desired clinical endpoints, together with methods for individualizing regimens in disease states such as renal failure. The evaluation of molecular effects on pharmacokinetics is a unique aspect of this text. Chapter 7 discusses how the structure can influence the time-course of drug in the blood in contrast to the influence of the formulation. It is aimed at casting aside many common misconceptions regarding comparisons of pharmacokinetic data for prodrugs and closely related analogs; several classes of antibiotics are reviewed to illustrate these effects. Finally, Chapter 8 addresses how the patient can influence the pharmacokinetic behavior of the drug and what compensatory measures are appropriate. It begins with a survey of factors which may alter drug pharmacokinetics beyond what is therapeutically acceptable. The monitoring of drug plasma levels and dosage adjustments of five agents are then reviewed as examples wherein risk dictates individualization. The level of expertise gained by completing this sequence should allow the reader to understand the literature and to enter a higher-level course with a thorough appreciation for the significance of the subjects.

One of the primary changes made in this edition is the stress on model-independent pharmacokinetics. A section on classical pharmacokinetic modeling is included for completeness, but its limitations are also emphasized. In keeping with this goal, the symbols published by the Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology (1982) have been adopted (see the Appendix, p. 405). This system allows a single model-independent definition for terms which otherwise require separate symbols for each model. For a more detailed explanation, see Nomenclature (p. xix). Other notable changes include an increased number of problems, an expanded treatment of bioavailability, and a reduction in

the fundamentals of those kinetics which precede pharmacokinetics, so that the reader's preparatory time to reach the title subject is minimized. Logarithmic tables are deleted from this edition as it is assumed that pocket calculators have made them obsolete. The reader will find a calculator that will handle exponentials to base e is convenient in the dosage regimen calculations.

Any criticisms, suggestions, or questions would be most gratefully received by the author.

Robert E. Notari

Preface to the Third Edition

The first edition, written during the 1960s and published in 1971, noted that "The approaches discussed here may seem a bit too sophisticated and costly to the reader who has not previously come upon the concept of an individualized dosage regimen." This statement followed a discussion suggesting that "pharmacokinetics will make an ever increasing contribution to the rational clinical use of drugs . . ." The second edition (1975) contained "a new addition covering dosage regimen calculations in patients with normal renal function or with renal failure," together with an additional chapter on the pharmacokinetic aspects of molecular modification. The latter was described as "a field which is relatively undeveloped." These applications of pharmacokinetics were minor components in the second edition and absent from the first edition.

The immense progress in these two areas, clinical pharmacokinetics and pharmacokinetic drug design, has necessitated the writing of this third edition. They now occupy roughly one-half of this text. Chapters 5 and 7 are devoted to clinical pharmacokinetics. The application of pharmacokinetics to drug design and evaluation comprises Chapter 6, the longest in the text. Progress in the development of prodrugs represents a major portion of this expanded chapter.

I must reemphasize that the text is not intended as a review but rather an introduction. Development of concepts is the primary goal, and examples have been selected to illustrate them. Problem solving by the reader remains the *modus operandi* for comprehending the principles and their applications. As in previous editions, it is the author's hope that this text will provide a starting place for those who wish to pursue further study or who want only a simplified but quantitative appreciation of the field.

The many inquiries I have received over the years have proven invaluable in identifying areas for revision. I am most grateful to all those who have

graciously given helpful comment or asked for clarification; both provide insight that an author cannot attain for himself. I particularly wish to acknowledge Dr. Adam Danek, Dr. Jacek Bojarski, and Dr. Halina Krasowska, who stimulated the publication of the second edition in Poland (1978) and who translated the English edition into Polish. This experience provided great encouragement to me, and the questions surrounding the translation called attention to several ambiguities that have led to rewording in the third edition. The continued beautiful art work of Yvonne Holsinger and the excellent typing of Sue Sheffield are most sincerely appreciated.

I would be grateful to receive any comments or questions from readers of the third edition as I truly regard both as a service to the author.

Robert E. Notari

Preface to the Second Edition

The objectives of this book are identical to those of the first edition. It is a place to begin your studies—an introduction. Hopefully, it is both simple and accurate. And the agreement between reader and author has also remained constant. This is a workbook. If you are willing to work the problems, the principles should become meaningful to you by the process of discovery.

To that end the second edition has been modified to make it more self-sufficient. As each new principle is introduced, two types of problems are presented. Sample problems are completely solved so that you can diagnose your error when your answer is not correct (and assuming that mine is!). Practice problems are designed to test your ability to apply what you have learned. They are generally slightly more difficult.

The constancy of objectives is not a reflection of a lack of progress in the field or a lack of change between the editions. Indeed, the second edition is largely a new book. In accomplishing the updating and improving of the book, the author gratefully acknowledges the indispensable contributions of co-authors Joyce L. DeYoung (Chapters 2 and 3) and Raymond C. Anderson (Chapter 5).

Those who are familiar with the first edition will find it helpful to know what changes have been made. Chapter 2 and 3 have been completely rewritten and restyled. While they cover the same subject matter, the order of presentation is different. Chapter 2 now contains pharmacokinetic models and the basic kinetics required to understand them. For example, a beaker is still used to teach two-compartment model kinetics, but it is immediately followed by the analogous situation in pharmacokinetics. The basic kinetics are therefore kept minimal and limited to models with pharmacokinetic counterparts. Chapter 3 contains methods and discussions for calculating pharmacokinetic parameters. Among the notable changes is the expansion of the section dealing with the apparent volume of distribution. This has

been completely updated to include both discussion and equations regarding variation in calculated values obtained by different methods for multicompartmental drugs.

Chapter 4 has been expanded. It begins with a revised section on the interpretation of blood level curves and ends with a new addition covering dosage regimen calculations in patients with normal renal function or with renal failure. This latter area is one of the most widely recognized contributions of pharmacokinetic sciences to improved clinical therapy.

Chapter 5 is a new addition to the book. It is aimed at fostering both an understanding and an interest in the effects of molecular manipulation on pharmacokinetic parameters and the resultant pharmacologic impact. This is a field which is relatively undeveloped (as compared with studies on dosage-form effects) but which will be a key to future evaluation and development of new drugs.

The second edition is amply referenced. Each chapter provides sufficient citations for the interested reader to check on the validity or limitations of the subject matter presented or to become more familiar with a particular field.

Again, I would greatly appreciate receiving comments, criticisms, suggestions, opinions, or notifications of errors regarding any section of the book. A similar invitation in the preface to the first edition was accepted by several people, whose comments had a direct influence on the production of the second edition. While I cannot cite them all, I would particularly like to thank Dr. Adam Danek, Dr. Gerald E. Schumacher, Dr. Donald A. Zuck, and Dr. James W. Ayres for their helpful suggestions, encouraging comments, and poignant questions.

Robert E. Notari

Preface to the First Edition

This book is designed as an introductory text for use in formal courses or for self-study. It is aimed at both biomedical researchers and practitioners. The book assumes no prior knowledge of either kinetics or calculus on the part of the reader. Derivations are provided for those who are mathematically inclined. Those who are not may simply make use of the final or "working" equations. None of the subjects is beyond the level of comprehension of an advanced undergraduate with no calculus background. However, one must approach this book "actively," with graph paper and pencil in hand and with desire to learn well in mind. The material is presented in "building-block" fashion, and it is imperative that the user solve the examples and practice problems to have all of the pieces necessary to build a solid foundation. Topics are covered in a cumulative manner, and skipping a principle will almost certainly result in an inability to understand a subsequent topic fully. Although it is not a programmed text, it must be approached in the same fashion—as a workbook. Casual reading will not suffice.

One problem that faces those who develop an interest in learning biopharmaceutics and pharmacokinetics for the first time is how to get started. Byron once wrote, "Nothing is more difficult than a beginning." This is certainly true for the present subject. Most current references are not written at the basic introductory level. They assume that the reader has some level of sophistication in either calculus or kinetics or both. In addition they do not provide for active participation in the form of problem solving. A teacher wishing to develop a course would have to do so from the literature. Yet it is difficult to read the literature without a fundamental knowledge of the field. This book is meant to provide that knowledge for teachers, students, biomedical practitioners, and research scientists in medicinal chemistry, pharmacology, pharmacy, and other biomedical disciplines. Chapters 2 and 3 comprise the basic introductory materials, and Chapter 4 illustrates some

of the applications. An understanding of this text should provide sufficient introduction to the field to allow further reading of more complex applications in the literature.

During the past six years I have been teaching biopharmaceutics to senior students in the College of Pharmacy of The Ohio State University. The absence of a textbook for the course has presented a number of difficulties. Although assigned readings of review articles and selected chapters have proven helpful, they fail to provide the structural foundation that a textbook achieves. Students repeatedly failed to visualize the total structure of the subject material until the course was nearly complete in spite of the fact that detailed syllabi and other outlines were distributed each quarter. Students were generally accustomed to working with a required text which serves to define the course goals in much more detail and provides a means for reading ahead. Furthermore, when a student experienced difficulties in solving homework problems, there was no reference book to provide additional information over and above that found in the lecture notes. Problem sets had to be created, printed, and distributed in lieu of an available source such as a required text. There was no provision for additional practice problems for the student who felt the need for such experience.

As a result, the outlines, problem sets, graphic demonstrations, classroom handouts, short presentations of principles, etc., grew in both number and in size until some of the materials distributed to the class approached the size of a chapter or even a small book. Most of the contents of this text have evolved from the development of these undergraduate teaching aids. Some of the subject matter was added later to accommodate an intermediate level graduate course. All of the examples and practice problems have been worked many times over by undergraduate and graduate students alike. Over the past two years (and prior to its publication) the book has been successfully used as a required text in both undergraduate and graduate courses here at Ohio State.

It would be impossible to list the names of all those students whose comments and general interest served to stimulate the writing of this book as well as to influence its contents and mode of presentation. Certainly I must acknowledge the graduating classes of the College of Pharmacy of The Ohio State University from 1965 through 1971, who had the dubious honor of serving as "guinea pigs" for the development of this course. Sincere thanks for their patience and enthusiasm. It is with pleasure that I thank the graduate students and faculty who read the text and in some cases helped develop the problems and examples. Among them I wish especially to acknowledge the efforts of Miss Marilyn Lue Chin, Mrs. Joyce DeYoung, Imtiaz Chaudry, Raymond Anderson, and Dr. Richard H. Reuning. The physical appearance

of the text is a testimonial to the fine art work of Mrs. Yvonne Holsinger and the excellent typing of Miss Carol J. Lusk.

Finally, any comments, criticisms, suggestions, errors or improvements would be most gratefully received by the author.

Robert E. Notari

Nomenclature

Those who are familiar with the nomenclature system involving A, α, B, β may find it helpful to examine its relationship to the system used herein [1]. For a complete listing of symbols and their definitions, please see the Appendix (p. 405). It is a simple system wherein each exponential multiplier is given the same symbol, λ, subscripted sequentially until the final entry, which is always given the subscript z, i.e., λ_z. Thus, the counterparts to the older systems are given by the following, where C is concentration in plasma following intravenous administration:

monoexponential

$$C = C_0 e^{-Kt}$$

$$C = C(0)e^{-\lambda_z t}$$

biexponential

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

$$C = C_1 e^{-\lambda_1 t} + C_z e^{-\lambda_z t}$$

triexponential

$$C = Ae^{-\alpha t} + Be^{-\beta t} + Ge^{-\gamma t}$$

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_z e^{-\lambda_z t}$$

A model-independent definition for biological half-life is thus $t_{1/2} = 0.693/\lambda_z$, which fits the mono-, bi-, and triexponential situation without having to rewrite the equation in terms of K, β, and γ. Similarly, clearance may be defined as $CL = \lambda_z V_z$, where V_z is defined as (DOSE)/(AUC)(λ_z). Both of these are model-independent definitions which apply to all three cases.

The remainder of the nomenclature is sufficiently similar to popularly employed systems to require no explanation. The primary change lies in the use of λ and the apparent volume of distribution, V_z. These are based on

sufficient logic to make them easily acceptable on usage especially since they afford such convenience in making model-independent definitions.

REFERENCE

1. *Manual of Symbols, Equations and Definitions in Pharmacokinetics*, Committee for Pharmacokinetic Nomenclature, American College of Clinical Pharmacology, Philadelphia, Pennsylvania, 1982.

Biopharmaceutics and Clinical Pharmacokinetics

1

Introduction

It is both an enlightening and astonishing experience to read the labels on so-called cure-alls and tonics on display in museums and occasionally found collecting dust in remote corners of storerooms in old established pharmacies. Since we are no longer obliged to take these medicines when we become ill, we may even see a great deal of humor in their claims. Therapeutic effectiveness was generally certified on the basis of testimonials or anecdotal evidence. Modesty was not a characteristic of promotional statements. *Hamlin's Wizard Oil*, "The Great Medical Wonder," recognized no limitations in stating, "There is no sore it will not heal. No pain it will not subdue." *Dr. King's New Discovery* was favorably compared with other recent inventions such as the steamship, steam engine, automobile, telephone, telegraph, and radio. According to the advertisement, it rated well as "The Greatest of All." "*No-To-Bac* made a man of me," another advertisement read, and, picturing a young man embracing a young woman, it noted that by use of this product he had "thrown away his pipe and tobacco and thereby won the love of this stunning girl." A delightful review of that era can be found in the book *One for a Man, Two for a Horse* [1]. That title in itself shows that individualization of dosage regimens (discussed in Chap. 6 of this text) is not as innovative as one might think. As a final example of immodest claims and an unbelievable dosage regimen, consider the statement regarding *Pond's Extract* and made by the popular fictional character Buster Brown: "From my own personal experiences, *Pond's Extract* is the best remedy for all inflammations, hemorrhages, sprains, cuts, bruises, chill blains, burns, scalds, frostbite." So much for the indications. Now for the clinical results: "It has made a better and healthier boy of me and is my best friend." And finally the dosage regimen: "Used externally, internally, and *eternally*."

How well did the products and claims of yesteryear measure up to the standards of today? One might use the following criteria:

1. Contents
2. Percent strength
3. Purity
4. Safety
5. **Clinical effectiveness**
6. **Bioavailability**

Not only did the contents of such products not appear on the label, but it is unlikely that the manufacturer knew the ingredients. If the contents are not known, the question of percent strength becomes meaningless. Plant sources sold for the production of drug products were often adulterated. Even if the plants used were pure, the active ingredients, if there were any, were not known. Chemical analyses were neither possible nor of great concern to a naive society. Some awareness of the danger in such a system probably evolved as a direct result of unfortunate experiences with products that not only failed to cure but also caused toxic effects which may have been worse than the malady. Initially, society responded with legislation aimed at ensuring that medicines were safe and free from adulterants. No doubt these seemingly simple goals presented tremendous problems, without adding concern for therapeutic effectiveness, which was generally certified on the basis of testimonials or anecdotal evidence.

The development of analytical chemistry brought about an acute awareness of the importance of controlling the contents of a product. That each drug should have an adequate purity rubric became the concern of those given the responsibility for setting standards for the protection of society. Tests for physical characteristics were introduced, and as analytical technology advanced, the sophistication of product tests increased. Trace analysis made limitations on allowable contamination practical. Chemical content and product purity advanced to a scientific level commensurate with the analytical technology of the day.

And so we can observe that since the turn of the century, product development has evolved from cure-all herb teas to stable, pure formations containing known amounts of chemicals that have been defined as drugs. It was quite natural that the scientific community and society at large had confidence in a product which adhered to its purity rubric. This philosophy dominated from 1938 (when the final drug safety amendments to the Federal Food, Drug, and Cosmetic Act were made) until relatively recent years. During that time it was widely assumed that all products containing equal doses of the same drug were equipotent when put to use by the clinician. The first four criteria in our list were regarded as sufficient. More recently we have come to the sometimes surprising realization that percentage chemical

strength is not the sole criterion for clinical effectiveness. In fact, formulations were produced and marketed that satisfied all of the required legal standards but which were not therapeutically active. It became obvious that a dosage form must not only contain the correct amount of the labeled drug but must also release that drug upon administration to the patient. *Clinical effectiveness* and *bioavailability* were thus added to the criteria for effective drug product development. A drug should be not only safe but beneficial as well, and its therapeutic claims must be based upon sound clinical evidence. Furthermore, a drug which has been proven effective can be rendered ineffective owing to lack of bioavailability.

What is bioavailability? The simplest concept to consider is that of a *bioavailable dose*. This is the dose available to the patient, in contrast to the dose stated on the label. Only a drug that is completely absorbed into the bloodstream will have a bioavailable dose equal to that stated on the label. In the case of tablets or capsules administered orally, the bioavailable dose will generally be less than the administered dose. Bioavailability therefore deals with the transfer of drug from the site of administration into the body itself as evidenced by its appearance in the general circulation. Since a transfer process is involved, it may be characterized by both the rate of transfer and the total amount transferred. The bioavailable dose refers only to the total amount transferred. A complete description of the bioavailability of a drug from a dosage form must include both the rate and the amount. Methods for such characterizations are discussed in this book. Bioavailability has been defined in various ways [2–5]. Those which ignore the rate of transfer [2,3] are inadequate to explain cases where products show differences in blood levels and/or clinical response due in total or in part to the rate of release of drug. A more acceptable definition for *bioavailability* is therefore [5] "a term used to indicate the rate and relative amount of the administered drug which reaches the general circulation intact."

The measure of success in the use of any drug is the degree to which the results obtained agree with those expected. Therefore the degree of success achieved by the use of a drug product may be altered by factors which affect bioavailability, such as certain foods, other drugs, the dosage regimen, the route of administration, a less than optimum formulation, or the inappropriate use of a suitable formulation. Biopharmaceutics deals with such problems. It is concerned with obtaining the expected therapeutic effect from a drug product when it is in use by the patient. One such definition has been offered as follows [5]: "*Biopharmaceutics* is the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical application."

Since studies involving the rates of drug transfer employ kinetic methods, biopharmaceutics is closely linked to pharmacokinetics. Indeed, the terms

have been interchanged often in the literature. In this book the following definition [5] will be used: "*Pharmacokinetics* is the study of the kinetics of absorption, distribution, metabolism, and excretion of drugs and their pharmacologic, therapeutic, or toxic response in animals and man."

Finally, consider the term *bioequivalency*. Like the others, it has been defined in various ways. We shall use the simplest interpretation. Two drug products containing equal doses of a drug will be said to be bioequivalent if they do not differ significantly in either their bioavailable dose or its rate of supply. Thus the time course for drug in the blood following the administration of either product would be identical. Bioequivalency therefore includes not only the amount of active ingredient available but also the rate at which it is available.

A corollary to the more recent concerns for product quality and effectiveness is the challenge to physicians and pharmacists to consider the impact of these sciences on clinical practice. For example, the clinician must be informed when the coadministration of other drugs or foods may influence the bioavailability of an active ingredient. As research defines the critical factors influencing the absorption of drugs, the information must be put to clinical use so that practitioners are aware of those situations that should be avoided.

This concept can be further extended into all areas of biomedical drug research. Let us consider pharmacology as a case in point. In a broader sense the concept of bioavailability cannot be circumvented by the choice of the route of administration. Regardless of where the experiment begins, the final observations are a function of the bioavailability of the drug to the site of action, and the factors influencing its arrival there are many. Since the movement of drug from the site of administration to the site of action requires time, the overall process may best be analyzed by pharmacokinetics. Thus the bioavailability time profile is again critical in the comparison of drugs or drug analogs. A pharmacological study is greatly enhanced by a knowledge of the amount of the drug that has reached the receptor as a function of time.

The concept of bioavailability in biomedical drug research, pharmaceutical product development, and the rational clinical use of formulations is the subject of this book.

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4. *Guidelines for Biopharmaceutical Studies in Man,* A.Ph.A. Academy of Pharmaceutical Sciences, Washington, D.C., February 1972.
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2

Rates, Rate Constants, and Order

I. ORDER

The concept of order and its application to rate processes originated in chemical kinetics. If the rate of decrease in the concentration, C, of reactant A to form product B,

$$\text{reactant } A \rightarrow \text{product } B \tag{1}$$

can be described as a function of time t by

$$\frac{dC}{dt} = -kC^n \tag{2}$$

then the reaction is nth order with respect to the concentration of reactant. This concept has been extended to pharmacokinetics, wherein its application has been limited to first-order ($n = 1$) and zero-order ($n = 0$) rate processes. The test for order is based upon whether or not the time-dependent concentration data can be described by the solutions to Eq. (2) when $n = 1$ or $n = 0$. The test will be conducted by attempting to fit the data to plots based on linear forms of the equations. One advantage of this approach is that rate processes of the same order can be compared by comparing the values obtained for their rate constants, k. The testing methods and their results are illustrated in the following sections.

II. RATES AND RATE CONSTANTS

A. First-Order Rates

Substituting $n = 1$ in Eq. (2) and solving provides

$$C = C(0)e^{-kt} \tag{3}$$

where $C(0)$ is the initial concentration and t is time. This equation can be changed to a linear form by taking its natural logarithm to yield

$$\ln C = \ln C(0) - kt \tag{4}$$

The test for a first-order rate process employs Eq. (4). If Eq. (1) is first order, then a plot of ln C versus t will be linear with a negative slope k (in units of time^{-1}) and an intercept of ln $C(0)$. The plot is easier to construct on semilogarithmic paper. The data may then be plotted directly without transforming each point to its corresponding natural logarithm. The logarithm must still be employed to calculate the slope. The determination of order, the use of semilogarithmic paper, and the calculation of a first-order rate constant are illustrated in the following example.

1. Hydrolysis

Hydrolysis represents a common drug instability problem during the storage of aqueous solutions and during passage through the gastrointestinal tract. The rates of hydrolysis in aqueous solutions are often first order with respect to the concentration of drug. For example, the β-lactam in penicillins undergoes hydrolysis to form the corresponding penicilloic acid; this results in decreased potency owing to hydrolysis in gastric acid:

$$\text{penicillin} \xrightarrow{\text{hydrolysis}} \text{penicilloic acid} \tag{5}$$

The rate of loss of penicillin through β-lactam hydrolysis has been observed to be first order in dilute solutions of penicillin in acid. Data treatment under these conditions is discussed in the following example.

Sample Problem 1

A dilute solution of penicillin *G* at pH 1.3, maintained at 37°C, is assayed for penicillin *G* concentration by sampling as a function of time to obtain the results in Table 1.

Table 1 Concentration of Penicillin G During Hydrolysis at pH 1.3 and 37°C

Time (min)	Concentration ($\times 10^2$ M)	Time (hr)	Concentration ($\times 10^2$ M)
0.0	9.00	6.0	2.75
1.0	7.40	7.0	2.25
2.0	6.05	8.0	1.85
3.0	5.00	10.0	1.25
4.0	4.08	—	—
5.0	3.34	24.0	0.00

(a) Test these data for first-order behavior.
Solution: The following suggestions, illustrated in Fig. 1, apply to first-order and zero-order plots in general.

1. Do not attempt to plot data points that are smaller than approximately 2/10 the initial value for the line. In Fig. 1, the initial value is $C(0) = 9.00$ and the final value (at 8 hr) is 1.85, or 0.2 $C(0)$.
2. Select and label the graph paper so as to expand the plots as much as possible. Figure 1 is on semilogarithmic, 1 cycle × 60 divisions, graph paper.
3. Plot the data using a generous circle around each data point.
4. Draw the line of best fit by attempting to touch each circle with a line or by a statistical fit (linear regression).

In the case of these data a first-order plot is linear, indicating that the data can be described by Eq. (4) and the rate expression, Eq. (2), may be written

$$\frac{dC}{dt} = -kC \tag{6}$$

where C is the penicillin concentration.

(b) What is the value of the first-order rate constant?

Solution: In accordance with Eq. (4), the negative slope of a plot for ln C versus t represents the estimate for k. This should be calculated from the line of best fit in Fig. 1. Since this is semilogarithmic paper, it is necessary to take the ln values for C in calculating the slope: For example, slope = $(\ln 9 - \ln 1.85)/(0 - 8)$, or $k = 0.198\ \text{min}^{-1}$.

The slope should always be calculated from the line of best fit. It should not be calculated by simply selecting two sets of data from the table without examining the plot. All of the data from Table 1 are on the line (Fig. 1), so that it will not matter which points are chosen. However, in the case of the usual expected experimental variability, selecting points without using the plot as a guide may lead to incorrect estimates. Figure 2b illustrates this problem, since these data points do not fall on the line of best fit; even though the rate constant is the same as that in Fig. 2a.

In Eq. (1) the total concentration C_A of reactant A and C_B product B at any time must equal the starting concentration $C(0)$, since only two

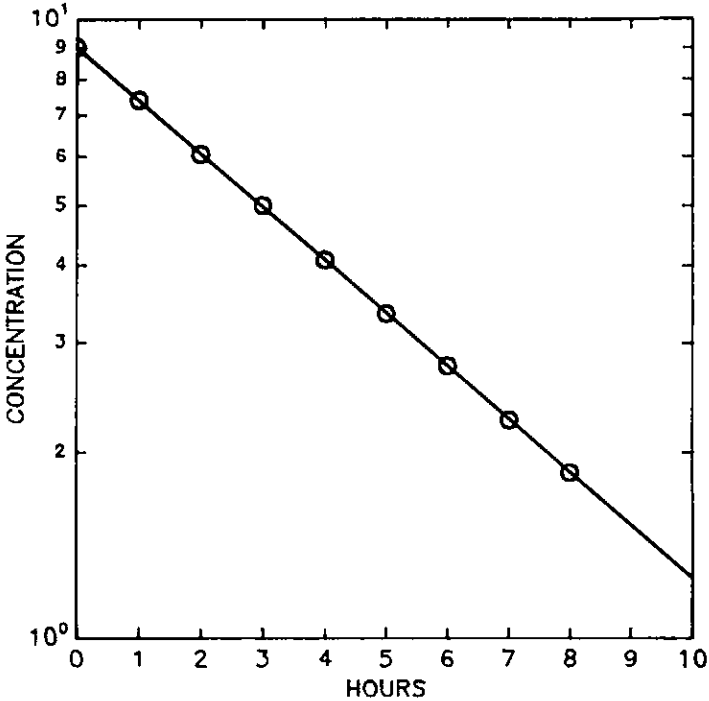


Fig. 1 A first-order (semilogarithmic) plot of the data in Table 1 for the hydrolysis of penicillin G at pH 1.3 and 37°C.

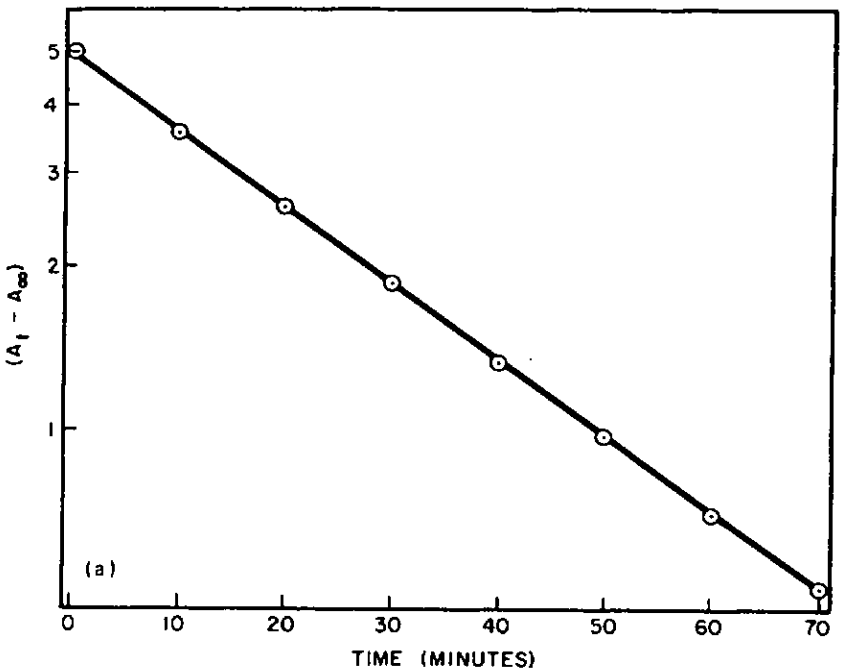


Fig. 2a A first-order plot of data which show no significant variability from the line of best fit.

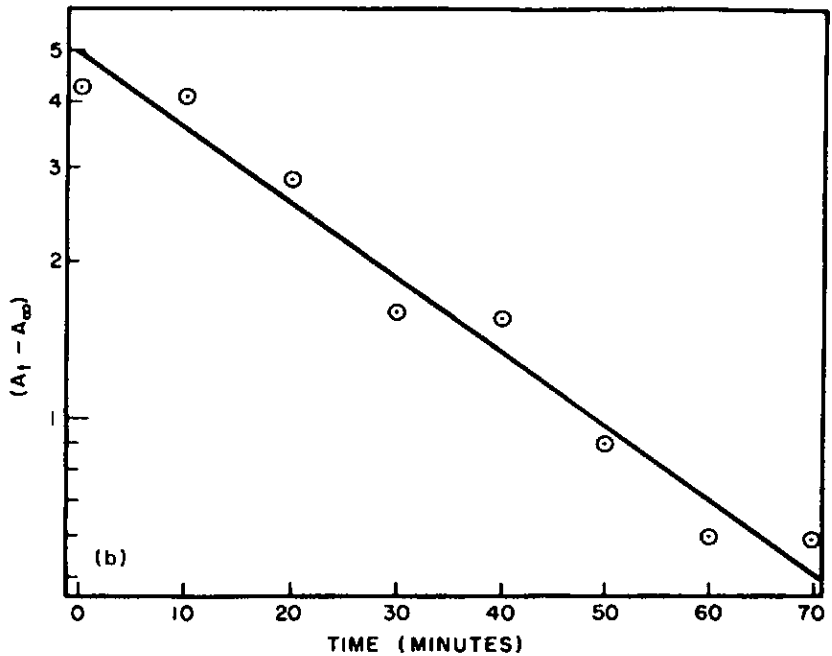


Fig. 2b A first-order plot of data which illustrate experimental error. The line of best fit is identical to that in Fig. 2a; however, choosing any pair of experimental points will not provide the value for k_1 which is estimated best from the negative slope of the line.

species are present. Therefore the value of C_A as a function of time may be calculated from assays for product B by using the mass balance equation, wherein $C_A = C(0) - C_B$. A first-order plot, using data for C_A calculated in this way, will also be linear with $-\text{slope} = k$, provided that Eq. (1) represents all of the species present.

Practice Problem 1

A solution of reactant A is maintained at constant pH and temperature under conditions where it is known to hydrolyze solely to a stable product B. The concentration of B is determined as a function of time and converted to its percentage of the initial concentration. Data are summarized in Table 2. Show that these data are first order and calculate the value of the rate constant.

Table 2 Percentage of Product *B* Relative to the Starting Concentration of Reactant *A* in Aqueous Solution at pH 5 and 25°C

Time (hr)	Concentration (%)	Time (hr)	Concentration (%)
1	3.4	30	64.8
5	16.0	39	74.3
8	24.3	54	84.7
12	34.1	86	95.0
17	44.7	—	—
22	53.5	120	100.0

Answer: A first-order plot based on data for reactant where $A\% = 100\% - B\%$ is linear, with $k = 0.0347\ \text{hr}^{-1}$ and intercept 100%.

B. Zero-Order Rates

Substituting $n = 0$ in Eq. (2) and solving provides

$$C = C(0) - k_0 t \tag{7}$$

which states that the concentration of reactant decreases as a linear function of time. If Eq. (1) is zero order, then a plot of C versus t will be linear with a negative slope k_0 (in units of concentration/time) and an intercept of $C(0)$. These data do not require any logarithmic transformation, as illustrated in the following example.

There are three commonly encountered zero-order rate processes which are discussed later in this text:

1. Constant-rate intravenous infusions
2. Sustained-release drug delivery systems (which may or may not be zero order)
3. Metabolism or enzyme transport rates under saturated conditions (this is really saturated Michaelis–Menten kinetics which behaves as apparently zero-order kinetics)

When the process involves the delivery of an amount of drug as a function of time, Eq. (7) may be rewritten in terms of mass:

$$A = A(0) - k_0 t \tag{8}$$

where A is the amount remaining and k_0 is in units of mass/time. Thus the time required to deliver an amount of drug is given by

$$t = \frac{A(0) - A}{k_0} \tag{9}$$

where $A(0) - A$ is the amount delivered.

Sample Problem 2

The rate of release of theophylline from a 300-mg sustained-release dosage form is measured over a 12-hr period. Table 3 provides the amount of theophylline remaining in the dosage form as a function of time.

(a) Test these data for zero-order behavior.
Solution: Figure 3 shows a plot of theophylline remaining versus t in accordance with Eq. 8) and graphed following the recommendations in Sample Problem 1. The agreement between the data and the line of best fit indicates that the data are described by Eq. (8) and the rate expression is $dC/dt = -k_0$.

(b) What is the value of the zero-order rate constant?
Solution: According to Eq. (8), the negative slope of this plot is k_0. Therefore slope = $(300 - 50)/(0 - 10)$, or $k_0 = 25$ mg/hr.

(c) How much time is required to release 90% of the total payload?
Solution: Equation (9) may be solved to give

Table 3 Amount of Theophylline Remaining in 300-mg Sustained-Release Dosage Form as a Function of Time

Time (hr)	Theophylline (mg)	Time (hr)	Theophylline (mg)
0.0	300	6.0	146
1.0	278	8.0	105
2.0	246	10.0	50
4.0	205	12.0	6

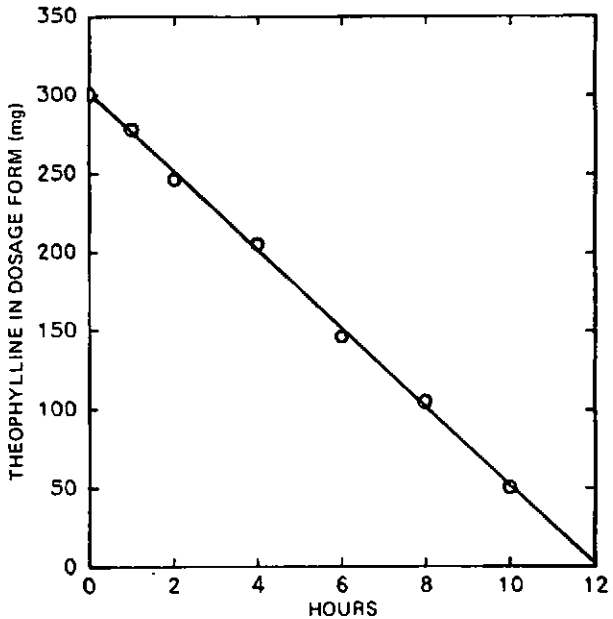


Fig. 3 A zero-order plot of theophylline remaining to be released from a 300-mg sustained-release dosage form based on the data in Table 3.

$$t = \frac{A(0) - 0.1A(0)}{k_0} = 10.8 \text{ hr} \qquad (10)$$

C. Negative Tests

In practice, it is prudent to demonstrate that only one of the two orders will describe the data. In Figs. 1 and 3, where all of the data points clearly fell on the line of best fit, the single positive graphical test for order was sufficient; however, when the data are subject to experimental error, a negative test showing deviation from linearity for one plot coupled with a positive result for the other plot may be combined to form an argument for one order in preference over the other.

The deviation from linearity will be most pronounced toward the end of the plot. It is helpful to know the characteristic shapes for these deviations as an aid to identifying their occurrence. The following examples are meant to illustrate the typical shapes of these deviations.

Sample Problem 3

The data in Table 1 have previously been shown to be first order (Fig. 1), whereas data in Table 3 are zero order (Fig. 3). Use the data from Tables 1 and 3 to illustrate the form of negative results as directed blow.

(a) If the data in Table 1 are tested for adherence to zero-order kinetics, what type of deviation from linearity is observed?
Solution: Figure 4 shows a plot of C versus t in accordance with Eq. (7). An attempt to draw a line to fit the initial data emphasizes the deviation which can be observed in the terminal phase. Since the data points are higher than this line, they are said to show *positive deviation* from linearity. A zero-order plot of first-order data will always show positive deviation from linearity in the terminal phase.

(b) If the data in Table 3 are tested for adherence to first-order kinetics, what type of deviation is observed?

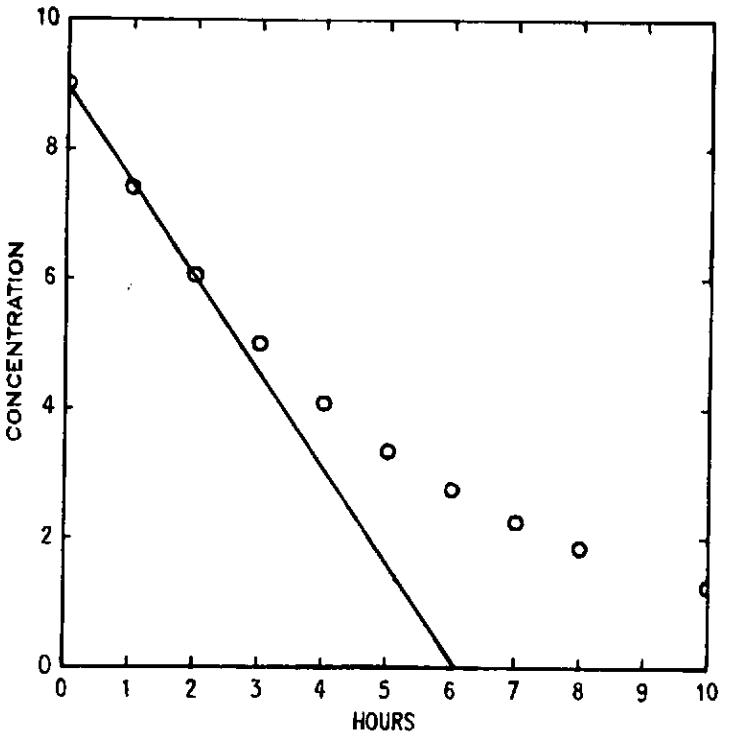


Fig. 4 A zero-order plot of the first-order data in Table 1 illustrating the characteristic *positive deviation* from linearity which constitutes a negative test for zero order.

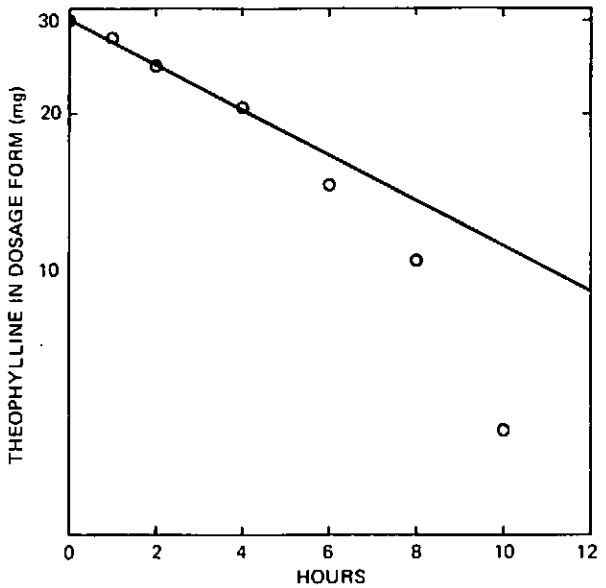


Fig. 5 A first-order (semilogarithmic) plot of the zero-order data in Table 3 illustrating the characteristic *negative deviation* from linearity which constitutes a negative test for first order.

Solution: Figure 5 shows a semilogarithmic plot of the data in Table 3 in accordance with Eq. (4). An attempt to draw a line through the initial data emphasizes the deviation in the terminal phase. Since the data points are below this line, they show *negative deviation* from linearity. A first-order plot of zero-order data will always show negative deviation from linearity in the terminal phase.

Practice Problem 2

(a) Can the rate process which produced the data in Table 4 be unequivocally described as first order or as zero order? If so, what is the value of the constant?

Answer: No. A first-order plot of these data will appear linear with $-\text{slope} = 0.087\ \text{hr}^{-1}$. A zero-order plot also appears linear with $-\text{slope} = 0.5 \times 10^{-2}$ M/hr. The order cannot be distinguished, because the last sample was taken at 8 hr, where only 50% of the process has occurred. It is necessary to have the terminal data (down to approximately 20%) in order to look for the characteristic deviation in one of the two plots, as illustrated next in part (b).

Table 4 Concentration of Drug Remaining as a Function of Time at 25°C and pH 7.2

Time (hr)	Concentration ($\times 10^2$ M)	Time (hr)	Concentration ($\times 10^2$ M)
0.0	7.95	4.0	5.80
1.0	7.40	6.0	4.85
2.0	6.95	8.0	4.00
3.0	6.38		

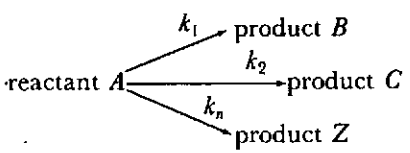
Table 5 Concentration of Drug Remaining as a Function of Time at 25°C and pH 7.2

Time (hr)	Concentration ($\times 10^2$ M)	Time (hr)	Concentration ($\times 10^2$ M)
10	3.42	16	2.03
12	2.88	20	1.44
14	2.41		

(b) Table 5 presents the rest of the data following the 8-hr sampling period already presented. Use the data from 0.0 to 20.0 hr to demonstrate that one plot is linear and one is not. What is the order of the rate process and the value of the rate constant?
Answer: A zero-order plot of the entire time course (C versus t) shows positive deviation from linearity between 10 and 20 hr. A first-order plot is linear, with $k = 0.0866\ \text{hr}^{-1}$.

D. Competing First-Order Rates

A single reactant may undergo simultaneous (or parallel) first-order reactions to form two or more products as represented by



(11)

The rate of loss of reactant A may be written as

$$\frac{dC_A}{dt} = -kC_a \tag{12}$$

As discussed earlier, this form of equation may be solved to give Eq. (3), but in this case the rate constant may be further defined as

$$k = \sum_{i=1}^{n} k_i \tag{13}$$

where k_i is the rate constant for the formation of each product and n is the total number of products.

For the simplest case where $n = 2$, $k = k_1 + k_2$ and the logarithmic form of Eq. (3) will be similar to Eq. (4), or

$$\ln C_A = \ln C_A(0) - (k_1 + k_2)t \tag{14}$$

Thus, if A undergoes simultaneous first-order loss to B and C, a semilogarithmic plot of C_A versus t will be linear with $-\text{slope} = k = k_1 + k_2$ and intercept $C_A(0)$.

Since the rate processes are competing for reactant A, the product yields are related to the relative values of the competing rate constants. Thus at any specified time the concentration of product B is related to the concentration of product C by the ratio of the rate constants:

$$\frac{k_1}{k_2} = \frac{C_B}{C_C} \tag{15}$$

Since a semilogarithmic plot based on Eq. (14) gives the sum of the rate constants, $k = k_1 + k_2$, a knowledge of the concentrations of products B and C at a common time allows the calculation of the individual rate constants using Eq. (15). These principles are not limited to the formation of two products and would hold true for any number of products in Eq. (11).

Upon completion of the reaction, it is possible to calculate the rate constant for a given species by knowing *only* its concentration time course, the value for k, and the mass balance. In Eq. (11) the sum of the final concentrations of products must equal the starting concentration of reactant A, that is, $C_A(0)$. Therefore k_1 may be calculated as follows. The final fraction of reactant A converted to product B, f_B, is the same fraction as that calculated from the individual rate constant k_1 relative to the total rate constant k, or

$$f_B = \frac{C_B(\infty)}{C_A(0)} = \frac{k_1}{k} \tag{16}$$

provided that the loss of reactant A is described by Eq. (11). This provides a means for calculating the individual rate constant from $k_1 = f_B k$, where k is obtained from a first-order plot of C_A and f_B is calculated using the final yield of product B, that is, $C_B(\infty)$. In contrast to the use of the ratios of the product concentrations, where the concentrations of all products are needed, as illustrated by Eq. (15), only the final yield of the product of interest is required for this approach.

A first-order plot using data from any one of the products in Eq. (11) may be constructed based upon the concentration of that product which remains to be formed. This is the difference between the concentration at time t and the final concentration. For example, a plot based on product B would employ ΔC_B calculated from

$$\Delta C_B = C_B(\infty) - C_B \tag{17}$$

where $C_B(\infty)$ is the final yield of product B and C_B is the time-dependent concentration at time t. A first-order plot would be based on

$$\ln \Delta C_B = \ln C_B(\infty) - kt \tag{18}$$

A semilogarithmic plot of ΔC_B versus t would be linear, with $-\text{slope} = k$ and intercept $C_B(\infty)$. Note that the *total* rate constant k is obtained from a ΔC plot for any product. The individual rate constant, in this case k_1, must be calculated by the methods illustrated in Eq. (15) or (16). The following problems illustrate the data treatment for competing first-order rate processes.

Practice Problem 3

A drug in solution in the gastrointestinal (g.i.) tract is known to undergo hydrolysis at a first-order rate with a hydrolysis constant value of $0.130\ \text{hr}^{-1}$. The data in Table 6 represent the amount of unhydrolyzed drug remaining in the g.i. tract as a function of time.

(a) What is the apparent first-order rate constant for loss of drug from the g.i. tract?
Answer: $k = 0.323\ \text{hr}^{-1}$.

(b) What is the fraction of drug absorbed and the apparent first-order absorption rate constant k_a?

Answer: Fraction hydrolyzed = k_h/k = 0.130/0.323 = 0.4. Therefore the fraction absorbed = 0.6 and k_a = (0.6)(0.323) = 0.194 hr^{-1}.

Table 6 Amount of Intact Drug Remaining in Solution in the Gastrointestinal Tract

Time (hr)	Amount (mg)	Time (hr)	Amount (mg)
0.0	800	2.5	355
0.5	680	3.0	305
1.0	580	4.0	218
1.5	492	5.0	160
2.0	420	12.0	0

Table 7 Cumulative Amount of Drug Excreted in the Urine as a Function of Time Following a 200-mg Intravenous Dose

Time (hr)	Cumulative amount (mg)	Time (hr)	Cumulative amount (mg)
2.0	22	16.0	110
4.0	42	20.0	121
8.0	72	24.0	129
12.0	94	48.0	150

Practice Problem 4

A rapid intravenous dose of 200 mg is administered to an adult subject and the cumulative amount of drug excreted in the urine is determined as a function of time (Table 7).

(a) What is the value of the apparent first-order rate constant (k) associated with these data?
Answer: A semilogarithmic plot of amount remaining to be excreted (ARE) versus time gives a k value of 0.0815 hr^{-1}, where ARE = (150 − cum. amt.) mg.

(b) Assuming Eq. (11), what is the value for the apparent first-order rate constants k_R for renal excretion and k_{NR} for nonrenal excretion?
Answer: The fraction f_u excreted in the urine is 150/200 = 0.75. Therefore k_R = (0.75)(0.0815) = 0.0611 hr^{-1} and k_{NR} = (0.25)(0.0815) = 0.0204^{-1}, since $k = k_R + k_{NR}$.

3

Active and Passive Transport

I. INTRODUCTION

Drugs are introduced into the body in a limited region referred to as the site of administration. This can be within a muscle following an intramuscular injection, within the gastrointestinal tract following an oral dose, and so on. This site of administration is not usually the site of action or the target organ

for the drug; however, the drug does not remain at the site of administration but, instead, distributes itself throughout the other regions of the body, one of which presumably is the site of action. The movement of drug throughout the body is known as drug transport. The change in drug concentration between regions as a function of time involves rate processes which may or may not include the participation of body enzymes. When enzymes or other drug carriers are involved, the rate process is called *active* transport and can often be described by the Michaelis–Menten equation or its equivalent.

Unassisted movement is due to diffusion and is called *passive* transport. Diffusion occurs in response to concentration gradients wherein molecules tend to move from a region of higher concentration to one of lower concentration. A passive transport process can often be described by a first-order equation. In this respect the data treatment is an extension of the first-order kinetics covered in Chapter 2. The present chapter employs compartmental models to illustrate the kinetics of active and passive transport.

II. PASSIVE TRANSPORT

A. Two-Compartment Closed Models

Consider the example where both compartments in Fig. 1 contain equal volumes of water. These compartments are therefore equivalent. Let us dissolve a drug in the water in compartment *A*. If the barrier is permeable to the drug, then the drug molecules will pass freely between the compartments; however, there will be a net transfer of the drug from the solution of

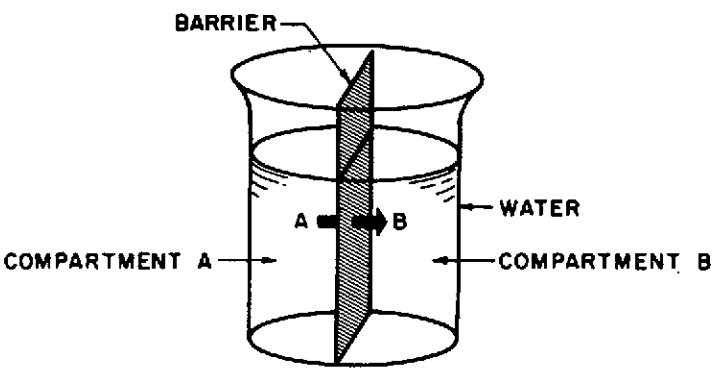


Fig. 1 Model illustrating passive diffusion between two equivalent compartments where the concentration gradient favors a net transfer from compartment *A* to *B*.

higher concentration to that of lower concentration, as indicated by the arrow in Fig. 1. The arrow does not imply that the passage of molecules through the membrane is a one-way process. This model represents a passive transport process wherein a net transfer of drug will occur from compartment A to B until the concentrations in both compartments become equal. At that time the system will be in equilibrium, which is to say that, although there is movement across the barrier in both directions, there is no net transfer in either direction. The concentrations in each compartment then remain equal. This process may be represented as

$$\text{concentration } A \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \text{concentration } B \tag{1}$$

where the first-order rate constant for transfer from compartment 1 to compartment 2 is k_{12} and the reverse rate process is represented by k_{21}.

The rate of transfer of drug may be studied by observing the decrease in C_A with time or the increase in C_B with time. Figure 2 illustrates typical results for such a transport process. A comparison of Fig. 2a and 2b will reveal that the rate process represented in Fig. 2a is slower than that in

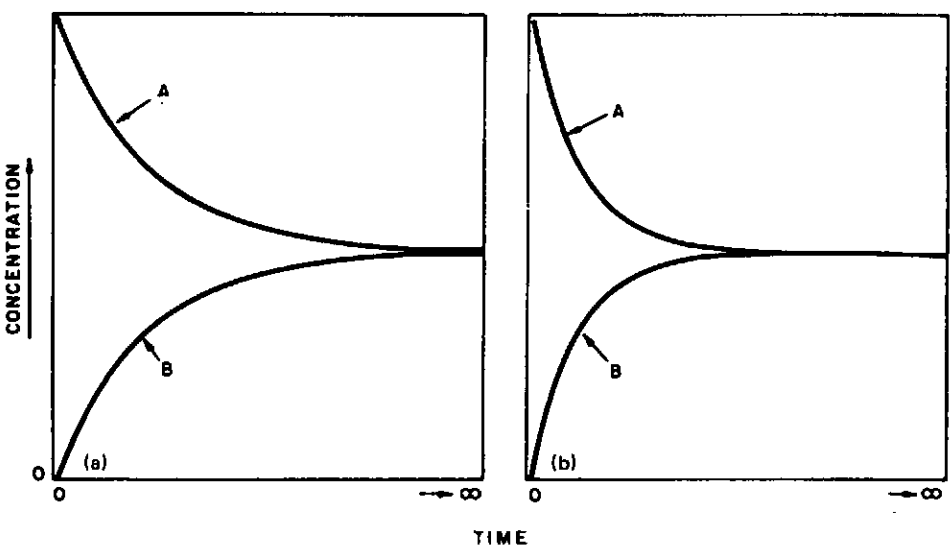


Fig. 2 Concentration time courses for a drug in compartments A and B following its introduction into compartment A in Fig. 1. The process in (b) is faster, as is evident by the fact that completion is more rapid.

Fig. 2b. This is obvious from the fact that the latter is finished sooner. But how much faster is it? It is not easy to compare rates per se. These plots of concentration versus time are curves in which the rate values are continuously diminishing throughout the process. The rate can only be defined at a particular time t, since it will have a different value at any other time. It is more convenient to compare the rate constants, since they remain constant during a given rate process.

This model may be called a two-compartment closed system, since drug cannot escape from the two compartments within the beaker. Thus $C_A(0) = C_A + C_B$ at any time. The observed rate constant k may be obtained from a first-order plot of $C_A - C_A(\infty)$ or $C_B(\infty) - C_B$, where

$$k = k_{12} + k_{21} \tag{2}$$

Since at equilibrium the forward and reverse rates must be equal,

$$k_{12}C_A(\infty) = k_{21}C_B(\infty) \tag{3}$$

the equilibrium constant may be written

$$K = \frac{C_B(\infty)}{C_A(\infty)} = \frac{k_{12}}{k_{21}} \tag{4}$$

Sample Problem 1

A drug is dissolved in the water contained in compartment A in the beaker illustrated in Fig. 1. Calculate the first-order rate constant for transfer using the concentration in compartment A measured as a function of time as given in Table 1.

Solution: The first-order rate constant for transfer from A to B may be calculated from a first-order plot where $C_A(\infty)$ is equal to 5.00, since the compartments are equivalent. The rate constant is calculated from this plot as follows:

$$k = (\ln 5.00 - \ln 0.98)/50 \text{ min} = 3.26 \times 10^{-2} \text{ min}^{-1}$$

Practice Problem 1

A drug transfer experiment was conducted in a beaker arranged as in Fig. 1. A solution containing 100 mg of drug in 100 ml of buffer was put into compartment A, with 100 ml of the same buffer in compartment B. The concentration of drug in B was assayed as a function of time (Table 2).

Table 1 Decrease in Drug Concentration in Compartment *A* as a Function of Time

Time (min)	Concentration (mg %)	Time (min)	Concentration (mg %)
0	10.00	100	5.20
10	8.56	110	5.17
20	7.58	120	5.14
30	6.88	130	5.11
40	6.35	140	5.09
50	5.98	150	5.06
60	5.70	160	5.04
70	5.51	170	5.02
80	5.39	180	5.01
90	5.29	190	5.00

Table 2 Drug Concentration in Compartment *B* as a Function of Time

Time (min)	Concentration (mg %)
0	0.0
10	9.2
20	18.5
35	27.0
60	35.3
80	41.0
115	45.5
240	50.4
360	49.7

(a) What is the rate constant for the transfer of drug from *A* to *B*?
Answer: $k = 2.12 \times 10^{-2}\ \text{min}^{-1}$.

(b) What value would be obtained for k using a plot based on data for the *A* compartment?
Answer: $k = 2.12 \times 10^{-2}\ \text{min}^{-1}$

Practice Problem 2

A weakly acidic drug is dissolved in compartment *A* of a beaker arranged as in Fig. 3. The results are given in Table 3. Compartment *B* has a pH of 4, and the pK_a of the drug is 3. Only un-ionized drug may pass through the membrane.

Table 3 Decrease in Drug Concentration in Compartment *A* as a Function of Time

Time (min)	Total concentration (mg %)	Time (min)	Total concentration (mg %)
0	6.60	40	0.68
5	4.15	50	0.63
10	2.69	60	0.61
15	1.89	70	0.60
20	1.32	80	0.60
30	0.85	90	0.60

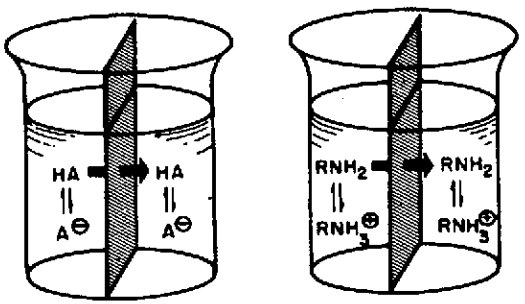


Fig. 3 Passive transport is limited to uncharged species in this model. Transfer of a weak acid *HA* or an amine base RNH_2 will be influenced by the pH values of compartments *A* and *B*, since the concentration of uncharged species must be the same in the two compartments when equilibrium is achieved.

(a) Calculate the value of the apparent first-order constant.
Answer: A semilog plot of $C_A - C_A(\infty)$ versus t is linear, with $k = 1.06 \times 10^{-1}\ \text{min}^{-1}$. Note that a plot of data for the *B* compartment would yield an identical line.

(b) What is the value of the apparent equilibrium constant *K*? What is the value of the equilibrium constant if only the concentration of un-ionized drug is considered?
Answer: In the first instance

$$K = \frac{C_B(\infty)}{C_A(\infty)} = \frac{6.00}{0.60} = 10$$

In the second case, however, we know that at equilibrium the concentrations of transferable species in both compartments must be equal, so

$$K' = 1$$

(c) What are the k_{12} and k_{21} values?
Answer: Since $K = 10$ and $k = 1.06 \times 10^{-1}$ min^{-1}, $k_{21} = 0.964 \times 10^{-2}$ min^{-1} and $k_{12} = 9.64 \times 10^{-2}$ min^{-1}.

(d) What is the pH of the A compartment?
Answer: This can be solved by employing the Henderson–Hesselbach equation:

$$\text{pH} = pK_a - \log\left(\frac{\text{protonated drug}}{\text{unprotonated drug}}\right)$$

We know the pH of compartment B is 4, the pK_a of the drug is 3, and the total concentration in B is 6.0 mg %. Therefore the concentration [HA] of transferable species in compartment B is

$$4 = 3 - \log\left(\frac{[HA]}{[A^-]}\right)$$

$$\frac{[HA]}{[A^-]} = \frac{1}{10}$$

$$[HA] = \frac{6.00 \text{ mg \%}}{11} = 0.545 \text{ mg \%}$$

Since $[HA]$ must be equal in both compartments and the total in compartment A is 0.60 mg %,

$$\text{pH of } A = 3 - \log\left(\frac{[0.545]}{[0.055]}\right) \simeq 2$$

Practice Problem 3

Sulfadimethoxine is placed into compartment A, which contains human blood serum. A membrane separates it from compartment B, which contains only water. The experiment is illustrated in Fig. 4. Free sulfadimethoxine (S_f) passes through the membrane, whereas the protein-bound sulfa (S—P) does not. The initial total concentration of sulfonamide in compartment A is 62 mg %. The data for the transfer process are found in Table 4.

(a) What is the apparent first-order rate constant?
Answer: $k = 9.36 \times 10^{-3}$ min^{-1}.

(b) What is the apparent K?
Answer: 0.148.

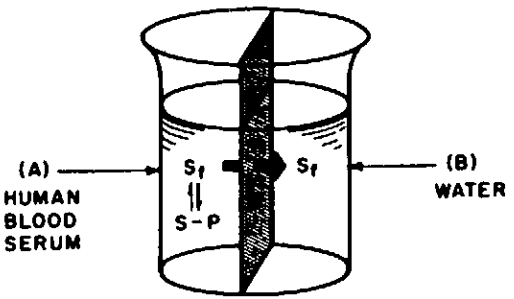


Fig. 4 In this model passive transport is limited to unbound (free) sulfadiamethoxine (S_f). The concentration of S_f is assumed to be in equilibrium with the sulfadiamethoxine bound to plasma protein (S—P).

Table 4 Concentration of Sulfadimethoxine Transferred from the Blood Plasma Compartment as a Function of Time

Time (min)	Total sulfadimethoxine concentration in B (mg %)	Time (min)	Total sulfadimethoxine concentration in B (mg %)
0	0.00	180	6.52
15	1.02	240	7.16
30	1.92	300	7.53
45	2.73	360	7.73
60	3.42	400	7.85
90	4.55	640	8.00
120	5.40	880	8.00
150	6.04		

(c) What are the values for k_{12} and k_{21}?
Answer: $k_{12} = 1.21 \times 10^{-3}$ min^{-1} and $k_{21} = 8.15 \times 10^{-3}$ min^{-1}.

(d) What is the concentration of sulfadiamethoxine (mg %) bound in compartment A at $t = 880$ minutes?
Answer: 46 mg %.

B. Two-Compartment Open Models

1. Biexponential Rates

All of the examples discussed so far were simple first-order, or monoexponential, rate processes. In every case the process could be described by an equation of the general form

$$\Delta C_A = \Delta C_A(0)e^{-kt} \tag{5}$$

where $\Delta C_A = C_A - C_A(\infty)$, $\Delta C_A(0) = C_A(0) - C_A(\infty)$, and k is the sum of the individual rate constants. When the process is reversible, k is an observed or apparent first-order constant equal to $k_{12} + k_{21}$. When loss of drug occurs by competing first-order processes, the observed k is the sum of all the competing rate constants. When the loss of drug is complete and by a single route, then $C_A(\infty) = 0$ and k is the true first-order rate constant, so that Eq. (5) becomes

$$C_A = C_A(0)e^{-kt} \tag{6}$$

Although the meaning of the observed first-order rate constant changed with the model, all the previous models followed the same monoexponential equation, Eq. (5), which can be linearized using a logarithmic transformation. Thus a first-order plot, $\ln \Delta C_A$ versus t, is linear.

The *minimum* requirements for a rate process that begins with an initial value of $C_A(0)$ to be biexponential are that the drug be involved in a reversible process, $A \rightleftarrows B$, and that at least one route exist for loss of the drug. Thus in all of the following C_A will be described by a single biexponential equation:

$$\leftarrow A \rightleftarrows B \tag{7}$$

$$A \rightleftarrows B \rightarrow \tag{8}$$

$$\leftarrow A \rightleftarrows B \rightarrow \tag{9}$$

$$\begin{matrix} \leftarrow A \rightleftarrows B \\ \quad \downarrow \end{matrix} \tag{10}$$

The time course for C_A in each of these schemes may be described by

$$C_A = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} \tag{11}$$

where the apparent rate constants λ_1 and λ_2 are made up of the various individual constants in the scheme. Each of these schemes may be called a two-compartment open model, since they involve two pools of drug, $A \rightleftarrows B$, which are eventually completely depleted. Since drug is lost, the system is open. Equations (7)–(10) are only a partial listing of all the models which could provide the biexponential loss of drug A. It follows that the description of a C_A time course by a biexponential equation does not in itself establish which one of the many models is in effect. It is necessary to have other data to distinguish between the possibilities.

If the values of the apparent constants are sufficiently different, then it is possible to solve for their values graphically. By convention, the larger value is assigned to λ_1 so that $\lambda_1 > \lambda_2$. The following examples illustrate this approach.

2. Loss of Drug from the First Compartment Only

In Eq. (7) the loss of drug occurs only from that compartment where the drug is initially introduced. This can be represented by

$$C \xleftarrow{k_{10}} A \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} B \tag{12}$$

where k_{12} and k_{21} are the first-order transfer constants between compartments 1 and 2 and k_{10} is the rate constant for the loss of drug. This is a two-compartment model in which all of the drug is eventually lost to C. With an open system drug is always being lost from one compartment, so that, depending on the rate of equilibration, the ratio of drug in B to drug in A may or may not approach the equilibrium value. The time course of the drug in each of these compartments is shown in Fig. 5, where, contrary to the case of the closed system shown in Fig. 2, the drug levels in A and B do not approach constant values, rather, but change continuously.

A drug placed directly into A will undergo simultaneous elimination and distribution processes. If the concentration of drug is measured as a function of time, it may be possible to observe biphasic loss. Although, in truth, all rate processes are occurring simultaneously throughout the curve, appropriate values for the constants in Eq. (11) make it possible to observe a rapid phase and a slower phase. During the rapid phase the fraction of dose in B is seen to pass through a maximum value, as shown in Fig. 5. The fraction of dose in A decreases owing to simultaneous loss to both B and C. During the slow phase the drug content decreases in both compartments A and B owing to elimination as a function of time. If these same data are plotted on semilog paper, the terminal phase will become linear. Figure 6 illustrates such a plot. The terminal phase is sometimes referred to as the "elimination" phase, and the negative value of the slope of its semilogarithmic plot is λ_2. Although the term in inaccurate, the reason for this nomenclature should become clear from the following mathematics.

The overall C_A time course is described by Eq. (11). Since $\lambda_1 > \lambda_2$, the term $C_1 e^{-\lambda_1 t}$ will become insignificant while the terminal phase is still evident. Equation (11) may then be written as

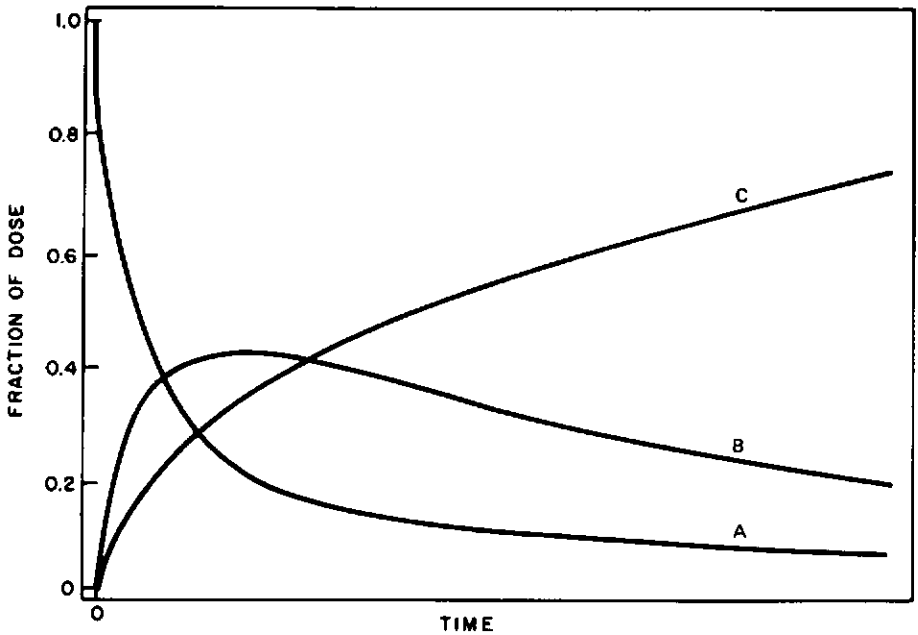


Fig. 5 Time course for each pool in Eq. (12) following introduction of the drug into compartment *A*. Since *A* and *B* are reversibly linked, their contents are eventually totally lost to *C*.

$$C_A \simeq C_2 e^{-\lambda_2 t} \tag{13}$$

where λ_2 represents the slower exponential.

When the λ values are sufficiently different from each other, they may be estimated using a graphical approach called feathering. This method is based on the fact that Eq. (13) is monoexponential so that a semilogarithmic plot of C_A versus t will become linear after the λ_1 phase becomes insignificant. This is illustrated in Fig. 6, where the λ_2 value can be estimated from the terminal slope in the same manner as a monoexponential, or first-order, plot. Since the early data points C_A are the sum of two monoexponential terms, Eq. (11), it is possible to create the plot for the faster exponential after establishing the terminal phase line. The difference between the actual data points C_A and the line attributed to the λ_2 phase in Fig. 6 represents the portion of the data not accounted for by the λ_2 phase and which must therefore be due to the λ_1 phase. To test this hypothesis, it is necessary to

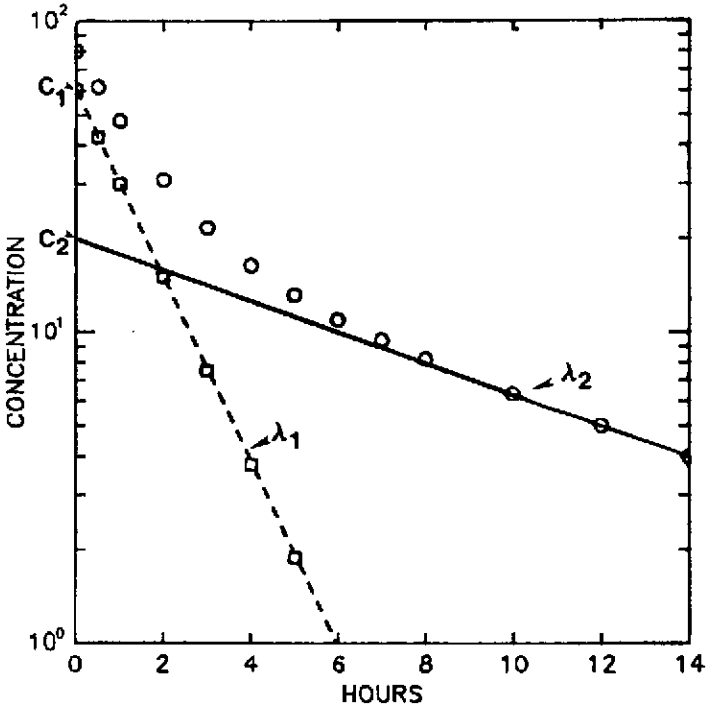


Fig. 6 Feathering data to show adherence to Eq. (11) for the biexponential loss of C_A. The negative terminal slope is λ_2 and the intercept of that line is C_2. The difference values between the data points (○) and the terminal line are plotted (□) to evaluate the rapid rate constant λ_1 and its intercept C_1.

subtract the values on the λ_2 line from the corresponding observed C_A data points and to test this set of difference values for monoexponential loss. A positive test in the form of a linear first-order plot is shown in Fig. 6. In this illustration the C_A values are adequately described by the sum of two exponentials and the graphical treatment provides estimates for all four of the required constants in Eq. (11), which are C_1, λ_1, C_2, and λ_2.

This may be called a model-independent equation for the data. It simply states that this biexponential equation adequately describes the data but it does not describe the individual rate contants for the model. This form is often both adequate and preferable in pharmacokinetics. Assigning a model requires more knowledge of the system than simply observing biexponential loss. In the present case we do know that the processes in Eq. (12) can be

defined in terms of the individual rate constants k_{12}, k_{21}, and k_{10}. Therefore the following relationships are in effect:

$$\lambda_1,\lambda_2 = \frac{1}{2}(k \pm \sqrt{k^2 - 2k_{21}k_{10}}) \tag{14}$$

where $\lambda_1 > \lambda_2$ and $k = k_{12} + k_{21} + k_{10}$. Since the only difference between λ_1 and λ_2 is the positive or negative sign of the square root, it follows that

$$\lambda_1 + \lambda_2 = k \tag{15}$$

Furthermore, assigning the fractional values $C_1' = C_1/C(0)$ and $C_2' = C_2/C(0)$, where $C(0) = C_1 + C_2$ and C_1 and C_2 are defined by Eq. (11) allows the following calculations:

$$k_{21} = (C_1')\lambda_2 + (C_2')\lambda_1 \tag{16}$$

$$k_{10} = \frac{\lambda_1\lambda_2}{k_{21}} \tag{17}$$

and, by rearrangement of Eq. (15),

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10} \tag{18}$$

The coefficients in Eq. (11) may then be defined by

$$C_1' = \frac{k_{21} - \lambda_1}{\lambda_2 - \lambda_1} \tag{19}$$

and

$$C_2' = \frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2} \tag{20}$$

where C_A' will now represent the fraction of the total in compartment A.

The previous example using Eq. (12) is theoretical. An experimentally observed analog to this model is the partitioning of penicillins between an

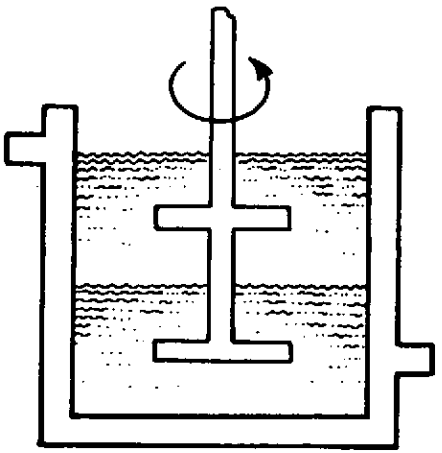


Fig. 7 Diagram of a two-phase transfer cell wherein ampicillin is allowed to distribute between aqueous acid and isobutanol while undergoing simultaneous hydrolysis in the aqueous phase. The system behaves in accordance with Eq. (12), as illustrated by the data in Table 5 and Practice Problem 4.

Table 5 Concentration of Ampicillin Remaining in the Aqueous Phase of a Stirred Transfer Cell Containing 0.3 N HCl and Isobutanol at 37°C with a Stirring Rate of 75 rpm[a]

Time (hr)	Concentration ($\times 10^2$ M)	Time (hr)	Concentration ($\times 10^2$ M)
0.0	4.00	2.0	1.32
0.2	3.46	4.0	0.77
0.4	3.01	6.0	0.54
0.6	2.67	8.0	0.40
0.8	2.34	10.0	0.30
1.0	2.09	12.0	0.22

[a]Data based on Refs. 1 and 2.

aqueous and a nonaqueous phase in a transfer cell (Fig. 7) wherein the drug is undergoing simultaneous hydrolysis in the aqueous phase. This may be represented by Eq. (12), wherein all of the drug is eventually hydrolyzed to the hydrolysis product *C*. The following problem illustrates the kinetic interpretation of this data treatment.

Practice Problem 4

A 4×10^{-2} M solution of ampicillin is prepared in a two-phase transfer cell (Fig. 7) containing 0.3 N HCl preequilibrated with isobutanol at 37°C with a constant stirring rate of 75 rpm. The ampicillin is known to undergo irreversible hydrolysis in the aqueous acid and reversible distribution (partitioning) into the isobutanol. The concentration C_A remaining intact in the aqueous phase was determined as a function of time, with the results shown in Table 5.

(a) Determine a model-independent equation to describe the time course for C_A throughout this experiment and obtain the numerical estimates required for that equation.
Answer: $C_A = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t} = (2.67 \times 10^{-2}\ \text{M})e^{-(1.05\ \text{hr}^{-1})t} + (1.33 \times 10^{-2}\ \text{M})e^{-(0.15\ \text{hr}^{-1})t}$

(b) Assuming that Eq. (12) describes the rate process, calculate the value for the partition coefficient K_D, the first-order constants k_{12}, k_{21}, and k_{10} and the hydrolysis constant k_h.
Answer: $k_{21} = (C_1')\lambda_2 + (C_2')\lambda_1 = (0.667)0.15\ \text{hr}^{-1} + (0.333)1.05\ \text{hr}^{-1} = 0.45\ \text{hr}^{-1}$; $k_{10} = \lambda_1\lambda_2/k_{21} = (1.05)(0.15)/0.45 = 0.35\ \text{hr}^{-1}$; $k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10} = 0.40\ \text{hr}^{-1}$. Since hydrolysis occurs in the aqueous phase, $k_h = k_{10} = 0.35\ \text{hr}^{-1}$. This value agrees with that observed independently for the hydrolysis of ampicillin in 0.3 N HCl at 37°C [2]. The partition coefficient may be calculated from $K_D = k_{12}/k_{21} = 0.40/0.45 = 0.89$.

Note that the alternative calculation given in Eq. (4), $K = C_B(\infty)/C_A(\infty)$, cannot be used here, as the final ampicillin concentration in both phases will be zero owing to hydrolysis. This further illustrates the difference between an open and a closed system. This open system is constantly losing ampicillin and the two phases will never achieve the ratio indicated by this K_D value of 0.89. When the ratio C_B/C_A becomes relatively constant, then both phases will be decreasing with the same apparent rate constant λ_2. Under this condition the C_B/C_A distribution ratio may be calculated from

$$\text{constant ratio} = \frac{k_{12}}{k_{21} - \lambda_2} \tag{21}$$

which gives a value of $0.40/(0.45 - 0.15) = 1.3$, instead of 0.89. The C_B/C_A distribution ratio will always be larger than the K_D value when loss is occurring from the aqueous phase. When the hydrolysis rate constant k_{10} becomes sufficiently small relative to the distribution constants k_{12} and k_{21},

then the actual distribution ratio will approach the partition coefficient K_D. In that case a semilogarithmic plot on a time scale that is appropriate for λ_2 would appear monoexponential, as the time required for distribution would appear nearly instantaneous by comparison.

III. ACTIVE TRANSPORT

A. Description and Properties

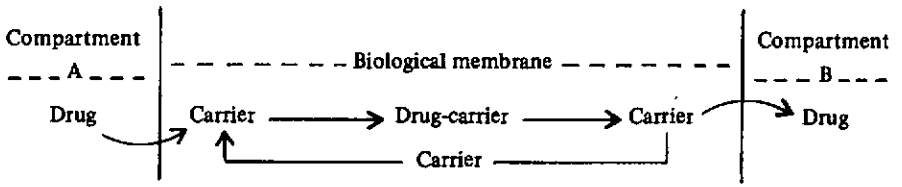
Up to this point all of the transport rate processes were examples of passive transport, that is, the membrane itself did not actively participate in the transfer process. Instead, it simply provided a physical barrier which permitted the formation of a concentration gradient when the drug was introduced into one of the compartments. However, the membrane may play an active role, transporting solute molecules against an electrochemical or concentration gradient. Molecules known to be transported in this manner include naturally occurring substances, with sodium and potassium ions representing the best-known examples. Others are amino acids, sugars, uracil, and many vitamins. Molecules such as 5-fluorouracil and 5-bromouracil are also actively transported, presumably owing to their similarity to natural pyrimidines.

The distinctions made between passive and active transport can be briefly summarized by comparing their major properties.

Passive transport may be characterized by the following:

1. Drug molecules move from a region of relatively high concentration to one of lower concentration.
2. The rate of transfer is proportional to the concentration gradient between the compartments involved in the transfer.
3. The transfer process achieves equilibrium when the concentration of the transferable species is equal on both sides of the membrane.
4. Drugs which are capable of existing in both a charged and a noncharged form approach an equilibrium state primarily by transfer of the noncharged species across the membrane.

In contrast to this, an active process involves participation by the membrane in the transfer of molecules between compartments. A "carrier," which may be an enzyme or some other component of the membrane, is responsible for effecting the transfer by a process which may be represented as follows:



Here the drug in compartment *A* is picked up by the carrier in the surface of the membrane. The drug–carrier complex then moves across the membrane and the drug is discharged to compartment *B* at the membrane surface open to *B*. The carrier then returns to the *A* compartment surface for another drug molecule.

This transfer system has characteristics that are decidedly different from those listed for the passive system:

1. This process consumes *energy*. There is energy involved in the work done by the carrier.
2. Since the transport involves consumption of energy, it may be subject to *poisoning* by metabolic poisons such as fluorides and dinitrophenol, lack of oxygen, and so on.
3. Unlike the passive transfer process, which is dependent upon a concentration gradient, an active transfer process can work *against the concentration gradient*; that is, the carrier may transport all of the drug from one compartment to the other without any regard for an "equilibrium state" which was the endpoint in the case of a passive transport process. Indeed, the carrier transfer system will generally be a "one-way" transport process.
4. The system will be relatively *structure specific*. The carrier will be designed to transport a specific chemical structure. Thus it will not be completely indiscreet in its activity.
5. However, the carrier system may transport a chemical structure which is sufficiently similar to the one for which it is allegedly "specific." The transfer system is thus subject to *competition* between similar chemical structures.
6. Since there are a finite number of carriers available, the system is capacity limited. If the total number of transferable molecules exceeds the number of carrier sites available for transfer, the system will become *saturated*. The system will then be working at full capacity and the

transfer of drug may thus occur at a constant rate until the concentration of drug falls below that of the capacity limit of the system.

B. Kinetics and Data Treatment

1. Mixed Order

In its two extremes active transport may appear to be first order or zero order. In fact, these are approximations which represent two limiting cases of the Michaelis–Menten equation. A system in which transfer occurs at a constant rate is described by zero-order kinetics. An example of such a system is the saturated active transport system just described. The same active transport system may also behave according to a first-order rate process. Consider the rate of transfer under conditions wherein the number of sites greatly exceeds the amount of drug available for transport. The transfer process will not operate at its maximum capacity under these conditions, since it is dependent upon the availability of drug.

When a fruitful collision occurs between drug and carrier, then the transport of drug across the membrane as a drug–carrier complex occurs in the normal manner previously outlined. However, at any given time a large number of available sites are not in operation. The rate is thus far below the rate at saturation. Now assume that the concentration of drug is doubled but that the available sites remain in large excess of transferable drug. We would expect the rate to double, since there are now twice as many collisions and thus twice as many chances for a fruitful carrier–drug collision. An increase in concentration will result in a proportional increase in rate as long as the carrier system does not become saturated and the solutions remain sufficiently dilute so that an increase in concentration is paralleled by an increase in thermodynamic activity. This process is apparent first order, since the rate is proportional to the concentration of transferable drug.

Thus an active transport rate can appear to be a first-order process when the concentration of drug is sufficiently dilute to be the limiting factor, rather than the capacity of the transfer system itself. Conversely, the kinetic order can change to apparent zero order when drug concentration is increased from dilute conditions to those of capacity-limited transfer.

2. Michaelis–Menten Kinetics

The above discussion of zero- and first-order kinetics, as indicative of saturated and nonsaturated active transport systems, are analogous to the Michaelis–Menten approach to enzyme-catalyzed reactions. Processes are

said to behave in accordance with Michaelis–Menten kinetics when the rate V can be described by the equation

$$V = \frac{V_{max} C_A}{K_m + C_A} \tag{22}$$

where V_{max} is the maximum possible rate (Fig. 8) and C_A is the concentration of drug that may undergo change. The Michaelis constant K_m is equal to that value of C_A which will result in $V = \frac{1}{2} V_{max}$. When C_A is much smaller than K_m, the denominator approaches the value of K_m and V becomes

$$V = \frac{V_{max} C_A}{K_m} \tag{23}$$

Since V_{max}/K_m is constant, this equation is of the form $-dC_A/dt = kC_A$, which is apparent first order. The rate is therefore proportional to the concentration of drug when $C_A < 0.1K_m$, as illustrated in Fig. 8.

At sufficiently high drug concentrations, where $C_A \gg K_m$, Eq. (22) becomes

$$V = V_{max} \tag{24}$$

which is a constant rate, as shown in Fig. 8 when $C_A > 10K_m$. When C_A is in the intermediate region, $0.1K_m < C_A < 10K_m$, then Eq. (22) must be employed and the approximations do not suffice.

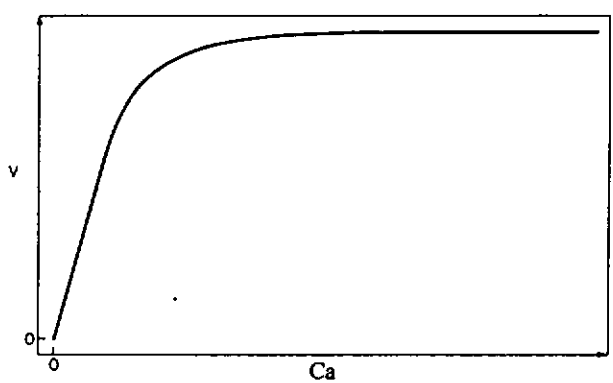


Fig. 8 An example of Michaelis-Menten kinetics where V is the rate of the process and C_A is the concentration of drug undergoing a change. At low C_A values, V is proportional to C_A, which is pseudo-first-order behavior. At high C_A values, V is independent of C_A, or pseudo-zero-order.

The elimination of a highly metabolized drug from the body is frequently found to exhibit what is called nonlinear kinetics. This terminology means that deviation from first-order behavior is observed at sufficiently high doses. These nonlinear data may sometimes be adequately described by an equation of the form of Eq. (22). In such a case the elimination is said to behave according to Michaelis–Menten kinetics. The K_m values have no simple theoretical significance. However, the approach has often proved to be of practical vlaue in successfully characterizing complex kinetic systems. Phenytoin multiple-dose calculations provide an excellent example of the analysis of nonlinear elimination kinetics using the Michaelis–Menten equation, and these are discussed in Chap. 8.

Sample Problem 2

A drug is being transferred from compartment A to compartment B during two experiments which are conducted under different sets of experimental conditions. In both cases the appearance of drug in compartment B is measured as a function of time. The volume of compartment B is identical to that of compartment A, and Table 6 gives the results in terms of the amount of drug transferred rather than the concentration of drug.

(a) What is the order of the transfer process in experiments 1 and 2?
Solution: A plot of $B(\infty) - B$ on coordinate graph paper results in a straight line for data from experiment 2, whereas data from experiment 1 are nonlinear. The same data on semilog paper, however, are linear in the case of experiment 1. Therefore experiment 1 illustrates a first-order process, and experiment 2 a zero-order process.

A first-order plot of data covering the first 15 min of each experiment (this includes almost 90% of the total process in experiment 1,

Table 6 Appearance of Drug (μg) in Compartment B Following the Introduction of 100 μg into Compartment A

Time (min)	Experiment		Time (min)	Experiment	
	1	2		1	2
0	0	0	25	97	42
3	34	5	30	98	50
5	51	8	35	99	58
10	76	17	40	99	67
15	88	25	50	100	83
20	94	33	60	100	100

but only 25% of the total in experiment 2) is linear for experiment 1, and is very nearly linear for experiment 2 as well. This emphasizes the importance of plotting data covering 80% of a process when trying to determine its order.

(b) What are the rate constants associated with both experiments?
Solution: In experiment 1

$$k = \text{slope} = \frac{\ln 100 - \ln 24}{10 \text{ min}}$$
$$= 0.143 \text{ min}^{-1}$$

In experiment 2

$$k_0 = -\text{slope} = \frac{100 \ \mu\text{g} - 0 \ \mu\text{g}}{60 \text{ min}}$$
$$= 1.67 \ \mu\text{g/min}$$

Practice Problem 5
Two separate experiments involving different dosage levels are carried out involving the active transport of a drug through a biological membrane. In each case the drug remaining in compartment *A* is assayed as a function of time (Table 7).

Table 7 Loss of Drug from Compartment *A* at Two Dosage Levels

	Concentration (mg %)			Concentration (mg %)	
Time (min)	Experiment 1	Experiment 2	Time (min)	Experiment 1	Experiment 2
0	10.0	100.0	60	0.02	32.6
5	6.0	94.5	70	0.00	21.4
10	3.5	89.0	80	0.00	10.0
15	2.1	83.5	85	—	6.0
20	1.2	77.8	90	0.00	3.5
25	0.70	72.0	95		2.1
30	0.41	66.5	100		1.2
35	0.24	60.8	105		0.7
40	0.14	55.0	110		0.4
50	0.05	43.8	115		0.0

(a) What is the order of the transport process at the 10 mg % dose level?
Answer: First order.
(b) What is the value of the rate constant?
Answer: 0.104 min^{-1}.
(c) What is the order of the transport process at the 100 mg % dose level?
Answer: Zero order.
(d) What is the value of the rate constant?
Answer: 1.1 mg %/min.
(e) What occurs between 80 and 115 min following the 100 mg % dose? (You might find it helpful to construct a plot of concentration versus time in answering this question).
Answer: At 80 min, when the concentration in A drops to 10 mg %, the active transport system is no longer saturated, so the process becomes first order.

Equation (22) can be written in several linear forms which allow graphical estimation of the V_{max} and K_m values. One such transformation follows. Solving for V_{max} gives

$$V_{max} = \left(\frac{K_m V}{C_A}\right) + V \tag{25}$$

which may be written

$$V = V_{max} - \left(\frac{K_m V}{C_A}\right) \tag{26}$$

A plot of V versus V/C_A is linear with slope $-K_m$ and intercept V_{max}.

Practice Problem 6
Under specified conditions (discussed in Chap. 8) phenytoin elimination in adults may be described using the Michaelis–Menten equation wherein the elimination rate V is equal to the daily drug intake R (in mg/day) and C_A is the corresponding average plasma concentration. The V_{max} and K_m values for the individual patient can be estimated from Eq. (26) by knowing the resulting C_A values for several dosing rates in that patient. Use the data in Table 8 to calculate K_m and V_{max} for the patient.
Solution: A plot of dosing rate R versus R/C_A is linear, with $-\text{slope} = K_m = 7.6$ mg/liter and intercept $= V_{max} = 675$ mg/day.

Table 8 Average Steady-State Phenytoin Plasma Concentrations Obtained from Three Dosing Rates in One Patient

Dosing rate (mg/day)[a]	Average plasma concentration (mg/liter)
240	4.2
300	6.1
360	8.7

[a]Given every 8 hr in equally divided doses.

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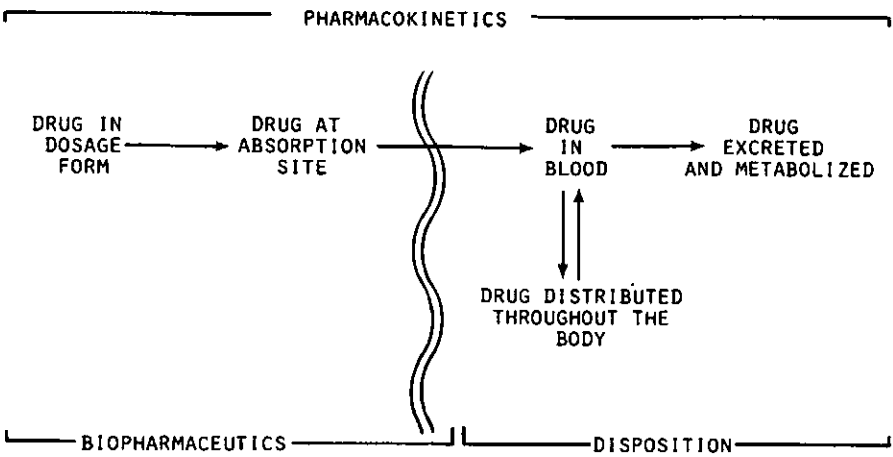
4

Pharmacokinetics

I. INTRODUCTION

Pharmacokinetics is the study of those rate processes involved in the absorption, distribution, metabolism, and excretion of drugs and their relationship to the pharmacological, therapeutic, or toxic response in animals or humans. Pharmacokinetic techniques attempt to mathematically define the time course for drug in the body by assaying for drug and metabolites in readily accessible fluids such as blood and urine. The goal is to quantitatively account for the amount which has entered the body (bioavailable dose) from the time of administration until it has been completely cleared. The mathematical descriptions that have emerged have proven extremely valuable to both drug research and drug therapy. Since the monitoring of drug concentration in patients' plasma by obtaining a few small blood samples at key times is clinically practical, individualization of dosage regimens has become a reality. This has dramatically altered certain types of drug therapy. These improvements are limited to cases wherein biological response can be related to drug blood levels, since the mathematics are capable only of describing the sampled fluids. Nonsampled fluids are considered as additional compartments or pools and described collectively using kinetic equations for mass balance. The results may be represented by a simplified scheme such as Scheme I.



Scheme I

As illustrated in Scheme I, pharmacokinetics includes the study of all of the controlling rate processes. It is sometimes called ADE kinetics for absorption, distribution, and elimination kinetics. Biopharmaceutics deals only with the absorption process. When a drug is administered by intravenous injection only distribution and elimination are in effect (DE kinetics). The study of DE kinetics is often called drug *disposition*. The site of administration and the properties of the dosage form can influence the bioavailability of the administered drug. Once absorbed, the drug is subject only to DE kinetics. Any or all of the ADE rate processes may be influenced by the physicochemical properties of the drug and the health, age, and sex of the patient.

Pharmacokinetic studies probably date back to 1924, when Widmark and Tandberg published two theoretical papers on the one-compartment open model [1]. In 1937 Teorell published two theoretical papers which are regarded today as a classic treatise marking the beginning of what is now called pharmacokinetics [1]. This work was largely disregarded for many years owing to the complexity of the equations and the lack of analytical tools. The advent of computers and the proliferation of sophisticated analytical methodology have removed these obstacles.

II. DRUG DISPOSITION

The rapid introduction of drug into the blood would result in a high blood concentration which would immediately begin to decrease owing to simultaneous loss to distribution, metabolism, and excretion as illustrated in Scheme I. Eventually the reversible transfer of drug between blood (the central

compartment) and the remainder of the body (peripheral compartment) would result in a constant ratio between the two pools and both would simultaneously decrease. After this initial period of equilibration between central and peripheral pools is complete, the rate of loss from blood would be due only to excretion and metabolism and would therefore be reduced. In practice, it may or may not be possible to observe the various phases of drug disposition involving a central and peripheral pool and elimination (i.e., excretion and metabolism). When distribution is sufficiently fast relative to elimination, it may be experimentally impossible to observe the equilibration period. It may also be possible to observe more than one period of apparent equilibration if the peripheral compartment behaves as though it were made up of a rapid and slow (deep) pool.

The compartmental interpretation of drug concentration versus time data, such as in Scheme I, is speculative. The peripheral compartments are treated as homogeneous pools, whereas anatomically it is well recognized that body regions will vary in drug content. However, it is not necessary to interpret the time course data in terms of a compartmentalized model. The equations which describe the sampled compartment (blood) are empirical and not, in themselves, speculative. These mathematical descriptions can be directly employed to calculate pharmacokinetic parameters. In the following section, and throughout this book, model-independent assessments of pharmacokinetic data will be emphasized. This means that the concentration of drug in the blood as a function of time, or an equation describing this data, will be used to calculate the pharmacokinetic descriptors directly. Here an equation to describe the concentration time course is not considered as a model. Attempts to relate this equation to nonsampled (i.e., peripheral) regions, as in Scheme I, are considered compartmental modeling. The methods and limitations of compartmental analyses are reviewed in a later section.

A. Model-Independent Descriptions

When a drug is rapidly introduced into the bloodstream (intravenous bolus) it is subject to countless physiological processes, all of which reduce the concentration of drug in the plasma. Despite this complexity, the plasma drug concentration C at any time t following a single intravenous bolus can often be described by

$$C = \sum_{i=1}^{n} C_i e^{-\lambda_i t} \tag{1}$$

If Eq. (1) is found to be empirically adequate, the drug is said to behave according to *linear* kinetics. This implies that the plasma concentration of

drug is linearly related to the dose and the profile C versus t, is the result of one or more first-order rate processes. One convention, used in this text, is to assign the slowest (or terminal) exponential term the rate constant λ_Z, and if $n > 1$, its intercept is termed C_Z. Thus, by this convention, the λ_i, C_i values, according to the n terms, are λ_1, C_1 and λ_Z, C_Z ($n = 2$) and λ_1, C_1, λ_2, C_2, and λ_Z, C_Z ($n = 3$). When $n = 1$, C_Z is assigned the symbol $C(0)$ making the pair λ_Z, $C(0)$.

1. Monoexponential Disposition, $n = 1$

The value of n in Eq. (1) is determined empirically. In the simplest case, where $n = 1$, the time course for the plasma concentration of drug, which is determined by sampling blood and assaying for drug, may be written

$$C = C(0)e^{-\lambda_Z t} \tag{2}$$

which is a monoexponential, or first-order, rate process with the apparent first-order elimination rate constant λ_Z (time^{-1}), and initial concentration $C(0)$. The log-linear transformation is

$$\ln C = \ln C(0) - \lambda_Z t \tag{3}$$

Thus a plot of C versus t on semilogarithmic paper is linear with negative slope λ_Z and intercept $C(0)$. The test commonly employed to determine the number of exponentials that are required consists of examining a first-order plot of plasma concentration data for the existence or nonexistence of positive deviation in the terminal phase. Of course, if the time between the injection and the first blood sample is long enough, a bi- or triexponential time course will appear to be monoexponential. Thus it is appropriate to sample shortly after injection in addition to sampling long term. If short- and long-term sampling fail to detect deviation, a monoexponential equation may describe the data.

Sample Problem 1

A 1.0-g intravenous dose of carbenicillin provided the following serum levels as a function of time:

Time (hr):	0.50	1.0	1.5	2.0	2.5	3.0
Serum level (μg/ml):	49.0	33.6	23.0	15.8	10.8	7.4

(a) Write a model-independent equation describing the time course for carbenicillin concentration during this experimental period and determine the values for the constants in the equation.
Solution: A plot of C versus t on semilogarithmic graph paper is linear over this time period. Therefore $C = C(0)e^{-\lambda_Z t}$, where $C(0) = 72$ μg/ml (the intercept) and $\lambda_Z = 0.756\ hr^{-1}$ (the negative slope).

(b) Is it valid to conclude that carbenicillin disposition can be described by a monoexponential equation in this patient? Explain your answer.
Solution: No. Earlier or later sampling could reveal additional exponential terms and increased dose size might demonstrate nonlinear kinetics. The only valid statement to be made is that serum levels following a 1.0-g intravenous dose were described by $C = C(0)e^{-\lambda_Z t}$ during the sampling period 0.5–3.0 hr.

Practice Problem 1
A 5-g intravenous dose of ticarcillin provided the following serum levels as a function of time:

Time (hr):	0.25	0.5	1.0	2.0	3.0	4.0	5.0	6.0
Serum level (μg/ml):	320.0	270.0	200.0	106.0	60.0	32.0	17.0	9.3

(a) Write a model-independent equation describing the ticarcillin concentration time course during this experiment and determine the values for the constants in the equation.
Answer: $C = C(0)e^{-\lambda_Z t} = (370\ \mu g/ml)e^{-(0.614\ hr^{-1})t}$

(b) Is it likely that this equation adequately described ticarcillin disposition following a 5-g intravenous dose to this patient? Why?
Answer: Very likely. The equation is shown to be adequate from 0.25 to 6.0 hr, where the C values of 320 and 9.3 μg/ml are 86 and 2.5% of the $C(0)$ value of 370 μg/ml. Although another exponential term could occur during the first 0.25 hr or after 6 hr, it is unlikely to be significant. In Sample Problem 1 the first sample had a serum level of 49 μg/ml, or 68% of the $C(0)$ value of 72 μg/ml. In that case, a more conservative conclusion was required owing to the increased uncertainty caused by that experimental protocol.

2. Biexponential Disposition, $n = 2$

When $n = 2$, Eq. (1) may be written

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \tag{4}$$

which is the sum of two apparent first-order processes of rate constants $\lambda_1 \neq \lambda_Z$. By convention, $\lambda_1 > \lambda_Z$, so that a plot of C versus t on semilogarithmic paper will eventually appear linear as the contribution of $C_1 e^{-\lambda_1 t}$ becomes insignificant and

$$C \cong C_Z e^{-\lambda_Z t} \tag{5}$$

Since the data are the sum of the two components and the terminal component can be described by this plot, the data for $C_1 e^{-\lambda_1 t}$ can be calculated from the difference. This may be done graphically by the method of "feathering." This process is illustrated in Fig. 1, where the terminal log-linear phase provides estimates for C_Z and λ_Z and the difference plot provides estimates for C_1 and λ_1. The value $C(0) = C_1 + C_Z$ represents the hypothetical concentration of drug in the volume of the sampled fluid at time zero. Although blood samples are withdrawn and assayed, the apparent volume of this sampled pool may be larger than the blood volume itself, since the drug concentration may equilibrate rapidly with some extravascular pools.

Thus, to describe drug disposition requiring a biexponential equation, it is necessary to estimate values for the constants C_1, λ_1, C_Z, and λ_Z. The following problems illustrate the use of feathering to make graphical estimates for these constants.

Sample Problem 2

A 3-g intravenous dose of ticarcillin was administered following a 1-g oral dose of probenecid to the same patient and the ticarcillin serum levels shown in Table 1 were determined as a function of time.

Table 1 Ticarcillin Serum Levels from a 3-g Intravenous Dose Administered after a 1-g Oral Dose of Probenecid

Time (hr)	Concentration (μg/ml)	Time (hr)	Concentration (μg/ml)
0.25	216.0	3.00	53.2
0.50	171.0	4.00	36.4
0.75	142.0	5.00	24.9
1.00	122.0	6.00	17.0
2.00	78.4		

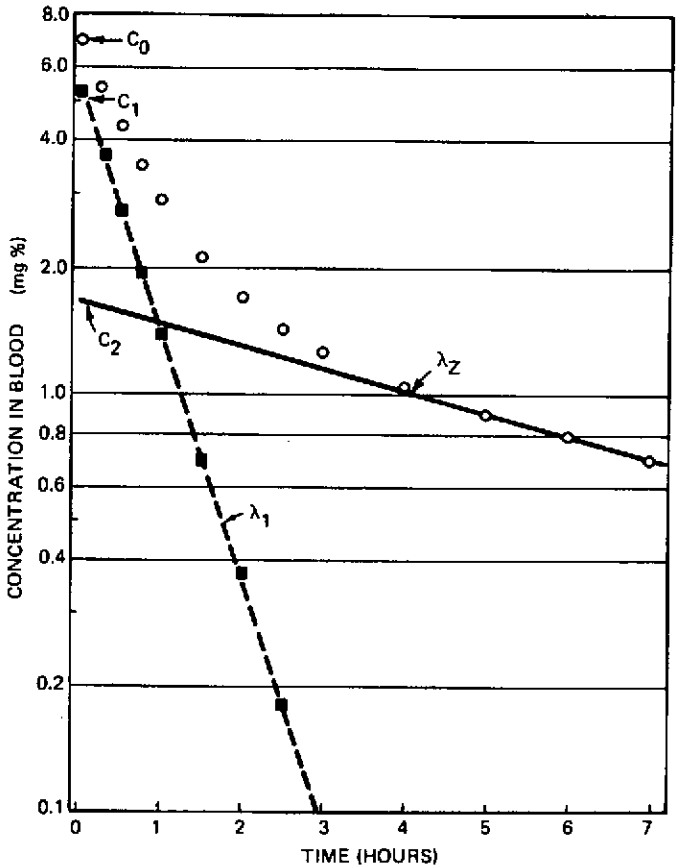


Fig. 1 Semilogarithmic plots illustrating the method of feathering biexponential data described by Eq. (4). The negative slope of the log-linear terminal phase is assigned the rate constant λ_Z and the intercept C_Z. The differences between the data points (○) and this line are then plotted (■) to evaluate the rapid rate constant λ_1 and the intercept C_1. The hypothetical initial concentration $C(0)$ is the sum of C_1 and C_Z.

(a) Write a model-independent equation describing the ticarcillin time course and determine the values of the constants in the equation.
Solution: A semilogarithmic plot of C versus t on a 2-cycle paper is linear from approximately $t > 2$ hr, with $\lambda_Z = 0.381\ \text{hr}^{-1}$ and $C_Z = 167\ \mu\text{g/ml}$. Feathering provides a linear plot for the difference values with $\lambda_1 = 2.75\ \text{hr}^{-1}$ and $C_1 = 127\ \mu\text{g/ml}$. The time course can be described by $C = C_1 e^{-\lambda_1 t} + C_Z e^{-\lambda_Z t}$.

(b) Why does ticarcillin appear to require a biexponential equation here whereas a monoexponential description was adequate in Practice Problem 1?
Solution: The primary difference may be attributed to probenecid, which appears to prolong the duration of ticarcillin, as is evidenced by comparison of the λ_Z values, which are 0.381 hr^{-1} in this case, decreased from 0.614 hr^{-1} in Practice Problem 1. This reduction in the elimination rate constant makes it easier to detect the initial rapid phase, $C_1e^{-\lambda_1 t}$.

Practice Problem 2
A 16.4-kg 4-year-old child with severe chronic asthma was given an intravenous dose of aminophylline equivalent to 3.2 mg/kg of the drug theophylline. Assays for theophylline concentration in plasma provided the results in Table 2.

(a) Write a model-independent equation describing the theophylline time course in this patient and determine the values of the constants.
Answer: $C = C_1e^{-\lambda_1 t} + C_Ze^{-\lambda_Z t} = (4.70\ \mu g/ml)e^{-(2.07\ hr^{-1})t} + (8.18\ \mu g/ml)e^{-(0.18\ hr^{-1})t}$.

(b) Would this equation be expected to describe the theophylline time course in other children of this age and weight? Why?
Answer: No. One should expect to observe biological variability. In fact, theophylline shows so much intersubject variability that it will be discussed later as a separate problem with the clinical pharmacokinetic examples in Chapter 8.

Table 2 Concentration of Theophylline in Plasma Following a 3.2-mg/kg Intravenous Dose of Theophylline (as Aminophylline) to a 4-Year-Old Asthma Patient

Time (hr)	Concentration (μg/ml)	Time (hr)	Concentration (μg/ml)
0.25	10.62	4.00	3.98
0.50	9.15	6.00	2.78
1.00	7.42	8.00	1.94
2.00	5.78	10.00	1.35
3.00	4.77		

The theophylline constants determined for an individual patient can only be used to calculate the correct dose for that particular patient. They cannot be applied to other patients. For example, the λ_1 values for the 10 children in the report used for this problem [2] varied from 2 to 17 hr^{-1} and the λ_Z values from 0.13 to 0.3 hr^{-1}. Unlike theophylline, the time courses for many drugs can be adequately predicted in individuals from average values for the general population without extraordinary risk to the patient.

3. Triexponential Disposition, $n = 3$

When $n = 3$, Eq. (1) may be written

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_Z e^{-\lambda_Z t} \tag{6}$$

which is the sum of three apparent first-order processes of rate constants $\lambda_1 > \lambda_2 > \lambda_Z$. A plot of C versus t on semilogarithmic paper will provide a terminal linear phase where $-\text{slope} = \lambda_Z$ and the intercept is C_Z, since Eq. (5) will describe the data when the contributions of $C_1 e^{-\lambda_1 t}$ and $C_2 e^{-\lambda_2 t}$ become insignificant. By subtraction of the terminal phase line from the data points (feathering of the λ_Z phase), the remainder is now the sum of the λ_1 and λ_2 phases, which leaves a biexponential rate process to be feathered once more. Then the terminal linear phase of these data provides estimates for C_2 and λ_2 and feathering once more produces data to estimate C_1 and λ_1. The first step estimates C_Z and λ_Z from the terminal data and the difference between this line and the data points leaves a set of data to be treated like a biexponential rate process. Because of the difference in relative rates, $\lambda_1 > \lambda_2 > \lambda_Z$, it may be necessary to use different time scales in order to achieve good estimates for all three slopes. Data treatment is illustrated in the following problem.

Sample Problem 3

A healthy 70-kg subject was given 150 mg of bis-hydroxycoumarin by intravenous injection. From the data in Table 3, calculate the slopes and intercepts of the three phases of the triexponential decrease in plasma concentration.

Solution: Three different phases of the curve can be resolved in a manner analogous to that used for the biexponential data. A semilogarithmic plot of the data shows a terminal linear portion with $-\text{slope} = \lambda_Z$ (Fig. 2). The extrapolated portion of this line is subtracted from the corresponding experimental points to yield a biphasic curve with a final slope of $-\lambda_2$. Finally, the extrapolated portion of the λ_2 line is subtracted from the nonlinear portion of this second plot to give the λ_1 line. The approximations of the slopes and y intercepts for the lines obtained by this process are the following:

Table 3 Concentration of Bis-hydroxycoumarin in Plasma After a 150-mg Intravenous Injection of Bis-hydroxycoumarin

Time (hr)	Concentration (mg/liter)	Time (hr)	Concentration (mg/liter)
0.17	36.2	3.0	13.9
0.33	34.0	4.0	12.0
0.50	27.0	6.0	8.7
0.67	23.2	7.7	7.7
1.0	20.8	18.0	3.2
1.5	17.8	23.3	2.4
2.0	16.5		

[a]Data from Ref. 3.

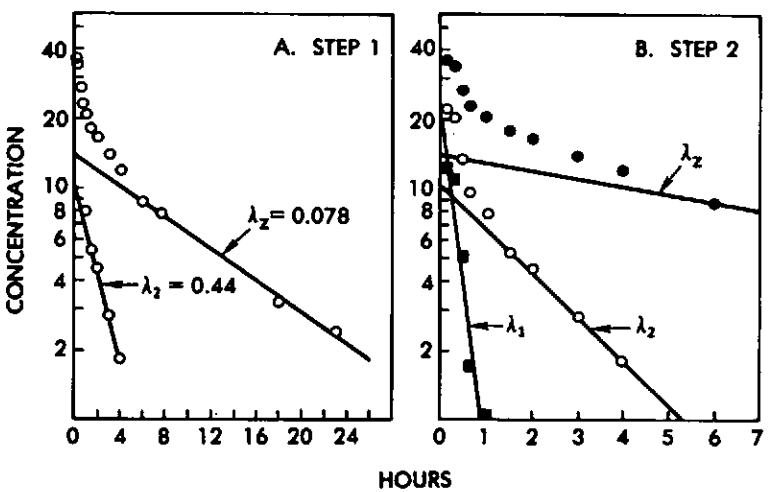


Fig. 2 Feathering the triexponential data in Table 3 described by Eq. (6). The negative terminal slope λ_Z and intercept C_Z of the semilogarithmic plot of the data are evaluated in step 1. The difference values between the data points and this line provide a biexponential data set of negative terminal slope λ_2 and intercept C_2, as shown in steps 1 and 2. The early data points ($\leq$1 hr) are above this line. The difference between these points and the λ_2 line are plotted to evaluate λ_1 and C_1, as shown in step 2, where the λ_Z line and the original data are shown for reference only.

Slopes	Intercepts
$\lambda_1 = 3.4\ hr^{-1}$	$C_1 = 24$ mg/liter
$\lambda_2 = 0.43\ hr^{-1}$	$C_2 = 11$ mg/liter
$\lambda_Z = 0.08\ hr^{-1}$	$C_Z = 14$ mg/liter

In theory, it is possible to have drug disposition requiring more than three exponentials, but there are practical limits on drug detection. The addition of each new phase requires an additional first-order plot in the graphical approach. Deciding how many phases actually exist can be a problem. The data seldom warrant proposing anything more complex than a triexponential rate of decrease in intact drug.

B. Model-Independent Calculations for Pharmacokinetic Parameters

1. Half-Life

a. Basis. The half-life concept is based on the characteristic time course of a monoexponential (first-order) rate process. Equation (2) can be rewritten in terms of the fraction of the concentration remaining to be lost at any time,

$$F = \frac{C}{C(0)} = e^{-\lambda_Z t} \tag{7}$$

where $0 \leq F \leq 1$. Once a given value is chosen for F, the time required to observe a decrease in $C(0)$ to that value is fixed, since λ_Z is constant. The logarithm of Eq. (7) is

$$\ln F = \ln\left(\frac{C}{C(0)}\right) = -\lambda_Z t \tag{8}$$

which is easily solved for the time t_F to reach any fraction,

$$t_F = -\frac{\ln F}{\lambda_Z} \tag{9}$$

The half-life associated with Eq. (7) is the time required for $C(0)$ to decrease to one-half of its value. In this case $F = 0.50$ and, since $-\ln 0.5 = 0.693$, Eq. (9) becomes

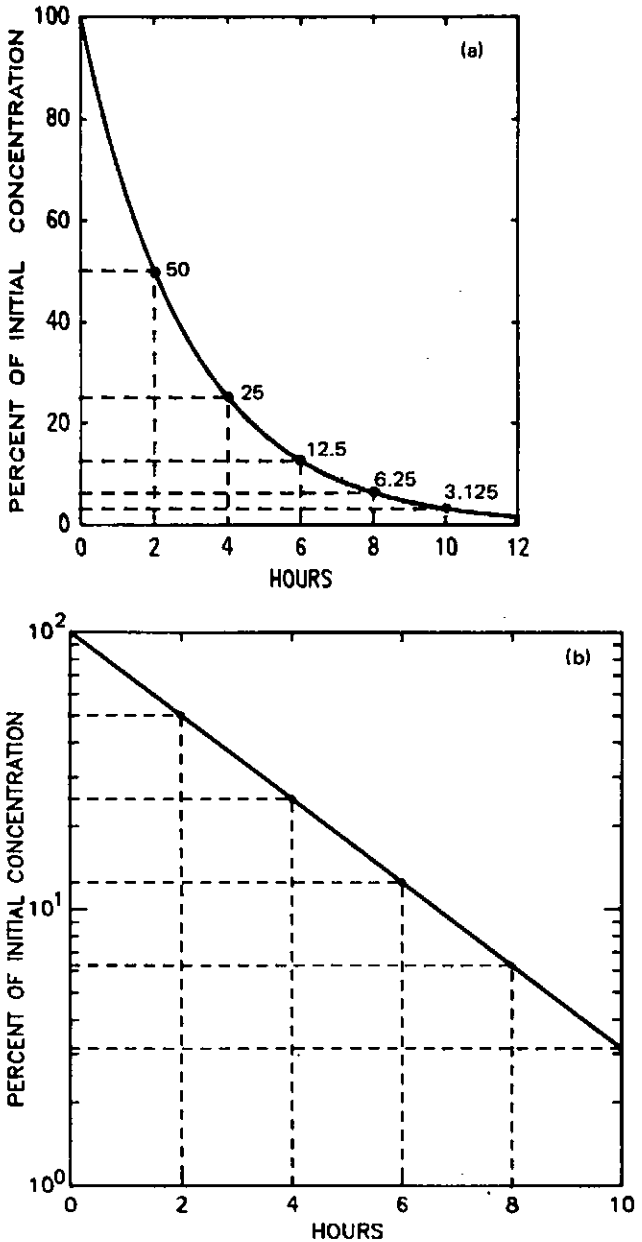


Fig. 3(a) Monoexponential (first-order) decrease in concentration with time where the half-life value is 2 hr. The concentration is reduced by a half during each subsequent 2-hr period. (b) A semilogarithmic (first-order) plot of the data in Fig. 3a. During each half-life period of 2 hr a 50% decrease in concentration takes place.

$$t_{1/2} = \frac{0.693}{\lambda_Z} \tag{10}$$

For a first-order process, the $t_{1/2}$ value is independent of the starting concentration, since $F = 0.5C(0)/C(0)$ and $C(0)$ cancels out of the expression. This is illustrated in Fig. 3. In this example the $t_{1/2}$ value is 2 hr. Table 4, taken from Fig. 3, shows that a constant $t_{1/2}$ estimate of 2 hr. will be obtained independent of the starting time. It will require one half-life for the concentration at any selected time to decrease by a half.

In Fig. 3 the plasma concentration, and therefore the amount remaining in the body, decreases exponentially with time in accordance with Eq. (2). The corresponding data describing the amount A_e excreted from the body, therefore increase with time and exponentially approach a final value $A_e(\infty)$ (Fig. 4). This plot of amount excreted is the mirror image of Fig. 3a, which reflects the amount remaining to be excreted (ARE). The data for the amount excreted can be converted to reflect the amount remaining through the relationship, $ARE = A_e(\infty) - A_e$. The ARE values would therefore be described by an expression similar to Eq. (2) which may be written

$$ARE = [A_e(\infty)]e^{-\lambda_Z t} \tag{11}$$

The log-linear transform yields $\ln(ARE) = \ln[A_e(\infty)] - \lambda_Z t$. Thus a semilogarithmic plot of ARE versus t would be linear with negative slope λ_Z and intercept $A_e(\infty)$. This is illustrated by Fig. 4b, which is identical to Fig. 3b, since both are based on an initial value of 100% with a 2-hr half-life. Figure 4 shows that the half-life estimate is based upon the amount remaining to be excreted; therefore, to analyze the data in Fig. 4a, the half-life must be defined as the time required for the ARE to decrease to one-half of its initial value. For example, at time zero $ARE = A_e(\infty) - A_e = 100\%$. One half of

Table 4 Percent Remaining at the End of Every Half-Life in Fig. 3, Where $t_{1/2}$ = 2 hr

Number of half-lives	Time (hr)	Percent remaining
0	0	100
1	2	50
2	4	25
3	6	12.5
4	8	6.25
5	10	3.125

this value is 50%, which corresponds to $A_e = 50\%$ and requires 2 hr to achieve. If one starts at 2 hr, $ARE = 100 - 50 = 50\%$ and one-half of this value is 25%. Then $A_e = 100 - ARE = 75\%$, which occurs at 4 hr, giving a half-life estimate of $t_{1/2} = 4 - 2 = 2$ hr. If the starting point is 4 hr, then one-half $ARE = 25/2 = 12.5\%$ and $A_e = 100 - 12.5 = 87.5\%$, which occurs at 6 hr. Therefore $t_{1/2} = 6 - 4 = 2$ hr. As previously shown in Table 4, the $t_{1/2}$ estimate will be independent of the starting time and concentration.

The half-life for a zero-order process is not like that of a first-order process. Applying the definition of half-life to the zero-order equation yields

$$0.5C(0) = C(0) - k_0 t_{1/2} \tag{12}$$

which arranges to

$$t_{1/2} = \frac{0.5C(0)}{k_0} \tag{13}$$

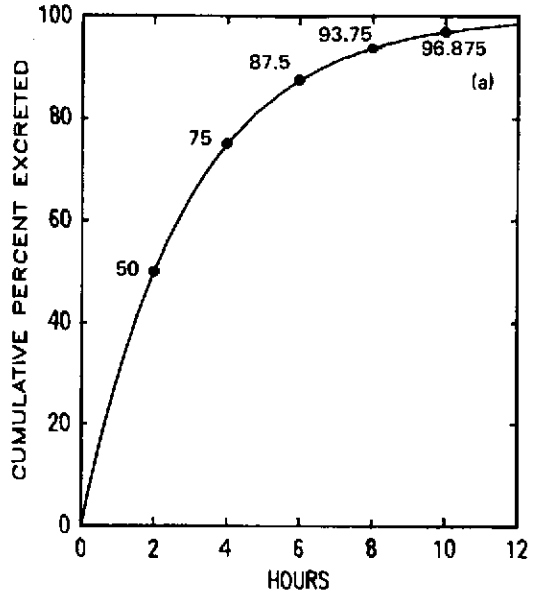
From Eq. (13) we see that $t_{1/2}$ *is dependent* on the initial concentration. In fact, the larger the initial concentration, the longer the half-life. This difference can be used to distinguish between a zero- and a first-order process by varying the initial concentration (or dose) and measuring its resulting half-life.

Sample Problem 4

Two different drugs are administered to a patient by intravenous injection on six different occasions. The time between each test is 1 week. In each case the time to eliminate one-half the dose is determined. Assuming that the disposition kinetics of the drug remain constant in the patient, answer the questions using the data shown in Table 5.

Table 5 Changes in Half-Life with Increasing Dose

Dose (mg)	Drug 1 $t_{1/2}$ (hr)	Drug 2 $t_{1/2}$ (hr)
40	10	3.47
60	15	3.47
80	20	3.47



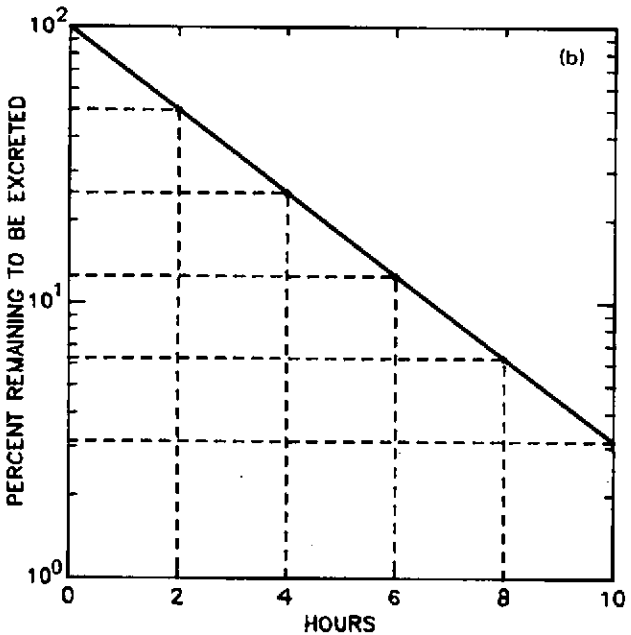


Fig. 4(a) The cumulative percent excreted for monoexponential loss of a drug with a 2-hr half-life. During each subsequent half-life period one-half of the amount remaining is excreted. The cumulative amount excreted at the end of each half-life is indicated on the curve. (b) A first-order plot of the data in Fig. 4a based on the amount remaining to be excreted (*ARE*) as defined by Eq. (11). The *ARE* value (shown as a percentage of the initial value) decreases by a half during each half-life period of 2 hr.

(a) What is the order of the elimination rate process of drug 1 and drug 2?
Solution: Drug 2 has a constant $t_{1/2}$, whereas the increase in $t_{1/2}$ for drug 1 is proportional to the dose. Therefore drug 1 must be eliminated by a zero-order process, and drug 2 by a first-order process.

(b) What is the value of the rate constant and the units of that constant for drug 1 and drug 2?
Solution: Solving Eq. (13) for k_0, using the dose D as the initial amount, we have

$$k_0 = \frac{0.5D}{t_{1/2}}$$

At a dose of 40 mg drug 1 has a $t_{1/2}$ of 10 hr, so that

$$k_0 = \frac{(0.5)(40\text{ mg})}{10\text{ hr}} = 2\text{ mg/hr}$$

The other doses give the same answer. The rate constant for drug 2 may be calculated from Eq. (10):

$$\lambda_Z = \frac{0.693}{t_{1/2}} = 0.2\text{ hr}^{-1}$$

(c) If a dose of 10 mg were given to the same patient, how much time would be required to eliminate 2 mg in the case of drug 1 and drug 2?
Solution: For drug 1

$$t = \frac{C(0) - C}{k_0}$$

$$= \frac{10\text{ mg} - 8\text{ mg}}{2\text{ mg/hr}} = 1\text{ hr}$$

In the case of drug 2 Eq. (9) may be solved for t to give

$$t = -\frac{\ln F}{\lambda_Z} = -\frac{\ln 0.8}{0.20\text{ hr}^{-1}} = 1.1\text{ hr}$$

Sample Problem 5

Figure 5 represents the concentration of drug on each side of a dialysis membrane which allows first-order equilibration of the drug between the donor and acceptor sides, as illustrated in Scheme II. Estimate the $t_{1/2}$ values from each plot and compare the values.

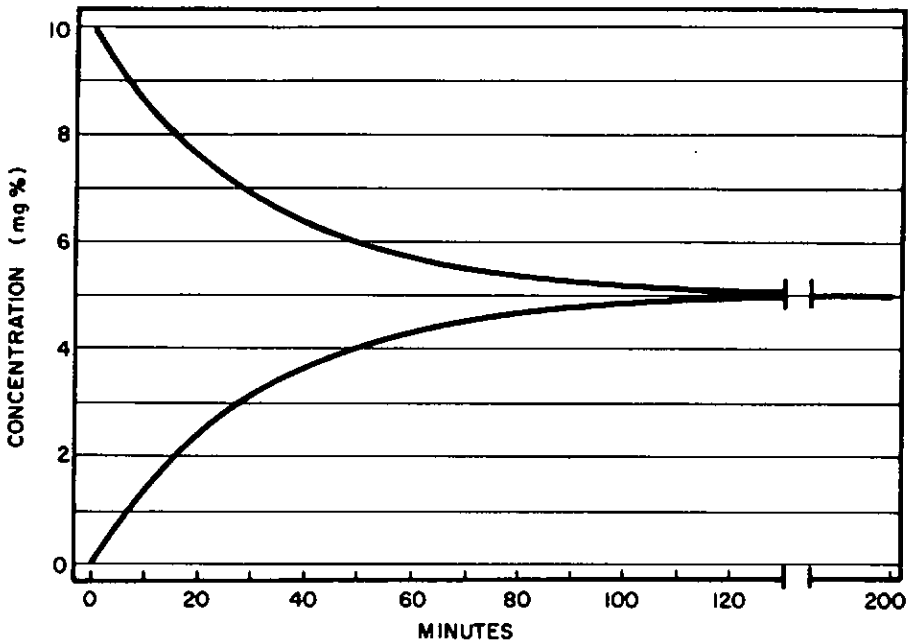
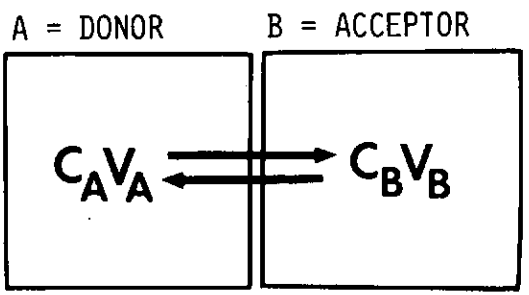


Fig. 5 The concentration of drug in the donor compartment, C_A, and that in the acceptor compartment, C_B, during a first-order rate process for drug transfer.



Scheme II

Solution: In each case the $t_{1/2}$ value is the time required for one-half of the remaining observed change to occur. The C_A value decreases from 10 to 5 for a total change of 5 mg %. The $t_{1/2}$ is therefore the time required to decrease by 2.5%, which corresponds to the time to reach 7.5%, or 21 min. The C_B data increase from 0 to 5 mg % so that one-half of the total change is 2.5 mg %, which occurs at 21 min. The $t_{1/2}$ value is a characteristic of the

rate process and may be estimated from either C_A or C_B. It is also independent of the starting time. If the time corresponding to C_A = 8 mg % and C_B = 2 mg % is chosen, then the total observed change remaining to occur is 8 − 5 = 3 mg %, or 5 − 2 = 3 mg %. One-half of the change is therefore 1.5 mg %. It requires 21 min for C_A to decrease from 8 to 6.5 mg % or for C_B to increase from 2 to 3.5 mg %. Thus this problem illustrates that a first-order half-life value may be estimated from data for either loss of accumulation of drug and is independent of the initial concentration.

b. Biological Half-Life The biological half-life (or elimination half-life) is the time necessary to decrease the drug concentration assayed in plasma, blood, or serum by a half during the "elimination" phase. The elimination phase is the terminal phase when

$$C \cong C_Z e^{-\lambda_Z t} \tag{14}$$

Thus $t_{1/2} = 0.693/\lambda_Z$ represents a single definition for biological half-life independent of the value of n in Eq. (1). The $t_{1/2}$ values for mono-, bi-, and triexponential disposition are all defined by Eq. (10). The $t_{1/2}$ values are properties of the drugs which are subject (to various degrees) to biological variation. The mean biological half-lives for a large number of drugs have been published [4–6]. Some typical examples are found in Table 6.

Practice Problem 3
What are the values for the biological half-lives of the drugs in the following problems in this chapter?

(a) Sample Problem 1
(b) Practice Problem 1
(c) Sample Problem 2
(d) Practice Problem 2
(e) Sample Problem 3

Answers: (a) 0.9 hr; (b) 1.1 hr; (c) the apparent $t_{1/2}$ is 1.8 hr but this is not the $t_{1/2}$ for ticarcillin, given in part (b) as 1.1 hr, since plasma concentrations are prolonged by the probenecid; (d) 3.9 hr; (e) 8.7 hr.

Practice Problem 4
A 100-mg dose of drug was administered to a 70-kg patient by intravenous injection. All of the patient's urine was collected by catheterization over a period of 36 hr. The urine samples were assayed for drug content (Table 7).

Table 6 Selected Drugs and Their Average Biological Half-Life Values in Normal Adults[a]

Drug	Approximate half-life (hr)
Acetaminophen	2–3
Amobarbital	24
Aprobarbital	12–36
Aspirin	0.25
Cephalosporins (in general)	0.5–2.0
Chloramphenicol	2–3
Chlordiazepoxide	6–24
Chlorphentermine	35–45
Diazepam	24–48
Digitoxin	96–192
Digoxin	32–45
Ephedrine	3–4
Ethambutal	4
Ethosuximide	56
Griseofulvin	13–24
Hydrocortisone	1–2
Indomethacin	1–2
Insulin	0.1–0.2
Lincomycin	5
Meprobamate	8–14
Morphine	2–3
Nalidixic Acid	1–2
Nitrofurantoin	0.3
Penicillins (in general)	0.5–1.0
Phenobarbital	2–4
Phenytoin	20–30
Salicylamide	1
Sulfisoxazole	5–6
Tetracyclines (in general)	10–20
Theophylline	3–20
Vancomycin	4–6
R-Warfarin	36–90
S-Warfarin	24–43

[a]From Refs. 4–6.

Table 7 Intact Drug Appearing in the Urine as a Function of Time Following Intravenous Injection

Time (hr)	Cumulative amount of drug in urine (mg)	Time (hr)	Cumulative amount of drug in urine (mg)
0	0	12	91
1	18	14	94
2	33	16	96
3	45	18	97
4	55	20	98
5	64	24	100
6	70	30	100
8	80	36	100
10	87		

(a) What is the value for λ_Z?
Answer: $\lambda_Z = 0.20\ \text{hr}^{-1}$.

(b) Compare the value calculated for $t_{1/2}$ from λ_Z to that chosen directly from a plot of A_r versus t.
Answer: The time at which the cumulative amount in the urine is 50 mg is approximately 3.5 hr as estimated from the plot. The calculated value is $t_{1/2} = 0.693/(0.2\ \text{hr}^{-1}) = 3.47$ hr.

2. Area Under the Curve Values

The area under the time course for concentration in plasma from time zero to infinity following a single dose is called the area under the curve (AUC). The AUC values are not pharmacokinetic parameters in themselves but are used to calculate clearance, volume of distribution, bioavailable dose, relative bioavailability, and so on. The AUC values can be calculated from the equation describing the curve or directly from a plot of C versus t on coordinate graph paper without the corresponding equation.

a. Calculating AUC Values from Time Course Equations for C. For an equation of the form

$$C = C_i e^{-\lambda_i t} \tag{15}$$

the area under the curve for C versus t from $t = 0$ to $t = \infty$ is the integral

$$AUC = \int_0^\infty C\,dt \tag{16}$$

which integrates to

$$AUC = \left[\frac{C_i e^{-\lambda_i t}}{-\lambda_i}\right]_0^\infty = \frac{C_i(1 - 0)}{\lambda_i} \tag{17}$$

or

$$AUC = \frac{C_i}{\lambda_i} \tag{18}$$

Therefore, for any monoexponential (or first-order) rate process, the AUC is the intercept of the semilogarithmic plot over the positive value for the slope. When the time course for C is made up of more than one exponential of the form given in Eq. (15), then the AUC is the sum of the parts. If an exponential term is negative in sign, its area would be subtracted. For each of the drug disposition equations discussed, the AUC values would be defined as follows. For *monoexponential* drug loss, described by Eq. (2).

$$AUC = \frac{C(0)}{\lambda_Z} \tag{19}$$

For *biexponential* drug loss, described by Eq. (4),

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_Z}{\lambda_Z} \tag{20}$$

For *triexponential* drug loss, described by Eq. (6)

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} + \frac{C_Z}{\lambda_Z} \tag{21}$$

Since the AUC value for Eq. (15) from 0 to ∞ is C_i/λ_i, it follows that the value from t to ∞ is C_i/λ_i, where t is a specified time. This is useful when data are truncated and one of the graphical methods (discussed next) is used. If the last data point is not sufficiently close to $C \cong 0$ but the data are

definitely in the terminal phase (λ_Z line), the remaining area can be estimated from

$$AUC(t\text{–}\infty) = \frac{C_t}{\lambda_Z} \tag{22}$$

This extrapolated area can then be added to the graphical estimate for $AUC(0\text{–}t)$ to provide the total area AUC.

Note that the AUC values are areas and the units must therefore be y axis $\times$ x axis, just as the area of a room will have the units of square feet. For example, if the C-versus-t plot has units of μg/ml versus hr, then AUC units are μg hr/ml.

Practice Problem 5

What is the AUC value in each of the following problems in this chapter?

(a) Sample Problem 1
(b) Practice Problem 1
(c) Sample Problem 2
(d) Practice Problem 2
(e) Sample Problem 3
(f) What is the relative contribution of each phase to the total AUC in parts (c), (d), and (e)?

Answers: (a) 95 μg hr/ml; (b) 603 μg hr/ml; (c) 485 μg hr/ml; (d) 48 μg hr/ml; (e) 208 mg hr/liter.

(f)

Part	1	2	Z
(c)	10%		90%
(d)	5%		95%
(e)	3.4%	12.3%	84.3%

The percentage contribution of each phase to the total AUC can provide an estimate of the relative significance of that phase in clinical pharmacokinetic calculations. Theophylline [part (d) above] is often described by monoexponential disposition by ignoring the λ_1 phase for simplicity. Although this is an approximation, that phase contributes only 5% to the total AUC, thus minimizing the error. Bis-hydroxycoumarin [part (e)] is an example wherein the terminal phase of the triexponential time course represents 84% of the total AUC, in contrast to the aminoglycosides (discussed later), which typically have three phases comprising ~20, ~70, and ~10% for λ_1, λ_2, and λ_Z, respectively.

When calculating renal clearance values, it is frequently necessary to determine the area under the plasma concentration time course during the period corresponding to the urinary collection interval. For example, suppose that a rapid intravenous injection resulted in monoexponential disposition and that the urine was collected at time t. The area under the plasma curve from 0 to t, $AUC(0\text{–}t)$, is the difference between the total area AUC and $AUC(t\text{–}\infty)$:

$$AUC - AUC(t\text{–}\infty) = \frac{C(0)}{\lambda_Z} - \frac{C(t)}{\lambda_Z} \tag{23}$$

Since $C(t) = C(0)e^{-\lambda_Z t}$, this may be written

$$AUC(0\text{–}t) = (1 - e^{-\lambda_Z t}) \frac{C(0)}{\lambda_Z} \tag{24}$$

Since $e^{-\lambda_Z t}$ is the fraction of $C(0)$ remaining at time t, this may be rewritten

$$AUC(0\text{–}t) = [\text{fraction of } C(0) \text{ lost}] \frac{C(0)}{\lambda_Z} \tag{25}$$

This same approach would be applied to each exponential in Eq. (1). For example, Eq. (20) would be rewritten

$$AUC(0\text{–}t) = (1 - e^{-\lambda_1 t}) \frac{C_1}{\lambda_1} + (1 - e^{-\lambda_Z t}) \frac{C_Z}{\lambda_Z} \tag{26}$$

When urinary excretion is collected between times t_1 and t_2, the same principle applies. For a monoexponential case $AUC(t_1\text{–}t_2)$ is the difference between $[C(t_1)]/\lambda_Z = AUC(t_1\text{–}\infty)$ and $[C(t_2)]/\lambda_Z = AUC(t_2\text{–}\infty)$, which may be written

$$AUC(t_1\text{–}t_2) = (e^{-\lambda_Z t_1} - e^{-\lambda_Z t_2}) \frac{C(0)}{\lambda_Z} \tag{27}$$

This would be applied to each exponential in the equation. The generalized expression for the contribution of each exponential would be

$$AUC(t_1\text{–}t_2) = (e^{-\lambda_i t_1} - e^{-\lambda_i t_2}) \frac{C_i}{\lambda_i} \tag{28}$$

where $e^{-\lambda_i t_i} = 1$ when $t_1 = 0$. The section on renal clearance will demonstrate the use of $AUC(0\text{–}t)$ and $AUC(t_1\text{–}t_2)$ values.

b. Calculating AUC Values Graphically. The advantage of using a graphical method is that the AUC calculation does not depend upon an equation to adequately describe the data. The areas are estimated directly from a C-versus-t plot (not semilogarithmic). These estimates may be obtained in several ways. One is by use of a planimeter; another involves plotting data for C versus t and then cutting out the curve and weighing it. The area may be calculated from the weight of the paper by determining the weight of a known area of paper cut as a square or a rectangle.

In a third method the area under a curve is estimated by dividing the curve into sections that approximate a series of trapezoids with a triangle at the end, as shown in Fig. 6. The individual areas of the trapezoids, $a(c + d)/2$, and of the triangle, $ab/2$, are summed to obtain the area under the curve. It is necessary to have the same units of concentration and time in order to

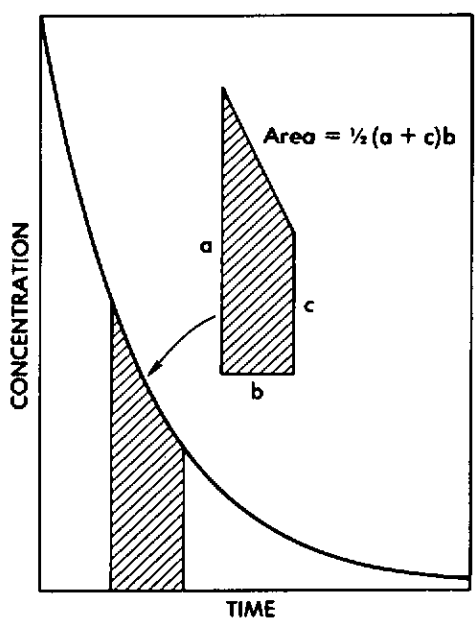


Fig. 6 The total area under a curve (AUC) may be estimated by summing the areas for a series of trapezoids, as illustrated here for one segment.

compare different curves. However, it is not necessary to have the same scale on the graph paper. The curves can be drawn to occupy the maximum amount of space on the graph paper.

Practice Problem 6

(a) Using the trapezoidal rule, estimate the AUC value during the 6-hr data period for ticarcillin in Practice Problem 1 by assuming $C(0) = 370$ μg/ml.
Answer: Approximately 597 μg hr/ml.

(b) The ticarcillin data were truncated at 6 hr, where $C = 9.3$ μg/ml. If the estimate in part (a) is corrected using Eq. (22), how does this corrected estimate compare with the estimate obtained using Eq. (19)?
Answer: $AUC(6\text{–}\infty) = 9.3/0.614 = 15$ μg hr/ml; $AUC_{\text{corrected}} = 597 + 15 = 612$ μg hr/ml; $AUC = C(0)/\lambda_Z = 370/0.614 = 602$ μg hr/ml. The corrected estimate is 1.7% larger than the estimate using Eq. (19).

3. Apparent Volumes

a. Apparent Volume of Distribution. The apparent volume of distribution V_Z of a drug is not literally a volume. It should not be regarded as a particular physiological space within the body. It is somewhat misleadingly described as the volume of body water which would be required to contain the amount of drug in the body if it were uniformly present in the same concentration in which it is in the plasma or blood. However, all regions of the body which contain drug will not have equal concentrations, so any volume calculated utilizing the drug concentration in plasma can be only an *apparent* volume. It is most prudent to avoid all analogies to volumes and define V_Z as a proportionality factor which, when multiplied by the concentration of drug in the plasma, yields the amount of drug present in the body, or

$$A = CV_Z \tag{29}$$

where A represents the total amount of drug in the body and C the concentration of drug in the plasma at some time t in the λ_Z phase.

It has been common practice to associate calculated values for V_Z with known values for the volumes of body water compartments. For example, the average volumes for body water compartments are roughly (in percent vol/wt of body weight) 5% plasma, 20% extracellular fluid, and 70% total body water. The inadequacy of interpreting V_Z values in terms of body "space" will become apparent after studying the limitations of the V_Z calculations themselves. Although the volume is hypothetical, and not real, it

is nonetheless a useful parameter which allows reliable calculations when used properly.

When the kinetics are linear, the area under the curve (AUC) from time zero to infinity will be a linear function of dose. The AUC value following an intravenous injection can be used to calculate V_Z from

$$V_Z = \frac{D_{iv}}{(AUC)\lambda_Z} \tag{30}$$

where D_{iv} is the intravenous dose (amount of drug). This value for V_Z (also called Vd_{area} or Vd_β in the literature) represents the factor which will provide the amount of drug in the body when multiplied by a value for C during the terminal or λ_Z phase in accordance with Eq. (29). For monoexponential disposition the V_Z values will be operative over the entire time course. For a bi- or triexponential it will apply only to the final phase, which occurs after the so-called distribution phases have equilibrated.

Since the AUC for a monoexponential time course is $C(0)/\lambda_Z$, substitution for AUC in Eq. (30) provides $V_Z = D_{iv}/C(0)$. This is called the method of extrapolation and the result is often referred to as Vd_{extrap}. It is important to note that this substitution for AUC is only valid for a monoexponential curve and not for a time course where $n > 1$. This is often overlooked in literature where the extrapolation method was employed to calculate values for bi- or triexponential data. The extrapolation method, when erroneously applied to biexponential loss, is carried out using the calculation D_{iv}/C_Z. Substituting $AUC = C_1/\lambda_1 + C_Z/\lambda_Z$ in Eq. (30) shows that D_{iv}/C_Z overestimates V_Z. Using Eq. (30) in all cases will provide a V_Z estimate that is operative during the λ_Z phase, regardless of the number of exponentials in the concentration time course equation.

Sample Problem 6

A physician wishes to inject sufficient drug to achieve a plasma level equal to 0.10 mg/ml in a patient weighing 70 kg. The apparent volume of distribution for the drug is given as 18% vol/wt. How many milligrams of drug must be injected into the blood in order to have a plasma level of 0.10 mg/ml just after the distribution phase, assuming that 10% of the dose is excreted unchanged by the kidney and no drug is lost via biotransformation during the distribution?

Solution: The apparent volume of distribution is

$$V_Z = 0.18(70 \text{ kg}) = 12.6 \text{ liters}$$

To achieve the desired concentration in the plasma, the amount that must be present in the body after distribution is complete is given by

$$A = CV_Z = (12.6 \text{ liter})(0.10 \text{ g/liter}) = 1.26\text{g}$$

Since 10% of the dose has been lost by this time, the dose given must be

$$D = \frac{A}{0.90} = 1.40 \text{ g}$$

Practice Problem 7

The pharmacokinetic parameters of a new drug are being studied. Concentrations in blood and total amounts eliminated following a 1.4-g intravenous dose were determined with the results shown in Table 8.

(a) What is the apparent volume of distribution as estimated from the blood concentration data only?
Answer: $V_Z = D_{iv}/(AUC)\lambda_Z = (1400 \text{ mg})/(700 \text{ mg hr/liter})(0.0536 \text{ hr}^{-1}) = 37$ liters.

(b) What is the V_Z value estimated from the amount eliminated relative to the dose and blood concentration?
Answer: This must be estimated during the λ_Z phase. At $t \geq 9$ hr, $V_Z = (D_{iv} - A_{el})/C = 37$ liters.

(c) What is the percentage error using the estimate obtained by the extrapolation method?
Answer: $V_Z(\text{extrap}) = D_{iv}/C_Z = (1400 \text{ mg})/(29.5 \text{ mg/liter}) = 48$ liters. The percentage error is 29.7%.

Table 8 Blood and Elimination Data Following a 1.4-g Intravenous Injection

Time (hr)	Blood concentration (mg/liter)	Total amount eliminated (mg)
1.0	80.0	—
2.0	51.0	—
3.0	36.5	—
4.0	29.3	—
5.0	25.0	555
7.0	20.8	—
9.0	18.2	730
12.0	15.5	835
15.0	13.0	920
18.0	11.2	995

Practice Problem 8

What is the apparent volume of distribution for ticarcillin using the data in Practice Problems 6 and 1?

Answer: $V_Z = D_{iv}/(AUC)(\lambda_Z) = (5000 \text{ mg})/(0.614 \text{ hr}^{-1})(602 \text{ mg hr/liter}) = 13.5$ liters. Since disposition is monoexponential, $V_Z = D_{iv}/C(0) = (5000 \text{ mg})/(370 \text{ mg/liter}) = 13.5$ liters.

b. Apparent Volume of the Central Compartment. The apparent volume of the sampled blood pool (central compartment) may be calculated from

$$V_C = D_{iv} / \sum_{i=1}^{n} C_i \tag{31}$$

following a rapid intravenous injection. When $n = 1$, this expression becomes $V_C = D_{iv}/C(0)$, which is identical to the monoexponential estimate for V_Z. In this case drug disposition behaves as though the body were a homogeneous pool with no kinetic distinction between the sampled fluid and the remainder of the body. When $n > 1$, the apparent volume of the sampled compartment can be differentiated from the overall volume of distribution. When $n = 2$.

$$V_C = \frac{D_{iv}}{C_1 + C_Z} \tag{32}$$

When $n = 3$,

$$V_C = \frac{D_{iv}}{C_1 + C_2 + C_Z} \tag{33}$$

Although the blood is the sampled compartment, the V_C is an apparent volume which may equal or exceed the actual blood or plasma volume. The apparent volume will include all tissues, organs, and binding sites which rapidly equilibrate with drug in the blood. Since concentraton is not homogeneous, the value is an *apparent* volume. Although both V_Z and V_C are fictitious volumes, they are operative in describing drug distribution. During the terminal phase the fraction of the body content in the sampled compartment may be estimated from the volume ratios:

$$(\text{fraction in central compartment})_Z = \frac{V_C}{V_Z} \tag{34}$$

Practice Problem 9

Calculte the apparent volume of the sampled compartment in Practice Problems 1–3.

Answer: PP1: $V_C = V_Z = D_{iv}/C(0) = 13.5$ liters. PP2: $V_C = D_{iv}/(C_1 + C_Z)$ = (53 mg)/(12.9 mg/liter) = 4.1 liters. PP3: $V_C = D_{iv}/(C_1 + C_2 + C_Z)$.= (150 mg)/(49 mg/liter) = 3 liters.

c. Steady-State Volume of Distribution. When a drug is introduced into the blood at a constant rate, the plasma concentration will increase until the rate of input is equal to the rate of elimination. The kinetics are described in detail in Sec. III on constant-rate intravenous infusion. When the input and output rates become equal, the plasma concentration remains constant (C^{ss}), and this condition is called the steady state. The amount of drug in the body during the steady state (A^{ss}) may be calculated from

$$A^{ss} = C^{ss}V_{ss} \tag{35}$$

where V_{ss} is the value for the apparent volume of distribution operative during the steady state. For a drug which undergoes monoexponential disposition, only one volume term is in effect, $V_Z = V_{ss} = V_C$. However, when $n > 1$, $V_Z \geq V_{ss} > V_C$. In many cases the value for V_Z is similar to that for V_{ss}. However, the difference may be dramatic. The V_Z/V_{ss} ratios have been found to approach 2 for some penicillins and 6 for some aminoglycosides. Model-independent estimates for V_{ss} assume that all rates are first order and that elimination occurs only from the central compartment. The estimates can be made using the disposition equations or by graphical means. The disposition equations may be employed as follows:

$$V_{ss} = D_{iv}\left(\sum_{i=1}^{n} C_i/\lambda_y^2\right)/\left(\sum_{i=1}^{n} C_i/\lambda_i\right)^2 \tag{36}$$

For example, when $n = 2$,

$$V_{ss} = D_{iv}\left(\frac{C_1}{\lambda_1^2} + \frac{C_Z}{\lambda_Z^2}\right)/\left(\frac{C_1}{\lambda_1} + \frac{C_Z}{\lambda_Z}\right)^2 \tag{37}$$

which may also be written

$$V_{ss} = D_{iv}\left(\frac{C_1}{\lambda_1^2} + \frac{C_Z}{\lambda_Z^2}\right)/(AUC)^2 \tag{38}$$

The value for V_{ss} may also be estimated graphically without describing the data by an equation. In this case

$$V_{ss} = \frac{D_{iv}(AUMC)}{(AUC)^2} \tag{39}$$

where $AUMC$ is the area under the first-moment curve from time 0 to ∞. The first moment curve is a plot of concentration $\times$ time versus time. The trapezoidal rule may be used to estimate $AUMC$ and AUC values.

When a drug is administered by constant-rate intravenous infusion to achieve the steady-state concentration C^{ss}, then V_{ss} may be calculated from

$$V_{ss} = \frac{D_{iv}[1 - AUC(0\text{–}T)]}{(AUC)C^{ss}} \tag{40}$$

where D_{iv} is the total infused dose, T is the infusion time, and AUC is the total area from 0 to ∞.

Practice Problem 10

A 250-mg intravenous dose of amoxicillin was administered to a healthy, 70-kg 28-year-old male. The disposition following administration was described by the equation

$$C = (11.3 \text{ mg/liter})e^{-2.19 \text{ hr}^{-1}t} + (2.83 \text{ mg/liter})e^{-0.398 \text{ hr}^{-1}t}$$

Compare the value for the apparent volume of distribution during the terminal phase λ_Z with that for the steady state, V_{ss}.

Answer: $V_Z = D_{iv}/(AUC)\lambda_Z = 250 \text{ mg}/(12.27 \text{ mg hr/liter})(0.398 \text{ hr}^{-1}) = 51.2$ liters; $V_{ss} = D_{iv}(C_1/\lambda_1^2 + C_2/\lambda_2^2)/AUC^2 = 250(20.22/150.8) = 33.5$ liters. Thus V_Z is 1.5 times larger than V_{ss}.

Practice Problem 11

Compare the values for V_Z and V_{ss} obtained in Practice Problem 2 and Sample Problem 3

Answer: PP2: $V_Z = D_{iv}/(AUC)\lambda_Z = 6.11$ liters. $V_{ss} = (C_1/\lambda_1^2 + C_2/\lambda_2^2)D_{iv}/(AUC)^2 = 5.85$ liters. They are nearly equal, with a difference of only 4%.

SP3: $V_Z = 9.03$ liters; $V_{ss} = 7.83$ liters. Here V_Z is 15% larger than V_{ss}.

4. Clearance

The concept of organ clearance can be visualized using Fig. 7. The drug is introduced as a single dose into the beaker compartment 1, from which it partitions into compartment 2. The solution is simultaneously circulated at

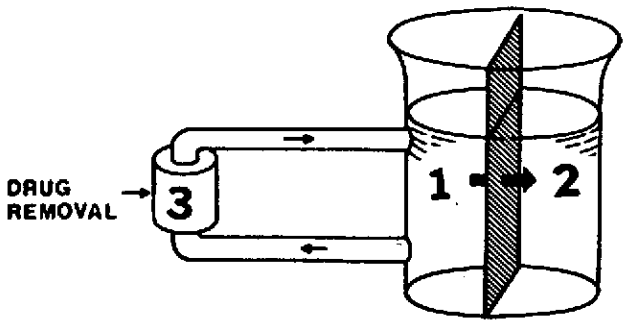
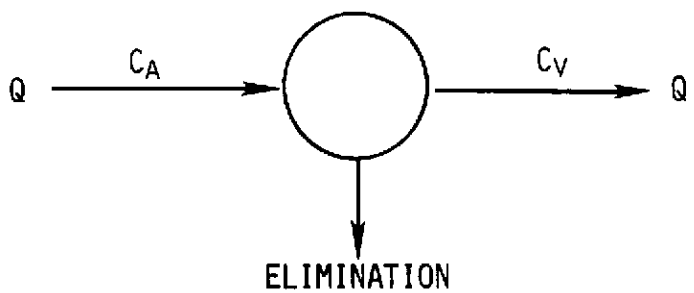


Fig. 7 Organ clearance is illustrated here by the introduction of drug into compartment 1, from which drug distributes into compartment 2. Solution is circulated at a constant rate Q through compartment 3 where drug is removed from a fixed volume per unit time.

a constant rate Q through compartment 3, where removal of drug from the solution represents elimination. This extraction of drug may or may not be complete. The degree to which extraction occurs is reflected by the difference between the concentration C_{in} entering the extracting compartment and that leaving, C_{out}. If drug is completely extracted, then $C_{out} = 0$; if none is extracted, then $C_{out} = C_{in}$. Thus the limits for the concentration leaving compartment 3 are $0 \leq C_{out} \leq C_{in}$.

a. Extraction Ratio. An organ capable of extracting drug may be represented by arterial blood flow into the organ and venous flow out, where Q is the flow rate [Scheme III].



Scheme III

By definition, the extraction ratio E is the fraction of drug extracted by the organ. This may be represented by

$$E = \frac{\text{rate of elimination}}{\text{rate of presentation}} \tag{41}$$

The rate of presentation of drug, in units of mass/time, is given by

$$\text{rate of presentation} = C_A Q \tag{42}$$

Based on mass balance, the rate of elimination may be calculated from the difference between the input and output rates:

$$\text{rate of elimination} = C_A Q - C_V Q \tag{43}$$

Substitution into Eq. (41) gives

$$E = \frac{Q(C_A - C_V)}{QC_A} = \frac{C_A - C_V}{C_A} \tag{44}$$

Thus, if drug is completely extracted, then $C_V = 0$ and $E = 1$. If none is extracted, then $C_A = C_V$ and $E = 0$. Therefore E has the limits $0 \leqslant E \leqslant 1$ and represents the fraction of drug mass which is extracted as blood flows through the organ.

b. Organ Clearance. Clearance is defined as the *volume* of drug apparently cleared per unit time. This may be written as

$$CL = QE \tag{45}$$

where Q is the flow rate and E is the fraction of drug removed. Substituting for E as defined in Eq. (44) gives

$$CL = \frac{Q(C_A - C_V)}{C_A} \tag{46}$$

which, according to Eq. (43), is

$$CL = \frac{\text{rate of elimination}}{\text{concentration presented}} \tag{47}$$

Thus the value for CL (in units of volume/time) may be calculated by dividing the elimination rate (in units of mass/time) by the concentration (in units of mass/volume).

c. Total Body Clearance. The rate of elimination from the body is the sum of all rates and may be expressed as dA_{el}/dt, where A_{el} is the cumulative amount of drug eliminated by all routes at time t. Using Eq. (47), the total body clearance may be expressed as

$$CL = \frac{dA_{el}}{dt}/C \tag{48}$$

The integral of the numerator and denominator with respect to time may be written

$$CL = \int_0^\infty \frac{dA_{el}}{dt}\,dt \Big/ \int_0^\infty C\,dt \tag{49}$$

This numerator represents the total amount of drug eliminated at infinite time, which must also equal the bioavailable dose, fD. The denominator represents the area under the concentration-versus-time curve (AUC). Substitution gives

$$CL = \frac{fD}{AUC} \tag{50}$$

Total body clearance may also be calculated from the product of the volume of distribution and the overall elimination rate constant. During the terminal phase following an intravenous injection the following expression holds:

$$\text{rate of elimination} = C\lambda_Z V_Z \tag{51}$$

Substitution into Eq. (47) yields

$$CL = \lambda_Z V_Z \tag{52}$$

By definition, the following equality exists during the steady state achieved by constant-rate intravenous infusion:

$$(\text{rate of presentation})^{ss} = (\text{rate of elimination})^{ss} \tag{53}$$

Since the rate of presentation is determined by the constant infusion rate R_0, it follows that

$$R_0 = (\text{rate of elimination})^{ss} \tag{54}$$

Substitution into Eq. (47) yields

$$CL = \frac{R_0}{C^{ss}} \tag{55}$$

Furthermore, following repetitive administration of a fixed dose D at a constant interval τ, the steady-state average plasma concentration during each dosage interval is defined as

$$C_{av}^{ss} = \frac{AUC}{\tau} \tag{56}$$

Substitution of $AUC = C_{av}^{ss}\tau$ from Eq. (56) into Eq. (50) provides

$$CL = \frac{fD}{C_{av}^{ss}\tau} \tag{57}$$

Since D/τ is the dosing rate (e.g., in mg/hr), this may be written

$$CL = \frac{f(\text{dosing rate})}{C_{av}^{ss}} \tag{58}$$

which can be regarded as the general case, which includes Eq. (55) as a specific example wherein the dosing rate is $R_0, f = 1$, and the concentration is C^{ss}. In summary, total body clearance is usually calculated from Eq. (50), (52), or (58), depending upon the pharmacokinetic information available.

Practice Problem 12

Figure 8 shows the blood concentration time course (in units of mg/liter) during an intravenous infusion at a constant rate R_0 of 1.68 g/hr. What is the total body clearance value (in ml/min) for this drug?

Answer: $CL = R_0/C^{ss}$ = (1680 mg/liter)/(80 mg/liter) = 21 liter/hr = 350 ml/min.

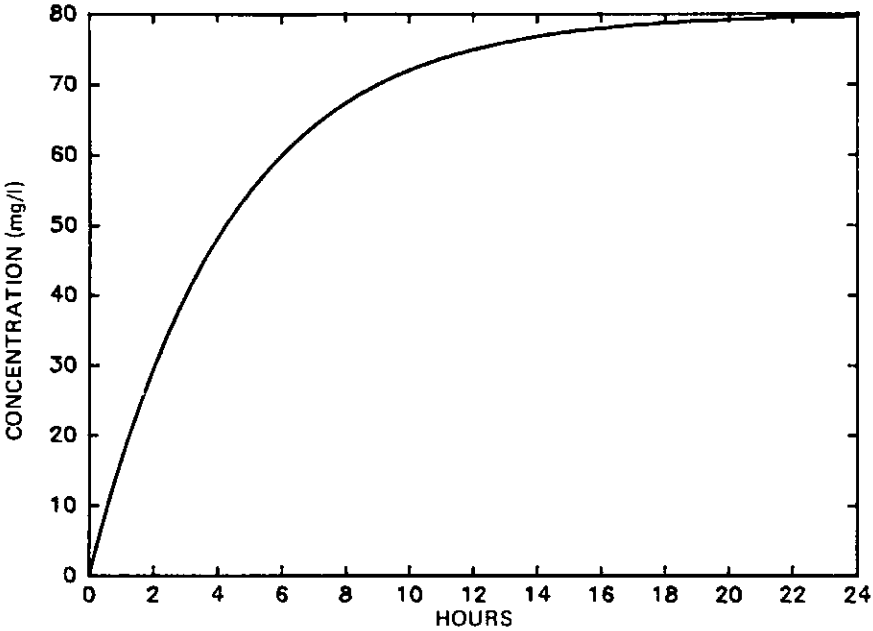


Fig. 8 Concentration of drug in blood during a constant-rate intravenous infusion (1.68 g/hr) which approaches a steady-state value C^{ss} at 24 hr.

d. Renal Clearance. The renal excretion rate of drug may be defined as

$$\text{rate of appearance in urine} = \frac{dA_e}{dt} \tag{59}$$

where A_e is the cumulative amount of unchanged drug excreted into the urine at time t. Substituting into the general equation for organ clearance, Eq. (47), renal clearance may be defined as

$$CL_R = \frac{\text{rate of appearance in urine}}{C_{av}} \tag{60}$$

which is equivalent to

$$CL_R = \frac{\Delta A_e}{\Delta t} \Big/ \frac{AUC}{\Delta t} \tag{61}$$

or

$$CL_R = \frac{A_e}{AUC(0\text{–}t)} \tag{62}$$

where A_e and $AUC(0\text{–}t)$ both represent the values during the same period of time. For the case where the time period is 0 to ∞, the equation becomes

$$CL_R = \frac{A_e(\infty)}{AUC} = \frac{f_e(fD)}{AUC} \tag{63}$$

or

$$CL_R = \frac{\text{total urinary recovery}}{AUC} \tag{64}$$

where f_e is the fraction of the bioavailable dose fD excreted intact in the urine.

A common approximation of Eq. (60) is

$$CL_R = \frac{\Delta A_e}{\Delta t}/C_{MID} \tag{65}$$

where the plasma concentration value C_{MID} at the midpoint of the time interval, $t_{MID} = (t_1 + t_2)/2$, is used in place of $C_{av} = AUC/\Delta t$. This will provide similar results when the urinary collection interval is less than twice the apparent half-life for loss of C during the time period t_1 to t_2. The shorter the urinary collection time interval, the closer the estimated value from C_{MID} will be to the correct value based on C_{av} [Eq. 62)].

Practice Problem 13

Serum concentrations of carbenicillin following a 1-g intravenous injection to an adult subject are given in Sample Problem 1. The subject voided once at 3.5 hr, and analysis showed the urine to contain 677 mg of carbenicillin.

(a) Compare the value for carbenicillin renal clearance calculated from C_{av} to that approximated using C_{MID}.
Answer: Using C_{av}, we have

$$CL_R = \frac{A_e}{AUC(0\text{–}3.5 \text{ hr})}$$

$$AUC(0\text{–}3.5\ hr) = \frac{C_Z}{\lambda_Z} - \frac{C(3.5)}{\lambda_Z} = 95.2 - 6.76 = 88.4 \text{ mg hr/liter}$$

$$CL_R = (677 \text{ mg})/(88.4 \text{ mg hr/liter}) = 7.66 \text{ liters/hr}$$

$$= 128 \text{ ml/min}$$

Using C_{MID}, we have

$$CL_R \simeq \frac{\Delta A_e}{\Delta t}/C_{MID}$$

$$C_{MID} = 72e^{-0.75(1.75)} = 19.4 \text{ mg/liter}$$

$$CL_R \simeq (193 \text{ mg/hr})/(19.4 \text{ mg/liter}) = 9.97 \text{ liters/hr} = 166 \text{ ml/min}$$

Therefore the estimated value is 30% larger than the true value. This is because the urinary collection period of 3.5 hr is roughly 3.8 times the half-life and the C_{MID} approximation is reliable over approximately two half-lives.

(b) Calculate the total body clearance and use the clearance values to estimate the fraction excreted in the urine, f_e.
Answer: $Cl = fD/AUC = (1000 \text{ mg})/(95.2 \text{ mg hr/liter}) = 10.5$ liters/hr = 175 ml/min; $f_e = CL_R/CL = 128/175 = 0.73$.

Practice Problem 14

A 2-g intravenous dose of ceftizoxime was administered to an adult subject. The subject was required to drink two glassfuls of water at the time of administration and again 2 hr later to induce urination. The subject voided at 2.5 and at 7.0 hr. The urine at 2.5 hr contained 1.44 g of ceftizoxime, and that at 7.0 hr contained 490 mg. The serum concentration (in mg/liter) as a function of time was found to be described by the biexponential equation

$$C = 64.8\, e^{-3.5 \text{ hr}^{-1}t} + 83.8e^{-0.47 \text{ hr}^{-1}t}$$

(a) What are the calculated renal clearance values for each of the two urinary excretion time intervals?
Answer: $CL_R = A_e'/AUC'$, where A_e' and AUC' both represent the specified time period.

At 2.5 hr: $AUC(0 - 2.5 \text{ hr}) = 141.7$ mg/liter
$CL_R = 1440/141.7 = 10.1$ liters/hr = 168 ml/min

At 7.0 hr: $AUC(2.5 - 7 \text{ hr}) = 48.5$ mg/liter
$CL_R = 490/48.5 = 10.1$ liters/hr = 168 ml/min

(b) What are the total body clearance and f_e values?
Answer: $CL = fD/AUC = 2000/196.8 = 10.16$ liters/hr = 169 ml/min; $f_e \simeq 1$, since $CL = CL_R$.

e. Renal Function Tests Based on Clearance. The determination of the degree of renal function is an important aspect in the individualization of dosage regimens for those drugs which exhibit significant excretion by the kidneys.

Furthermore, recognition of the mechanism by which renal excretion takes place provides a basis for understanding certain pharmacokinetic drug interactions which are reviewed in Chap. 8 on clinical pharmacokinetics.

The functional unit of the kidney is the nephron, which is composed of glomerulus and tubule. Urinary excretion of drug may involve any or all of the following processes:

1. Glomerular filtration
2. Active tubular secretion
3. Passive tubular resorption

The relative importance of these processes in the elimination of a drug may be indicated to some extent by the drug's observed renal clearance value. Before discussing these clearance values, it is instructive to consider some tests employed for kidney function. The substances creatinine, inulin, mannitol, and sodium thiosulfate are *filtered by the glomeruli* and completely excreted in the urine. The term *filtration* is perhaps misleading. Actually, water and all the dissolved material from plasma pass through the glomeruli, leaving behind only proteins and colloidal material. The filtrate is thus of the same concentration as the blood itself; however, most of the water is resorbed from the tubules. The normal clearance value for such substances is equal to the glomerular filtration rate (*GFR*), which is roughly 125–130 ml/min.

Creatinine is a by-product of muscle metabolism and its production is influenced by the creatinine content of the body, the body surface area, and the lean body weight. Patients with a muscle-wasting disease, as well as geriatric patients, often experience decreased creatinine production. Creatinine clearance values CL_{CR} are often useful for individualizing a dosage regimen for a patient with renal impairment. Normal creatinine clearance values are in the range of 100–150 ml/min for men and 95–125 ml/min for women. Since the clearance value varies with body size, it is often normalized by multiplying the observed clearance value by the fraction 1.73/(patient's surface area, in m^2). The value 1.73 corresponds to a normal clearance value of 120 ml/min. In cases of severe renal impairment clearance values are often included as part of the patient's profile, whereas less serious cases more commonly include creatinine serum levels obtained as part of blood analyses. Clearance values may be estimated from serum creatinine concentrations [7], as illustrated in Chap. 8 on clinical pharmacokinetics.

Low-threshold substances, such as urea, uric acid, and certain phosphates and sulfates, are *filtered by the glomeruli* and *passively resorbed* in the tubules. Since this resorption is passive, there is a concentration gradient involved

and thus some of the substance will be excreted. The amount will be less than in the previous case. Normally the clearance value for urea is less than 75 (approximately 73). The urea is not injected for this test, since it is already present in the blood.

High-threshold substances, such as glucose, ascorbic acid, Na, K, Ca, Mg, P, Cl, and S, are normally completely resorbed by *active tubular resorption.* The glucose clearance test thus has a normal value of zero (Table 9).

The reabsorption of water is regulated by hormonally controlled adjustments in the permeability of the collecting duct. Typically, during 1 min, 130 ml of normal glomerular filtrate is obtained; of this, approximately 106 ml of water is reabsorbed in the proximal tubule, 9 ml in the thin segment, and 14 ml in the distal tubule. Thus the body has conserved all but 1 ml of the 130 ml of filtrate. This concentrating effect also provides the concentration gradient for the passive reabsorption of drugs.

Iodopyracet, sodium o-iodohippurate, and p-aminohippuric acid (PAH) are completely removed from the plasma in a single passage through the kidneys when present in blood in low concentrations. They are *actively secreted by the tubules,* in addition to glomerular filtration. Thus, as long as the capacity of the active system is not exceeded, the blood will be completely cleared. The clearance value is therefore equivalent to the plasma flow in the kidneys. When a dose of PAH sufficient to provide a 1 mg % plasma level is administered, the clearance value is equal to the plasma flow. The normal rate for men is 654 ± 163 ml/min and that for women is 592 ± 153 ml/min. However, a dose providing 50 mg % is capable of saturating the capacity-limited active

Table 9 Amounts of Substances in the Glomerular Filtrate and Recovered in the Urine at a GFR of 130 ml/min

	Amount filtered	Amount recovered in urine
Urea	46 g	20–35 g
Uric acid	7.2 g	0.1–2 g
Creatinine	1.2 g	1.2–1.5 g
Glucose	180 g	—
Albumin	36 g	—
Sodium	600 g	4–6 g
Chloride	640 g	6–9 g
Potassium	7.2 g	2.5–3.5 g
Inorganic phosphate	5.6 g	1–5 g
Water	180 liters	1.5 liters

tubular secretion. The clearance value obtained will therefore decrease. Although the clearance value is less at the dose which is above saturation, tubular secretion is nevertheless operating at maximum capacity. Thus the value at the 50-mg % dose can be used as a measure of overall kidney function, since it will reflect tubular secretion at maximum capacity plus glomerular filtration. Independent analysis of GFR and conversion to mass allows calculation of tubular excretory mass by difference.

Thus the renal clearance value for a drug is a first approximation of how the kidney is excreting that particular drug. In general, a value near 130 ml/min would indicate *glomerular filtration,* a value greater than 130 ml/min would indicate both *filtration* and *secretion,* and a value of less than 130 would indicate *passive resorption.* It should be noted here that this is only a first approximation, since combinations can give clearance values which are misleading. However, if a value is large, such as the case of CL_R = 650 ml/min, there is no doubt that active secretion is involved. Since this is an active transport system, it will be subject to all of the properties previously discussed under Michaelis–Menten kinetics. We have already discussed the *saturation* of the system at high doses of PAH. This same principle can be responsible for a change in the apparent kinetic order of elimination and thus the apparent half-life. At low doses filtration and secretion will be apparent first-order. However, if secretion becomes saturated because of a large dose, then elimination will be the sum of apparent zero-order secretion and first-order filtration. Thus the effect of dose on the $t_{1/2}$ will depend upon the relative contribution of secretion to the overall elimination process.

If secretion is saturated, the rate cannot increase further with increased dose. The filtration rate, however, can increase, since it is a function of plasma concentration. Thus, at sufficiently high plasma concentrations, the elimination rate may again become apparent first order if the primary component of the elimination process becomes filtration. Similarly, a dose which was just sufficient to saturate the secretion process would result in mixed kinetics only until the plasma level decreases to the point where the elimination system is no longer saturated. At that time it would return to a first-order process.

This active secretion will also be subject to *competition*; that is, two drugs which are sufficiently similar to be secreted by the same active process will enter into competition for the available enzymes. It is important to realize that any drug with a large clearance value, indicating active secretion, is potentially capable of competing with other actively secreted drugs. The coadministration of two actively secreted drugs can, in effect, increase the apparent $t_{1/2}$ for both drugs, since the total available sites for transfer are decreased in number. This could result in the accumulation of drug and untoward effects from an otherwise normal dosage regimen, as discussed in Chap. 8 on clinical pharmacokinetics.

Competition for tubular secretion has been put to therapeutic usage. The compound probenecid is actively secreted and is thus capable of competitively inhibiting the tubular secretion of other acidic compounds which are excreted by this route. It has therefore been employed as an adjuvant in penicillin therapy, where it inhibits penicillin tubular secretion and thus increases the duration of the antibiotic; for example, compare the $t_{1/2}$ values in Practice Problem 1 and Sample Problem 2. Probenicid also inhibits excretion (renal or hepatic) of such agents as p-aminosalicylic acid (PAS), p-aminohippuric acid (PAH), phenolsulfonphthalein (PSP), pantothenic acid, 17-ketosteroids, sodium iodomethamate, and sulfobromophthalein (BSP). The PSP excretion test may be used to determine the adequacy of probenecid blood levels for penicillin therapy. The PSP renal clearance is reduced to about one-fifth the normal value when probenecid levels are sufficient to inhibit penicillin secretion. Probenecid also inhibits the tubular resorption of urate. Thus serum uric acid levels are decreased, making probenecid useful in treating gout and gouty arthritis.

Substances which undergo passive resorption in the tubules will be subject to the principles previously discussed under passive transport. The tubular resorption of drugs is predominantly by passive diffusion of the uncharged species. Accordingly, resorption will be a function of the pH of the urine and the pK_a of the drug. For example, the $t_{1/2}$ of salicylic acid may be increased by acidifying the urine with NH_4CL and thus enhancing the passive resorption of undissociated salicyclic acid. Conversely, alkalinization of the urine with sodium bicarbonate will decrease the $t_{1/2}$ of salicylic acid by increasing the salicylate concentration and thus decreasing the passive resorption. This latter approach has been employed to treat cases of salicylate poisoning. Similar results have been demonstrated upon adjustment of the pH of the urine during sulfonamide excretion, where the $t_{1/2}$ was shortened from 11 to 4 hr upon alkalinization of the urine.

The use of infusion to study renal clearance has several advantages. The excretion rate and plasma concentration can be maintained constant during the steady state. A minor clearance route may be detected by comparing urinary drug output with infusion input during steady state, whereas a minor elimination route might be overlooked in a single-dose study. Examining clearance at several steady-state blood levels allows the detection of capacity-limited processes.

Sample Problem 7

A patient is given 1000 ml of water followed by 200 ml every 30 min until completion of the test. Inulin is administered intravenously 2 hr after the first intake of water and 1 hr later the bladder is emptied and the urine

discarded. Then urine and blood samples are collected hourly for 2 hr and analyzed for inulin: At the end of the first hour the urine contained 1.32 g and after the second hour the urine contained 1.79 g. The plasma concentration at the midpoint was 0.2 mg/ml. What is the estimate of the GFR?
Solution: The average excretion rate is (1555 mg/hr)/(60 min/hr) = 26 mg/min; $CL_R = \Delta A_e/\Delta t)C_{MID}$ = (26 mg/min)/(0.2 mg/ml) = 130 ml/min = GFR.

Sample Problem 8
Assume that PAH is infused at a constant rate to provide a steady-state plasma concentration of 2 mg per 100 ml. During the steady state 390 mg of PAH is excreted in the urine during a 30-min interval.

(a) Calculate the renal clearance value for PAH.
Solution: $CL_R = (\Delta A_e/\Delta t)/C^{ss}$ = (13 mg/min)/(0.02 mg/ml) = 650 ml/min.

(b) What is the renal plasma flow and why?
Solution: PAH is actively secreted. At low doses, such as this one, the capacity of the system is not exceeded, so the blood is completely cleared. Therefore plasma flow equals the clearance value, or 650 ml/min.

(c) Would you expect this value to change at a PAH plasma level of 50 mg per 100 ml? How would it change and why?
Solution: At this concentration the capacity-limited system would be expected to be saturated. In this case CL_R will decrease, since the rate of excretion will be lower relative to the plasma concentration than it was in part (b).

Practice Problem 15
(a) A table of data is presented below for six hypothetical drugs. Assuming that no biotransformation is involved, rank the drugs in order of decreasing $t_{1/2}$.

Drug	V_Z (liters)	CL_R (ml/min)
A	50	130
B	50	40
C	50	700
D	15	700
E	50	1
F	70,000	1

Answer: F > E > B > A > C > D.

(b) Compare each of the drugs with drug A. In each case choose one or more of the following reasons as probable explanations for the difference in elimination rates:

a. renal tubular resorption
b. renal tubular secretion
c. low V_Z
d. extensive tissue binding
e. poor absorption
f. decreased glomerular filtration

Answer:

Drug	Reason
B	a, f
C	b
D	c, b
E	a, possibly f
F	a, d, possibly f

f. Nonrenal Clearance. The difference between total body clearance of drug from plasma (CL) and renal clearance (CL_R) is called nonrenal clearance (CL_{NR}). Nonrenal clearance represents the sum of all other routes of drug elimination, including metabolism, excretion via the skin or lungs, and biliary excretion. If metabolism represents the only alternate route to renal excretion, then nonrenal clearance will equal metabolic clearance (CL_{MET}). Metabolism occurs in several organs and tissues throughout the body, notably the liver, lungs, kidneys, gut wall, and intestinal tract. In general, the liver represents the primary organ for metabolism, and when it is known to be responsible for nonrenal elimination, the clearance value may be called the hepatic clearance (CL_H). In all cases of linear kinetics the clearance values are additive:

$$CL = CL_R + CL_{NR} \tag{66}$$

III. CONSTANT-RATE INTRAVENOUS INFUSION

A. The Drug Concentration Time Course

A constant-rate intravenous infusion delivers a fixed amount of drug per unit time directly into the bloodstream. This represents a zero-order rate process. This type of administration is most commonly employed with anti-infective

agents (such as antibiotics), heparin, lidocaine, procaine, pentobarbital, thiamylal, methoxyhexital, nutrients, electrolytes, vitamins, anticancer agents, steroids, and several other drugs. This discussion will be limited to the drug plasma concentration time course following a single constant-rate infusion. Multiple-dosage regimens of constant-rate infusions are discussed in Chap. 6 on dosage regimens.

1. Accumulation of Drug in the Body

A plasma concentration time course during and after drug administration by constant-rate intravenous infusion is illustrated in Fig. 9. When a parenteral drug solution is continuously presented to the bloodstream at a constant rate, the concentration of drug in the plasma and the total amount in the body will initially increase until a constant level is maintained. The resultant time-independent constant drug concentration in the plasma is called the steady-state concentration and given the symbol C^{ss}. The C^{ss} value desired for optimum therapy can be achieved by employing the appropriate infusion rate, which can be calculated using the total body clearance of the drug.

Why does this increase in plasma drug concentration occur? During this period of accumulation the rate of drug input to the body (R_0, in units of amount/time) exceeds the rate R_d of drug elimination, where

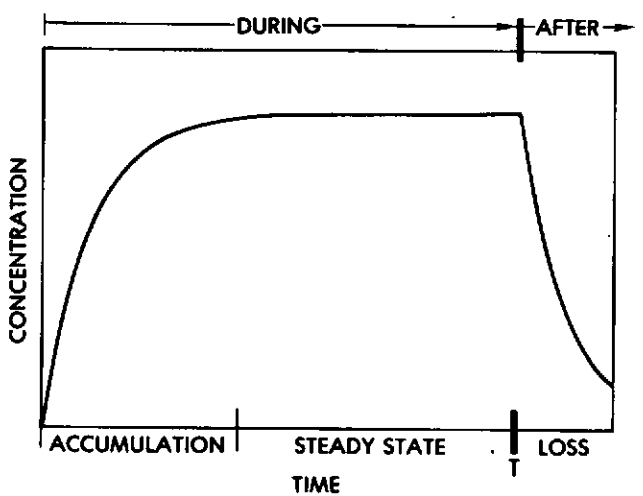


Fig. 9 The three phases of a plasma concentration time course resulting from a constant-rate intravenous infusion with a duration equal to T.

$$R_{el} = C(CL) \tag{67}$$

Since the concentration in plasma, C, is small, $R_0 > R_{el}$. Therefore when $C < C^{ss}$, then

$$R_0 > C(CL) \tag{68}$$

and

$$\text{rate in} > \text{rate out} \tag{69}$$

This represents the accumulation phase, wherein the amount of drug in the body (and thus the concentration in plasma) increases with time.

2. Steady State

During the accumulation period the amount in the body increases until $C \approx$ constant $= C^{ss}$ and the rate of elimination becomes equal to the rate of infusion:

$$\text{rate in} = \text{rate out} \tag{70}$$

which may be expressed as

$$R_0 = R_{el}^{ss} = C^{ss}(CL) \tag{71}$$

The steady-state concentration may be calculated from the infusion rate and the drug clearance value by rearranging Eq. (71) to give

$$C^{ss} = \frac{R_0}{CL} \tag{72}$$

3. Loss of Body Drug Content

When the infusion has stopped, rate in $= R_0 = 0$. Since only rate out $= R_{el} = C(CL)$ is in effect, the body content of drug decreases owing to elimination. The duration of the infusion is the time T required to deliver the total dose, which may be calculated from

$$T = \frac{D}{\mathrm{R_0}} \tag{73}$$

where D is the total amount of drug delivered by the infusion.

B. Concentration Time Course Equations for Constant-Rate Infusions

1. During the Infusion ($t \leq T$)

a. Monoexponential Drug Disposition. During the constant-rate intravenous infusion of a monoexponential disposition drug, the concentration of drug in plasma as a function of time t may be described by

$$C = \frac{R_0}{CL}(1 - e^{-\lambda_Z t}) \tag{74}$$

where $t \leq T$. Since $C^{ss} = R_0/CL$, substitution provides

$$C = C^{ss}(1 - e^{-\lambda_Z t}) \tag{75}$$

This equation applies only while the infusion is occurring. In Fig. 9 it would describe the period of increase and the steady state. It would also apply to the period of increase when the infusion is stopped before C^{ss} is achieved. The time applicability is $0 \leq t \leq T$, which includes the calculation of the concentration at the instant the infusion is stopped, $t = T$.

b. Biexponential Drug Disposition. During the constant-rate intravenous infusion of a biexponential disposition drug, the concentration in plasma as a function of time t may be described by

$$C = \frac{C_1}{\lambda_1 T}(1 - e^{-\lambda_1 t}) + \frac{C_Z}{\lambda_Z T}(1 - e^{-\lambda_Z t}) \tag{76}$$

where $t \leq T$. The values C_1 and C_Z are the observed coefficients to the two exponential terms when the drug is administered by rapid intravenous administration and the concentration time course is biexponential. As in Eqs. (74) and (75), Eq. (76) may also be employed up to and including the time when the infusion is stopped, $0 \leq t \leq T$.

Since $T = D/R_0$, Eq. (76) may also be written as

$$C = \frac{C_1 R_0}{\lambda_1 D}(1 - e^{-\lambda_1 t}) + \frac{C_Z R_0}{\lambda_Z D}(1 - e^{-\lambda_Z t}) \tag{77}$$

2. After the Infusion ($t > T$)

When the infusion has stopped, only the disposition kinetics remain in effect and the loss of drug from the body will be described by the number of

exponential terms normally required for that drug. The initial plasma concentration, marking the beginning of the decay phase, may be calculated from the equation which applies during the infusion by setting $t = T$ to calculate $C(T)$, the concentration at the instant of termination of drug input. This may or may not be equal to C^{ss}, depending on the length of time of the infusion.

a. Monoexponential Drug Disposition. At the end of the infusion, then $t = T = D/R_0$, the concentration may be defined as $C = C(T)$. During the final phase, shown as the period of decrease in Fig. 9, the decreasing concentration will be described by a monoexponential equation with an initial value $C(T)$ and an initial time T. This postinfusion time may be measured as $t_{pi} = t - T$ to provide a disposition equation which is similar to that following a rapid intravenous injection,

$$C = C(T)e^{-\lambda_z t_{pi}} \tag{78}$$

When the infusion has been continued to steady state before termination, then $C(T) = C^{ss}$ and

$$C = C^{ss}e^{-\lambda_z t_{pi}} \tag{79}$$

Equation (78) applies to monoexponential disposition independent of the length of time of the infusion. The steady state may or may not have been achieved. The initial concentration $C(T)$ may be calculated by setting $t = T$ in Eq. (75) to obtain

$$C(T) = C^{ss}\,(1 - e^{-\lambda_z T}) \tag{80}$$

which may also be written in the same form as Eq. (74) by substituting R_0/CL for C^{ss}.

Equation (78) is a simple equation in the familiar style used to describe the time course following a rapid intravenous injection when $C = C(0)e^{-\lambda_z t}$. The postinfusion equation is often written by substituting for $C(T)$ in Eq. (78) using Eq. (80) to obtain

$$C = C^{ss}(1 - e^{-\lambda_z T})e^{-\lambda_z t_{pi}} \tag{81}$$

This is equivalent to Eq. (78), but its more complex appearance tends to hide the fact that it is a similar phenomenon to monoexponential disposition with an initial value of $C(T)$. Substitution of R_0/CL for C^{ss} provides an equivalent form of this equation.

b. Biexponential Drug Disposition. When a constant-rate infusion of a biexponential disposition drug is stopped, the plasma drug concentration decreases in accordance with

$$C = F_1C(T)e^{-\lambda_1 t_{pi}} + F_2C(T)e^{-\lambda_2 t_{pi}} \tag{82}$$

where F is the fraction of $C(T)$ which is associated with each disposition constant. The values for $F_1C(T)$ and $F_2C(T)$ represent the intercepts obtained by feathering the postinfusion concentration data, where C is a function of $t_{pi} = t - T$.

The value for $C(T)$ can be calculated from Eq. (76) by substituting T for t to obtain

$$C(T) = \frac{C_1}{\lambda_1 T}(1 - e^{-\lambda_1 T}) + \frac{C_2}{\lambda_2 T}(1 - e^{-\lambda_2 T}) \tag{83}$$

where C_1 and C_2 are the coefficients to the exponential terms when drug is administered by rapid intravenous administration. Equation (82) can also be written in terms of the C_1 and C_2 coefficients observed following rapid intravenous administration:

$$C = \frac{C_1(1 - e^{-\lambda_1 T})e^{-\lambda_1 t_{pi}}}{\lambda_1 T} + \frac{C_2(1 - e^{-\lambda_2 T})e^{-\lambda_2 t_{pi}}}{\lambda_2 T} \tag{84}$$

where $F_1C(T) = (1 - e^{-\lambda_1 T})C_1/\lambda_1 T$, and $F_2C(T) = (1 - e^{-\lambda_2 T})C_2/\lambda_2 T$.

If the steady state has been attained before the infusion is stopped, then $1 - e^{-\lambda_1 T}$ and $1 - e^{-\lambda_2 T}$ in Eq. (84) both approach unity.

C. Calculations for Clinical Use of Constant-Rate Intravenous Infusions

Constant-rate intravenous infusions may be used to prolong the duration of action or avoid problems arising from rapid intravenous injections. In the latter case short-term constant-rate infusions may be repeated at fixed time intervals. The calculations for repetitive administration of short-term intravenous infusions are presented in Chap. 6 on dosage regimens. The following calculations apply to the maintenance of steady-state drug plasma concentrations over an extended period of time using a single intravenous infusion.

1. Recommended Infusion Rate

The rate of infusion required to provide a desired steady-state concentration may be calculated on the basis that rate in = rate out during the steady state. Since $R_{el}^{ss} = C^{ss}(CL)$, then $R_0 = R_{el}^{ss}$, and the infusion rate may be calculated from

$$R_0 = C^{ss}(CL) \tag{85}$$

which was given previously as Eq. (71). This may also be written as $R_0 = C^{ss}\lambda_Z V_Z$, since $CL = \lambda_Z V_Z$. Once the desired value for C^{ss} has been chosen, the infusion rate necessary to achieve this value can be calculated from Eq. (85).

2. Onset Time

If it is assumed that the steady-state concentration of drug in plasma represents the desired therapeutic level, then the time to achieve C^{ss} may be regarded as the onset time.

How much time will be required to achieve therapeutic levels? For the purpose of standardizing this text, the onset time will always be defined as

$$\text{onset} = 4t_{1/2} \tag{86}$$

where $t_{1/2} = 0.693/\lambda_Z$. This actually represents the time for achieving 94% of C^{ss} for monoexponential disposition.

a. Monoexponential Disposition. Equation (75) can be written

$$C = C^{ss} - FC^{ss} \tag{87}$$

where $F = e^{-\lambda_Z t}$ is the fraction of the steady-state value remaining to be achieved at time t. Equation (87) provides a simple means to consider the time required for onset of the steady state. According to Eq. (87), $C \simeq C^{ss}$ when $F = e^{-\lambda_Z t}$ approaches zero. This fraction remaining can be expressed in terms of the number n of half-life values. Since $t_{1/2} = 0.693/\lambda_Z$, substituting $nt_{1/2}$ for t provides $F = e^{-n(0.693)}$. Thus, after one half-life, $F = 0.5$ and $C = 0.5C^{ss}$. When $n = 2$, $F = e^{-1.386} = 0.25$ and $C = 0.75C^{ss}$; when $n = 3$, $F = 0.125$ and $C = 0.875C^{ss}$; when $n = 4$, $F = 0.0625$ and $C = 0.937C^{ss}$. Therefore after four half-lives the concentration would be 94% of the steady-state

value. If we look at the question mathematically, $C \simeq C^{ss}$ when t approaches ∞, so that $e^{-\lambda_Z t}$ approaches zero. This mathematical limit is not a practical answer.

However, a useful approach is to select an acceptable compromise. The time course for C during the accumulation period is analogous to that of product in the first-order process. Equation (87) can be rearranged to the form

$$C^{ss} - C = C^{ss}e^{-\lambda_Z t} \tag{88}$$

which, in logarithmic form, is

$$\ln(C^{ss} - C) = \ln C^{ss} - \lambda_Z t \tag{89}$$

Therefore a plot of $C^{ss} - C$ versus time on semilogarithmic paper is linear with $-\text{slope} = \lambda_Z$ and intercept C^{ss}, as shown in Fig. 10. Figure 10 shows that the time for C to reach C^{ss} is dependent on λ_Z (or the biological half-life of the drug, since $t_{1/2} = 0.693/\lambda_Z$). It is not dependent on the rate of

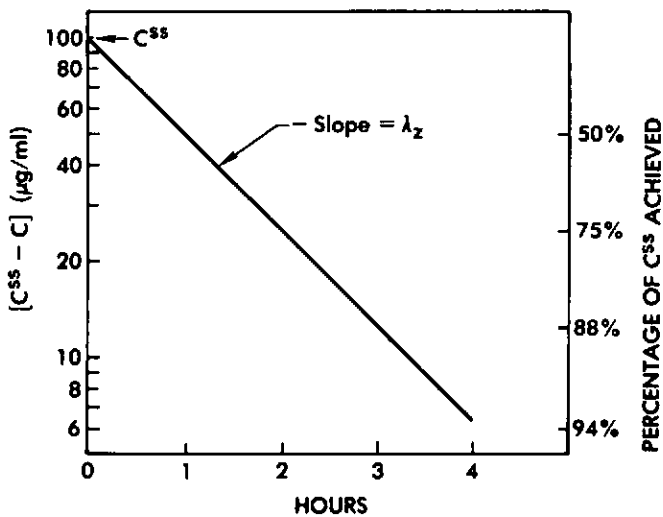


Fig. 10 The y axis on the left corresponds to a semilogarithmic plot based on Eq. (89) for the steady-state onset period during constant-rate intravenous infusion of a monoexponential disposition drug of half-life 1 hr. The y axis on the right shows the approach to C^{ss} as a function of the number of half-lives, where 94% of the steady-state concentration is achieved in four half-lives.

infusion R_0. Examination of Fig. 10 will reveal that the $t_{1/2}$ value is 1 hr. During each hour the concentration change remaining to occur, $C^{ss} - C$, decreases by half. During the first hour the ΔC value decreases from 100 to 50, during the second hour from 50 to 25, and so on.

The scale on the right side of Fig. 10 shows the percentage of C^{ss} achieved at the end of each half-life. These same data are also shown as the accumulation period in Fig. 11. Here it can be seen that the concentration increases by one-half of the remaining ΔC value, $C^{ss} - C$, every half-life, as summarized in Table 10. It requires four half-lives to achieve 94% of C^{ss}, five to achieve 97%, and so on. The choice of a practical criterion is arbitrary. For some research experiments five or six half-lives may be warranted. For the purpose of standardization throughout the text, we will define the onset time based on 94% of the steady-state, as shown by Eq. (86). Thus the onset of steady state will require four times the biological half-life of drug, accepting 94% C^{ss} as sufficiently close.

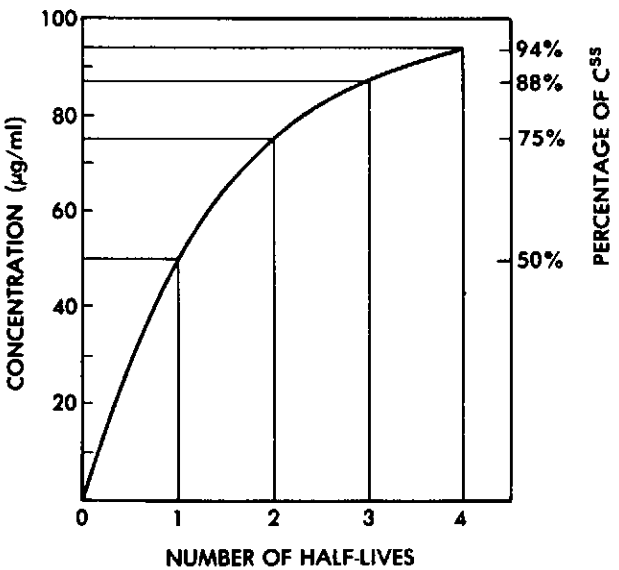


Fig. 11 The accumulation of a monoexponential disposition drug during the onset period of a constant-rate intravenous infusion. During each subsequent half-life the steady-state concentration remaining to be achieved, $\Delta C = C^{ss} - C$, decreases by half. The y axis on the right shows the resultant percentage of C^{ss} achieved at the end of each half-life. The first-order plot for this period is shown in Fig. 10, and Table 10 summarizes the onset behavior as a function of the half-life.

Table 10 Percentage of C^{ss} Achieved as a Function of Time in Half-life Values (Fig. 11)

Half-life number	Percentage of final concentration		Percentage C^{ss} achieved
	Beginning	End	
1	0	50	50
2	50	75	75
3	75	87.5	88
4	87.5	93.75	94
5	93.75	96.875	97
6	96.875	98.438	98

The time to achieve the steady state is therefore a function of the biological half-life of the drug, and not the infusion rate. Equation (86) does not contain the term R_0. What, then, is altered if the rate of infusion is changed? The answer is the steady-state concentration, C^{ss}. The direct relationship between R_0 and C^{ss} is shown in Eq. (85).

b. Biexponential Disposition. During constant-rate intravenous infusion the concentration time course for a biexponential disposition drug is given by Eq. (76). Since $\lambda_1 > \lambda_Z$, $e^{-\lambda_1 t}$ will become insignificant first, so that

$$C \simeq \left(\frac{C_1}{\lambda_1 T}\right) + \left(\frac{C_Z}{\lambda_Z T}\right)(1 - e^{-\lambda_Z t}) \tag{90}$$

The approach to steady state is therefore dependent upon λ_Z. When $e^{-\lambda_Z t}$ is negligible relative to unity, then

$$C^{ss} \simeq \frac{C_1}{\lambda_1 T} + \frac{C_Z}{\lambda_Z T} \tag{91}$$

The approach of $1 - e^{-\lambda_Z t}$ to unity will follow the same pattern as that discussed under Eq. (87). Therefore we again use Eq. (86), wherein the onset time was the time required to reach 94% C^{ss}. This estimate will be based on four times the biological half-life, regardless of the number of exponentials in the disposition equation following rapid injection, since the slowest exponential defines half-life:

$$t_{1/2} = \frac{0.693}{\lambda_Z} \tag{92}$$

As seen by Eq. (76), the terminal exponential for the achievement of steady state is λ_Z. Thus data for the onset period can also be employed to calculate the drug half-life from λ_Z. A semilogarithmic plot of $C^{ss} - C$ versus time will become linear when $e^{-\lambda_1 t}$ becomes insignificant. The negative terminal slope value will be equal to λ_Z.

3. Loading Dose

Assume that a constant-rate intravenous infusion is to be administered at a rate of R_0, which will provide a C^{ss} value that is desired for the therapeutic goal of the drug. Equation (86) will then provide an estimate of the time required to achieve this goal. This onset period may be too long for effective therapy. For example, a drug with a 12-hr half-life would require 2 days. The accumulation period can be reduced to minutes by simultaneously administering a rapid intravenous loading dose DL. Since the infusion itself is capable of maintaining C^{ss}, the steady state can be rapidly achieved by providing a rapid dose sufficient to produce C^{ss}. The infusion rate R_0 would then maintain this level.

For simplicity, the loading dose calculation will be based on monoexponential disposition for problems within this text. Problems associated with the use of this approach for biexponential drugs will be discussed.

For a monoexponential case at steady state,

$$R_{el}^{ss} = R_0 = C^{ss}(CL) = C^{ss}V_Z\lambda_Z \tag{93}$$

and $C^{ss}V_Z$ is the amount of drug in the body at steady state:

$$R_0 = A^{ss}\lambda_Z \tag{94}$$

$$\left(\begin{matrix}\text{amount}\\ \text{in body}\end{matrix}\right)^{ss} \left(\begin{matrix}\text{overall elimination}\\ \text{rate constant}\end{matrix}\right)$$

Thus the dose required to rapidly achieve the steady state amount in the body is

$$DL = A^{ss} = C^{ss}V_Z = \frac{R_0}{\lambda_Z} \tag{95}$$

The loading dose will be calculated from Eq. (95). This may be an overestimate in the case of biexponential disposition, but this will be disregarded in the practice problems.

Unlike the case of monoexponential drug disposition, there are several approaches to calculating loading doses to be used concomitant with the infusion of a drug which exhibits biexponential disposition. In this text the loading dose DL will be calculated from Eq. (95) to be consistent with the monoexponential case. In practice, this approach appears acceptable for many drugs, but a reduced dose may be required for a drug with a low therapeutic index. An alternate approach together with a summary of the problem follows.

When the rapid intravenous loading dose $DL = C^{ss}V_Z$ is administered with the infusion of a monoexponential drug, the C^{ss} value is achieved immediately and maintained by the infusion. In the case of a drug with biexponential disposition the initial concentration will be higher than C^{ss} and will decrease to the desired value with time (Fig. 12, curve A).

In order to avoid exceeding C^{ss}, a loading dose has been suggested which is based on initially providing C^{ss} with the rapid intravenous dose. In this approach the plasma concentration will fall to some minimum below the desired value and then gradually recover (Fig. 12, curve B). The dose required to provide this initial C^{ss} value is $C^{ss}V_c$, where $V_c = D_{iv}/(C_1 + C_2)$. By calculating both estimates, $C^{ss}V_Z$ and $C^{ss}V_c$, one has defined the range for consideration as a rapid intravenous loading dose. While it is impossible to avoid either elevated levels (Fig. 12, curve A) or reduced levels (Fig. 12, curve B), it may be possible to establish a compromise which is more satisfactory for a specific drug. Alternative methods employing consecutive infusions can also be used. These control the onset of steady state but do not eliminate the period of elevated or reduced concentrations.

The total body clearance CL is the same during the steady state as it is during the λ_Z phase following a rapid intravenous injection, $CL = \lambda_Z V_Z$. The rate of infusion to maintain C^{ss} is therefore described by the same equation as that for a monoexponential drug [Eq. (85)]. In spite of this simplicity, the amount of drug A^{ss} in the body during the steady state may be overestimated if V_Z is employed for the calculation. The actual amount in the body during steady state will be less than or approximately equal to $C^{ss}V_Z$. This is due to the fact that the volume of distribution V_{ss} during the steady state will be less than that during the λ_Z phase ($V_{ss} < V_Z$). The amount of drug in the body is correctly estimated from

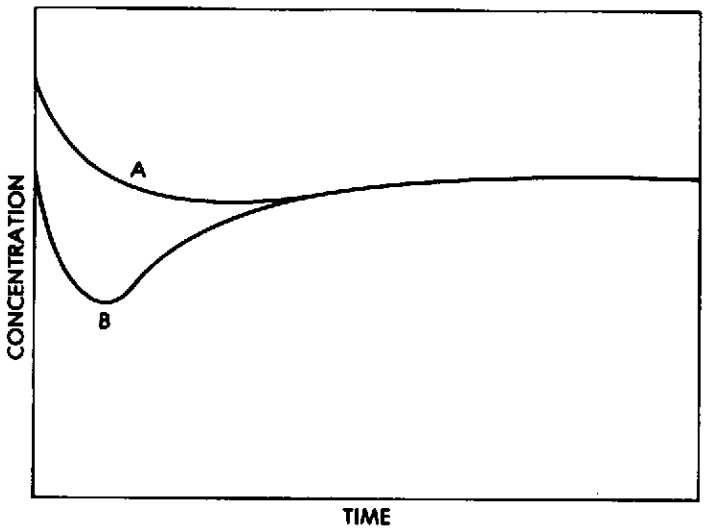


Fig. 12 Plasma concentration time courses resulting from two different rapid intravenous loading doses administered with a constant-rate intravenous infusion of a biexponential disposition drug. The loading dose in curve A is based on the apparent volume of distribution, $DL = C^{ss}V_Z$, and curve B is based on the volume of the central compartment, $DL = C^{ss}V_c$.

$$A^{ss} = C^{ss}V_{ss} \tag{96}$$

where

$$V_{ss} = D_{iv}\frac{C_1/\lambda_1^2 + C_Z/\lambda_Z^2}{(C_1/\lambda_1 + C_Z/\lambda_Z)^2} \tag{97}$$

provided that the elimination of drug occurs solely from the sampled volume (central compartment). A graphical method to estimate V_{ss} is

$$V_{ss} = D_{iv}\frac{AUMC}{(AUC)^2} \tag{98}$$

where $AUMC$ is the area under the first-moment curve constructed by plotting concentration × time versus time. The area may be estimated using the trapezoidal rule in the same manner as it is employed in estimating AUC.

The difference between A^{ss} estimated from V_{ss} and V_Z may be small or large. For many drugs the difference is not significant. There are few practical instances when the A^{ss} value is required; there are none in this text. This omission reflects the lack of a need for the A^{ss} value rather than an effort to circumvent the uncertainty in the volume term.

Practice Problem 16

The $t_{1/2}$ values, distribution volumes, and renal clearance values for patients with normal renal function are given in Table 11.

(a) A physician wishes to maintain a carbenicillin plasma level of 15 mg %. If 1 liter of intravenous solution is to be constantly infused for a 10-hr period, how much carbenicillin must be dissolved in the solution?
(b) If the calibration of the intravenous injection delivers 10 drops/ml, how many drops per minute must be infused into the patient?
(c) How much carbenicillin should be administered in rapid intravenous dose to reduce onset time?
(d) How much more oxacillin would have to be dissolved in 1 liter to be used for intravenous infusion in order to accomplish the same result as defined in part (a) above? How would you explain this difference?
(e) Using calculated values for total body clearance (CL) and reported values for renal clearance (CL_R), calculate the fraction of drug eliminated intact (f_e) in the urine for carbenicillin and ampicillin.
(f) Using the renal clearance values, what estimates might be made regarding the mechanism by which the kidneys eliminate carbenicillin and penicillin G? Which one would you expect to be most affected by probenicid and why?

Table 11 Mean Values of Pharmacokinetic Parameters for Several Antibiotics in Human Subjects

Penicillins	Normal $t_{1/2}$ (hr)	V_Z (liters)	CL_R (ml/min)
Carbenicillin	1.0	9.0	86
Ampicillin	0.8	25	210
Dicloxacillin	0.7	9.4	114
Cloxacillin	0.6	10.8	162
Nafcillin	0.55	27.0	160
Penicillin G	0.5	24	386
Oxacillin	0.4	13.0	190

(g) If each penicillin were infused at a constant rate of 250 mg/hr, which would have the longest onset period to achieve steady state and what time would be required?

Answers: (a) 9.35 g; (b) 17 drops/min; (c) 1.35 g; (d) 24.4 g more; (e) carbenicillin (0.83); ampicillin (0.58); (f) penicillin *G* is actively secreted, since CL_R is significantly larger than 120–130 ml/min; (g) carbenicillin, 4 hr.

Practice Problem 17

Table 12 compares pharmacokinetic parameters of furosemide in patients with normal renal function after administration of spironolactone or probenicid.

(a) What fraction of furosemide is excreted in the urine in a normal subject who is not taking other drugs?

(b) Furosemide product information states, "If the physician elects to use high-dose parenteral therapy, it should be administered as a controlled infusion at a rate not exceeding 4 mg/min. Furosemide injection is a mildly buffered alkaline solution which should not be mixed with acidic solutions of pH below 5.5." What steady-state concentration (in mg %) would result from using this maximum infusion rate in a normal subject who is not taking other drugs?

(c) What constant infusion rate R_0 (in mg/min) is required to provide this same C^{ss} value if the patient is pretreated with spironolactone?

(d) What constant infusion rate R_0 (in mg/min) is required to provide this same C^{ss} value if the patient is pretreated with probenecid?

Table 12 Pharmacokinetic Parameters of Furosemide in Six Normal Subjects Who Received 40 mg of Furosemide Intravenously on Three Occasions Without Pretreatment and After Administration of Either Spironolactone or Probenecid

	Mean		
Parameter	Control	Spironolactone	Probenecid
Volume of distribution (liters)	14.9	11.7	7.7
Half-life (min)	38.4	25.0	54.5
Total clearance (ml/min)	268	322	98
Renal clearance (ml/min)	90	99	20
Nonrenal clearance (ml/min)	178	223	78

Data from Ref. 8.

(e) Why does the infusion rate have to be increased in the case of spironolactone but decreased with probenecid?

(f) In parts (b), (c), and (d), how much time is required to achieve 94% of the C^{ss} value of 1.49 mg %?

Answers: (a) 0.336; (b) C^{ss} = 1.49 mg %; (c) 4.8 mg/min; (d) 1.46 mg/min; (e) since $R_0 = C^{ss}CL$, it is increased with an increase in CL to 322 ml/min (spironolactone) and reduced with decreased CL (98 ml/min for probenecid). It appears that spironolactone increases furosemide metabolism, since CL_{NR} increases from 178 to 223 ml/min, while CL_R is constant. Conversely, probenecid, which is known to be able to compete for active tubular secretion, reduces both CL_R and CL_{NR}. (f) For parts (b), (c), and (d), respectively, the times are 2.6, 1.7, and 3.6 hr.

Practice Problem 18

(a) The data shown in Fig. 13 represent the concentration of drug in the plasma during a constant-rate intravenous infusion. If the volume of distribution is 0.2 liter/kg and the patient weighs 72 kg, what infusion rate was used? (answer in mg/hr)

(b) Assuming that the definition for "onset time" is the time required to achieve 94% of C^{ss}, what is the onset time in hours?

(c) What rapid intravenous loading dose DL would you recommend in order to avoid the onset period? (answer in grams)

Answers: (a) R_0 = 499 mg/hr; (b) onset hour = 16 hr; (c) DL = 2.88 g.

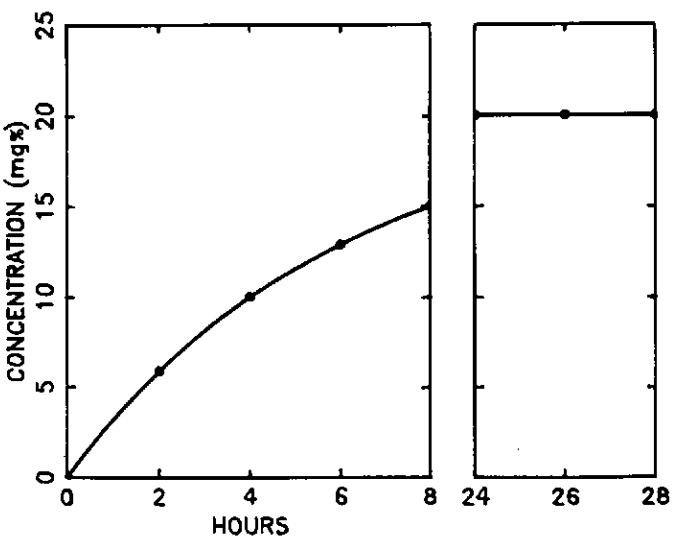


Fig. 13 The concentration time course for drug in plasma during a constant-rate intravenous infusion.

Practice Problem 19

Figure 14 shows a 16-hr segment of the plasma drug concentration (μg/ml) time course resulting from a 24-hr constant-rate intravenous infusion.

(a) If the apparent volume of distribution V_Z for this drug is 39 liters, what is the rate of infusion R_0 (in mg/hr) used to obtain the data in Figure 14?
(b) What is the total body clearance value CL (in ml/min) for this drug?
(c) What is the value for the onset of 94% of the steady-state concentration?
(d) What loading dose DL (in grams) should be given in connection with the infusion in Fig. 14?
(e) If the fraction of the total dose excreted intact in the urine is 0.8, what value for C^{ss} (in μg/ml) would be observed if the infusion rate used in Fig. 14 were applied to a patient in renal shutdown?

Answers: (a) 900 mg/hr; (b) 150 ml/min; (c) 12 hr; (d) 3.9 g; (e) 500 μg/ml.

Practice Problem 20

Assume the results in Table 13 are based upon an analysis of total drug in plasma for a drug that is 50% plasma-protein bound.

(a) A constant-rate (in μg/min) intravenous infusion is to provide a *free* (unbound) plasma concentration of 5 μg/liter in an average subject. What is the calculated infusion rate (in μg/min) based on these data?

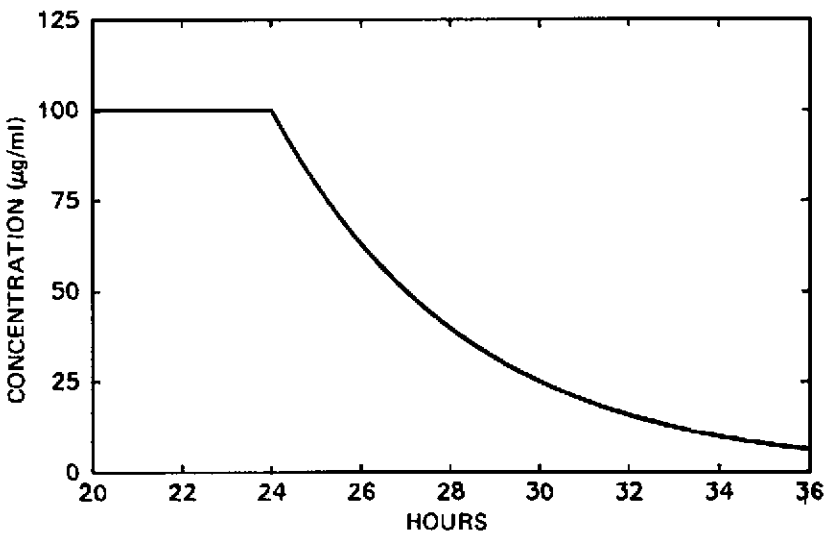


Fig. 14 The plasma drug concentration time course during the 20- to 36-hr time interval of a 24-hr constant-rate intravenous infusion.

Table 13 Estimates of Kinetic Parameters from Total Concentrations After Intravenous Dose of Drug

Subject	V_z (liters)	Clearance (liters/min)	$t_{1/2}$ (hr)
1	298	0.60	5.8
2	367	1.10	3.8
3	417	1.32	3.6
4	473	0.95	5.8
Mean	389	0.99	4.75

(b) Assuming that 94% of C^{ss} is an acceptable clinical endpoint, what is the "onset time" (in hours) for achieving a 5 μg/liter free drug concentration in the average patient?

(c) What intravenous stat loading dose DL (in mg) would you recommend in order to avoid this delayed onset?

(d) Assume that each subject is to be given a constant-rate intravenous infusion which is based on the mean values for the pharmacokinetic parameters. Which subjects would develop the highest steady-state plasma levels and how would these levels relate to the predicted mean?

Answers: (a) 9.9 μg/min; (b) 19 hr; (c) 3.9 mg; (d) subject 1 would have a C^{ss} value 1.7 times that predicted from mean values.

IV. COMPARTMENTAL MODELS AND THEIR LIMITATIONS

A. One-Compartment Open Model, $n = 1$

Equation (1) is used to empirically determine the value for n in drug disposition. Once determined, the rate process may also be categorized as an n-compartment open model (generally $n = 1$, 2, or 3). The term *open* refers to the fact that $C_\infty = 0$, which implies that the system has lost the dose initially introduced.

When $n = 1$, the rate process behaves as though the sampled compartment (blood) were homogeneous with the rest of the body over the entire time course. This is unlikely from an anatomical or physiological point of view. It is important to realize that compartmental analysis is a mathematical treatment. Equation (2) is a mathematical description of the time course for a drug which behaves kinetically as though it were instantaneously distributed throughout the body and eliminated by a first-order process. Thus

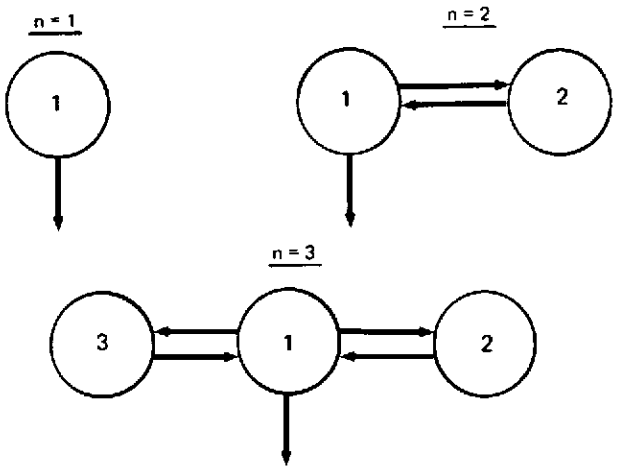


Fig. 15 The commonly employed one- ($n = 1$), two- ($n = 2$), and three- ($n = 3$) compartment models with elimination from the central compartment.

monoexponential disposition is synonymous with *one-compartment open model.* This model is illustrated in Fig. 15. The monoexponential Eq. (2),

$$C = C(0)e^{-\lambda_z t}$$

is an adequate description of the kinetics and as such it allows dependable and useful predictions in spite of the inadequacy of visualizing the body as a homogeneous single compartment. The apparent volume of distribution may be calculated from any simple mass balance equation together with a known plasma concentration value. For example, the value for $C(0)$ may be obtained from Eq. (3) to give

$$V_Z = \frac{D_{iv}}{C(0)} \tag{99}$$

where D_{iv} is the intravenous bolus dose. If the amount of drug eliminated by all routes is known at time t, then

$$V_Z = \frac{A}{C} \tag{100}$$

where A is the drug remaining in the body at time t and C is the corresponding concentration. The volume determined by the area method or the steady-state volume may also be used to represent the apparent volume of distribution. For the case where $n = 1$, all methods will provide similar estimates.

While V_Z is not a real volume, it is an operative value which, when multiplied by C, will estimate the amount of drug in the body.

Since the time course equation for C also reflects the time course for total body content, $A = CV_Z$, the one-compartment open model does not have the speculative aspect that will be discussed next for cases where $n > 1$. There is no practical consequence of describing the disposition as a "one-compartment model" rather than monoexponential disposition; they are equivalent.

However, it is possible, even when $n = 1$, to have a pharmacologically important region or organ wherein the drug time course is independent of the time course for C. This would occur when the organ exhibited such a small capacity for drug that its time course would not influence the pharmacokinetic analysis. It could simultaneously have a strong affinity for a small fraction of the dose so that on subsequent doses it might tend to accumulate drug. This could go on undetected pharmacokinetically but ultimately result in toxicity. Alternatively, if this region were the site of action, the pharmacological response could continue beyond the time during which blood levels were detectable. The compartmental model is therefore mathematically compatible with the kinetic observations but does not claim to represent the physiological situation.

B. Two-Compartment Open Model, $n = 2$

The equations and techniques discussed in Sec. II.A are operationally valid. They allow the prediction and management of plasma drug levels and thus of body content based on empirical descriptions. In this regard they can significantly improve drug therapy. But they do not provide information regarding the time course for either drug or metabolite in a specific organ. The further extension of these equations to compartmental schemes does not alter this limitation. The choice of an appropriate model is generally an arbitrary selection from kinetically equivalent models [9].

If drug disposition is biexponential, then the kinetics require the sampled compartment (compartment 1) to reversibly transfer drug to at least one other compartment (compartment 2), with one or both compartments giving rise to elimination pathways. Assuming linear kinetics, this is the minimum model which will produce data showing biexponential loss from compartment 1. By convention, the model chosen to explain such data is the two-compartment open model with elimination from the central compartment, as illustrated in Fig. 15. In fact, further proliferation of compartments and exit constants could also be made to fit the data, but $n = 2$ does not

justify complicating the model beyond the required two compartments. However, even this restriction still allows the three following possibilities:

$$\leftarrow ① \rightleftarrows ② \tag{101}$$

$$① \rightleftarrows ② \rightarrow \tag{102}$$

$$\leftarrow ① \rightleftarrows ② \rightarrow \tag{103}$$

All three of these models will result in biexponential loss of drug from compartment 1 (C versus time), which can be described by Eq. (4):

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t}$$

which has often been reported in the literature as

$$C = Ae^{-\alpha t} + Be^{-\beta t} \tag{104}$$

The reversible first-order rate process between compartments 1 and 2 is necessary. For example, none of the following will provide biexponential loss from compartment 1:

$$\leftarrow ① \rightarrow \tag{105}$$

$$① \rightarrow ② \rightarrow \tag{106}$$

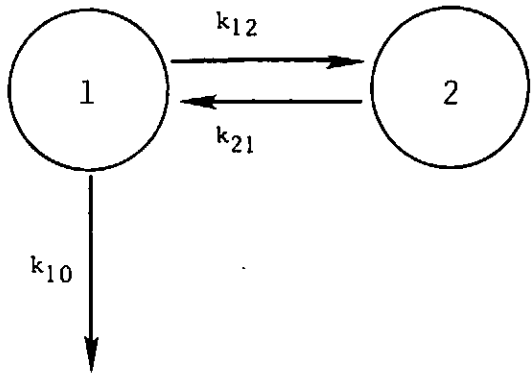
$$\leftarrow ① \rightarrow ② \rightarrow \tag{107}$$

However, the three reversible models (Eqs. (101)–(103) are kinetically equivalent, since in each case the time course for drug in compartment 1 can be described by Eq. (4). Therefore all three are kinetically indistinguishable based on blood level data. The number of rate constants for which numerical values may be estimated is given by

$$R = 2n - 1 \tag{108}$$

where n is the number of compartments with one or more exit constants [10]. Thus in the models of Eqs. (101)–(103), $R = 3$. If the model of Eq. (103) is assumed, the four rate constants cannot be evaluated. The three rate constants can be solved if one of the remaining models is chosen.

The model commonly assumed is that shown in Fig. 15, which is presented in Scheme IV with the three solvable microconstants:



Scheme IV

In the linear two-compartment open model the rates are apparent first order and the rate constants for transfer between central and peripheral compartments are represented by k_{12} and k_{21}, while that for elimination from the central compartment is designated k_{10}. The model allows one to generate the time course for the amount $A2$ in compartment 2 through its relationship to the sampled compartment 1:

$$\frac{k_{12}D_{iv}}{\lambda_1 - \lambda_2}\left(e^{-\lambda_2 t} - e^{-\lambda_1 t}\right) \tag{109}$$

This is illustrated in Fig. 16, where the central compartment is designated as blood and the peripheral as tissue. A semilogarithmic plot of this data is shown in Fig. 17, where the total body content $B + T$ is the sum of $A1 + A2$, where

$$A1 = D_{iv}\left[\left(\frac{k_{21} - \lambda_1}{\lambda_2 - \lambda_1}\right)e^{-\lambda_1 t} - \left(\frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2}\right)e^{-\lambda_2 t}\right] \tag{110}$$

It can be readily observed that the terminal slope λ_2 represents the overall rate constant for loss from the body, since all three plots become parallel. During the terminal phase there exists a constant relationship between $A1$ and $A2$, and the fraction of the total body content f_c in the central compartment may be calculated from

$$f_c = \frac{V_c}{V_2} \tag{111}$$

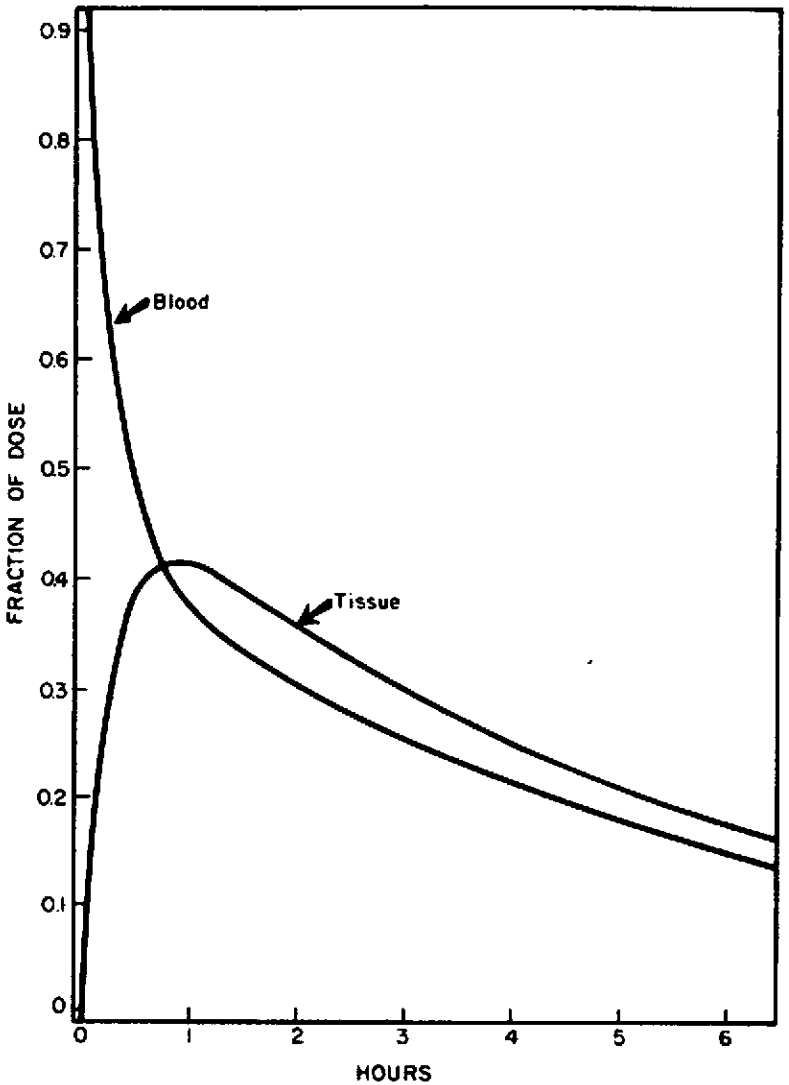


Fig. 16 Time course for drug in compartments 1 (blood) and 2 (tissue) of Scheme IV where the amounts are described by Eq. (110) for $A1$ and by Eq. (109) for $A2$.

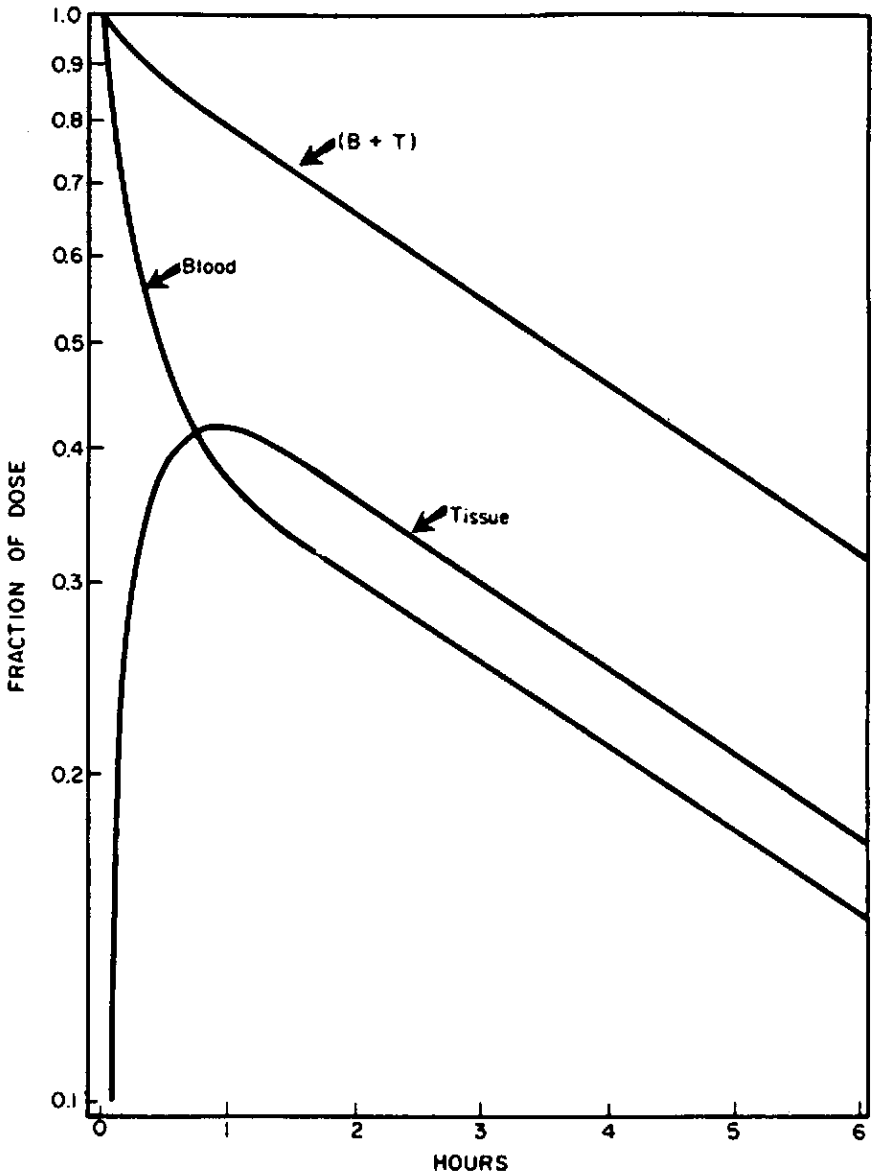


Fig. 17 A semilogarithmic plot of the data in Fig. 16 where the sum of blood and tissues is represented by $B + T$. Since the slope of the line for total body content $B + T$ is the same as that for blood, the elimination rate constant λ_Z, calculated from blood samples represents loss from the body.

Furthermore, clearance is defined as

$$CL = \lambda_Z V_Z = k_{10} V_c \tag{112}$$

and it therefore follows that

$$\lambda_Z = f_c k_{10} \tag{113}$$

Equations (1)–(6) are model independent, since they empirically describe the blood concentration time course with no assumption as to the scheme which best describes the data. In this regard they are operative, not speculative. But, once a single model is chosen out of several possible models, then predictions for compartment 1 (sampled compartment) remain operative but predictions for compartment 2 become speculative. For example, both Eqs. (100) and (101) can be described by Eq. (4), but the definitions for the coefficients will change, as shown in Table 14. In both models Eq. (109) describes the time course for $A2$. However, the value for k_{12} is model dependent. Therefore the time course predicted for $A2$ in Eq. (101) can be significantly different from that predicted for Eq. (102) even though the central compartment time course remains constant, as illustrated in Fig. 18.

In the model commonly employed (Scheme IV), elimination occurs solely from the central compartment (compartment 1). This may be envisioned as

Table 14 Comparison of the Exponential Multipliers (C_1, C_2) and Coefficients (λ_1 λ_Z) When Drug Elimination Is from Compartment 1, Model of Eq. (101), Compared to Elimination from Compartment 2, Model of Eq. (102)

Parameter[a]	Model of Eq. (101)		Model of Eq. (102)
C_1	$\dfrac{\text{dose}\ (k_{21} - \lambda_1)}{V_1(\lambda_Z - \lambda_1)}$		$\dfrac{\text{dose}\ (k_{21} + k_{20} - \lambda_1)}{V_1(\lambda_Z - \lambda_1)}$
C_2	$\dfrac{\text{dose}\ (k_{21} - \lambda_Z)}{V_1(\lambda_1 - \lambda_Z)}$		$\dfrac{\text{dose}\ (k_{21} + k_{20} - \lambda_Z)}{V_1(\lambda_1 - \lambda_Z)}$
$\lambda_1 > \lambda_Z$		$\dfrac{K_1 \pm \sqrt{K_1^2 - 4K_2}}{2}$	
K_1	$k_{12} + k_{21} + k_{10}$		$k_{12} + k_{21} + k_{20}$
K_2	$k_{21}k_{10}$		$k_{12}k_{20}$

[a]Here V_1 is the apparent volume of compartment 1 and k_{ij} is the first-order rate constant from compartment i to j.

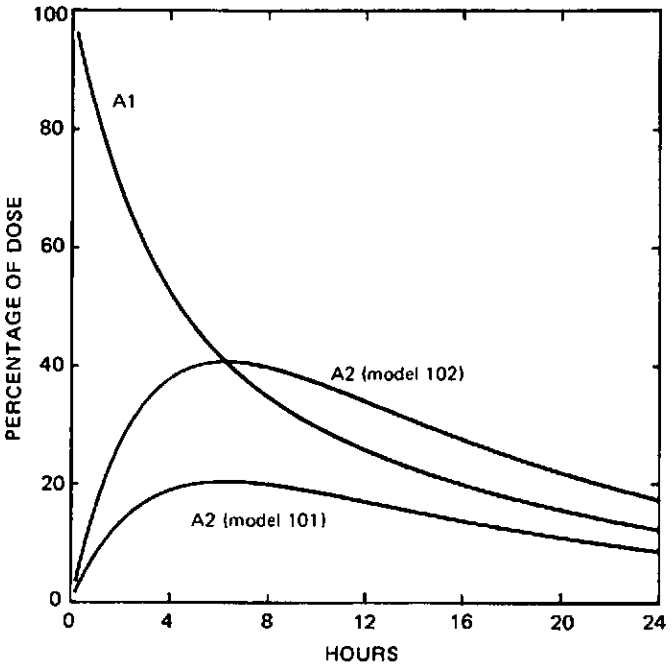


Fig. 18 An illustration of how the model chosen influences the predicted time course for the nonsampled compartment $A2$. The sampled compartment $A1$ is described by a single biexponential equation in both cases, Eq. (4). When elimination occurs from the central compartment [model of Eq. (101)] the time course generated for the peripheral compartment $A2$ will differ from that generated with elimination from the peripheral compartment [model of Eq. (102)]

the blood being cleared of drug by excretion and/or metabolism as it passes through the kidneys and the liver. This apparent first-order elimination rate constant represents the sum of all rate processes which remove drug. This model has probably predominated because it is easy to imagine that drug distributed throughout some regions in the peripheral compartment (compartment 2) is not accessible to elimination by kidney or liver except via return to blood. However, it is certainly possible that metabolism or excretion might occur in compartment 2.

In addition, the same problem of undefined regional differences exists as discussed in Sec. IV.A. Compartment 1 is generally considered to be blood and those fluids and tissues which kinetically appear to achieve spontaneous equilibrium with blood. When $n = 2$, compartment 2 is the entire remaining unsampled portion of the body. No doubt many regional differences in concentration exist, but the model pools all of the remaining drug mass not

accounted for by elimination and compartment 1 into compartment 2. It is a mathematical compartment which is treated as a homogeneous pool in the equations. In reality, it is not homogeneous and the site of action for the drug may have a time course that is independent of the pool. This renders attempts to correlate the time course for compartment 2 with such considerations as structural changes or observed pharmacological activity even more speculative.

Values for the microconstants k_{12}, k_{21}, and k_{10} in Scheme IV may be calculated from the four parameters C_1, λ_1, C_Z, and λ_Z in Eq. (4). These estimates are obtained by feathering the biexponential data, as previously illustrated in Fig. 1. The values for λ_1 and λ_Z are the two routes of a quadratic equation:

$$\lambda_1, \lambda_Z = {}^1/_2(K_1 \pm \sqrt{K_1^2 - 4K_2}) \tag{114}$$

where $K_1 = k_{12} + k_{21} + k_{10}$, $K_2 = k_{21}k_{10}$, and, by convention, $\lambda_1 > \lambda_Z$ [10,11]. Two identities arise from this solution:

$$\lambda_1 + \lambda_Z = k_{12} + k_{21} + k_{10} \tag{115}$$

$$\lambda_1\lambda_Z = k_{21}k_{10} \tag{116}$$

After feathering of the data, the individual rate constants may then be calculated from

$$C(0) = C_1 + C_Z \tag{117}$$

$$F_1 = \frac{C_1}{C(0)} \tag{118}$$

$$F_Z = \frac{C_Z}{C(0)} \tag{119}$$

$$k_{21} = F_1\lambda_Z + F_Z\lambda_1 \tag{120}$$

$$k_{10} = \frac{\lambda_1\lambda_Z}{k_{21}} \tag{121}$$

$$k_{12} = \lambda_1 + \lambda_Z - k_{21} - k_{12} \tag{122}$$

Sample Problem 9

A drug was administered by rapid intravenous injection into an adult male. An indwelling venous catheter was used to withdraw blood samples over a 7-hr period. Samples were assayed for intact drug and results are given in Table 15. Calculate the values for k_{10}, k_{21}, and k_{12}.

Table 15 Concentration of Drug in Blood Following Intravenous Administration

Time (hr)	Concentration (mg %)	Time (hr)	Concentration (mg %)
0.00	7.00	2.50	1.43
0.25	5.38	3.00	1.26
0.50	4.33	4.00	1.05
0.75	3.50	5.00	0.90
1.00	2.91	6.00	0.80
1.50	2.12	7.00	0.70
2.00	1.70		

Solution: Construct a first-order plot representing drug concentration in the blood as shown in Fig. 1. The negative slope of the second phase λ_Z is derived from the best line drawn through the terminal portion of the plot. The intercept of this line is C_Z. The λ_1 line, marked by solid squares, is obtained by feathering. A plot of these values yields a line of slope $-\lambda_1$ and intercept C_1.

The following values were obtained from Fig. 1:

$$C_1 = 5.25 \text{ mg \%} \quad C_Z = 1.75 \text{ mg \%} \quad C(0) = 7.00 \text{ mg \%}$$
$$\lambda_1 = 1.34 \text{ hr}^{-1} \quad \lambda_Z = 0.13 \text{ hr}^{-1}$$

Application of Eqs. (115)–(120) leads to

$$k_{10} = 0.40 \text{ hr}^{-1} \quad k_{21} = 0.43 \text{ hr}^{-1} \quad k_{12} = 0.64 \text{ hr}^{-1}$$

Practice Problem 21

A drug was administered by intravenous injection to a patient and the blood level data given in Table 16 were obtained. Calculate the values for k_{10}, k_{21}, and k_{12}.

Answer: $k_{21} = 0.61 \text{ hr}^{-1}$, $k_{10} = 0.39 \text{ hr}^{-1}$, $k_{12} = 0.84 \text{ hr}^{-1}$.

C. Three-Compartment Open Model

Equation (6) describes the drug time course in plasma for triexponential disposition. The minimum model consistent with this time course must have three compartments reversibly related to one another and at least one elimination constant. The model is generally interpreted as having rapid transfer

Table 16 Concentration of Drug in Blood as a Function of Time

Time (hr)	Concentration (μg/ml)	Time (hr)	Concentration (μg/ml)
0.2	5.65	2.0	1.78
0.4	4.58	3.0	1.43
0.6	3.80	4.0	1.22
0.8	3.23	5.0	1.06
1.0	2.78	24.0	0.00

to one of the peripheral compartments and slower transfer (or return) for the other. The commonly employed three-compartment open model with elimination from the central compartment is shown in Fig. 15. That model is kinetically equivalent to

$$\begin{array}{c} ① \rightleftarrows ② \rightleftarrows ③ \\ \downarrow \end{array} \tag{123}$$

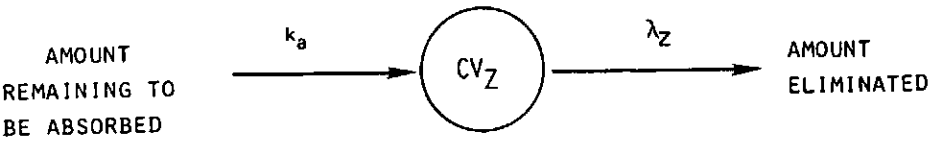
Furthermore, each of these models may be represented by kinetically equivalent models having one elimination constant from any one compartment (three possibilities), one each from any two compartments (three possibilities), or one from each compartment (one possibility). Thus each model has 7 possibilities for a total of 14 kinetically equivalent models. Since $R = 2n - 1 = 5$, only 6 of the 14 models could be solved for the values of the microconstants. Methods for solving for the microconstants in the three-compartment open model in Fig. 15 have been published [12] and those for Eq. (123), which is the model corresponding to Sample Problem 3, may be found in Ref. 13 on bis-hydroxycoumarin.

V. ABSORPTION RATE CONSTANTS

A. One-Compartment Model with First-Order Absorption

1. Data That Cannot be Feathered

The simplest case is that of a one-compartment model with first-order absorption (Scheme V):



Scheme V

A time course for each pool in Scheme V is shown in Fig. 19.

The equation describing the amount in the body, when $k_a \neq \lambda_Z$, is

$$CV_Z = \frac{k_a D}{k_a - \lambda_Z} (e^{-\lambda_Z t} - e^{-k_a t}) \tag{124}$$

In Fig. 19 one can observe that the duration of the time course for the amount remaining to be absorbed (*ARA*) approaches that for the amount in the body. In other words, both exponentials are in effect throughout the curve for CV_Z versus time. This will occur whenever the values for k_a and λ_Z are similar. As a consequence, the two exponentials cannot be separated by feathering. In order to feather the plasma concentration data into a λ_Z phase and a k_a phase, it is necessary that the value for the ratio of these two

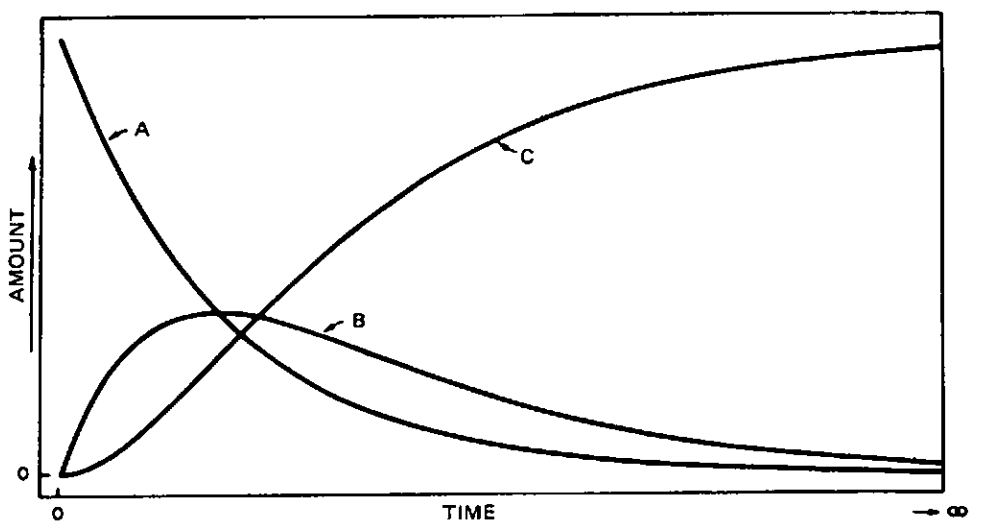


Fig. 19 The time course for each pool in Scheme V, where *A* is the amount remaining to be absorbed (*ARA*), *B* is the amount in the body (CV_Z), and *C* is the amount eliminated.

rate constants be equal to or greater than 3 [14]. The smaller of the two constants represents the rate-controlling step as discussed next. When neither step is rate controlling, that is, when the ratio is less than 3, feathering the data may provide apparent solutions but the answers will not represent either k_a or λ_Z.

2. "Flip-Flop" Phenomenon

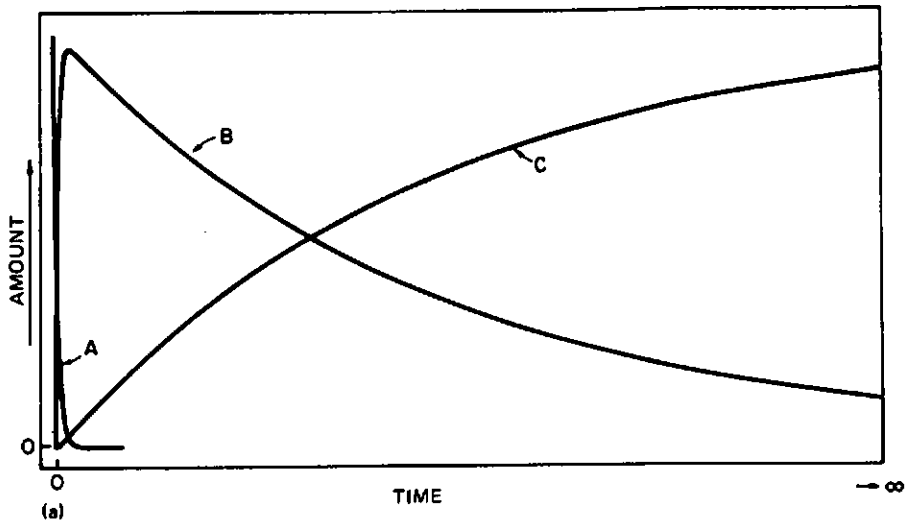
The overall rate process, from beginning to end, is limited by the slowest step in the sequence, provided that one step is sufficiently slower than the rest. This may be likened to a bucket brigade with one lethargic member. In the simple series of two consecutive, irreversible first-order rate processes (Scheme V), either step may be rate limiting.

If the initial step is rapid, it may be possible to calculate both k_a and λ_Z from blood or urine data. This is illustrated in Fig. 20, where two different time scales have been chosen to display the same data. It is obvious that data for *ARA* will always provide an estimate for k_a; however, blood level data may be used to calculate λ_Z by a simple first-order plot of the data shown in Fig. 20a or to calculate k_a using the data in Fig. 20b. This is because the ratio for the example is $k_a/\lambda_Z = 500$. This estimate for k_a will be reasonable as long as $k_a/\lambda_Z > 10$. Urine data can also be used to calculate λ_Z by applying a first-order treatment to the data in Fig. 20a.

A method which can be applied to cases where $3 \leq k_a/\lambda_Z$ with reasonable success ($\pm 10\%$) is that of "feathering" [14]. This is illustrated in Fig. 21. The first-order plot for the terminal portion of the blood data is extrapolated to zero time and a difference plot is made using the line and the experimental points.

It is necessary that *ARA* approach zero and $k_a > \lambda_Z$ for the terminal slope to yield λ_Z. Linearity of this plot is not sufficient evidence for the acceptability of the plot. This is why biological half-life values from data following oral administration may not be accurate. The terminal slope may or may not represent λ_Z. If k_a/λ_Z exceeds 3, the terminal slope will estimate λ_Z, and the feathered line k_a; however, if λ_Z/k_a exceeds 3, the terminal slope estimates k_a, and the feathered line λ_Z. This phenomenon is called "flip-flop," since the slopes of the two linear plots have exchanged their meanings. When the ratios lie between these limits, $0.3 < k_a/\lambda_Z < 3.0$, the feathered lines will *not* reliably estimate either value [14].

The flip-flop phenomenon is illustrated in Fig. 22, where the ratio $\lambda_Z/k_a = 20$. Here the elimination is sufficiently rapid relative to absorption to make the absorption step rate controlling. In Fig. 22 the curve representing the blood time course data has been multiplied by a factor of 20 to allow



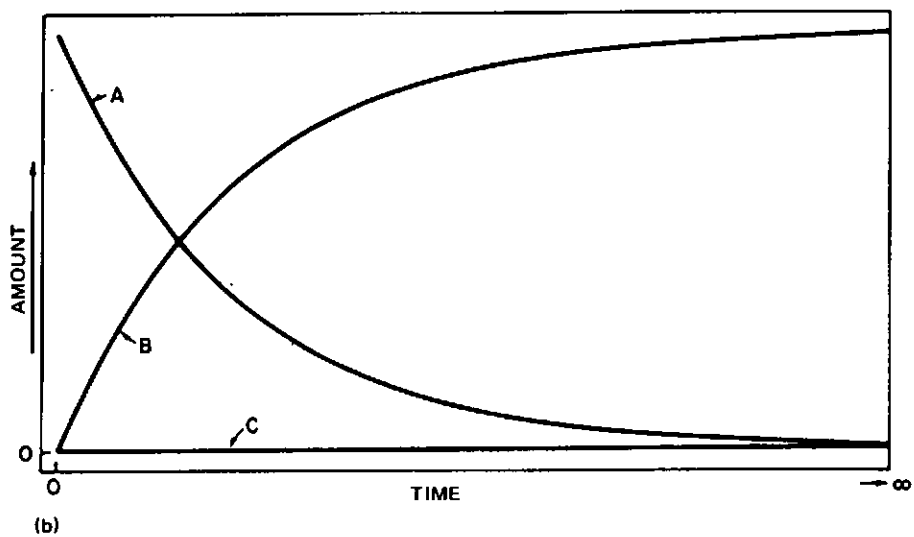


Fig. 20(a) The time course for each pool in Scheme V when absorption is much faster than elimination ($k_a >> \lambda_Z$): *A* is the amount remaining to be absorbed (*ARA*), *B* is the amount in the body, and *C* is the amount eliminated. This time scale illustrates primarily elimination. (b) The same data in Fig. 20a shown on a time scale which illustrates only the early period. Elimination (C) is insignificant and the curves primarily represent the absorption phase.

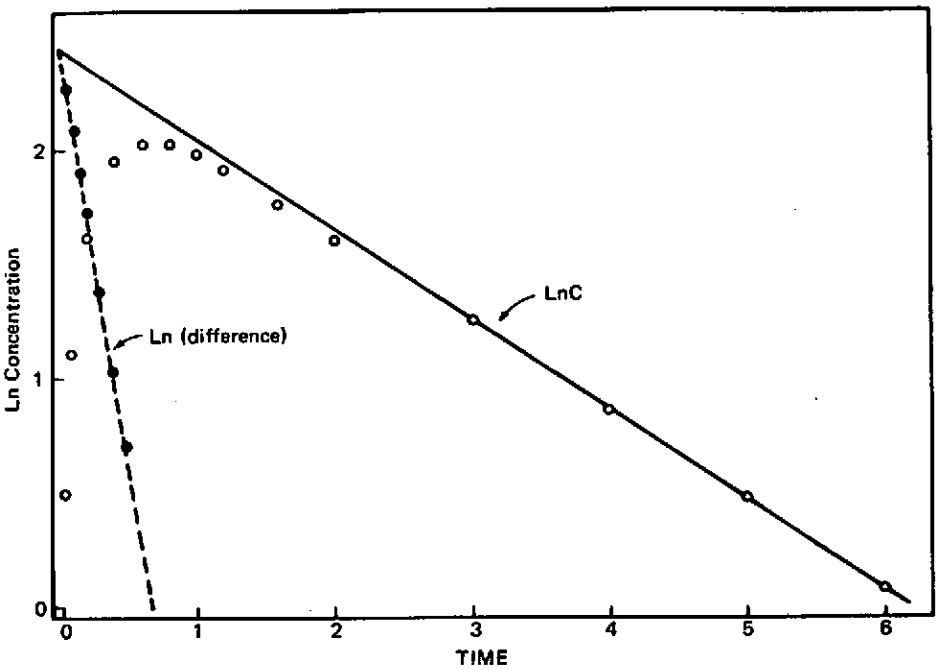


Fig. 21 Feathering biexponential drug plasma concentration data following oral administration. When $k_a \geq 3\lambda_Z$, the negative slope of the terminal log-linear plot represents λ_Z. The negative slope of the log-linear plot of the values for the difference between the data points and the terminal line provides an estimate for k_a. When $\lambda_Z \geq 3k_a$, the meanings for the slopes are interchanged, which is termed "flip-flop" phenomenon [14].

comparison to the *ARA* time course. The resulting curve shows that the two are superimposable over most of the sampling period. Since a first-order plot for *ARA* data would estimate the k_a value, it is clear in Fig. 22 that the terminal slope of the blood level would also estimate k_a. The value obtained from a feathered line would then be λ_Z.

Since the terminal slope may be either k_a or λ_Z, and because of the possibility of a "vanishing exponential" (discussed next), the following equation is used in this text to describe a biexponential plasma concentration curve following extravascular administration:

$$C = C_i e^{-S_Z t} - C_i e^{-S_1 t} \tag{125}$$

This is a model-independent empirical description which designates the terminal slope as S_Z, the rapid slope obtained by feathering S_1, and the common

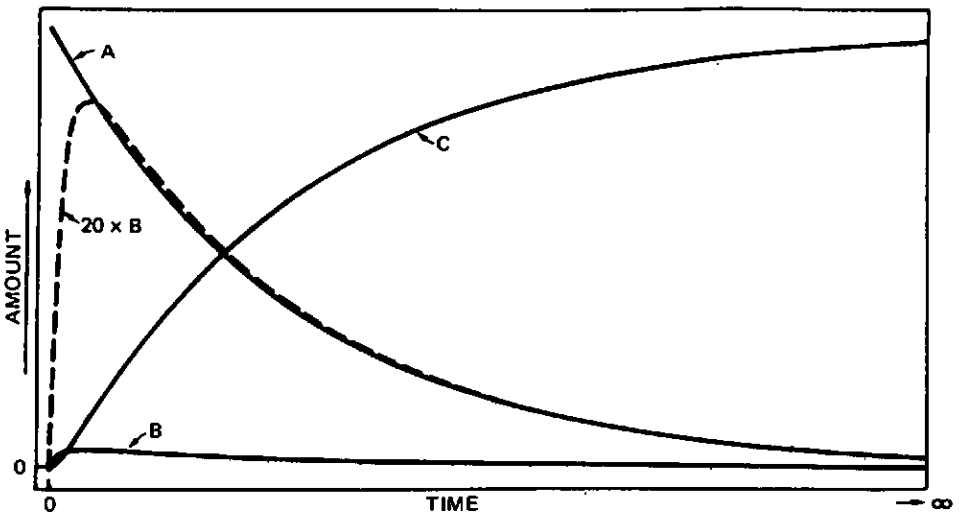


Fig. 22 Illustration of the flip-flop phenomenon, where *A* is the amount remaining to be absorbed (*ARA*), *B* is the amount in the body, and *C* is the amount eliminated (Scheme V). Since $\lambda_Z = 20\ k_a$, the negative terminal slope for plasma concentration data would estimate the rate-limiting step k_a. The common curve for decrease in *ARA* and the terminal phase for *B* is demonstrated by the expanded *B* curve.

intercept C_i as illustrated in Fig 7 in Chap 6. When the feathered lines intersect at a negative value for time, rather than at zero time, as shown in Fig 7 in Chap 6, the difference is ascribed to a lag time in the absorption process. This general approach allows such calculations as dosage regimens without having to assign a meaning to S_1 or S_Z or choosing a model.

3. The "Vanishing Exponential"

In theory, a drug exhibiting biexponential disposition following intravenous administration would require an additional exponential term to describe the blood concentration time course following extravascular administration. When the absorption rate constant is sufficiently fast, $k_a > \lambda_1 > \lambda_Z$, the expected equation is

$$C = \frac{k_a f D}{V_c}\left(C_1' e^{-\lambda_1 t} + C_Z' e^{-\lambda_Z t} + C_3' e^{-k_a t}\right) \tag{126}$$

where $C_1' = (k_{21} - \lambda_1)/(\lambda_Z - \lambda_1)(k_a - \lambda_1)$, $C_Z' = (k_{21} - \lambda_Z)/(\lambda_1 - \lambda_Z)(k_a - \lambda_Z)$, $C_3' = (k_{21} - k_a)/(\lambda_1 - k_a)(\lambda_Z - k_a)$, and no lag time is

in effect. When a lag time exists, Δt is substituted for t, where $\Delta t = t - t_{lag}$. In place of Eq. (126), it is often possible to describe the data using Eq. (125), where the values for S_1 and S_Z may or may not represent k_a, λ_1, or λ_Z. In this case the characteristic nose associated with Eq. (126) is not visible (Fig. 23). Equation (125) has been shown to adequately describe data from an extravascular dose of a known two-compartment model drug when the k_a value approaches either λ_Z or k_{21} [15]. Attempts to calculate k_a when $k_a \simeq k_{21}$ provided the known value for λ_1 which often overestimated k_a by more than a factor of 2. When k_a approached λ_Z, the errors in estimating k_a became quite large.

This phenomenon, called the "vanishing exponential" because Eq. (125) has one less exponential than Eq. (126), has been addressed by several authors [15–18]. It is not limited to extravascular administration. For example, an intravenous injection of a four-compartment model drug may appear quadraexponential ($E_2 \neq E_3 \neq E_4$), tricxponential ($E_2 = E_3 \neq E_4$ or $E_2 \neq$

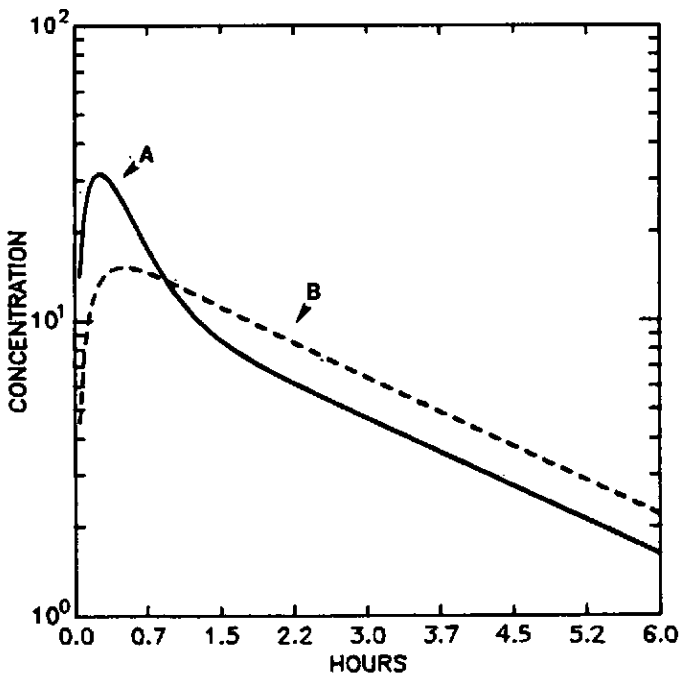


Fig. 23 Illustration of the "vanishing exponential" following the oral administration of a biexponential disposition drug. The expected shape is shown in curve *A*, which requires a triexponential equation, Eq. (126); however, when the absorption rate constant for the same drug is decreased, the resulting curve *B* is described by the biexponential Eq. (125).

$E_3 = E_4$), or biexponential ($E_2 = E_3 = E_4$), where E_n represents the sum of the rate constants out of compartment n [17].

In Chap. 6 in the development of dosage regimens, it will be assumed that extravascular administration can be adequately described by Eq. (125). No further assumptions are required regarding the meaning of the equation parameters. The potential error which would result from the existence of a nose, which is not described by Eq. (125), would be minimal in most cases.

4. The Loo–Riegelman and Wagner–Nelson Equations

Both of these equations calculate the percentage of drug remaining to be absorbed at any time. This percentage is based on the absorbable fraction of the dose in the case of incomplete absorption [19]. An appropriate plot (first order or zero order) of these data allows calculation of the absorption rate constant (k_a or k_0). We will first look at the application of the Loo–Riegelman equation to a drug described by a two-compartment open model and absorbed by a first-order rate process. Vaughan and Dennis [20] and Wagner [21] have shown that the Loo–Riegelman equation, though based on the model of Eq. (101) (Scheme IV), is applicable even though the model of Eq. (102) or (103) is in effect. In this respect it is model independent so long as input is into compartment 1.

The equation to be used is

$$\left(\frac{AB}{V_c}\right)_{t_n} = C_{t_h} + k_{10}AUC(0\text{–}t_A) + T_{t_n} \tag{127}$$

where $(Ab/V_c)_{t_n}$ represents the total amount absorbed, Ab, at a time t_n, expressed in terms of V_c, the volume of the central compartment. Concentrations of

Table 17 Plasma Levels of Drug Following Oral Administration of 490 mg

Time (hr)	Concentration (mg %)	Time (hr)	Concentration (mg %)
0.5	3.2	4.0	4.8
1.0	4.8	5.0	4.1
1.5	5.5	7.0	3.1
2.0	5.7	9.0	2.2
2.5	5.7	11.0	1.8
3.0	5.4	13.0	1.4

Table 18 Answers to Stepwise Calculations for the Loo–Riegelman Equation

Step 1					Step 2			Step 3		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
t_n	Δt	C_{t_n}	ΔC	T_{t_n}	Area t_{n-1} to t_n	Area t_0 to t_n	$k_{10} \times$ col. 7	$Ab/V_c =$ cols. 3 + 5 + 8	Percent Ab/V_c	100% − col. 10
0.5	0.5	3.2	3.2	0.240	0.80	0.80	0.20	3.64	26.8	73.2
1.0	0.5	4.8	1.6	0.752	2.00	2.80	0.70	6.25	46.0	54.0
1.5	0.5	5.5	0.7	1.32	2.58	5.38	1.35	8.17	60.1	39.9
2.0	0.5	5.7	0.2	1.84	2.80	8.18	2.04	9.58	70.4	29.6
2.5	0.5	5.7	0.0	2.28	2.85	11.03	2.76	10.7	78.7	21.3
3.0	0.5	5.4	−0.3	2.62	2.78	13.81	3.45	11.5	84.6	15.4
4.0	1.0	4.8	−0.6	3.00	5.10	18.91	4.73	12.5	91.9	8.1
5.0	1.0	4.1	−0.7	3.09	4.45	23.36	5.84	13.0	95.6	4.4
7.0	2.0	3.1	−1.0	2.78	7.20	30.56	7.65	13.5	99.3	0.7
9.0	2.0	2.2	−0.9	2.26	5.30	35.86	8.96	13.4	98.5	1.5
11.0	2.0	1.8	−0.4	1.80	4.00	39.86	9.96	13.6	100.0	0.0
13.0	2.0	1.4	−0.4	1.43	3.20	43.06	10.8	13.6	100.0	0.0

drug in plasma and tissue are given by C and T. The most convenient and simple way to explain the use of Eq. (127) is to work through an example. The first-order rate constant for absorption will be calculated from the data in Table 17.

A drug is found to exhibit biexponential disposition following intravenous injection. The calculated values for the two-compartment model rate constants are $k_{12} = 0.30$, $k_{21} = 0.40$, and $k_{10} = 0.25$ (hr^{-1}). The same drug was administered orally, and the data given in Table 17 were obtained. This information will be used to calculate the three unknown quantities in Eq. (127): T_{t_n}, $AUC(0\text{–}_{t_n})$, and (Ab/V_c). The results of our stepwise calculations are entered in Table 18.

Step 1. Calculation of tissue concentrations as a function of time. The equation to be used is

$$T_{t_n} = T_{t_{n-1}} e^{-k_{21}\Delta t} + C_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) \frac{k_{12}}{k_{21}} + {}^1/_2 k_{12} \Delta C \, \Delta t \qquad (128)$$

This equation will be solved for each data point. In our example the first set of points is 0.5 hr, 3.2 mg %. Thus $\Delta t = 0.5$, $\Delta C = 3.2$, and t_{n-1} is zero, since it refers to the time of the previous data point. Thus $C_{t_{n-1}}$ and $T_{t_{n-1}}$ are also zero, since no drug is in the body at time zero. The first entry in Table 18 under step 1 is calculated from

$$T_{0.5} = 0 + 0 + {}^1/_2(0.3)(3.2)(0.5) = 0.24 \tag{129}$$

and the second entry from

$$T_{1.0} = 0.24e^{-0.20} + (1 - e^{-0.2})\frac{(3.2)(0.3)}{0.4} + {}^1/_20.3(1.6)0.5 = 0.751$$

and so on. Each of the entries of T_{t_n} is given in Table 18.

Step 2. Calculation of elimination as a function of time. We have now calculated the values for T_{t_n}. Since we have data for C_{t_n}, there is only one part of Eq. (127) yet to be calculated and that is $AUC(0–t_n)$, which represents the area under the plasma time–concentration curve from time zero to time t_n. Accuracy may be increased by including interpolated points [22] and employing the logarithmic trapezoidal rule during the terminal log-linear portion [23,24] and the trapezoidal rule up to the peak. In this example it can be done most easily by use of the trapezoidal rule. Thus the curve for C versus t must be drawn and the individual areas calculated for each trapezoid (or triangle) as described by the data points. The answers are illustrated in Table 18, column 6. These are the areas of the various trapezoids. Therefore each area up to and including t_n must be summed to obtain the total value of the $AUC(0–t_n)$ in Eq. (127), as shown in column 7 of Table 18. Each of these values is then multiplied by the elimination constant $k_{10} = 0.25$ to obtain the values in column 8 of Table 18.

Step 3. Calculation of Ab/V_c. The three component parts of Eq. (127) are now calculated (columns 3, 4, and 8 in Table 18) and are to be summed to obtain the values given in column 9. Examination of the entries in column 9 as a function of time will reveal that Ab/V_c appears to approach a maximum value of about 13.6. The values of Ab/V_c are next converted to a percentage of this maximum value according to

$$\text{percent}\,\frac{Ab}{V_c} = \frac{100Ab}{13.6V_c} \tag{130}$$

and the results are shown in column 10 of Table 18. Column 11 represents the percentage of drug unabsorbed as a function of time and is calculated by subtracting column 10 from 100%. The first-order plot of percent unabsorbed versus time yields a value of 0.60 hr^{-1} for k_a.

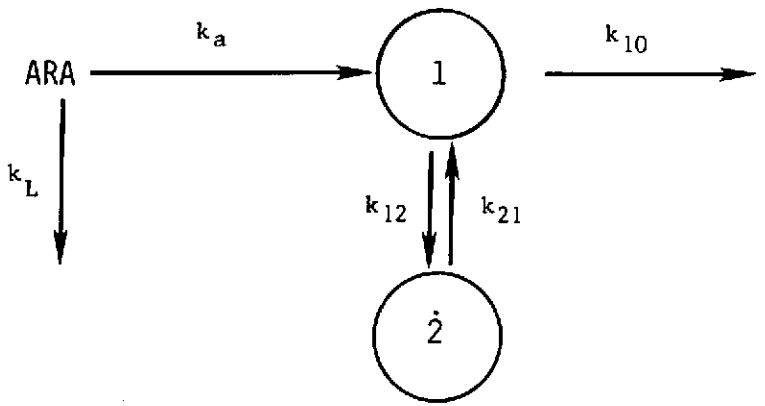
The calculation of k_a for a drug distributed according to a one-compartment model is done by means of the Wagner–Nelson [25] equation:

$$\left(\frac{Ab}{V_Z}\right)_{t_n} = C_{t_n} + (\lambda_Z)AUC(0 - t_n) \tag{131}$$

The procedure for solving this equation to obtain k_a is the same as that just described for Eq. (127).

5. First-Order Loss of Drug from Depot

The rate constant calculated using Eq. (127) or (131) does not represent absorption if part of the drug in the depot is lost to some parallel process that competes with absorption. Examples of such processes might be chemical degradation, biotransformation by enzymes or intestinal bacteria, or transfer to a compartment other than the blood. This kind of process is shown schematically in Scheme VI,



Scheme VI

where k_L represents the rate constant for drug loss by the competing process. In such a system and where k_L is a first-order rate constant, it has been shown that the calculated absorption rate constant k_{app} is the sum of k_a and k_L, provided that these represent the only routes for loss of drug from the depot [19]. The rate constant for absorption may be obtained from $k_a = fk_{app}$, where k_{app} is the apparent rate constant for absorption and f represents the fraction absorbed. Loss of drug by a competing non-first-order process cannot be treated in this simple manner.

Thus false impressions of rapid absorption may result from a competing process such as rapid hydrolysis. Studies employing the Wagner–Nelson or

Loo–Riegelman method should therefore include a calculation of the fraction of dose absorbed. If the drug is well absorbed, the calculated absorption rate constant should represent a good estimate of the actual value. If absorption is poor, the reason must be established before a physical meaning can be assigned to the apparent rate constant.

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5

Biopharmaceutics

I. EXTRAVASCULAR ADMINISTRATION

A drug administered by an extravascular route must be transferred from the dosage form to the blood in order to be bioavailable. Therefore bioavailability entails both the amount of drug entering the bloodstream and the rate at which it enters. Biopharmaceutics is the study of those factors which influence bioavailability and the subsequent use of this knowledge to optimize clinical success in the use of drug products.

Drugs administered by extravascular routes (oral, buccal, rectal, topical, intramuscular, subcutaneous, etc.) result in plasma concentration time courses which exhibit an initial increase and subsequent decrease (Fig. 1). Initially the rate of absorption is faster than elimination from the blood, so the concentration increases. In the terminal portion the concentration decreases as the elimination rate exceeds the rate of absorption. There exists a brief moment during which the concentration neither increases nor decreases. This occurs at the peak or maximum concentration C_{max}. At that specific time, t_{max}, the rate of drug input to blood is equal to the rate of loss, so there is no net change in concentration.

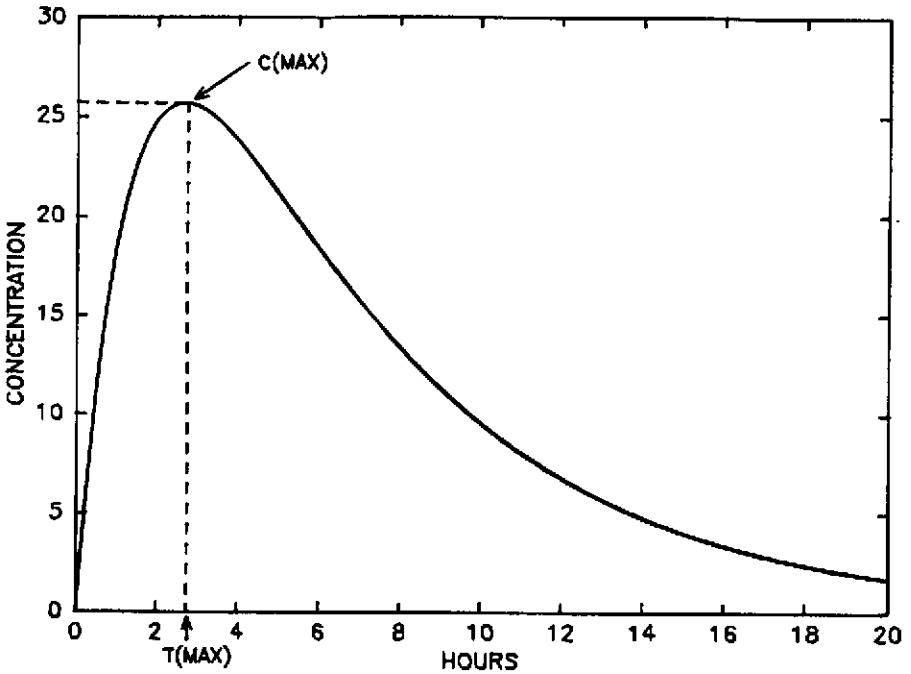
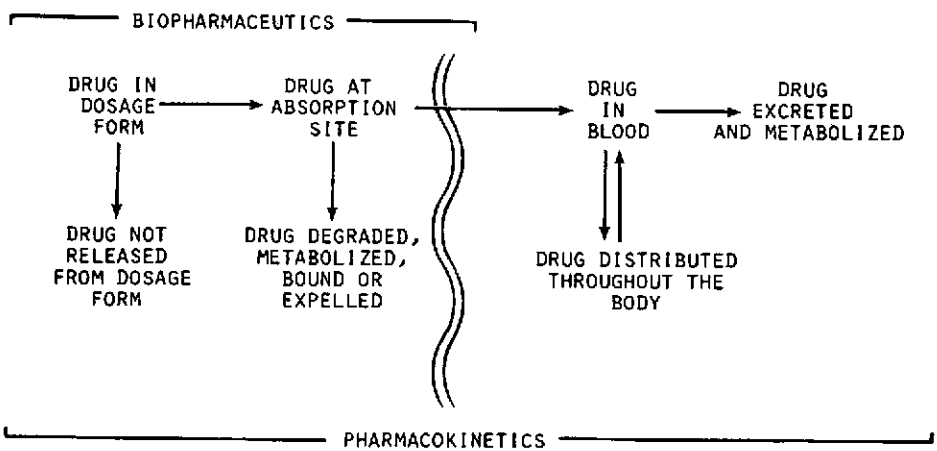


Fig. 1 Drug plasma concentration time course following administration by an extravascular route. The concentration passes through a maximum value C_{max} at time t_{max}.

Since the drug must be released from the dosage form and be transferred through various physiological barriers to arrive in the blood (Scheme I), the study of this process must include assessment of (1) the total amount of drug



Scheme I

absorbed and (2) its rate of absorption. The rate and amount of drug absorbed (i.e., the bioavailability of drug) can be influenced by many factors. The extent to which bioavailability is influenced by these factors may be evaluated using the plasma concentration time course data, as discussed in Sec. IV on the evaluation of bioavailability.

II. ABSORPTION OF DRUGS FROM THE GASTROINTESTINAL TRACT

A. Processes

1. Passive Diffusion

Drugs pass from the gastrointestinal (g.i.) tract into the bloodstream primarily by passive diffusion. Few drugs are actively absorbed, and these will be discussed later. The absorption of drugs by passive transport is a function of the concentration gradient between the g.i. tract and the blood. A drug moves from the g.i. tract into the bloodstream because diffusion occurs from a region of higher concentration to that of a lower concentration. This point has been dramatically illustrated by the demonstration that parenterally administered drugs can be secreted into the gastric juice [1]. Although we are accustomed to thinking about drugs passing into the blood, this experiment reminds us that passive transport is described by the principles of physical chemistry, wherein the rate and direction of mass transport are due to the concentration gradient of the diffusing species.

Since this gradient refers to the diffusing species only, we must define the kind of chemical entities that can permeate this membrane. The g.i. membrane is composed of a lipoidal sheet, covered on both sides by protein, oriented perpendicularly to the cell surface. The lipoid film contains what appear to be small water-filled pores. Although these aqueous pores have not been observed microscopically, there exist highly polar regions of the membrane that are more aqueous than the lipoidal regions and through which small molecules, of radius less than about 4 Å, may pass. This convective absorption of small molecules is a function of the number of pores and the size of the pores relative to the molecules themselves. There are few substances capable of passing from the g.i. tract into the blood by the pore route. Small atoms such as K^+ and Cl^- can fit through these openings, and they may be carried through the membrane by water passing through the pores, thus creating what is sometimes called solvent drag.

Drugs, however, are generally large molecules with molecular weights in excess of 100. They are therefore too large to permeate these pores. Since the membrane is lipoidal in nature, it is believed that drugs undergo a partitioning process from the aqueous g.i. fluids into the membrane. After diffusion through the membrane, they then partition from the membrane into the aqueous blood and tissue fluids. This concept of absorption by an oil–water partitioning process is generally attributed to Hogben et al. [2]. In general, we will assume that drugs are passively absorbed and that their absorption is related to their ability to leave the aqueous fluids of the g.i. tract and partition into the g.i. membrane and finally into the blood. For the following discussion the membrane may be viewed as a continuous layer of mineral oil with a number of small water-filled channels much smaller than molecules of the drugs themselves. This is not a physiological model but, rather, an oversimplified reference that will allow predictions regarding the permeability of some organic molecules.

2. pH Partition Theory

Using this simplified model of the g.i. membrane, one would predict that uncharged drug molecules would permeate with more facility when charged species; that is, neutral species would be expected to be more soluble in mineral oil than ionic species. Many drugs are Bronsted acids or bases, which may be described by the following:

$$\text{Acids:}\quad \underset{\substack{\text{absorbable}\\\text{form}}}{HA} \rightleftarrows H^+ + \underset{\substack{\text{poorly absorbable}\\\text{form}}}{A^-} \qquad (1)$$

$$\text{Bases:}\quad \underset{\substack{\text{poorly absorbable}\\\text{form}}}{R_3NH^+} \rightleftarrows \underset{\substack{\text{absorbable}\\\text{form}}}{R_3N} + H^+ \qquad (2)$$

where *HA* represents carboxylic acids, sulfonamides, imides, phenols, and so on, and R_3N represents amines, such as alkyl amines, phenylalkylamines, alkanolamines, pyridines, quinolines, imidazoles, piperidines, indoles, and phenothiazines. The only word of caution is to remember that the protonated form is *neutral for acidic compounds* (*HA*) and *charged for basic amines*. Then the Henderson–Hasselbach equation can be employed to calculate the relative amount of the charged species from the pK_a of the drug (*HA* or RNH_3^+) and the pH of the environment:

$$\text{pH} = pK_a - \log\left(\frac{\text{protonated}}{\text{unprotonated}}\right) \tag{3}$$

Although the pH partition theory is generally attributed to Hogben et al. [2], evidence of such behavior in the literature has existed for some time [3]. An intriguing demonstration of this principle was carried out by Travell in 1940 [1]. When the pH of the stomach of experimental animals was kept low, there were no toxic effects from large doses of alkaloids; however, when the stomach contents were made alkaline, the animals died rapidly. Thus the g.i. membrane was shown to be permeable to the neutral form of the alkaloid but relatively impermeable to the ionic species:

$$\underset{\text{not absorbed}}{RNH_3^+} \overset{OH^-}{\underset{H}{\rightleftharpoons}} \underset{\text{absorbed}}{RNH_2} \tag{4}$$

It is often convenient to consider the ratio of protonated to unprotonated species, prot/unprot, at 1 or 2 pH units above or below the pK_a of the drug. A ratio of 10/1 coincides with a pH 1 unit below the pK_a, as shown by Eq. (3), when $\log 10 = 1$. Conversely, a ratio of 1/10 provides $\log 0.1 = -1$, which coincides with a pH 1 unit above the pK_a. This simplification may be summarized as follows:

$\text{pH} - pK_a$:	-2	-1	0	$+1$	$+2$
prot/unprot:	100/1	10/1	1/1	1/10	1/100

(5)

Thus, at a pH value 2 units above the pK_a, an amine would be 1 part charged and 100 parts free base, whereas a carboxylic acid would be 100 parts carboxylate anion and 1 part undissociated acid. Some representative pK_a values are listed in Table 1.

The pH partition theory can provide a basis for useful first approximations, but it is not a predictive rule. In accordance with the theory, a drug which exists both as an ion and a neutral species may be assumed to be preferentially absorbed in the neutral form. But one cannot predict the g.i. absorption site or the degree to which the ionic species will be absorbed. One overriding factor is the efficiency with which intestinal absorption often takes place despite the nonideal nature of the absorbing species. It may be said that weak acids of low pK_a values (i.e., 2 or 3) will be charged throughout most of the g.i. tract and may therefore present a bioavailability problem.

Table 1 Approximate pK_a Values for Selected Acidic Drugs and Protonated Forms of Basic Drugs

Acids	pK_a	Protonated bases	pK_a
Acetaminophen	9.5	Allopurinol	9.4
Ascorbic Acid	4.2, 11.6	Amantadine	10.4
Aspirin	3.5	Amphetamine	9.9
Barbiturates	7.8	Antipyrine	1.4
Cephalosporins	2.7	Atropine	9.2
Ethosuximide	9.3	Benzocaine	2.8
Fluorouracil	8.0, 13.0	Carbachol	4.8
Furosemide	3.9	Carbinoxamine	8.1
Hippuric acid	3.6	Chlordiazepoxide	4.8
Ibuprofen	5.2	Chlorpheniramine	9.0
Indomethacin	4.5	Cimetidine	6.8
Mandelic acid	3.4	Codeine	8.2
Nalidixic acid	6.7	Dextromethorphan	8.3
Nicotinic acid	4.9	Erythromycin	8.8
Nitrofurantoin	7.1	Heroin	7.8
Penicillins	2.6	Histamine	5.9, 9.8
Phenylbutazone	4.5	Isoniazid	2.0, 3.9
Phenytoin	8.3	Isoproterenol	8.6
Salicylamide	8.2	Lidocaine	7.9
Salicylic acid	3.0, 13.4	Procaine	8.8
Sulfamethoxazole	5.6	Pseudoephedrine	9.7
Tolbutamide	5.4	Quinine	4.2, 8.8
Warfarin	5.0	Reserpine	6.6

Weak bases of $pK_a > 8$ will also be ionized and may give rise to similar problems. However, their degree of absorption cannot be predicted. Some general acids and bases provide nearly complete bioavailability despite being charged species throughout most of their g.i. transit. Quaternary drugs, which are cationic and independent of pH, very widely in bioavailability but are often absorbed sufficiently to be administered orally. The mechanism by which the absorption of ions occurs remains unclear. Ion pair formation has frequently been suggested as the means by which charged species undergo passive absorption. Ion pair formation has been demonstrated in vitro. There is no unequivocal evidence that orally administered drugs combine with a counterion and are absorbed as the ion pair. Although this is a potential explanation, it has yet to be demonstrated.

Ampicillin, amoxicillin, and the tetracyclines are notable examples of ampholytes which bear some charge over the pH range of the g.i. tract. Such drugs appear to be passively absorbed in accordance with the pH partition theory; that is, the maximum partition coefficient values coincide with the pH of minimum net charge on the compound and that is the optimum pH for absorption. In the case of a zwitterion at its isoelectric point, absorption involves an ion of both positive and negative charge, even though the entire molecule is electrically neutral.

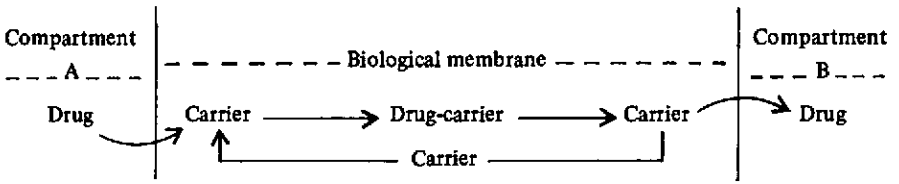
The passive absorption of ionic species does not invalidate the pH partition theory. It simply emphasizes that the theory is applicable on a relative basis rather than in absolute terms. In Chap. 7 the improved absorption of drugs via the formation of analogs and prodrugs which result in more favorable partitioning behavior will be discussed. The enhanced bioavailability of an ester relative to the parent acid is dramatic proof of the pH partition theory in operation.

3. Active Transport in Absorption

Most drugs are absorbed by passive diffusion. The driving force for this absorption is the concentration gradient across the membrane. The rate of absorption is proportional to the concentration gradient of the transferable species. If this concentration is equal on both sides of the membrane, the net transfer is zero.

In contrast, some substances are transported by active processes. Here a carrier is involved in the transfer. The characteristics of an active process are therefore quite different from those of a passive process (Scheme II). Transfer can occur from a region of low concentration to one of higher concentration, against the concentration gradient. If an enzyme behaves as a carrier, for example, this does not depend on the concentration gradient. The process consumes energy because there is energy required in the work carried out by the enzymes. Transfer may be subject to inhibition by a substance that can either interfere with enzyme activity or compete for the available enzymes. The limited number of enzymes makes the system capacity limited. If the total number of transferable molecules exceeds the availability of the enzyme sites, the system will become saturated. This may be visualized as an enzyme system working at full capacity while additional drug molecules await transfer. Those molecules that are waiting can undergo passive absorption. One characteristic of active transport is the great increase in rate over that which can be expected from passive diffusion. If we assume that transport is much faster than diffusion, the rate at saturation will appear

to be zero order. This occurs because the enzymes will transfer drug at a constant rate so long as the drug is in excess of the available sites.



Scheme II

It appears that many vitamins, minerals, amino acids, sugars, and pyrimidines are absorbed by carrier-mediated transport systems. The antitumor drugs 5-fluorouracil and 5-bromouracil are actively absorbed by way of the pyrimidine transport system, presumably owing to their structural similarity to the natural pyrimidines uracil and thymine. Thus a system that may be designed to ensure the absorption of building blocks for DNA and RNA may result in the absorption of drugs that are similar in structure. Closely related pyrimidines have been shown to compete for this active process. in animals the absorption of uracil was inhibited by thymine, 5-bromouracil, and 5-fluorouracil. Vitamins such as thiamine, niacin, vitamin B_6, vitamin B_{12}, and riboflavin are notable examples of substances that are actively absorbed.

Specialized absorption sites appear to be most dense in specific sections of the intestinal tract. While this is generally in the upper portion of the intestines, it is not necessarily identical for all carriers. A limited area in which a carrier system is most dense is often referred to as an "absorption window." Drugs that are absorbed by a window in the upper intestines would make poor candidates for dosage forms designed to delay release, for the active ingredient may be released after it has passed the window. A sustained-release product that releases drug over a long period of time may thus result in a decreased bioavailable dose. Sustained-release vitamins and iron preparations have been shown to reduce bioavailability.

Absorption rates that are much greater than expected for passive diffusion have been termed facilitated diffusion when they appear to involve a carrier but do not transport against a concentration gradient. They do show capacity-limited behavior when high concentrations exceed the availability of the carriers. Capacity-limited absorption is generally evidenced by examining the absorption rate, or the amount absorbed in a given time period, as a function of dose. Although subject to biological variability, the theoretical plot for passive absorption would be a linear function. In contrast, the absorption by a carrier-mediated process will approach a finite limit wherein increased

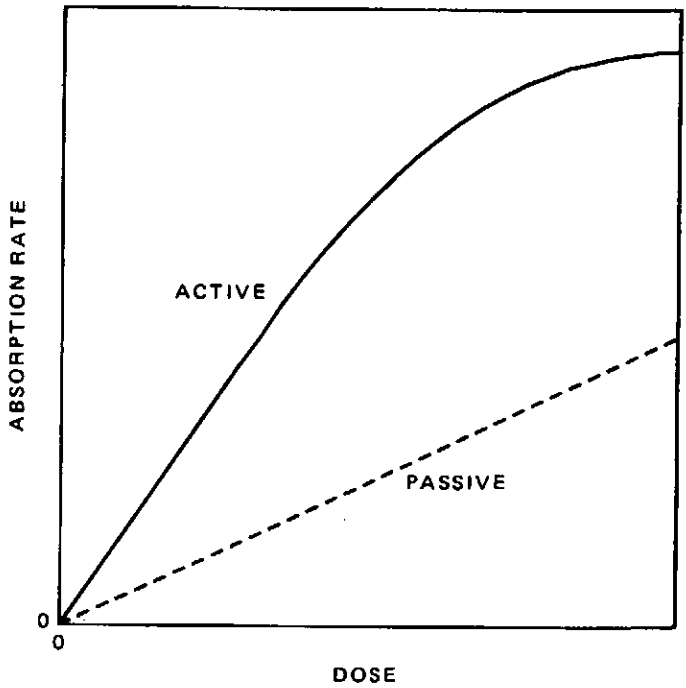


Fig. 2 The passive absorption of a drug will depend on the concentration gradient and is characterized by a linear dependency on administered dose. An active absorption process may appear linear in the low dose range but become saturated at high doses, at which point the absorption may remain nearly constant as the dose is further increased.

dosage will not show a proportional increase in absorption. These examples are illustrated in Fig. 2.

B. Absorption of Drugs from Solutions

1. Rate-Determining Step

The fastest rate of absorption by the oral route can be achieved by administering a solution of the drug. If the goal is a high C_{max} and a rapid onset of action, the drug would best be administered in the form of an elixir, syrup, or aqueous solution. The rate-determining step would then be the passive transfer of drug from the g.i. fluids through the g.i. wall to the systemic

circulation. For a neutral drug this process could be relatively independent of position in the g.i. tract, if the process were simple passive absorption. Many drugs are either general acids or general bases and their partitioning behavior is therefore influenced by the pH of the g.i. fluids.

2. pH of the Gastrointestinal Tract

Figure 3 is a schematic representation of the digestive tract showing a gradual decrease in acidity when moving from the stomach to the lower intestine. The stomach varies in pH from 1 to 3.5, but pH 1–2.5 is probably the most common range. Stomach pH is affected by foods and can be clinically increased by the administration of antacids. Cimetidine is used in ulcer patients, since it inhibits gastric acid secretion stimulated by food, caffeine, insulin, histamine, and pentagastrin. A 300-mg dose given with a meal has been shown to result in a gastric pH of 3.5–6.1 during the 1- to 4-hr postprandial period. With a placebo control, the gastric pH during the same period of time was 2.08 (SD = 0.43). By comparison, the intestinal pH is relatively independent of such foreign influences. The duodenum has a pH of 5–6 and the lower ileum approaches a pH of 8.

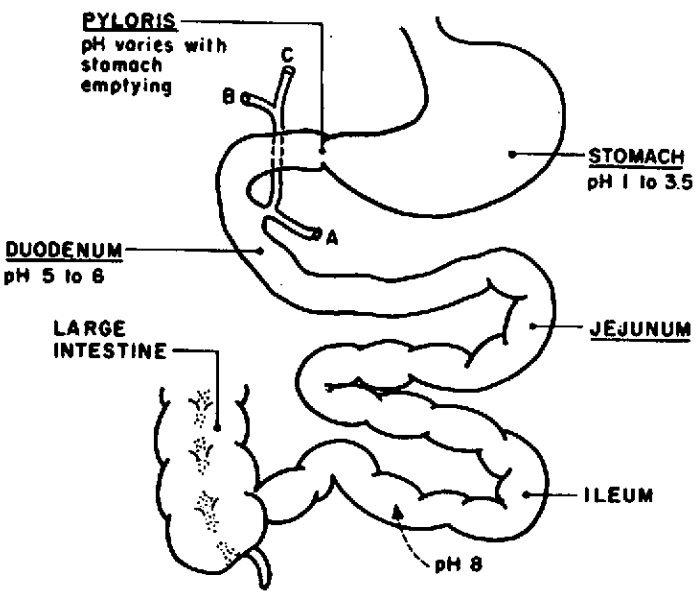


Fig. 3 Diagram illustrating the pH of various regions in the g.i. tract.

This difference in pH of the g.i. fluids can be a key factor in determining the primary site for absorption of a drug from an orally administered solution. We have already discussed the absorption behavior for a drug that can exist in both a charged and an uncharged form. According to the pH partition theory, the primary mode of absorption will be by passive diffusion of the neutral species. If we consider all drugs as acids (in the protonated form), we can generalize their dissociation by considering the two groups represented by Eqs. (1) and (2).

Since the rate-determining step in the g.i. absorption of drugs that are orally administered in solution is the partitioning of the neutral species, the preferred site for absorption would be expected to be that area where the neutral species is at its maximum. For example, if we consider the ingestion of a solution of a weak acid HA of pK_a in the range 4–5, we would expect it to exist primarily in the neutral form in the stomach, where the pH is 1–3.5. Thus we would predict tht such a drug would be absorbed primarily from the stomach, and this is reasonably true, at least in a semiquantitative sense. But this does not rule out intestinal absorption. When the solution of drug is ingested, it will first arrive in the stomach. Since the neutral species will predominate, absorption would be expected to occur. If the drug solution passes into the intestines, its absorption may not be limited by the less than ideal pH of the intestines. Absorption may still occur in spite of the fact that a drug of type HA with a pK_a of 4 would be predominately charged throughout the intestines. The reason for this behavior lies in the anatomy of the intestinal tract. The intestinal tract is extremely long. In addition to its length, it is composed of large numbers of villi, which serve to increase the overall surface area of the intestines. When drug is exposed to this long tract of great area, it becomes relatively easy for absorption to occur across the thin, 25-μm epithelial layer, which also has 6000 ml/min of blood plasma circulating on the systemic side, thereby maintaining a high concentration gradient. Thus the intestine is anatomically adapted for the absorption of drugs and other substances.

Predictions for R_3N types of drugs might be even more reliable. Since the stomach is relatively small, a drug that exists in the charged form, R_3NH^+, will probably not be well absorbed from the stomach. Using the same pKa value of 4 for the protonated amine, we would predict that absorption from the stomach would be poor, since the drug would exist almost entirely in the protonated (and in this case charged) form in the stomach. Once the drug passed into the intestines, it would be in the neutral form and would be expected to show good absorption by the intestinal route.

It should be recognized here that we have referred to absorption in a rather nonspecific manner; that is, we have not differentiated between the absorption rate and the amount absorbed. The large intestinal surface may

in certain cases result in complete absorption at a rather slow rate. As previously discussed, the time profile may be all important clinically. We will discuss this aspect further in Sec. II.C on solid dosage forms. It might also be mentioned here that a drug absorbed primarily from the intestines could have stomach emptying time as its rate-determining step. Since this would be more pronounced with a solid dosage form, it will also be discussed in Sec. II.C.

C. Absorption of Drugs from Solid Dosage Forms

1. Rate-Determining Step

In the previous discussions the absorption process began the instant the drug arrived at the site for absorption. This is not the case when a drug is administered in a solid dosage form. In order for a drug to be absorbed, it must first be in solution. Let us consider the absorption of an acidic drug HA from a tablet. The usual steps involved in the absorption process are

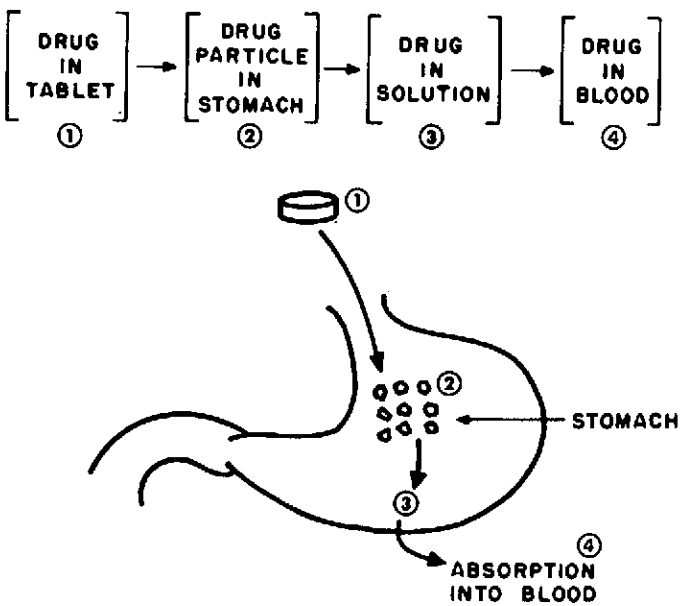
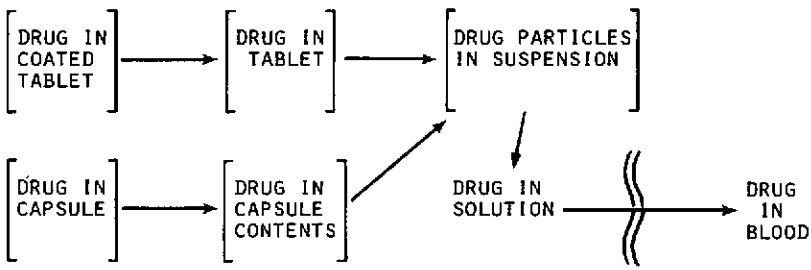


Fig. 4 Illustration of the usual steps involved in the absorption of a drug following oral administration of a tablet: disintegration, dissolution, and absorption.

represented in Fig. 4. Once the tablet is swallowed, it normally undergoes disintegration, dissolution, and finally absorption, as illustrated in Fig. 4.

It is important to distinguish between disintegration and dissolution. Disintegration is the breaking apart of the compressed tablet into primary particles. By including certain disintegrating agents in the formula, one can produce a tablet that will literally explode when submersed in water. Although disintegration is a prerequisite to absorption and rapid disintegration certainly enhances a speedy onset, it does not ensure absorption. If the drug particles do not dissolve after disintegration takes place, then the drug will never reach the bloodstream. This would be no different from swallowing the ancient "perpetual pill" of gold which was retrieved for continuous use throughout a person's lifetime and passed along with the family inheritance. It is easily recognized that such treatment never resulted in blood levels of gold. A negative disintegration test is certainly evidence of a poor tablet, for if the first step does not occur, dissolution will be difficult and absorption may never take place. Fast disintegration will aid in predicting uniform behavior from the tablets, but it will not, in itself, ensure efficacy.



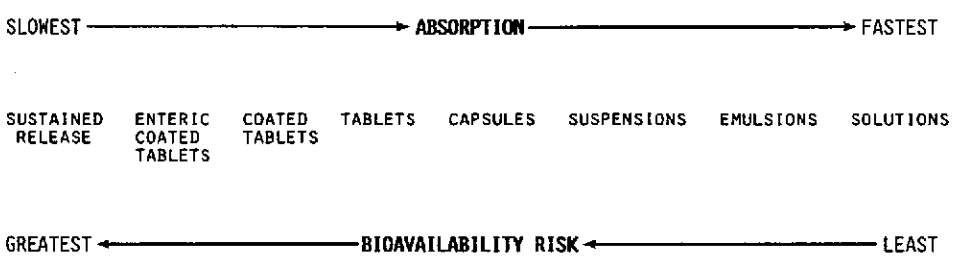
Scheme III

Scheme III illustrates the usual absorption steps following the oral ingestion of capsules or coated tablets. In theory, any one of these steps could become rate limiting. In practice, the dissolution rate is generally the slowest step following oral administration of a solid dosage form. One rule of thumb suggests that drugs which have an aqueous solubility of less than 1% of pH 1–7 at 37°C are predisposed to bioavailability problems. Under similar conditions, a rate of dissolution that is less than 0.1 mg/ml per square centimeter using a rotating disk of constant surface area is a predictor of dissolution-rate-limited absorption.

Drugs whose solubility characteristics are less than ideal require optimum formulations to avoid exacerbating an inherent bioavailability problem. Although less likely, it is possible to observe poor bioavailability with a solid

dosage form of a highly soluble drug. In Scheme III this can occur in the steps preceding disintegration to form drug particles in suspension. Drug bioavailability could be impaired by failure of the tablet's coating to expose the contents or failure of the enclosed tablet to readily disintegrate. If both of these steps are fast, the dissolution of particles in suspension would be expected to become rate limiting. If this is also rapid, then absorption of the drug itself would be the rate-limiting step.

Thus the more complex the dosage form, the greater the number of potential rate-limiting steps and the greater the risk for incomplete bioavailability. The degree to which a formulation can influence absorption rate and thereby potentially play a role in bioavailability can be predicted on this basis. The anticipated results are shown in Scheme IV.



Scheme IV

As a first approximation, most marketed drugs are well absorbed from the intestine if they are in solution. However, dosage forms vary with regard to the rate at which they can present drug in solution to the g.i. wall. Drugs administered in solution (syrups, elixirs, and solutions), are most rapid in presenting drug for absorption, because rate-limiting dissolution is eliminated by the dosage form. Sustained- or prolonged-release dosage forms would be expected to be the slowest, since the release of drug is intentionally retarded. Enteric-coated tablets are designed to prevent drug release prior to arrival in the intestines. The coating must first dissolve in the case of a coated tablet. Tablets themselves are next. Rapid dissolution of the drug in the tablet will not occur until the tablet itself disintegrates. Capsules must have the capsule shell dissolved before the contents are available for dissolution. Whereas the capsule contents might behave as a tablet if they were compressed, it is more likely that they will behave like a suspension and distribute quickly into the g.i. fluids. Suspensions have no coating to remove, no tablet to disintegrate, and no capsule shell to dissolve; however, they are slower than emulsions, because the suspended drug must still undergo dissolution in the g.i. fluids. Emulsions contain dissolved drug which must partition between the immiscible phases. Finally, solutions present the drug directly on the g.i. wall for

absorption. Any one of the other dosage forms can be as rapidly bioavailable as the solution if the steps preceding absorption are sufficiently rapid. Generally, a drug in one of the nonsolution dosage forms would not be absorbed more rapidly than that of a solution.

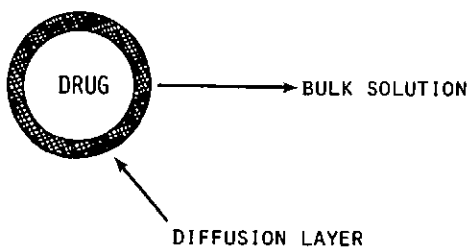
2. Noyes–Whitney Dissolution Rate Law

In the presence of fast disintegration with a rapidly absorbed drug, the dissolution rate of the drug particles themselves will limit the rate of appearance of drug in the blood. These conditions may be considered as the usual case. Often, one can increase the absorption rate by increasing the rate of dissolution. Since dissolution rate is the limiting factor, it follows that to control dissolution rate is to control absorption. This is the ultimate goal in any product development: to control the behavior of that product when it is in use in the clinic. In the case of solid dosage forms, it is therefore necessary to control dissolution rate. Let us begin by examining the factors that influence dissolution rate. By controlling these factors by either the design or the use of the product, we should be able to control the dissolution rate of drug.

For the purpose of this discussion it is convenient to examine a modified form of the Noyes–Whitney dissolution rate law given as

$$\frac{dC}{dt} = (C_s - C)\frac{kDS}{Vh} \tag{6}$$

where dC/dt is the rate of increase in C, the concentration of drug in a bulk solution in which dissolution of the solid particles is taking place; k is a proportionality constant; D is the diffusion coefficient of the drugs in the solvent; S is the surface area of undissolved solid; V is the volume of the solution; h is the thickness of the diffusion layer around a particle; and C_s is the solubility of the drug in the solvent.



Scheme V

When a particle of drug undergoes dissolution, it is surrounded by a layer

considered to be saturated with regard to drug, as shown in Scheme V. This saturated solution is the diffusion layer. Drug moves from the diffusion layer into the bulk solution. The rate-controlling step in this process can be a function of agitation. Dissolution into the diffusion layer may be slower than diffusion to the bulk solution under high rates of stirring. The degree of agitation within the g.i. tract may be considered relatively mild so that diffusion from the saturated layer to the g.i. wall is generally rate limiting. If we consider a given drug under well-defined conditions (such as controlled liquid intake), we may assume that D, V, and h are relatively constant values. Thus we can reduce Eq. (6) to

$$\frac{dC}{dt} = k'S(C_s - C) \tag{7}$$

Equation (7) shows that two variables which may be controlled by the formulation are the surface area and the solubility of the drug. These two variables can be altered by the following techniques:

1. Control the solubility of a weak acid or base by buffering the entire dissolution medium, the "microenvironment," or the diffusion layer surrounding a particle.
2. Control the solubility of the drug through choice of the physical state, such as the crystal form, its hydrate, and its amorphous form.
3. Determine the surface area of the drug through control of particle size.

If we further assume that dissolution is rate limiting to the point that the accumulation of drug in the g.i. fluids is negligible relative to the solubility of the drug itself, or $C_s >> C$, then

$$\text{dissolution rate } \alpha \text{ surface area} \times \text{solubility} \tag{8}$$

Equation (8) will be particularly important in the design of certain sustained-release products which are discussed later in this chapter.

a. Buffering Stomach pH to Increase Solubility. It should be kept in mind that we are dealing with *solubility* as a means of increasing or decreasing *dissolution rate*. The difference between these terms should be clear to the reader before proceeding. Equation (8) emphasizes that the terms are different although usually related. There are exceptions to the generality that dissolution rate is proportional to solubility, but they are sufficiently rare that we will assume there is a direct relationship. Solubility is a thermodynamic parameter; that

is, it represents the concentration of a solution of drug at equilibrium with undissolved solute. The dissolution rate is a kinetic term that describes how fast a drug dissolves in a solvent. We are now considering increasing or decreasing the total solubility C_s of a drug in the g.i. fluids in order to affect the rate of dissolution and thus the rate of absorption.

The total solubility S_T of a weak acid is the sum of the ionized (A^-) and the un-ionized (HA) forms and increases with pH according to the equation

$$S_T = S_0 (1 + 10^{pH - pK_a}) \tag{9}$$

where S_0 is the intrinsic solubility of the undissociated form and is therefore relatively constant independent of pH. Equation (9) is valid at pH values below that pH at which the solution becomes saturated by the ionic species. As the pH of the solvent is increased, the total solubility of a weak acid will increase owing to increased formation of the anion A^-.

One approach to increasing dissolution rate woutld be to coadminister an antacid with a weak acid drug *HA*. Since the stomach pH can be buffered toward alkalinity, the total solubility of the drug would increase in accordance with Eq. (9). The dissolution rate would be enhanced as described in Eq. (8). The alert reader may question the wisdom of converting a weakly acidic drug to its charged form in order to enhance absorption. However, the principle can be documented by considering some studies done on aspirin. When aspirin was dissolved in water in the presence of buffers and administered orally, the onset for salicylate blood levels was found to be faster than that obtained by swallowing either plain or buffered aspirin tablets, in spite of the fact that the pH of the stomach was raised to 7 by the buffered solution. One must keep in mind that two different rate-limiting steps are being compared here. In the case of the buffered solution the dissolution step has already taken place before swallowing. Absorption occurs primarily through the uncharged form of aspirin, but this is in rapid equilibrium with a reserve of the charged form. In the case of the tablets the rate-limiting factor is that of dissolution. One explanation for the difference in absorption rates is that dissolution of aspirin at pH 1–3.5 is slower than partitioning of aspirin from a solution of pH 7 into the g.i. membrane. This is partially due to the fact that the total amount of aspirin in solution is much greater at pH 7 than at pH 1–3.5, as can be seen from Eq. (9). In general, we will assume that speeding up the dissolution rate will result in increased absorption, in spite of the problem associated with the effect of pH on the concentration of the absorbable species. Adjusting the pH of the entire gastric fluid content is not commonly employed as a means of increasing dissolution rate in clinical practice.

The total solubility of a weak base is also the sum of the ionized (R_3NH^+) and un-ionized (R_3N) forms. In this case total solubility increases with decreasing pH according to

$$S_T = S_0(1 + 10^{pK_a - pH}) \tag{10}$$

The solubility of weakly basic drugs, such as ephedrine, should be favored by the normally acidic pH of the stomach, which would increase the difference pK_a − pH and increase solubility. In contrast, the total solubility for a weak base would be reduced in the intestinal pH relative to the stomach. While the pH of the stomach can be controlled by the use of antacids, adjusting the intestinal pH is not clinically feasible. Weak base drugs are often administered as their hydrochloride salts to overcome the intestinal pH problem, as discussed next.

b. Soluble Salts. Weak acids are often administered as sodium or potassium salts, while weak bases may be given as their hydrochloride salts. Since their total solubility in the g.i. fluids depends upon pH, Eqs. (9) and (10), the salt form per se does not determine total solubility. A typical dose of a drug could not be expected to alter the pH of the g.i. fluids, but the salt will alter the pH of the diffusion layer and thereby the dissolution rate.

When a weak acid is dissolved in water, the pH may be approximated from

$$\text{pH} = \frac{1}{2}(pK_a - \log C) \tag{11}$$

where C is the total concentration of the acid in the solution. If a salt of a weak acid and a strong base is dissolved in water, the pH may be approximated from

$$\text{pH} = \frac{1}{2}(pK_w + pK_a + \log C) \tag{12}$$

Thus for moderately concentrated solutions the pH of a solution of the salt of a weak acid and a strong base will be higher than that of a solution of the same weak acid. Consider 1 M solutions using an acid of pK_a 4 as an example. Since log 1 = 0 and pK_w, the pK for water, is 14, the pH of a 1 M solution of the acid will be 2 and the pH of a 1 M solution of its sodium or potassium salt will be 9.0. We can now easily understand why salts are more soluble than the free acids. They are not more soluble in the literal sense of the word, since the total solubility in both cases is described by Eq. (9). We

can expect a higher total solubility in the case of a salt owing to the buffering of the solvent to a higher pH by the strong base cation. In the example just discussed, the pH was 7.0 units higher for the salt than for the acid. Placing the acid in solvent of pH 9 would produce identical results for both.

Consider the dissolution rate difference which might be observed in the preparation of two solutions, an acid and its sodium salt, each in a breaker of water. As the free acid dissolves, the pH of the water would be lowered and the total solubility would approach the value of S_0 in Eq. (9); however, as the acid's sodium salt dissolves, the pH would be increased and the total solubility S_T would also increase. If we were to measure the rate of dissolution, we would find that the sodium salt is dissolving at a much faster rate. This is easily understood by examining Eq. (8) for the case where the surface area for the acid and its salt are equal, so that

$$\frac{dC}{dt} \alpha S_T \tag{13}$$

Since we are speaking of one acid, the value for S_0 is constant in both beakers. The ratio of the dissolution rates will be equal to the ratio of the total solubilities, as indicated by

$$\frac{S_T}{S'_T} = \frac{1 + 10^{pH - pK_a}}{1 + 10^{pH' - pK_a}} \tag{14}$$

where S'_T and pH′ are the values for the free acid and S_T and pH are the values for the sodium salt. For the sake of illustration, assume that an acid of pK_a 3 had a pH of 2 at saturation while its salt produced a pH of 6. The ratio S_T/S'_T would thus be 910. If all the other variables are held constant, then Eq. (13) would predict that the dissolution rate for the salt of the acid would be 910 times faster than the free acid.

So far we have discussed dissolution rates in beakers of water. How significant are these calculations in vivo? Certainly the salt form of an acidic drug would not be capable of buffering the pH of the gastric fluids. The dose of the salt form of the active ingredient would be much smaller than the required doses for antacid tablets. It is easily recognized that this salt would not affect the pH of gastric juice.

There are many examples illustrating that the sodium or potassium salt of a weak acid drug is more rapidly absorbed than the free acid itself when each is administered orally in tablets. A few examples are the sodium and potassium salts of penicillins, cephalosporins, barbiturates, sulfonamides, and salicylates [4]. If the pH of the stomach is unchanged by these salts, how do they increase absorption rate?

We can assume that each particle of undissolved drug is surrounded by a thin zone of saturated solution called the diffusion layer. Dissolved drug diffuses from this zone into the bulk solution, creating a nonsaturated space in the diffusion layer. As this occurs, more drug is dissolved from the particle into the layer. Thus the diffusion layer remains at a steady-state concentration that would approach the saturation solubility of the drug in the area immediately adjacent to the solid. We might diagram this as

$$\begin{bmatrix}\text{drug in}\\ \text{solid state}\end{bmatrix} \rightleftarrows \begin{bmatrix}\text{drug in}\\ \text{diffusion layer}\end{bmatrix} \overset{\text{diffusion}}{\rightarrow} \begin{bmatrix}\text{drug in}\\ \text{bulk solution}\end{bmatrix} \qquad (15)$$

The migration of drug from the layer surrounding the particle into the bulk solution would take place owing to the concentration gradient. Agitation would occur constantly, and the movement of drug into the bulk solution would be due primarily to this mixing rather than the diffusibility of the drug itself.

This model is simplified, since a continuous concentration gradient would exist between the solution near the particle and that in the bulk. However, we will assume that the diffusion layer is in the steady state and that it is a saturated solution of the drug. If the pH of this layer were increased, then one would expect the solubility of a weak acid in the layer to increase. A sodium or potassium salt of a weak acid would be expected to have a diffusion layer of higher pH than that of the free acid. In spite of the fact that the bulk solution will have the same pH in both cases, the salt would have a faster dissolution rate.

If we consider the dissolution rate of an acidic drug in the stomach at pH 1–3, it is obvious that the total solubility in the bulk solution is rather limited. The question is Which form will saturate this gastric fluid first, the acid or the salt? Since the salt form has a higher pH in the diffusion layer, the dissolution of the particle will take place faster. If absorption is rapid, we may assume that the bulk solution will also be in a near steady state and that the particle which dissolves faster into its diffusion layer will result in faster absorption. Thus it is a general observation that the sodium or potassium salts of acidic drugs are absorbed faster. One might expect reprecipitation of the free acid to occur in the bulk solution if the pH is several units lower than that surrounding the particle, since total solubility is described by Eq. (9). It is likely that this precipitation would result in very fine crystals with a resultant increase in surface area as compared to the free acid form itself. While this may or may not represent an additional advantage of the salt form, it does not negate the fact that a saturated solution of free acid in stomach fluids occurs faster beginning with the salt form.

The discussions to this point have centered around increasing the rate of absorption of weak acids. There are somewhat analogous examples for weak

base drugs, R_3N. As previously discussed, these drugs would be absorbed from the intestines. Since they must first pass through the stomach, there is an opportunity for rapid dissolution in acidic medium, as the total solubility of a base increases when it is protonated to form the charged species. However, the variability in stomach emptying time precludes any dependability in predicting that dissolution will take place in the stomach before the tablet is passed into the intestines. For this reason several basic drugs are administered in the protonated forms as the hydrochloride salts. Since the basic drug is administered as the salt ($R_3NH^+Cl^-$), the passage of undissolved particles to the alkaline intestines will be somewhat compensated by the more soluble form. A few examples of such drugs are tetracyclines, antihistamines, phenylalkylamines such as amphetamine and pseudoephedrine, and most alkaloids [5].

Thus the absorption rate of both acidic and basic drugs from solid dosage forms may be increased by administration of their salts. In terms of Fig. 1, increasing the absorption rate would decrease t_{max}, increase C_{max}, and decrease the duration. For example, the shortest duration for a given dosage would result from rapid intravenous injection. If onset and peak height are the most signficant parameters for a given drug therapy, then rapid absorption should be the goal in the development of that solid dosage form. However, it may be a therapeutic advantage to have a lower peak level and a longer duration. Controlled drug delivery is discussed in Sec. V.

We might consider the problem of developing an oral tablet for the control of blood sugar levels (an oral hypoglycemic agent). If the drug is absorbed quickly, a fast dissolution rate would result in a high blood level and a possible temporary state of hypoglycemia in the patient. A very short duration would require frequent dosing in order to control blood sugar. The onset of the action would not be so critical here, since the treatment would be a chronic one and not subject to the same considerations as treating a systemic infection with an antibiotic, where onset and peak height might be paramount. Since the patient will continue to take the hypoglycemic agent, a more constant blood level of longer duration may be more ideal. A case in point is that of tolbutamide and tolbutamide sodium. It has been reported that the sodium salt has a very rapid, strong, but short-acting effect on the lowering of blood sugar levels, whereas the control with the free acid was more suitable for therapy [6]. The commercial tablets are in the free acid form. Thus the control of dissolution rate can be tailored to the specific needs of the disease under treatment. From the standpoint of optimum clinical effectiveness, there is an ideal time course for the presentation of every drug.

c. Buffered Tablets. Buffered aspirin tablets and buffered penicillin tablets are two well-known examples of this approach. The incorporation of buffering agents controls the pH in the solution surrounding the undissolved particles of drug. In the case of an acidic drug this may be accomplished by

including such agents as sodium bicarbonate, sodium citrate, magnesium oxide, and magnesium carbonate. The amount of these agents in a typical buffered tablet is not sufficient to alter the pH of the stomach contents. For example, a typical buffered aspirin tablet contains 0.1 g of magnesium carbonate and 0.05 g of aluminum dihydroxyaminoacetate. Another contains 0.15 g of magnesium and aluminum hydroxide. A typical antacid dose of magnesium carbonate is 0.6 g, for aluminum dihydroxyaminoacetate it is 1 g, and for magnesium and aluminum hydroxide combined it is 0.8–1.6 g. It is obvious that the doses in aspirin tablets are not sufficient to raise the pH of gastric juice. In fact, it has been experimentally determined that the pH of the stomach remains unchanged following the ingestion of buffered aspirin. It has also been demonstrated that the dissolution and absorption rates of aspirin are increased for buffered tablets relative to plain aspirin tablets [7–9].

Although the exact mechanism remains unclear, the enhancement might be due to increasing the pH of the microenvironment, since the pH of the bulk solution is not changed but the dissolution rate is increased. Thus the area immediately surrounding the aspirin particles may be elevated in pH owing to the proximity of the buffer components of the dosage form itself.

d. Soluble Polymorphs. Polymorphism is the ability of a drug to crystallize as more than one distinct crystal species [10]. These forms can differ in such properties as melting point, density, x-ray diffraction, hardness, infrared spectra, and, most important to this discussion, solubility. Thus, while the solution phase will have only one form of the dissolved drug, the solid phase can contain two or more forms. Only one form will ultimately be stable, and if the solution is allowed to stand, it will approach an equilibrium containing a single type of crystal. If this transformation is sufficiently slow, the thermodynamically unstable polymorph is called *metastable*. The most stable polymorph usually has the highest melting point and the lowest solubility. The amorphous form is always more soluble than the crystalline form. Since the dissolution rate is proportional to solubility and the drug must be dissolved in order to be absorbed, the conversion from a metastable to a stable form can represent a real problem in bioavailability.

Novobiocin in suspension provides one example of this phenomenon [10]. The amorphous form of novobiocin is orally absorbed, whereas the crystalline form is not. At 25°C in 0.1 N HCl the amorphous form was found to be 10 times more soluble than the crystalline form. In novobiocin aqueous suspensions the equilibrium

$$\begin{bmatrix}\text{amorphous}\\ \text{novobiocin}\\ \text{solid}\end{bmatrix} \rightleftharpoons \begin{bmatrix}\text{novobiocin}\\ \text{in}\\ \text{solution}\end{bmatrix} \rightleftharpoons \begin{bmatrix}\text{crystalline}\\ \text{novobiocin}\\ \text{solid}\end{bmatrix} \tag{16}$$

will slowly convert to the more stable crystalline precipitate, with decreasing oral effectiveness to the point where the therapeutic effect is finally lost. Aqueous suspensions of amorphous novobiocin can be stabilized against conversion to the inactive crystalline form for sufficient periods of time to be clinically useful by including such agents as methylcellulose, povidone, sodium alginate, and propylene glycol algin.

There are many drugs which exhibit polymorphism, among them chloramphenicol palmitate, cortisone acetate, sulfathiazole, methylprednisolone, hydrocortisone, prednisolone, and aspirin (where a 50% difference in dissolution rate between two polymorphs has been reported). Poole et al. [11] have demonstrated that the solubility of anhydrous ampicillin is 20% higher than that of the trihydrate, and this resulted in both an increased rate and an increased amount of drug absorbed after oral administration of suspensions and capsules to humans.

The previous examples serve to illustrate the fact that the bioavailability of a drug from a solid dosage form can be increased by controlling the physical state of the drug. They also demonstrate that a product can assay for 100% potency yet be clinically inactive owing to the use of the wrong polymorphic form of the drug.

e. Controlling Drug Surface Area Through Particle Size. Equation (8) contains two variables that can be controlled in the development of solid dosage forms: surface and solubility. Presenting a large surface area by using finely powdered drug can enhance the dissolution rate. While we are prone to think in terms of fast absorption, an ideal absorption pattern for each individual drug should be the goal of modern product development. Two examples have been chosen to illustrate this point. In one case we will review the rationale behind a microcrystalline product, and in the other case that behind a macrocrystalline product.

Griseofulvin is a white, thermostable powder of needlelike crystals with a solubility in water between 1 and 10 μg/ml. When given orally, griseofulvin often exhibits irregular absorption owing to its limited solubility [12]. Once absorbed, griseofulvin is distributed into tissues, fat, skeletal muscle, and keratin and is also bound to protein in the bloodstream. Tissue levels parallel blood levels, and the apparent biological half-life is 18–24 hr following oral administration. The most common reason for clinical failure with griseofulvin therapy is poor absorption. Since absorption is the limiting factor for effective griseofulvin therapy, several methods for increasing dissolution rate have been examined. The effect of sodium lauryl sulfate was deemed insignificant in multiple-dose therapy. Marvel et al. [12] and Kraml et al. [13] demonstrated that 0.5 g of microcrystalline griseofulvin produced blood levels equal to or higher than 1.0-g doses of regular griseofulvin. Since griseofulvin is fat

soluble, high-fat diets were also examined. It was shown by Crounse [14] that 1 g of microcrystalline griseofulvin gave blood levels roughly twice as high as those in fasting patients administered regular griseofulvin and that a high-fat diet more than doubled the levels from the microcrystalline material. The average serum levels from microcrystalline griseofulvin doses of 0.5 g are equal to or better than those obtained from 1.0 g of the regular form.

The potential for side effects from administration of a drug increases as the percentage of absorption decreases. If a drug is only 5% absorbed, for example, the patient is really swallowing 20 doses. If for some reason erratically high absorption takes place, there is an increased chance for toxicity. The advantage of microcrystalline griseofulvin is clear. It produces higher blood levels and, weight for weight, is more effective than the original form. A high-fat diet seems to be a rational adjunct.

There are other examples of micronized drugs, such as sulfadiazine, sulfaethylthiadiazole, aspirin, and tetracycline. However, this does not imply that micropulverization of drugs for solid dosage forms is a general panacea. Let us examine the rationale behind at least one exception, nitrofurantoin.

Nitrofurantoin has a solubility of about 200 mg/liter at pH 7. The usual dose is about 50–100 mg taken four times a day. Since it is a weak acid and the volume of stomach fluid is about 100 ml, one would not expect an entire dose to dissolve easily. However, it would appear that about 36% of the amount ingested in the form of fine crystals (10-μm range) is absorbed [15]. An unspecified percent incidence of nausea and vomiting has been reported in patients taking nitrofurantoin. It was thought that these side effects might be linked to the rate of absorption. Rapid absorption can result in high peak blood levels which may be associated with side effects. In the present case unabsorbed drug in solution in contact with the surface of the g.i. tract might also cause some irritation, contributing to the nausea and vomiting. In either case proper control of the dissolution rate would be expected to decrease the untoward response. The rate constant for release from the capsules is a function of particle size. The effect of crystal size on the rate and amount absorbed was studied by determining the percentage excreted as a function of time. Data indicate that the blood level peak height, as well as the total amount absorbed, decreased with increasing crystal size. However, it was possible to choose a large crystal size (80–200 mesh) that represented about 31% absorption, which was roughly equivalent to the originally marketed crystals (10 μm), which are 35% absorbed. The macrocrystals give lower peak blood levels, as reflected by the maximum amount excreted in a fixed time interval, which was 20% for the fine crystals and about 15% for the macrocrystals. Capsules of macrocrystals were used clinically in 112 patients who experienced nausea and vomiting with the tablets (fine crystals), and

89 (79%) tolerated the macrocrystals. Of these, 22 were rechallenged with the tablets and 85% of these again experienced nausea and/or vomiting. Thus, in this case, the use of large crystals reduced the side effects without significantly reducing the percentage of absorption. It should be noted that total absorption is not a valid criterion for therapeutic equivalency. Nitrofurantoin is indicated for the treatment of genitourinary tract infections. The therapeutic equivalency claimed for the macrocrystals is based on equivalent urinary concentrations [16] and effectiveness in treating urinary tract infections as measured by clinical and biological criteria [17].

Sample Problem 1

Three formulations for aspirin tablets were prepared and their bioavailability was tested in 10 subjects. The formulations were described as (A) tablets, (B) buffered tablets, and (C) buffered tablets of micronized aspirin. Results are given in Fig. 5. Assuming that tablets A and B give similar results (the

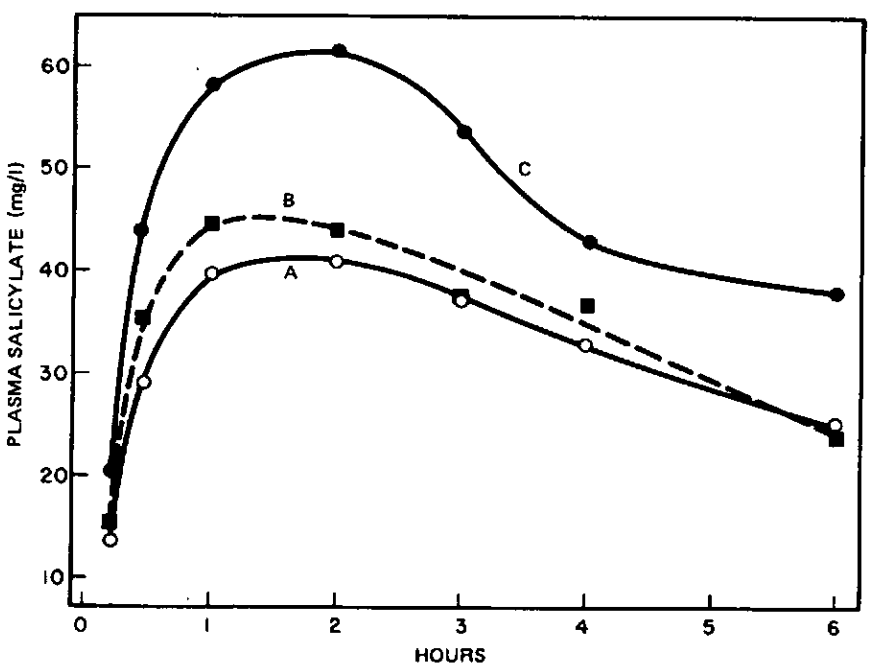


Fig. 5 Average total plasma salicylate levels following the ingestion of three commercial aspirin tablets by 10 patients: (A) plain aspirin tablets, (B) buffered tablets, and (C) buffered tablets of micronized aspirin.

difference being due to biological variation), what is the percent increase of aspirin absorbed from product C?

Solution: A rough estimate can be obtained from the peak heights which occur at about 2 hr. It would appear that approximately 50% more is absorbed from product C. However, in such an evaluation of products it is necessary to know the dose. Product C contains 7.5 grains of aspirin per tablet while products A and B contain 5 grains each. If this comparison were made with equal numbers of tablets (rather than equal doses), the 50% increase would be attributed to 50% more aspirin administered. The time course for aspirin per se is also masked by the fact that this figure represents total salicylate in blood. Unfortunately, it is not difficult to observe such presentations in the advertising media.

Practice Problem 1

(a) What is the concentration in moles per liter of the diffusion layer surrounding penicillin G potassium if the pH of the layer equals 8? (The pK_a of penicillin G is 2.76.)
Answer: 0.174 mol/liter.

(b) What is the *solubility* of penicillin G (not the potassium salt) at a pH sufficiently low to allow only the nondissociated form? [Hint: Use your answer from part (a) and Eq. (9). Consider the diffusion layer to be saturated.]
Answer: 1×10^{-6} mol/liter.

(c) Consider the initial rates of absorption of penicillin G potassium and penicillin G from identical solid dosage forms. Calculate the value you would predict for the ratio R_1/R_2, where R_1 is the rate of absorption from penicillin G potassium and R_2 is the rate of absorption from penicillin G. [Assume the solubilities that you calculated in parts (a) and (b).]
Answer: 1.74×10^5

Practice Problem 2

(a) Calculate the pH of a 4×10^{-3} M solution of sodium sulfathiazole. (The pK_a of sulfathiazole is 7.1.)
Answer: 9.35.

(b) Calculate the pH of a 4×10^{-3} M solution of sulfathiazole.
Answer: 4.75.

(c) Assuming the diffusion layers in cases (a) and (b) have the pH values you calculated, calculate the *total* solubility of sodium sulfathiazole and of sulfathiazole in their respective stagnant layers. The intrinsic solubility is given above, 4×10^{-3} M.

Answer: Sodium sulfathiazole, 0.716 mol/liter; sulfathiazole, 0.004 mol/liter.

(d) Given in similar tablets (same binders, same disintegration, etc.), which would be absorbed faster? Explain your choice.
Answer: The sodium salt.

Practice Problem 3

(a) Explain, using equations, why the rate of dissolution of sodium phenobarbital is faster than that of phenobarbital.

(b) Why would you expect to find a difference in absorption between sodium phenobarbital tablets and phenobarbital tablets but not between enteric-coated sodium phenobarbital tablets and enteric-coated phenobarbital tablets?
Answer: The more alkaline pH of the intestines would mask the advantage of the sodium salt which would increase dissolution rate in the stomach.

Practice Problem 4

(a) Consider the absorption following oral administration of an elixir containing two drugs, where drug A is RCOOH and drug B is RNH_2. The pH of the stomach is 2. Which would you expect to be better absorbed from the stomach and why?
Answer: Drug A; see text for discussion.

(b) Write the rate expression for the absorption of each drug.
Answer: Absorption rate of drug A = k_1[RCOOH]; absorption rate of drug B = k_1'[RNH_2].

(c) What kinetic order are these rates?
Answer: First order.

(d) The pK_a of drug A is 2, the pK_a of protonated drug B is 3, the dose of each drug is 1 g, and the volume of gastric juice is 100 ml. Write the expression for the *initial* rate of absorption, substituting the concentration of the absorbable species in grams per 100 ml for each case.
Answer: (absorption rate of drug A)$_0$ = k_1(0.5 g/100 ml); (absorption rate of drug B)$_0$ = k_1(0.09 g/100 ml).

Practice Problem 5

(a) Consider transport from blood (pH 7.4) to stomach (pH 2.0) following an intravenous injection. Which would appear to a larger extent in the stomach, phenobarbital (pK_a = 7.4) or morphine (pK_a = 7.9, aminium) and why?
Answer: Morphine (consider uncharged form in blood and stomach).

(b) Explain why the rates of absorption of prednisone, prednisolone, testosterone, and androsterone esters given orally in sesame oil solutions were greater than for the corresponding aqueous suspensions.
Answer: Change in the rate-limiting step.

(c) Explain why the absorption rate of tetracyclines was increased by reducing the particle size, but the absorption rate of tetracycline hydrochloride was not affected by the same treatment.
Answer: Dissolution was not rate limiting for the hydrochloride. Why?

(d) Consider the following data:

	Percent absorbed by oral route
Hexamethonium chloride	5
Pentolinium tartrate	4
Mecamylamine hydrochloride	50

Why are hexamethonium chloride and pentolinium tartrate poorly absorbed compared with mecamylamine hydrochloride? Why is the apparent volume of distribution of drugs such as hexamethonium chloride and pentolinium tartrate only about 7–21%? Why are drugs such as hexamethonium chloride and pentolinium tartrate particularly dangerous if administered orally? Would you expect to find any difference in absorption between tablets of mecamylamine and of mecamylamine hydrochloride and why?
Answer: Hint: Mecamylamine hydrochloride is not a quaternary, but the others are.

(e) A commercial for buffered aspirin states that two of the buffered tablets deliver almost twice as much acetylsalicylic acid as two of the plain aspirin tablets. If the aspirin is completely absorbed in both cases, what is the meaning of the statement?
Answer: The statement arises from the difference in rates and is true only at an early limited time period.

(f) It has been stated by Hogben et al. [2] that acids with pK_a values below 2 and bases with pK_a values above 9 are poorly absorbed when taken orally. Do you agree or disagree and why?

(g) Heparin is marketed only as an injection because the weak acid heparin is not absorbed at a pH above 4, thus limiting oral availability. Esterification has been shown to result in absorption at pH values of 5, 6, and 7. Offer an explanation for this difference in g.i. absorption.

(h) For each of the following cases explain why the particular form of the drug has been selected for incorporation in solid dosage forms: *potassium* penicillin V; tetracycline *hydrochloride*; tolbutamide *free acid*.

III. FACTORS INFLUENCING BIOAVAILABILITY

A. Biological Variability

1. Gastrointestinal Motility

Stomach emptying has been approximately described as an apparent first-order process following the ingestion of test meals. The process can be accelerated by administering large volumes of liquids while food delays stomach emptying. Some poorly soluble antacids, such as aluminum hydroxide, can retard gastric emptying, whereas ingestion of an aqueous alkaline solution may accelerate it. Physical activity, disease states, the emotional state of the patient, the viscosity of stomach contents, and fatty foods can all alter gastric emptying time. Obviously, there will be pronounced biological variability which, coupled with the influence of food, pH, and other drugs, makes predictions speculative. Since the intestines represent an efficient site for drug absorption, the passing of drug from the stomach contributes significantly to the variability in bioavailability by the oral route. It has been suggested that promoting gastric emptying will generally increase the bioavailability of drug. While this will not hold true for all cases, it is frequently true. The most significant point is that g.i. motility can be a variable in the absorption of orally administered products. The experimental protocol employed to compare products which deliver the same drug must control this factor. This is one of the reasons why clinical tests often involve oral administration on an empty stomach.

2. Food or Other Drugs

Stomach pH is temporarily increased by food, requiring 1–2 hrs for recovery to normal acidity. Food (especially fatty foods) also closes the pyloric sphincter, thus delaying stomach emptying. The simultaneous ingestion of food with drugs may influence g.i. absorption by altering dissolution rate, changing gastric emptying time, altering the pH of the stomach fluid, or complexing drug to food or food components. Reducing tetracycline bioavailability by the concomitant administration of milk or certain antacids will be discussed in the Sec. III.B.3 on complexation. Penicillin and cephalosporin absorption is decreased following meals, as discussed in Sec. III.B.2 on instability. However, a reduction in the bioavailability of acid-stable semisynthetics

implies that hydrolysis due to stomach acidity is not the only factor reducing penicillin absorption in the presence of foods.

Aspirin, propanthelene, levo-dopa, and rifampin absorption has been reduced in the presence of food. Delayed absorption of sulfonamides, acetaminophen, digoxin, furosemide, and some cephalosporins has been observed in the presence of food. In contrast, griseofulvin absorption has been enhanced by meals with a high fat content owing to an increase in contact time with the epithelium of the small intestine together with some increase in griseofulvin solubility.

Inhibition of the absorption rate of a drug with a short biological half-life can result in decreased plasma levels and therapeutic failure. Drugs having long biological half-lives would accumulate in the plasma despite some reduction in absorption rate. In general, drugs are very well absorbed from the small intestine, and absorption from the stomach is relatively insignificant. Therefore any drugs which influence the rate of gastric emptying can potentially alter the absorption rate. For example, the absorption rate of acetaminophen, a weak acid of pK_a 9.5, appeared directly related to the gastric emptying rate. Propanthelene, which delays gastric emptying, nearly doubled t_{max} for orally administered acetaminophen. The bioavailable dose did not appear to change. Metoclopramide both stimulated gastric emptying and increased the rate of absorption.

Age, Weight, Activity, and Disease State

Both inter- and intrasubject biological variability can affect g.i. absorption. Bioavailability studies must therefore eliminate or minimize the influence of such factors on the data. Normally, healthy individuals of controlled age and weight are given the test products on fasting stomachs or with controlled diets. Some patients may be alchlorhydric relative to the normal stomach pH. In one report a slowly dissolving tetracycline product showed decreased bioavailability in a group of patients known to be achlorhydric.

The absorption from an effervescent aspirin product was delayed in patients experiencing a migraine attack. This delay was correlated with the severity of the headache and the g.i. symptoms and was assumed to be due to a delay in gastric emptying. This explanation was consistent with an observed increase in aspirin absorption together with a relief of symptoms upon intramuscular administration of metoclopramide, which increases gastric emptying.

Bacterial overgrowth in the upper small intestine is a pathological condition most prevalent in the elderly. It can be of clinical significance during chronic digoxin administration. Bacterial overgrowth has been reported to enhance the g.i. conversion of digoxin to one of its inactive metabolites (dihydrodigoxin), with a resultant decrease in the bioavailability of digoxin [18,19].

Pyloric stenosis impaired the absorption of acetaminophen. It has been suggested that this phenomenon can lead to therapeutic failure in patients with gastric stasis. Prolonged gastric emptying has been cited as the reason for an increase in t_{max} when digoxin and several antibiotics are administered with food. Diseases which delay gastric emptying would be expected to show similar effects. Levo-dopa is poorly absorbed in some patients with Parkinson's disease. This has been attributed to delayed gastric emptying resulting in destruction by gastric decarboxylase.

Gastrectomy decreased the C_{max} of cephalexin while the absorption of ampicillin was unchanged. Iron and folic acid were poorly absorbed, whereas p-aminosalicylic acid was well absorbed. While oral administration would not normally be employed in the presence of intestinal obstruction, undetected changes in gastric emptying, as in pyloric stenosis, can alter the absorption of orally administered drugs.

Four different patterns have been observed for drug absorption in celiac patients: (1) no effect (celiac patients in remission showed normal levels) (2) delayed absorption (lincomycin, amoxicillin), (3) increased absorption (sodium fusidate, trimethoprim, and sulfamethoxazole), and (4) reduced absorption (propranolol, pivampicillin). The increased plasma concentrations observed for cephalexin, sodium fusidate, sulfamethoxazole, and trimethoprim in untreated celiac disease may be due to increased mucosal permeability. A deficiency of esterase in the wall of the g.i. tract of the small intestine could explain impaired pivampicillin activity, since this ester must be hydrolyzed to ampicillin. However, the prodrug ester pivmecillinam showed normal absorption in patients with celiac disease.

There are few examples of altered therapeutic response due to malabsorption associated with disease, but the potential does exist. The difficulty in establishing convincing examples is due to the wide variability of plasma concentrations in patients with malabsorption, making clear-cut, statistically significant conclusions difficult. The physiological state of the patient, including the degree of physical activity, may alter the bioavailability of drugs. Thus malabsorption due to patient variability as well as disease state can simultaneously affect the results.

B. Factors That Decrease Bioavailability

1. Presystemic Metabolism

First-pass metabolism implies that an absorbed drug, following oral administration, passes directly to the liver before reaching the systemic circulation. This can increase the degree of metabolism relative to an intravenous dose.

In dogs the area-under-the-curve values for aspirin and lidocaine are significantly greater when the drug is infused into a peripheral vein than following infusion into the portal vein. Introduction directly into the portal vein is analogous to oral absorption. This reduction is attributed to the exposure of drugs to the liver before reaching the blood, which dilutes and distributes drug to other sites. A rapid intravenous dose will also simultaneously distribute throughout the body while blood passes through the liver. Drug distributed to other organs is temporarily protected from hepatic metabolism.

There are other mechanisms for drug metabolism before arrival in the systemic circulation. Presystemic metabolism can occur, not only in the liver but also in the intestine itself or during passage through the intestinal wall. In all cases the consequences are a loss of intact drug. Unless the mechanism is clearly identified as first-pass metabolism, it is appropriate to describe such loss as presystemic metabolism. Table 2 lists drugs for which presystemic metabolism is considered significant.

This phenomenon may prohibit the oral use of a drug. Lidocaine exhibits poor and variable bioavailability owing to high first-pass metabolism; only 21–46% of orally administered lidocaine reaches the blood. Nortriptyline bioavailability is reduced by approximately 40% following an oral dose relative to intramuscular administration. The low and variable bioavailability of vimipramine (30–75%) has also been attributed to first-pass metabolism.

When first-pass metabolism is subject to saturation, it will produce a nonlinear dependency for the area under the curve (AUC) as a function of

Table 2 Selected Examples of Drugs That Can Undergo Presystemic Metabolism When Given Orally

Acetaminophen	Meperidine
Aldosterone	Methadone
Alprenolol	Methylphenidate
Aspirin	Morphine
Chlorpromazine	Nitroglycerin
Cortisone	Nortriptyline
Desipramine	Papaverine
Dopamine	Pentazocine
Estrogens	Phenacetin
Flurazepam	Propoxyphene
Hydralazine	Propranolol
Imipramine	Salicylamide
Isoproterenol	Terbutaline
Lidocaine	Testosterone

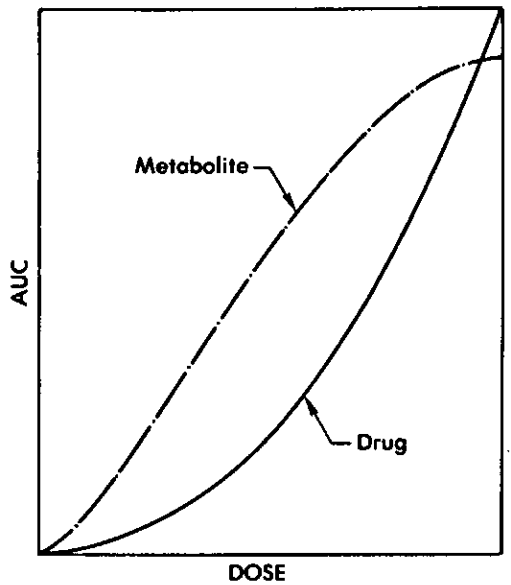


Fig. 6 The area under the plasma concentration–time curve (*AUC*) following the oral absorption of a drug which undergoes saturable first-pass metabolism. At low doses nearly all of the absorbed drug appears in the plasma as metabolite. When the dose is sufficiently high to saturate metabolism, the metabolite formed approaches a constant value and *AUC* values for the drug increase with dose.

dose. The *amount* of surviving drug which arrives in the blood is increased by saturation of the enzymes, thus producing positive deviation from linearity (Fig. 6).

A similar phenomenon is observed for the *rate* of presentation of drug. For example, it has been reported that intact aspirin ester arriving in the bloodstream is decreased when slowly released from a sustained-release dosage relative to a rapidly released aspirin product. In both products the bioavailability of total salicylate was similar. The product that presented aspirin at a faster rate provided a greater *AUC* for aspirin per se by reducing presystemic metabolism [8].

2. Instability

Drugs may be unstable to gastric acid or enzymes present in the g.i. tract. Hydrolysis in the stomach fluids is rather common. If a drug undergoes hydrolysis in the g.i. tract, it becomes involved in parallel rate processes, as respresented by

$$\begin{array}{ccccc} \text{drug} & & \text{drug in} & & \text{drug} \\ \text{in blood} & \xleftarrow{k_a} & \text{g.i. fluids} & \xrightarrow{k_h} & \text{hydrolysis} \\ & & & & \text{products} \end{array} \tag{17}$$

and the apparent first-order rate constant k_{app} may be defined by

$$k_{app} = k_a + k_h \tag{18}$$

The ratio of the rate constants will define the ratio of the competing rate processes so that

$$\frac{k_h}{k_a} = \frac{\text{hydrolysis product}}{\text{drug absorbed}} \tag{19}$$

where the numerator is the amount of degradation product and the denominator is the amount of drug delivered to the blood. What does this mean in terms of absorption? Let us suppose that k_h/k_a was 2; that is, the rate constant for degradation was twice as fast as that for absorption. For every molecule of drug absorbed, two molecules would undergo degradation. Thus the maximum absorption would be 33%.

We will consider the problem of hydrolysis in gastric fluids for two categories of drugs: those for immediate absorption and those whose absorption can be delayed until reaching the intestines. The second category will be considered separately, since it presents the problem of getting the drug through the stomach without degradation.

Hydrolysis of Weak Acid Drugs in Gastric Juices. A good example of this problem is that of penicillins. The carboxylic acid group of the parent structure, 6-aminopenicillanic acid, has a pK_a value in the range 2–3. Rapid absorption, which can begin in the stomach, is clinically desirable. The primary difference in the structure of the penicillins is in the substituent group on the amide. This group is largely responsible for the observed differences in gastric stability, enzyme stability, protein binding, and pharmacokinetics. This is discussed in Chap. 7 on molecular effects.

The β-lactam ring is extremely susceptible to hydrolysis, with a resultant loss in activity. One of the major limitations in systemic activity is instability to penicillinase, an enzyme produced by microorganisms (especially staphylococci). Instability to gastric acid represents another limitation in oral effectiveness. The half-lives for the hydrolysis of penicillins in aqueous acid at 35°C are summarized in Table 3. It is obvious from Table 3 why methicillin is available only in injectable form. It is less obvious why penicillin G would ever be chosen for oral administration; its bioavailability is variable and not

Table 3 Half-Lives for the Hydrolysis of Various Penicillins at pH 1.3 and 35°C[a]

Penicillin	$t_{1/2}$ (min)
Methicillin	2.3
Penicillin G	3.5
Phenethicillin	68
α-Methoxybenzyl	77
Oxacillin	160
Penicillin V	160
α-Chlorobenzyl	300
Amoxicillin	540
Ampicillin	660

[a]Refs. 6 and 11 in Chap. 7.

dependable, since it is extremely labile to stomach acid. As an injectable, methicillin has the advantage of being relatively stable to penicillinase, along with oxacillin and cloxacillin; penicillin G is the least stable of the penicillins, and the rest lie between these extremes.

In order to calculate the percentage of hydrolysis of a penicillin relative to its absorption, it is necessary to have a value for the absorption rate constant for each case. Lacking this data, one can estimate the hydrolysis which would occur in the absence of parallel absorption. The following problem serves to illustrate this point.

Practice Problem 6

For the purpose of solving this problem, use the $t_{1/2}$ values for hydrolysis given in Table 3; these estimates will serve to compare the stability of penicillin G to that of penicillin V at pH 1.3, and 35°C, which is closer to the pH of the stomach than to that of orange juice. The present example is meant to simplify the calculations by eliminating absorption from the problem.

(a) A mother wishes to crush penicillin G tablets in orange juice and administer them to a child. If the process takes 2 min, how much penicillin (in percent of dose) will the child swallow? What if the process takes 5 min?
Answer: 67% (2 min); 37% (5 min).

(b) What answers would you get for part (a) if penicillin V were employed?
Answer: 99% (2 min); 98% (5 min).

(c) Consider the case where the tablets are mixed with juice at 8 a.m. and used throughout the day. For each penicillin listed, how much active drug would remain at 6 p.m.?

Answer: Methicillin, 0%; penicillin G, 0%; phenethicillin, 0.2%; α-methoxybenzyl, 0.5%; oxacillin, 7.6%; penicillin V, 7.6%; α-chlorobenzyl, 25%; amoxicillin, 46%; and ampicillin, 53%.

(d) Why is it recommended that penicillin G oral tablets (including buffered ones) be taken on an empty stomach at least 2 hr after meals yet no such statement is found in the prescribing information for penicillin V?
Amount: Penicillin V is nearly 50 times more stable to stomach acid than penicillin G, which has a 3.5-min half-life. Food delays stomach emptying, thus trapping drug in an environment that is more acidic than the intestines.

b. Delaying Absorption Until Reaching the Intestines. According to pH partition theory, the uncharged form of a drug is better absorbed than the charged species. This might lead one to expect that the intestinal pH of 6–8 would principally allow the absorption of weakly basic and non-ionizable drugs. In practice, the absorption efficiency of the intestines predominates over theory. Of those drugs which are orally bioavailable, most are generally amenable to intestinal absorption even though they are primarily ionized as calculated by Eq. (3). However, the rate of intestinal absorption of an ionized species will probably be reduced relative to the neutral form. If the clinical use of the drug does not require immediate onset of action, as is the case with chronic dosing, then intentionally protecting against gastric dissolution is a viable alternative.

The antibiotic erythromycin is one example of an acid-unstable drug that is available in a number of different dosage forms. Erythromycin is most stable at pH 6–8 and is rapidly destroyed at pH values less than 4. The protonated form of the erythromycin base has a pK_a of approximately 8.9. Thus erythromycin would be primarily in the protonated form throughout the g.i. tract. One would expect that the combination of gastric instability and charged species would make oral absorption poor or perhaps irregular at best. Intestinal absorption should be better than absorption from the stomach. Gastrointestinal absorption can be increased by protecting erythromycin from the gastric fluids. Several approaches have been employed in this case.

The most obvious solution is to use enteric coating. This simple approach is not without its problems. In addition to the fact that certain types of enteric coatings become unacceptable upon aging [20], there is the "all-or-none effect" in using enteric-coated tablets, discussed by Wagner [21]. Average times for passing an enteric-coated tablet from the stomach to the intestines have been reported as 3.61 and 2.63 hr [20]. However, an average obtained from a group of individuals can be misleading when a single tablet swallowed by one patient is considered. In this case the tablet may leave the stomach right away or it may remain in the stomach for anywhere from 0

to 12 hr [21], depending on food ingested, physical activity and body position. This presents the potential for a patient experiencing periods of no medication or receiving a double dose if two tablets are simultaneously passed. However, if the drug is divided into many small particles, then the passing of the particles within a given patient can be randomized and the effect will be a gradual and more predictable emptying. In the case of erythromycin this has been achieved by enteric-coated pellets in capsules, ERYC. The increased bioavailability is illustrated later in Practice Problem 8.

Other forms of erythromycin in common usage are ethylsuccinate, stearate, and estolate. These are available in addition to enteric-coated tablets of erythromycin free base. The erythromycin stearate is a salt of the tertiary aliphatic amine of erythromycin and stearic acid. Although the coated tablet of the stearate disintegrates rapidly in the stomach, the salt does not dissolve readily and its degradation is thus retarded. Once in the intestine, the salt dissociates, yielding free erythromycin base to be absorbed at a pH more favorable to its stability. Since disintegration occurs in the stomach, the passing of the drug is more predictable as a divided powder.

One prodrug of erythromycin is the lauryl sulfate salt of erythromycin propionate ester. This promotes absorption in two ways. Salts of weak carboxylic acids and erythromycin base tend to dissolve in human gastric juice and lose antibiotic activity quickly. Lauryl sulfuric acid is a sufficiently strong acid to resist deplacement by gastric juice. Thus the estolate remains undissolved and retains its potency in acid for long periods of time [22]. In addition the propionyl ester being protected from stomach acids by the lauryl sulfate salt, its intestinal absorption is enhanced by its partition coefficient and its pK_a of 6.9, which is 2 units below that of the free base, resulting in more uncharged drug [22,23]. Once in the blood, the propionyl ester would hydrolyze to yield the free erythromycin. The half-life for hydrolysis in human serum at pH 7.5–7.8 has been reported to be 93 min [24].

There have been conflicting opinions with regard to the advantages of obtaining high blood levels of the propionyl ester prodrug as opposed to the lower levels of drug obtained by administration of the stearate salt. Stephens et al. [25] have reported that the levels in humans after the fifth dose contained 20–35% free base and 65–80% ester, which gives a higher net average of free base than that obtained from the salt. Part of the confusion regarding the advantage of the ester can be attributed to assay procedures and the question of the bioactivity of the prodrug itself. Since the in vitro half-life for hydrolysis of the prodrug ester is 0.5 hr at pH 8, increasing to 5.0 hr at pH 5 [26], it has been suggested that hydrolysis would occur in buffered culture media during microbial assays, with a resultant increase in activity due to a free form. This is discussed further in Sec. III on prodrugs in Chap. 7. It should also be noted that the estolate (and not the free base,

stearate, or ethylsuccinate) can infrequently result in a reversible idiosyncratic cholestatic hepatitis that has been found to subside upon switching to an alternate form of erythromycin [27].

Methenamine is an example of a prodrug that is converted to ammonia plus the antibacterial agent formaldehyde in acidic media at pH values of 5.5 or less. The formaldehyde that is released in this manner in the urine provides the basis for the utility of methanamine in treating urinary tract infections. However, this same mechanism can act to destroy methenamine in the stomach. It has been stated that approximately 10–30% of orally administered methenamine is prematurely converted in the stomach but that enteric-coated preparations will avoid this problem [28]. An interesting approach to the combined problem of instability in gastric juice coupled with the necessity for acidic urine is that of enteric-coated methenamine mandelate. This is a salt of the methenamine base and mandelic acid. The mandelic acid aids in acidification of the urine, while the enteric coating protects the methenamine from conversion in the stomach. It should be remembered that foods or other substances, such as $NaHCO_3$, which would buffer the urine toward alkaline pH would result in decreased effectiveness of methenamine.

Capsules containing enteric-coated aspirin particles, Encaprin, are indicated for arthritis, rheumatism, and chronic pain. They would not be indicated for prompt relief of headache, since the enteric coating will result in delayed absorption. However, on chronic administration the random delivery of aspirin to the intestines should become relatively constant. In this case the goal is to overcome erosion of the gastric mucosa associated with high and chronic aspirin dosage. This is another example of intestinal absorption of a predominantly charged species. Aspirin is a weak acid of pK_a 3.6, making its dissociation to carboxylate anion nearly complete at the intestinal pH.

3. Complexation

The problem of the decreased absorption of drugs by complexation with other agents in the g.i. tract has been widely publicized through the examples of tetracyclines and heavy metals [29,30]. Aluminum hydroxide gels, milk, and milk products have been coadministered with tetracyclines to decrease nausea and vomiting. The complexation of tetracyclines by aluminum, calcium, and so on, might decrease such symptoms, since the complex becomes inactive and unable to penetrate biological membranes. Since tetracyclines sometimes upset the normal g.i. flora, complexation might result in decreased g.i. distress, but the same results would be obtained by not administering the tetracyclines. The extent is illustrated later in Practice Problem 10.

C. Formulation

1. General

Factors such as inert ingredients, manufacturing processes, the form of the drug, and many other formulation variables can markedly influence both the amount and rate of drug release from the dosage form. Several reviews have summarized the resultant differences in bioavailability [31]. In the earlier discussion (Scheme III) it was suggested that tablet disintegration should not limit bioavailability, since competent technology can ensure fast disintegration. However, this does not rule out disintegration as a potential problem. In order to illustrate formulation effects, as well as emphasize the importance of dependable technology, an example will be presented in which disintegration was the problem. The example is one of a capsule, and the disintegration of the capsule mass might better be termed deaggregation or dispersion. This would be analogous to the processes outlined for a tablet, since absorption from a capsule would proceed according to Eq. (20),

$$\begin{bmatrix}\text{drug in}\\ \text{capsule}\end{bmatrix} \xrightarrow{\text{deaggregation}} \begin{bmatrix}\text{solid}\\ \text{drug}\\ \text{particles}\end{bmatrix} \xrightarrow{\text{dissolution}} \begin{bmatrix}\text{drug in}\\ \text{solution}\end{bmatrix} \rightarrow \begin{bmatrix}\text{absorbed}\\ \text{drug}\end{bmatrix} \quad (20)$$

The problem of slow deaggregation limiting the absorption of a drug from a capsule was observed for the antibiotic chloromycetin. Four commercial lots of capsules produced by different manufacturers were compared with respect to deaggregation rate, dissolution rate, particle size, analysis of fill, labeled strength, and absorption profiles in human subjects [32]. These studies emphasize the importance of pharmaceutical formulation in controlling the bioavailability of chloromycetin from capsules. Although all four products contained equivalent quantities of drug, their blood level curves were dramatically different. A qualitative correlation was found to exist between the absorption of chloromycetin and the deaggregation rates of the capsules. In one case the deaggregation rate was so slow that the capsule mass still maintained its capsule shape after 3 hr in simulated gastric fluid even though the gelatin capsule had dissolved. The dramatic differences in the absorption rates are demonstrated in Practice Problem 11.

2. Surface-Active Agents (Surfactants)

Surfactants may influence the absorption of orally administered drugs, but it is difficult to predict the effect. In fact, the wettability of chloramphenicol in the best of the capsules discussed above was achieved using surfactants.

A surfactant may interact with the biological membrane or with the drug itself. Since dissolution of a solid dosage form is often rate determining, solubilization of drug by surfactant may increase the absorption rate. Once a solution is obtained, a further increase in surfactant concentration may increase micellarization of the drug. The absorption of this drug micelle species is generally negligible. Small concentrations of surfactant can also increase membrane permeability.

Small amounts of surfactants in capsule formulations that are difficult to wet can increase deaggregation and enhance absorption. Bile salts are significant for the intestinal absorption of fats, fat-soluble vitamins, and cholesterol. They can increase the solubility of a number of poorly soluble drugs, including glutethimide, griseofulvin, hexestrol, and dienestrol, but the clinical significance is unclear. An increase in riboflavin absorption accompanying sodium deoxycholate administration may be due to decreased gastric emptying. Because riboflavin absorption is predominantly an active process in the proximal intestine, a reduction in the rate of drug presentation would favor absorption.

Much about the clinical effects of surfactants on drug absorption remains speculative. Surfactants may increase or decrease absorption and should not be indiscriminately added to a formulation.

IV. EVALUATION OF THE BIOAVAILABILITY OF A SINGLE DRUG

The bioavailability of a given drug can be influenced by

1. The formulation
2. The route of administration
3. The physiology of the patient
4. Interactions with foods or other drugs

If the goal is to compare two formulations of the same drug, then the experimental design must maintain the remaining factors constant. The resultant bioavailability may differ with respect to the amount absorbed (i.e., bioavailable dose), the rate of absorption, or both. The bioavailable fraction f is the fraction of the administered dose that enters the systemic circulation:

$$f = \frac{\text{bioavailable dose}}{\text{administered dose}} \tag{21}$$

Rarely does a patient receive the administered dose which is the dose on the label. For example, ampicillin, a widely used penicillin, has an f value of

Table 4 Approximate Bioavailable Fractions f of Selected Orally Administered Drugs

Drug	f
Amoxicillin	0.9
Ampicillin	0.5
Bacampicillin	0.8
Cephradine	>0.9
Cloxacillin	>0.9
Digoxin	
Solution	0.7–0.9
Tablets	0.6–0.8
Lanoxicaps	0.9–1.0
Digitoxin (solution)	0.9
Grisefulvin (micronized)	0.4
Hydrochlorothiazide V	0.6–0.8
Lidocaine	0.3
Metronidazole	>0.9
Oxacillin	0.6
Penicillin V, potassium	0.5
Phenylvutazone	0.9
Pivampicillin	0.9
Propoxyphene	0.2–0.3
Quinidine sulfate	0.9
Talampicillin	0.9
Ticarcillin	<0.1
Tocainide	>0.9

0.5. This means that if you swallow a 250-mg capsule, you absorb only 125 mg. Some representative bioavailable fractions are given in Table 4.

The term *linear pharmacokinetics* applies to cases where the concentration of drug in blood is directly proportional to the bioavailable dose. Consider the oral administration of equal doses of such a drug in two tablet formulations which differ *only* in their bioavailable fractions. For example, let the bioavailable fraction for tablet A be twice that of tablet B. As illustrated in Fig. 7, the concentration of drug in blood following the administration of A will be twice that of B at any specified time. Thus the bioavailable dose will not change the shape of the concentration time course but only the amplitude.

In contrast, the rate of absorption will alter the shape of the curve. Consider a drug described by linear pharmacokinetics administered as equal oral doses in two tablet formulations C and D. In this case the bioavailable fractions are equal, but absorption from C is twice as fast as that from D.

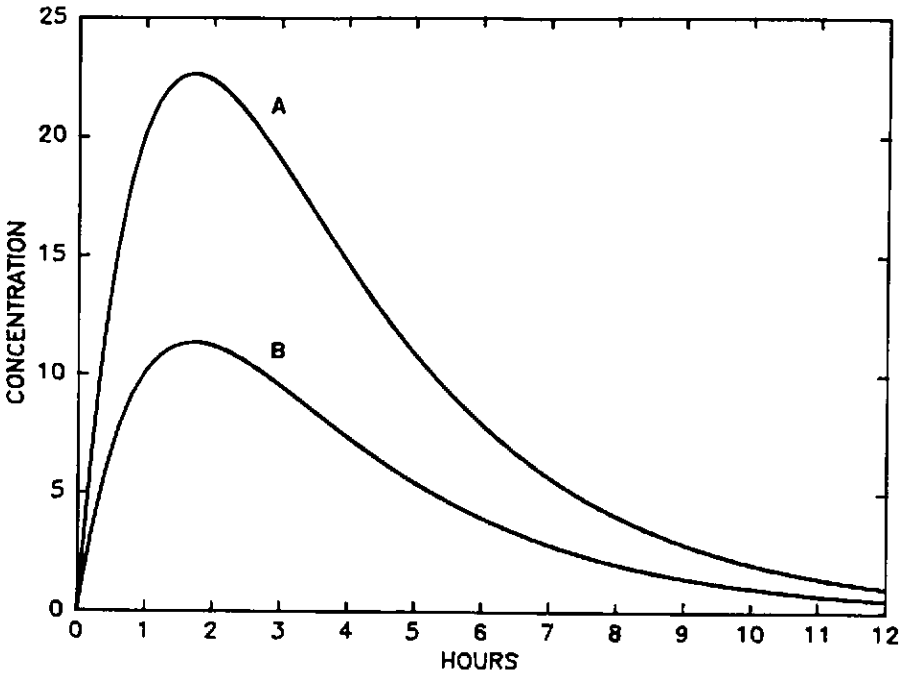


Fig. 7 Plasma concentration time courses for one drug from two different tablets, the bioavailable dose from tablet A being twice that of tablet B.

As shown in Fig. 8, tablet C produces a higher peak concentration at a shorter time interval. Tablet *D* prolongs the concentration time course. The curves cross one another, which is not observed when only f is changed (see Fig. 7).

In summary, bioavailability involves both the rate and the amount of administered drug which reaches the general circulation intact. These two aspects will alter the resultant drug plasma concentration time course in different ways.

A. Clinical Significance of Blood Level Curves

The previous paragraphs described the effect of changing f or absorption rate upon the shape of blood level curves. We are concerned with blood level patterns because only the blood and urine compartments are readily accessible, and the concentration of intact drug and metabolites are therefore determined in these compartments. Figure 9 illustrates the fraction of the initial dose in each compartment following the extravascular administration

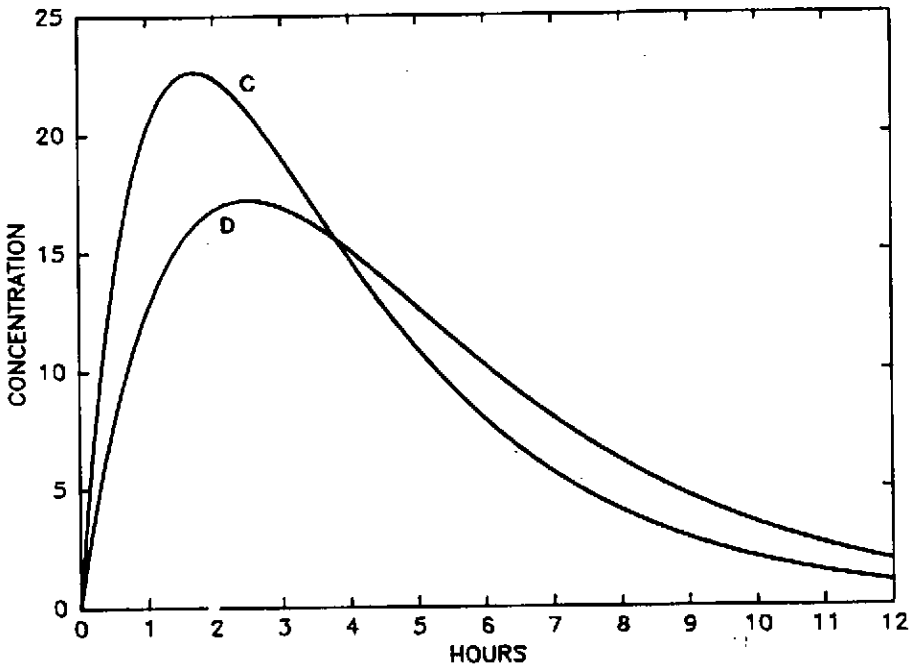


Fig. 8 Plasma concentration time courses for one drug from two different tablets where the bioavailable dose is constant but the absorption rate from tablet C is twice as fast as that from tablet D.

of a drug. A figure such as this can be constructed from data representing assays for blood and urine as a function of time. By fitting these data to the model in Scheme I, one can generate curves for nonsampled compartments such as the tissue and the fraction remaining at the site of administration. However, the only actual data are those for blood and urine. The so-called tissue compartment actually represents the entire nonsampled remainder of the body. The shape of this curve is therefore dependent upon the model chosen. The tissue curve is both schematic (since the remainder of the body may not be uiform in drug content) and speculative (since other models may apply). Control of clinical response must therefore rely upon the assays for drug concentrations in plasma. Urinary data are more variable and their concentrations are subject to variable urine volumes.

Let us assume that the intensity of a drug's pharmacological activity is a function of the drug's concentration at the site of action. We will also assume that the site of action is either unknown or, if known, inaccessible to the analyst except by sacrifice of the subject. That is, we cannot directly

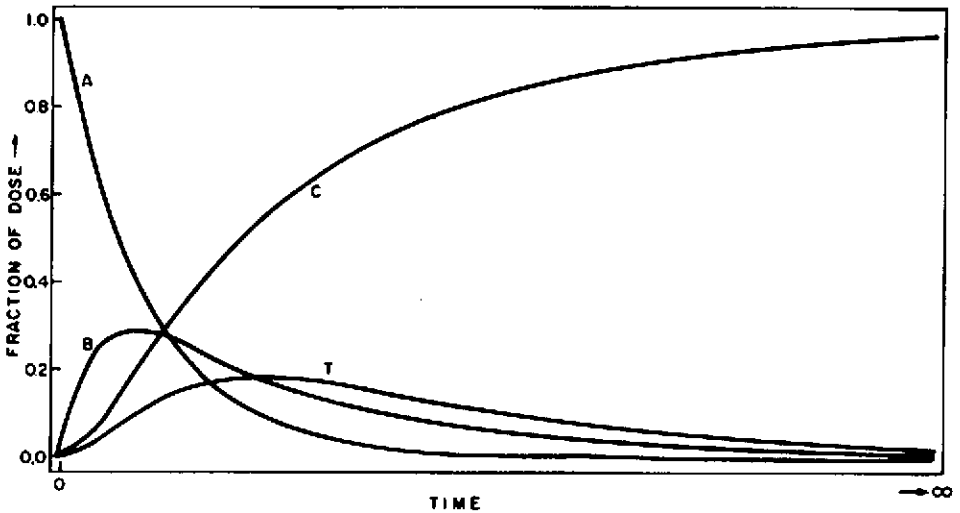


Fig. 9 The fraction of an extravascular dose in each pool as a function of time: *A* is amount remaining to be absorbed (*ARA*), *B* is the blood (sampled compartment), *C* represents cumulative elimination by all routes, and *T* is the "tissue" compartment which represents the model-dependent profile for the remaining drug distributed throughout the body. All of the dose is absorbed, since the initial amount is recovered in *C*.

determine a dose–response curve based upon the concentration of drug which is actually at the site of action. Assuming that this site of action is not in the blood itself, Scheme I shows that drug in the blood diffuses reversibly into the tissues where the site is located. This does not imply that the site is assumed to be in a particular tissue, but only that it is somewhere outside the bloodstream. It then follows that the concentration at that site corresponds to some concentration in the blood.

Since the concentration in blood is readily accessible, it is often possible to relate blood concentration to response. Recognizing that it is not the concentration in the blood per se that is responsible for the pharmacological activity, it may be possible to define dose responses based on blood levels, which in turn have some relationship to the concentration at the site of action. Consider as an example the three drug blood concentration time courses following oral administration in Fig. 10. In each case the bioavailable dose and the drug disposition factors have been held constant. It is obvious that bioavailability differs among the three dosage forms in spite of the constant bioavailable dose; therefore the rate of absorption also differs. One can deduce from the peak heights and their times of occurrence that the

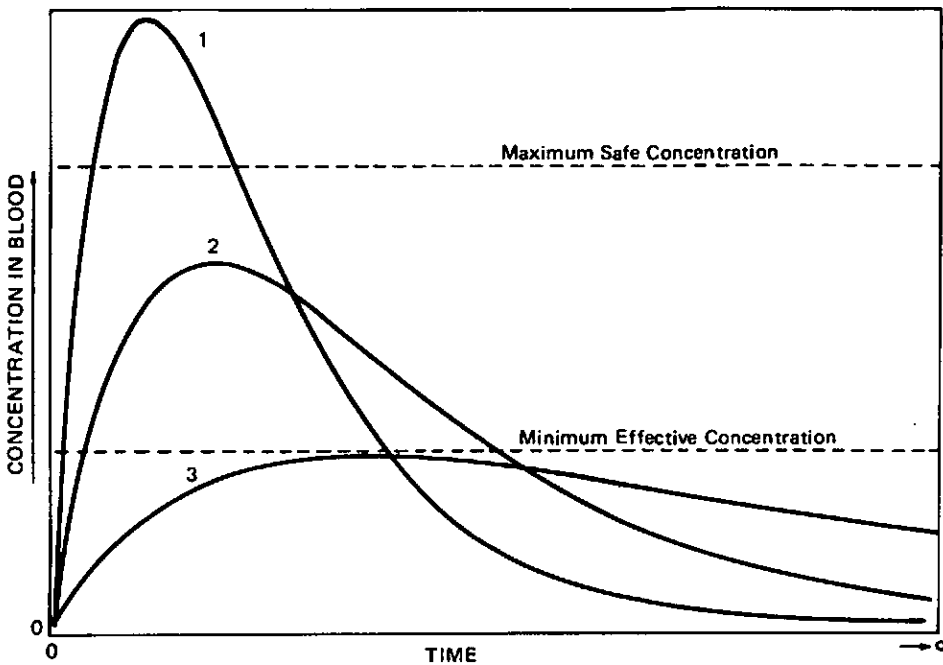


Fig. 10 Plasma concentration time courses for one drug from three different oral dosage forms which all provide equal bioavailable doses. The relative rates of absorption are 1 > 2 > 3.

relative rates of absorption are in the order 1 > 2 > 3. The following discussion based on these single dose curves also applies to multiple dosage regimens and will be extended to those examples in Chap. 6.

1. Minimum Effective Concentration or Minimum Inhibitory Concentration

The minimum effective dose may be defined as the minimum dose required to achieve the desired therapeutic effect. Assuming that this represents a minimum effective concentration at the site of the action, the corresponding blood concentration can be determined by appropriate dose–response experiments. In this way a *minimum effective blood concentration* can be defined as that concentration corresponding to the desired therapeutic effect. In Fig. 10 the minimum effective concentration is indicated by a dashed line. Thus we can observe that curves 1 and 2 achieve therapeutic results, whereas curve 3 does

not. This illustrates that ensuring the bioavailable dose does not ensure clinical effectiveness. Since each of the cases in Fig. 10 represents $f = 1$, then drug in formulation 3 is 100% absorbed yet clinically ineffective.

It is common for many antibiotics to define a minimum inhibitory concentration (*MIC*). For a given antibiotic the *MIC* will vary with the infecting organism. The dosage regimen for a given antibiotic can therefore vary, depending upon the organism. A product which fails to provide the required antibiotic blood concentration time course will result in clinical results that are less than optimum. In some severe cases this could lead to therapeutic failure and loss of life.

2. Onset

Once the minimum effective concentration has been determined, it is possible to define onset and duration on this basis. Onset may be defined as the beginning of the desired therapeutic effect which may be regarded as occurring when the drug concentration exceeds the required minimum. The onset time may be defined as the time required to achieve the minimum effective concentration following administration of the dosage form. In Fig. 10 the onset time for curve 1 is less than that for curve 2, whereas that for curve 3 is nonexistent, since it never achieves an effective concentration. The onset time for curve 2 is approximately three times longer than that of curve 1.

3. Duration

The duration of action may be defined as the length of time that the drug concentration in blood remains above the minimum therapeutic level. In Fig. 10 the duration of curve 2 is 30% longer than that of curve 1, and curve 3 has no duration, since it never achieves an effective level.

4. Maximum Safe Concentration

That dose which, if exceeded, results in side effects or undesirable effects may be called the *maximum safe dose*. The maximum safe concentration may be defined as the drug concentration in the blood which, if exceeded, results in these unwanted effects, and this is indicated by a dashed line in Fig. 10. Of the three blood level curves illustrated in Fig. 10, curve 1 is not desirable, since it exceeds the maximum safe concentration. Thus the rate of delivery from formulation 1 is too fast, resulting in increased side effects and decreased duration.

B. Bioavailability and Bioequivalency

1. Bioequivalency

Products may differ in bioavailability with respect to the rate of absorption or the amount absorbed. If two products are to be considered bioequivalent, they must not differ significantly in either their bioavailable dose or its rate of supply. This would be evidenced by their drug blood concentration time courses, which would be the same, regardless of which product was administered. They would then be bioequivalent and would therefore provide equivalent clinical responses.

2. Absolute Bioavailable Dose

The absolute bioavailable dose is the dose which the patient actually absorbs, in contrast to the dose which the patient takes. The bioavailable dose may be calculated from the value for f by rearranging Eq. (21) to obtain

$$\text{bioavailable dose} = f \times \text{administered dose} \tag{22}$$

Methods for estimating f will be discussed next.

For a drug described by linear pharmacokinetics, the total body clearance value CL is independent of the dosage and route of administration:

$$CL = \frac{fD}{AUC} \tag{23}$$

From Eq. (23) the bioavailable dose following extravascular administration may be defined as

$$fD_{ev} = AUC_{ev}CL \tag{24}$$

Thus the bioavailable dose fD_{ev} is directly proportional to AUC_{ev}, since CL remains constant. When a drug is administered by the intravenous route, then, by definition, $f = 1$, since all of the administered dose reaches the blood. Since CL is constant, AUC_{iv} is directly proportional to the administered dose.

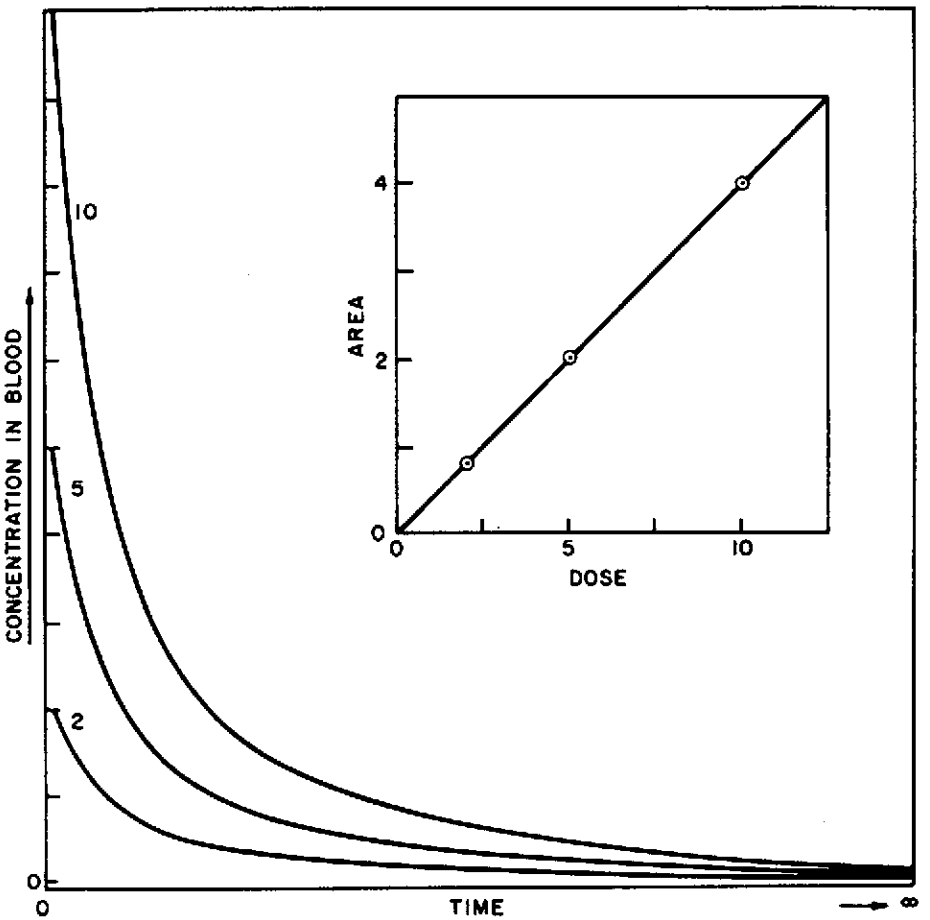


Fig. 11 Blood concentration time courses for one drug given by rapid intravenous doses of 2, 5, and 10 mg/kg. The insert shows that the area under the curve (AUC) is proportional to the dose, indicating linear disposition kinetics.

$$D_{iv} = AUC_{iv}CL \tag{25}$$

as illustrated in Fig. 11. Chapter 4 provides methods for determining AUC. Since CL is constant, the ratio of Eq. (24) to Eq. (25) is given by

$$\frac{fD_{ev}}{D_{iv}} = \frac{AUC_{ev}}{AUC_{iv}} \tag{26}$$

If equal doses are administered by both routes, $D_{ev} = D_{iv}$, then

$$f = \frac{AUC_{ev}}{AUC_{iv}} \tag{27}$$

This shows that at equal administered doses the bioavailable fraction is simply the ratio of the observed AUC values. When the doses are not equal, then the following form of Eq. (26) may be employed:

$$f = \frac{AUC_{ev}/D_{ev}}{AUC_{iv}/D_{iv}} \tag{28}$$

This form shows that the bioavailable fraction is the ratio of the dose-adjusted AUC values, which are written as the AUC per dose for each route.

There are several approaches to calculate the AUC value for the extravascular route, where

$$AUC = \int_0^\infty C\,dt \tag{29}$$

as defined previously. The total AUC may be estimated using the trapezoidal rule, as in the intravenous case. As illustrated in Fig. 12, the curve is divided

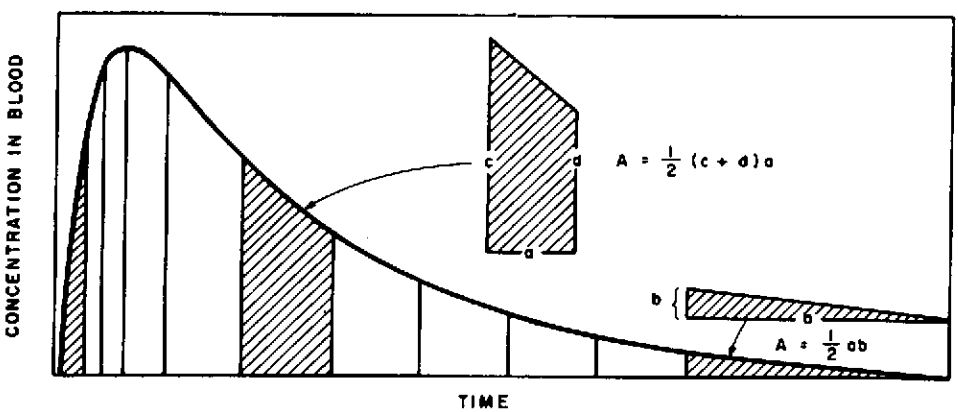


Fig. 12 The total area under the concentration time course following extravascular administration may be estimated by summing the areas of the trapezoids and triangles which approximately comprise it. This is illustrated for intravenous administration in Fig. 6 in Chap. 4.

into a series of trapezoids with a triangle at each end. The individual areas of the trapezoids, $\frac{1}{2}a(c+d)$, and of the triangles, $\frac{1}{2}ab$, are summed to estimate the total AUC. In order to compare the AUC values for different curves, it is necessary to use the same concentration and time units. It is not necessary to use the same scales in plotting the data. Both curves could be made to occupy a full sheet of graph paper.

This latter characteristic is not true for the cut and weigh approach. In this approach a calibration plot can be prepared by cutting several squares from the graph paper and plotting their weights versus their areas, which are easily calculated. The curve to be estimated may then be cut out and weighed and the AUC value estimated from the reference plot. The advantage is that irregularly shaped curves may be easily assessed. All of the plotting, squares and curves, must be done on the same concentration–time scale.

Drug blood concentration time profiles following oral administration can often be described by the biexponential equation

$$C = C_i e^{-S_Z t} - C_i e^{-S_1 t} \tag{30}$$

where S_Z and S_1 are the negative slopes of the first-order plots for the terminal (S_Z) and feathered (S_1) data. As shown in Fig. 13, C_i is the common intercept and S_Z represents the slower of the two exponentials. When there is an observable lag time before absorption begins, these lines will meet at a negative time. The difference between this time and zero time may ascribed to the lag period and the observed intercepts for the two lines will not be equal. It is not possible to assign an absorption and an elimination phase to an oral curve without further information. The slower phase, S_Z, will correspond to the slower step. This is called the flip-flip phenomenon, since either S_1 or S_Z may correspond to the absorption process [33]. Furthermore, these slopes can represent hybrids of several rate processes. Competing g.i. hydrolysis rates will appear with the absorption rate constant while disposition rates can be part of the elimination phase. For this treatment it is not necessary to assign rate processes to the two slopes; it is only required that data are described by Eq. (30).

Since the AUC for a monoexponential concentration time course may be written

$$AUC = \frac{\text{intercept}}{-\text{slope}} \tag{31}$$

it follows that the area of a curve described by Eq. (30) is the difference between two such terms:

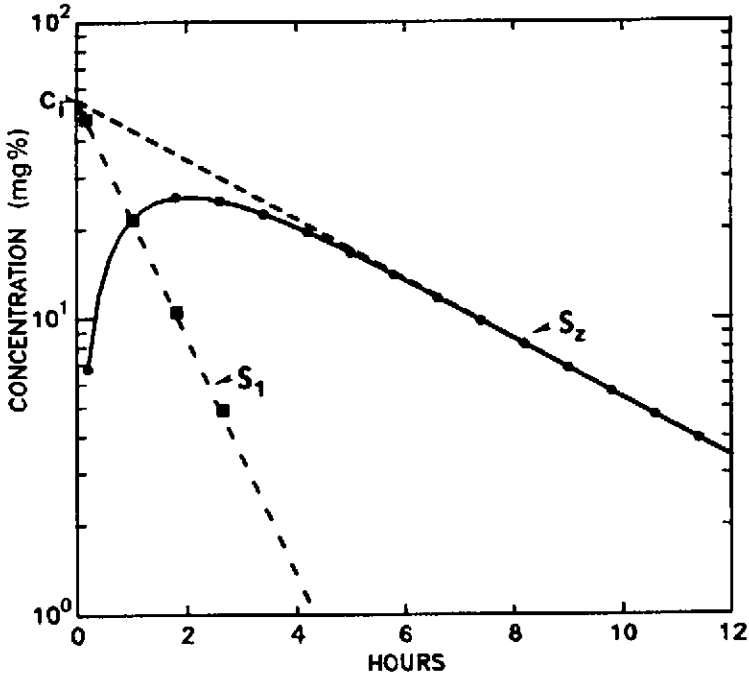


Fig. 13 Feathering a biexponential drug plasma concentration time course described by Eq. (30). The negative slope of the terminal log-linear plot is S_Z. The difference between the S_Z line and the actual data points (●) are plotted (■) to estimate S_1, the negative slope of the log-linear difference plot.

$$AUC = \frac{C_i}{S_Z} - \frac{C_i}{S_1} \tag{32}$$

This principle may also be employed to supplement the trapezoidal rule when data are truncated. If the final data point C_t is located on the S_Z line (i.e., $C_t e^{-S_1 t} \approx 0$), then the missing area can be estimated from

$$AUC(t\text{–}\infty) = \frac{C_t}{S_Z} \tag{33}$$

The total area is the sum of the graphical estimate $AUC(0\text{–}t)$ and the extrapolated estimate $AUC(t\text{–}\infty)$

Practice Problem 7

What is the value of the AUC for the data given in Fig. 13?
Answer: AUC = 180 mg % hr using Eq. (32).

Practice Problem 8

(a) A 70-kg subject is given a 500-mg oral dose of a drug which behaves in accordance with linear pharmacokinetics as described by Eq. (30), where $S_Z = 0.087\ \text{hr}^{-1}$, $S_1 = 0.72\ \text{hr}^{-1}$, and $C_i = 23\ \mu\text{g/ml}$. When a 250-mg dose was given by rapid intravenous injection to the same subject, the concentration time course was described by $C = (16.7\ \mu\text{g/ml})e^{-(0.087\ \text{hr}^{-1})t}$. What is the bioavailable dose?
Answer: The bioavailable dose fD_w is 300 mg.

(b) What does the S_Z value represent?
Answer: Since S_Z is equal to the monoexponential rate constant obtained by intravenous administration, it represents the elimination constant associated with the biological half-life $t_{1/2} = 0.693/S_Z = 8$ hr.

3. Relative Bioavailability

Absolute bioavailability refers to the amount absorbed as calculated using the bioavailable fraction f. This requires data following intravenous administration. Such data may not be available for a number of reasons. For example, the drug may only be used by the oral route. The relative bioavailability may be assessed for several dosage forms of the same drug without knowing the absolute bioavailable dose.

Consider a comparison between two different formulations of one drug. For each formulation the bioavailable dose will be defined by Eq. (24). The ratio for the two formulations using this equation is

$$\frac{f_1 D_1}{f_2 D_2} = \frac{AUC_1}{AUC_2} \tag{34}$$

where CL cancels out, since it is constant. If equal doses are administered, Eq. (34) becomes

$$\frac{f_1}{f_2} = \frac{AUC_1}{AUC_2} \tag{35}$$

When the doses are not equal, Eq. (34) may be employed or rewritten as

$$\frac{f_1}{f_2} = \frac{AUC_1/D_1}{AUC_2/D_2} \tag{36}$$

which uses dosage-adjusted AUC values. Thus the relative bioavailability of product 1 compared to product 2, f_1/f_2, is simply the ratio of the AUC values:

$$(\text{relative bioavailability})_{1 \text{ to } 2} = \frac{AUC_1}{AUC_2} \tag{37}$$

Practice Problem 9

The bioavailability of the following forms of erythromycin were compared in six separate studies: enteric-coated beads of erythromycin base in capsules, erythromycin ethylsuccinate film-coated tablets, erythromycin stearate film-coated tablets, enteric-coated base tablets, and erythromycin estolate capsules. Doses were administered every 6 hr and AUC values were determined following an overnight fast. The time between this test dose and the next meal varied from 0 to 4 hr. Results are summarized in Table 5.

Table 5 AUC Values During the 6-hr Time Interval Following Oral Administration of Erythromycin Products Every 6 hr[a]

Study	Product	Dose (mg)	Hours before meal	AUC (μg hr/ml) ($t_1 - t_2$)	Time interval (hr)
1	Enteric-coated beads	250	3.5	5.65	48–54
	Ethylsuccinate	400	3.5	0.74	48–54
2	Enteric-coated beads	250	1.0	9.06	24–30
	Stearate	250	1.0	5.76	24–30
3	Enteric-coated beads	250	1.0	9.54	24–30
	Enteric-coated base (tablets)	250	1.0	7.24	24–30
4	Enteric-coated beads	250	1.0	9.50	24–30
	Stearate	250	Before food	4.41	24–30
5	Stearate	500	4.0	15.4	24–30
	Estolate	500	4.0	7.3	24–30
6	Stearate	500	After food	11.7	24–30
	Estolate	500	After food	7.7	24–30

[a]Values were determined after an overnight fast and the time to the next meal is specified. For discussion and references see Chap. 7, Sect. III.C.2.b.

(a) Rank the products in decreasing order of relative percentage of absorption using enteric-coated beads as a reference state (assigned 100%).
Answer:

Enteric-coated beads	100% (reference)
Enteric-coated base tablets	76%
Stearate	63%
Stearate (before food)	46%
Estolate	30% (using stearate as 63%)
Estolate (after food)	32% (using slight increase from 7.3)
Ethylsuccinate	8% (after dose adjustment)

(b) What is the effect of the time interval between the dose and the following meal on the relative bioavailability of enteric-coated beads, the stearate, and the estolate?
Answer: The average *AUC* for the beads 1 hr before meals is 9.37 μg hr/ml. The relative absorption taken 3.5 hr before meals is 60% of this value. The stearate administered just before meals is 76% (4.41/5.76) of that given 1 hr before. The estolate given immediately after food is roughly equivalent to that given 4 hr before.

Practice Problem 10: Decrease in Gastrointestinal Absorption Due to Complexation

Table 6 contains reported concentrations for Declomycin following equal oral doses under four different experimental conditions.

(a) What percentage of absorption takes place when Declomycin is taken orally with 8 oz of milk, as compared with the case of an equal dose taken after 8 hr of fasting?
Answer: 13% (by the cut and weigh method)

(b) What percentage of absorption occurs when Declomycin is coadministered with aluminum hydroxide gel, 20 ml, in comparison to the fasting state?
Answer: 22%.

(c) What is the effect of taking Declomycin during a meal that contains no dairy products?
Answer: Appears to have increased absorption (140%); see discussion in Ref. 30.

Practice Problem 11: Decrease in Gastrointestinal Absorption Due to Formulation

In Practice Problem 10 the relative amounts of drug absorbed were compared by comparing the weights of the curves. Another method for determining the relative areas under a series of curves was illustrated in Fig. 12, where

Table 6 Effect of Heavy Metal Complexation on Absorption of Declomycin in Human Subjects[a] Following 300 mg Taken Orally

	Average[b] serum concentration of Declomycin (μg/ml)			
Time (hr)	After 8 hr of fasting	Meal without dairy products	With 8 oz of whole milk	With 20 ml of Amphojel
0	0.0	0.00	0.0	0.0
1	0.7	1.0	0.1	0.2
2	1.1	1.2	0.3	0.3
3	1.4	1.7	0.4	0.4
4	2.1	2.0	0.4	0.5
5	2.0	—	0.4	0.5
6	1.8	2.1	0.4	0.5
12	1.4	1.8	0.3	0.4
18	—	—	0.2	0.3
24	0.8	1.1	0.1	0.2
48	0.4	0.7	0.0	0.1
72	0.2	0.3		0.0
96	0.1	0.2		

[a]Data from figures in Ref. 30.
[b]Six volunteers in the fasting group and four volunteers in each of the others.

Table 7 Average Plasma Levels for Groups of 10 Human Subjects Receiving 0.5-g Oral Doses of Chloramphenicol in Capsules[a]

Time (hr)	Mean plasma levels (μg/ml)			
	Capsule A	Capsule B	Capsule C	Capsule D
0.0	0.0	0.0	0.0	0.0
0.5	5.8	1.1	1.4	0.6
1.0	9.4	2.4	3.9	1.3
2.0	9.1	4.5	5.7	2.2
4.0	6.7	4.7	5.2	2.2
6.0	5.2	3.4	3.6	2.1
8.0	3.8	2.5	2.6	1.8
12.0	2.3	1.1	1.4	1.0
24.0	0.6	0.2	0.2	0.3

[a]Data from Table V in Ref. 32b.

the *AUC* was estimated by the trapezoidal rule. One of the advantages of the trapezoidal method is that the curves can be drawn to occupy the maximum amount of space on the graph paper and the estimates of the lengths of the sides involved in the calculations are therefore improved. In the method of cutting and weighing, a small blood level profile would be difficult to determine. The data in Table 7 illustrate the chloromycetin case previously discussed. Use the trapezoidal method for estimating areas under the curves, answer the questions regarding chloromycetin absorption.

(a) If capsule A is used as the standard of reference, what is the percentage of chloromycetin absorbed from capsule D?
Answer: 35%.

(b) What relative percentage of absorption takes place from capsules B and C as compared with capsule A?
Answer: 52% (B); 61% (C).

(c) Why is it not possible to calculate the absolute percentage of absorption rather than the relative percentage of absorption from Table 7, and what type of data would be required to calculate the absolute percentage of absorption?
Answer: An intravenous dose is required.

4. Peak Height C_{max} and Time of Occurrence t_{max}

The *AUC* value reflects the fraction of the dose that is absorbed, but this is independent of the absorption rate. The shape of the plasma concentration curve as a function of time, from one dosage form to the next, is not reflected by the *AUC* value. If the same amount of drug is absorbed from two dosage forms but the rate of absorption differs, then the *AUC* values will be equal but the shapes of the curves will differ. The concentration of drug in the blood is the net difference between drug input and drug output. If all other factors are constant, such as the fraction absorbed and the elimination constant, then the peak height C_{max} is proportional to the rate of absorption. The faster the absorption rate, the higher the observed peak height. Conversely, if the absorption rate is constant, the peak height is proportional to the fraction absorbed, f, since the shape of the curve must remain constant and f is proportional to *AUC*. Thus the *AUC* values can be compared for relative bioavailability, but the C_{max} values reflect both relative bioavailability and absorption rate. Peak heights may be employed as a rough indication of the amount absorbed when all the rate constants—including absorption, distribution, and elimination—are constant.

The time required for the concentration of drug in plasma to reach its highest value C_{max} following extravascular administration is designated t_{max}. For a given dose and bioavailable fraction, t_{max} is inversely dependent on

absorption rate. As the absorption rate constant increases, the time to achieve the peak is decreased. The limiting case representing the fastest rate of absorption is a rapid intravenous injection, wherein the peak occurs at time zero.

The t_{max} value will remain constant if all the rate constants in the process are held constant. For a given drug with a fixed elimination rate constant, two dosage forms of equal absorption rate constants will have similar t_{max} values despite differences in bioavailable dose. Therefore, when t_{max} values are equal, one may conclude that the absorption rate constants are also equal. In this case a comparison of two peak height values (adjusted for dose size) provides a rough estimate of the relative bioavailability, since the absorption rate is eliminated as a potential influence on peak heights.

This comparison of C_{max} at constant t_{max} values for different products is an approximation. Accurate assessment of bioavailability can be obtained using AUC values. However, peak height comparisons can provide a rapid first approximation under circumstances where a quick decision is needed.

5. Limitations on Direct Comparisons of Oral Blood Level Curves

Direct comparisons based on values for AUC, C_{max}, and t_{max} evaluate dosage form effects. In these comparisons it is assumed that only the fraction absorbed and/or the absorption rate have changed but all other rate processes remain constant. Total body clearance must remain constant in order to use AUC values as indicators of bioavailable fractions. Structural modifications of a drug can change any or all of the rate processes shown in Scheme I, independent of the dosage form. The dissolution and the absorption may be altered by changes in the chemical structure. Following absorption, molecular modification can influence the distribution, excretion, and metabolism of the drug. All of these processes impact on the time course for the drug in the blood. Therefore it is not valid to directly compare the blood levels of two structurally related analogs. Only if two analogs have identical clearance values can one compare the AUC values as a measure of their relative bioavailability. One should not expect structurally different chemicals to have similar clearance values.

Structurally related analogs should be compared using absolute bioavailability. This is discussed in Chap. 7, which discusses molecular modifications.

6. Limitations in the Use of Urinary Data

Urinary excretion data are often misinterpreted as a means of evaluating bioavailability. Typically, data for the total amount of drug and metabolite excreted in the urine are used to measure bioavailability. This approach is

valid when the excretion of drug and/or metabolite is shown to be related to the bioavailable dose of drug. Many drugs are excreted both intact and partially metabolized. The ratio of the amount of drug excreted intact to that excreted metabolized may increase with dosage. This is observed when drug metabolism is capacity limited at high doses. At increased doses less drug is metabolized relative to that excreted intact. Thus drug excreted intact in the urine would not indicate the bioavailable fraction. For example, one could administer various doses by intravenous injection and the fraction excreted intact would not be related to the dose. For an assessment of extravascular bioavailability to be valid, one must first demonstrate that the total excretion of drug is proportional to the intravenously administered dosage.

Still, the total urinary excretion of a drug is of limited utility in the evaluation of dosage forms and is not recommended as a substitute for blood concentration time course data. At best, data for the total amount of drug excreted can be employed as a rough estimate of the bioavailable fraction. However, such data do not evaluate the bioequivalency, absorption rate, duration, or C_{max} and t_{max} values. Theoretically, a time course for the cumulative amount of drug excreted in the urine could be used to assess bioequivalency and duration. In practice, these estimates are subject to a high degree of variability and are less reliable than those from concentration time courses in blood.

Even the relatively simple assessment of the bioavailable fraction using the total urinary excretion of drug presents several problems. It is necessary to collect data for a period of time equal to five times the half-life of the rate-determining step in order to achieve 97% recovery following a single totally bioavailable dose. The control experiment normally would be the intravenous administration of drug together with urinary collection during a period five times the biological half-life. The percentage of recovery should be independent of the drug dose over the range of urinary excretion data which apply to the final product evaluation. Oral administration would require urinary collection over a period of time representing five times the half-life corresponding to the terminal phase of the drug concentration time course. This cannot be assumed to be equal to the biological half-life of the drug. The oral terminal-phase half-life may reflect slow drug absorption. If a successful long-acting product provides a very slow release of drug, then the resulting low urinary concentrations may become too dilute to assess.

7. Experimental Design

A common goal is to compare the relative bioavailability of a single drug from formulations prepared by two different manufacturers. The clinical study must evaluate the influence of the two dosage forms. The remaining

potential influences must be eliminated or evenly dispersed among the study subjects. Physiological factors such as age, weight, physical activity, disease, foods, and other drugs can potentially influence the absorption of drugs. All of these factors must be controlled to isolate the influence of the dosage form on bioavailability.

Generally, healthy adults are divided into two different groups of equal size in a random, unbiased fashion. Either the diets are controlled or the dosage forms are administered in the morning after an overnight fast. If the tablets from the two manufacturers are A and B, then each member in group 1 would receive tablet A and each menber in group 2 would receive tablet B. The protocol would be kept constant; for example, each tablet would be taken with an 8-oz glass of water. The concentration of drug in the blood would be determined as a function of time for each member of the group, and the *AUC* values calculated.

A second dose would be administered after a sufficient period of time had elapsed to allow complete elimination of the first dose. Group 1 would then receive tablet B and group 2 would receive tablet A. This is called a crossover design. The original studies would be repeated and the individual *AUC* values again calculated. The *AUC* values for each patient can then be compared and the relative bioavailability of tablet A to tablet B evaluated. All subjects serve as their own control.

These *AUC* comparisons evaluate the relative bioavailable dose. They are limited to the question of how much drug is absorbed from one dosage form relative to another. Two dosage forms providing equivalent bioavailable doses may provide different clinical effects. If one dosage form is more rapidly absorbed, it may elicit side effects not observed with the slower one; conversely, if one is absorbed too slowly, it may fail to produce therapeutic results.

Equivalent bioavailable doses do not ensure bioequivalency. Bioequivalency means that two dosage forms of the same drug exhibit no statistical differences between their plasma concentration time profiles (time to peak, peak height, and *AUC*). The data collected in the crossover studies can also be compared for bioequivalency. Again, all individuals should be used as their own control. Often the pooled results and average values are compared. This can obscure significant information, such as the variability in data. One product may show a high degree of variability yet on the average appear bioequivalent to the reference product, which has much less variability. Although the averages may be similar, a product with the most uniform behavior and the least variability would be the most dependable in clinical use.

There is often confusion with respect to the acceptability of a product which exhibits a bioavailability lower than that of the reference standard

but nonetheless exceeds the known minimum effective plasma concentration. This should not be regarded as a satisfactory product. A product which barely exceeds minimum required concentrations in the blood but that has poor bioavailability is predisposed to higher variability in clinical use. Since many factors can influence absorption in the therapeutic use of drugs, optimum bioavailability is required of every dosage form to reduce the uncertainty. Bioavailability studies are conducted under ideal, controlled conditions. If performance is minimal under ideal conditions, then the potential for therapeutic failure is increased during usage under conditions encountered during illness.

In general, the smaller the bioavailable fraction, the greater the variability encountered in widespread use. For example, if only 20% of the drug is absorbed from a dosage form, than that dosage form contains five potentially bioavailable doses. The possibility exists for the patient to absorb more than the expected 20% determined in the bioavailability study. This may result in toxicity or side effects. Conversely, if 90% is absorbed, then the maximum bioavailable dose is limited to that expected for the dosage form. Furthermore, a patient stabilized on a poorly absorbed dosage form may experience unexpected toxicity when switched to one of optimum bioavailability. This has been experienced with a number of drugs, including prednisolone and digoxin. Depending upon the order in which the dosage forms are employed, switching can cause either side effects or therapeutic failure. If all dosage forms show optimum bioavailability, then problems associated with switching brands and those of unpredictability due to clinical usage conditions can be minimized.

V. DRUG DELIVERY TO PROLONG DURATION

A. Controlled-Release Oral Dosage Forms

Controlled release is a nonspecific term describing any formulation designed to predetermine the kinetic pattern for the presentation of a drug to a patient. The goals range from reducing the C_{max} value for decreased side effects to prolonging steady-state plasma concentrations for increased duration. Mechanisms for achieving these goals vary from simply increasing drug particle size to decrease the C_{max} to constructing a sophisticated metering device which provides zero-order release. Throughout the range of drug delivery systems a common trait is the control of drug release from the formulation relative to a rapidly dissolving tablet or capsule.

I. Definitions

There are several types of oral dosage forms designed to increase duration of action. These products are often similar in appearance but not in release time profiles. Often the descriptive phrases accompanying the products do not accurately describe the mechanism controlling the release pattern. General terms, such as *controlled release, extended action,* and *long acting,* may or may not be meant to indicate that the formulation is a sustained-release preparation. Unfortunately, there are no standard definitions or classifications. The descriptions which follow provide a foundation. More precise terminology and definitions will be developed by a discussion of specific examples. In this text controlled-release dosages are divided into three major groups: repeat action, sustained release, and prolonged action.

a. Repeat Action. Repeat-action tablets are designed to release one dose immediately and a second dose after some period of time has elapsed (Fig. 14). The release of the subsequent dose is delayed by either a time barrier or an enteric coating. These products provide patient convenience. They can mean the difference between a continuous night of sleep and having to arise to take medication. However, they are not designed for continuous constant plasma levels; instead, they provide the usual "peak-and-valley" type of blood level pattern. The primary advantage is that additional doses are provided without the administration of another tablet. Plasma concentration time courses are similar to those obtained with the repetitive administration of the fast-acting tablets.

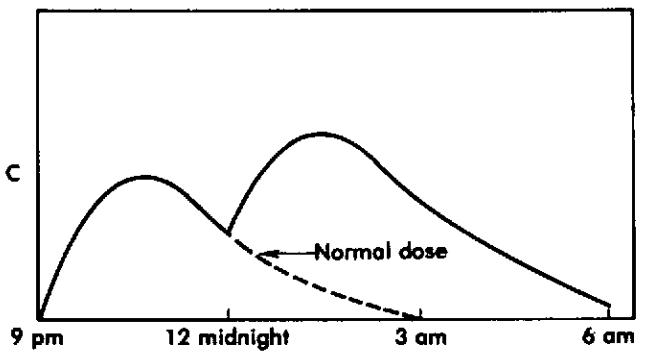


Fig. 14 The concentration (C) of drug in blood following the oral administration of a single repeat-action tablet. The broken line shows the time course which would result without the built-in second dose.

b. Sustained Release. Sustained-release dosage forms provide a rapidly absorbed dose followed by a gradual release of medication over a prolonged period of time. The goal of this type of dosage form is to achieve a therapeutic blood level quickly and then maintain that level with the prolonged-release dose, as shown in Fig. 15. Ideally, the resultant blood levels would be continuously maintained in the therapeutic range without the intermittent, peak-and-valley effect of a normal dosage regimen or a repeat-action tablet.

c. Prolonged Action. Prolonged-action preparations provide the slow release of a drug at a rate which will provide a longer duration of action than a single dose of the normal dosage form. They may differ from sustained-release products only in that no initial dose is included in the prolonged-action formulation (see Fig. 15).

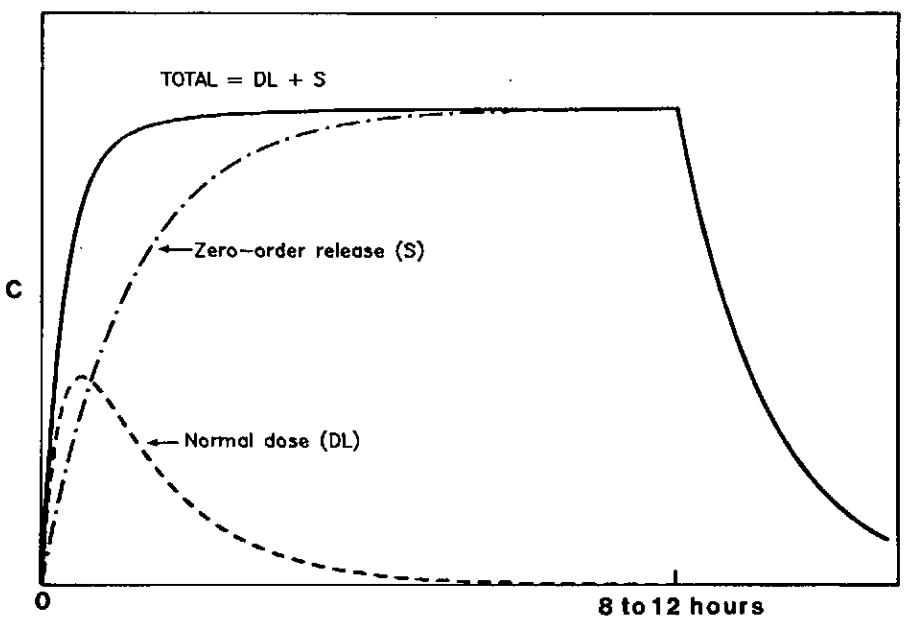


Fig. 15 The concentration (C) time course of drug in blood following the oral administration of a sustained-release dosage form with a loading dose *DL* is shown by the solid line. The time course from *DL* alone would appear as a normal dose curve. The remaining profile (—·—) shows the result without a loading dose, which typifies a prolonged-action product.

2. Advantages and Disadvantages

The advantages generally claimed for sustained-action products include improved therapy, decreased side effects, increased compliance, patient convenience, and/or economy. Improved therapy and less toxicity result from continuous therapeutic blood levels, as opposed to an intermittent or peak-and-valley pattern. While continuous blood levels are not necessarily ideal for all drugs and disease states, there are certainly conditions in which clinical or therapeutic advantages can be realized. Typical examples are those cases where depletion of the drug from the body or low blood levels would result in symptom breakthrough, such as might be encountered with antihistamines, tranquilizers, sedatives, anorectic agents, antitussives, ataractics, antispasmodics, and so on. It is also possible to decrease side effects associated with high C_{max} values.

Patient convenience and compliance represent a common reason for using a sustained-release product. It has been shown that sustained-release forms help eliminate the possibility of forgotten doses. Improved compliance occurs because the patient may take one daily dose, or one morning and night, rather than three or four times a day during what may be a busy schedule. We have already mentioned the advantage of not waking a sick person during sleeping periods.

Economy may be realized from one of two points of view. Sometimes the sustained-release form may provide a less expensive replacement for equivalent therapy, even though a single-dosage form is more expensive than the normal one; that is, a daily treatment may cost less. Economy may also result from decreasing the cost of administering drugs in institutions.

The primary disadvantages are the loss of flexibility in the dosage regimen and the potential for increased risk from technology failure. The payload, normally sufficient to last 8–12 hr, represents several times the normal single dose. Also, the release pattern cannot be altered to accommodate individual patient requirements. If a patient experiences some undesirable effect, such as drowsiness from an antihistamine, the regimen cannot be readily adjusted, as with a schedule of every 3–4 hr, where one dose can be skipped intentionally. Although it may be more economical to take a drug in a sustained-release dosage form, there are also examples where it is more costly owing to the technology involved in the formulation. Because these devices are more sophisticated and complex, it can prove unwise to employ sustained-release forms of toxic or potent drugs owing to the increased risk of administering the large doses in a long-acting preparation. This will be discussed later with regard to appropriate candidates for sustained-release dosage forms.

3. Theory

There are several models that could be employed in considering the theory governing the design of a prolonged-release oral dosage form. The ideal prolonged-release pattern is zero-order release over a time period equal to the dosage interval. This would mimic the results achieved by a constant-rate intravenous infusion. The oral administration of such a zero-order drug delivery system (DDS) can provide a constant steady-state concentration of drug in plasma on a multiple-dosage regimen. Figure 16 illustrates the time course resulting from an oral dose of a zero-order DDS of 12-hr duration given every 12 hr.

In practice, all oral sustained-release devices are not zero order. Some are more adequately described by a mono- or biexponential rate of drug release. While these cannot provide constant values for C^{ss}, they can nonetheless prolong the drug concentration in the plasma by controlling the rate of release from the DDS, and therefore the subsequent absorption rate. Figure 17 illustrates a 24-hr period during the steady state achieved by oral administration of a DDS with a slow first-order release rate constant. The DDS is designed to maintain the time course within the limits of 10–20 μg/ml on a 12-hr schedule. This drug would normally require a dose to be given every 4–6 hr, using the elixir or rapidly dissolving tablets.

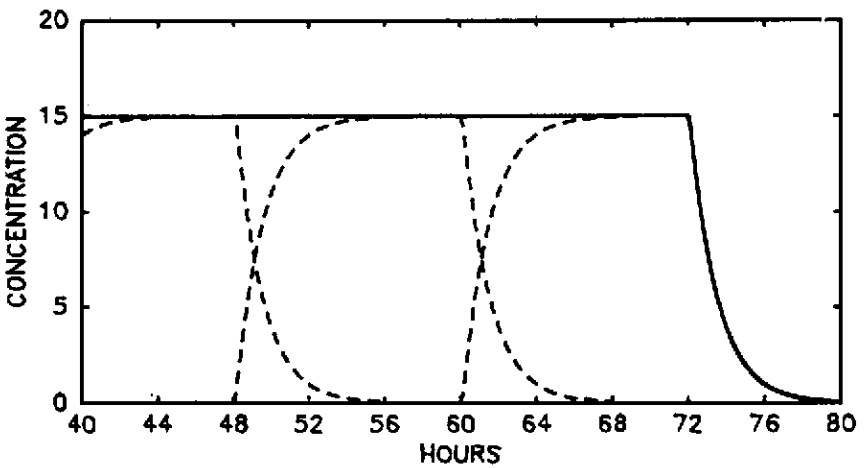


Fig. 16 The concentration of drug resulting from oral administration of a 12-hr zero-order release drug delivery system given every 12 hr. The broken line shows the individual time courses resulting from each dose and the solid line is the resultant blood level time course.

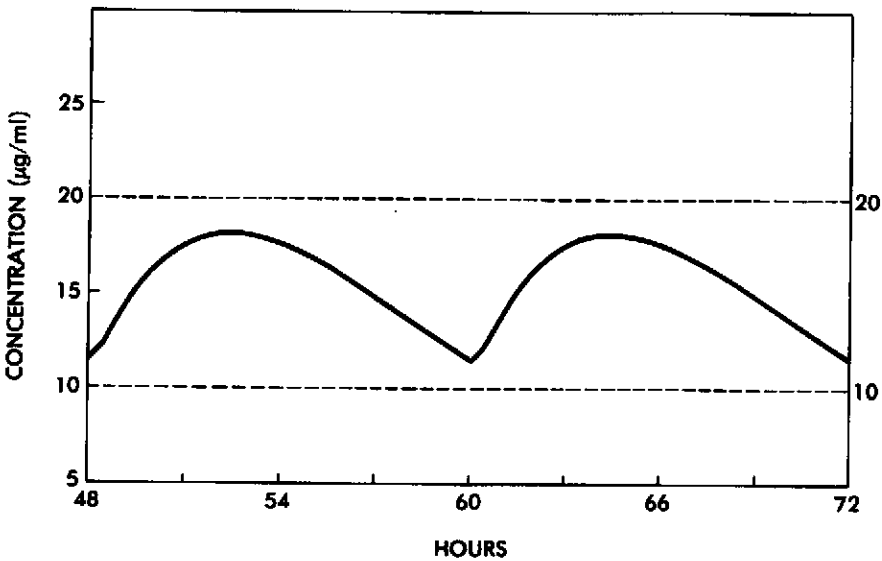
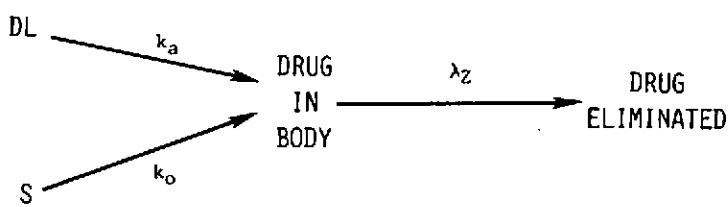


Fig. 17 Steady-state drug concentration time course in plasma from oral administration of a slow first-order release drug delivery system given every 12 hr to maintain levels between 10 and 20 μg/ml. A fast-acting tablet or the elixir would require dosing every 4–6 hr.

The following model is analogous to an intravenous infusion with an initial rapid loading dose. The only difference is that both the initial and sustained doses have an absorption step before entering the blood (Scheme VI).

SUSTAINED RELEASE
DOSAGE FORM WITH
LOADING DOSE



Scheme VI

In Scheme VI DL is the loading dose, S is the sustained-release dose, and λ_Z represents the overall apparent elimination rate constant, where $t_{1/2} = 0.693/\lambda_Z$. It is assumed that the dose DL is rapidly absorbed following oral administration, with a first-order absorption rate constant k_a, and that the zero-order release of drug from S (k_0) is rate determining. Thus DL is designed to achieve a rapid therapeutic blood level and S is meant to maintain it. The steady-state elimination rate may be calculated in the same way as for intravenous infusions, letting k_0 replace R_0 (see Chap. 4).

Practice Problem 12

Specifications for a sustained-release oral DDS are to be calculated using the above model and its assumptions. A sustained-release tablet having an immediately available dose DL and a slow-release core S is to be formulated. The desired blood level is 0.4 mg % and the distribution volume in a 70-kg person is 50 liters. It is found that the drug is quickly and completely absorbed upon oral administration and that 200 mg is sufficient to provide a therapeutic blood level. The biological half-life is 4 hr. If 200 mg is used as the DL dose, how much drug must be placed in the sustained-release core to maintain the desired therapeutic blood level for 12 hr.
Answer: 415 mg.

Practice Problem 13

A prolonged-action formulation of sulfaethidole is to be designed. The optimum blood level range is 8–16 mg %. The average biological half-life is 8 hr. A 1.5-g dose administered in a rapidly dissolving tablet to a 90-kg patient yields a blood level of 6 mg % after 3 hr. All of the dose is absorbed, and the total amount eliminated during this time is 300 mg. At what rate must the drug be supplied in order to maintain a 12 mg % blood level, and how much must be placed in the tablet to result in a 12-hr duration?
Answer: Rate = k_0 = 208 mg/hr; 2.5 g.

Practice Problem 14

A semilogarithmic plot of drug plasma concentration versus time in hours gave two apparently linear regions with slopes of -2.8 and $-0.18\ hr^{-1}$. How much drug must be placed in the S compartment to maintain the blood level for 8 hr if the DL compartment contains 0.40 g and this amount produces a therapeutic level without significant loss of drug?
Answer: 576 mg.

Practice Problem 15

Each of the drugs in Table 8 is to be formulated into a zero-order 12-hr sustained-release dosage form. In each case $f = 1$ and absorption from a capsule is rapid. Consider the total number of doses to be contained in

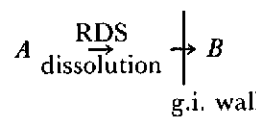
Table 8

Drug	C^{ss} (mg/liter)	V_Z (liters)	$t_{1/2}$ (hr)
A	1.0	20	8
B	1.5	20	6
C	2.0	10	4
D	3.0	8	2

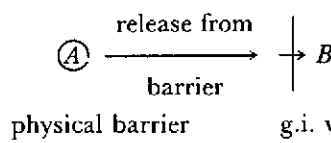
a 12-hr dosage form *relative* to a normal single dose. Rank-order the 12-hr dosage forms from *most* to *least* in terms of the number of doses contained.
Answer: $D > C > B > A$.

4. Product Design and Typical Examples

The release rate from a sustained-release dosage form must be slower than both the absorption and the elimination rate of the drug; that is, release must be the rate-limiting step. The slowest step in the absorption process from tablets is generally dissolution. If the dosage form is to control absorption, it must limit the dissolution rate. Thus the normal absorption pattern,



must be rate limited by some physical barrier. This may be represented as



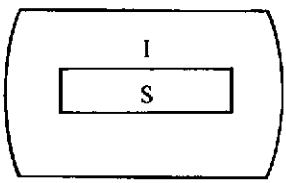
There are many methods by which the physical barrier is built into the oral dosage form, including coatings, embedding drug in a wax–fat matrix, incorporation into a porous plastic base, binding to ion-exchange resins, complexation with colloidal material, and microencapsulation. The type of mechanism employed for each sustained-release product is important, since

it also governs the rational use of that product. For this reason the commonly used structures for controlled-release oral dosage forms will be surveyed here.

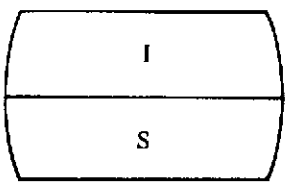
The titles used are not standard and, in some cases, may not be found outside this text; however, these descriptive categories will be helpful in remembering the types of dosage forms and in considering new products as they are introduced. Examples are listed in Table 9.

a. Repeat-Action Tablets. As previously defined, repeat-action tablets do not provide continuous release but present intermittent dosing by the administration of a single dosage form (see Fig. 14). They are controlled release but should not be confused with prolonged, or sustained-release tablets. When a repeat-action tablet is cut in half, the cross-sectional appearance will often reveal a tablet within a tablet. However, honest labeling and product descriptions should differentiate the repeat-action release pattern from a continuous pattern.

b. Slow-Erosion Core with Loading Dose. The drug is incorporated into a tablet with insoluble materials, usually fats and waxes of high molecular weight. This tablet does not disintegrate but, rather, maintains its geometric shape throughout the g.i. tract. The drug release is due to surface erosion from the intact tablet. The initial dose may be in a pan-coated or press-coated outer shell or in a separate layer in the case of a laminated tablet.



Tablet in a tablet



Laminated tablet

The principle of this dosage form can be explained using the Noyes–Whitney dissolution rate law, under the conditions of rate-limiting dissolution, wherein

$$\text{dissolution rate} \propto \text{surface area} \times \text{solubility} \tag{38}$$

which approaches zero order only when the surface area and solubility remain constant. Since the solubility term may be considered constant for a given drug, the overall rate may be made constant by maintaining a constant surface area. The surface cannot be constant in the absolute sense, since the dosage form will become smaller on erosion; however, the tablets are designed

Table 9 Partial Listing of Marketed Long-Acting Oral Dosage Forms and Their Probable Categories

	Designation	Typical product
(a)	Repeat-action tablets	
	Repetab	Chlor-Trimeton Long-Acting Repetab Demazin Repetab Polaramine Repetab Trilafon Repetab
	Timed release	Triaminic TR Tablets Triaminic Juvelets
(b)	Slow-erosion core with loading dose	
	Chronotab	Disophrol Chronotab
	Enduret	Preludin Endurets
	Extentab	Donnatal Extentabs Dimetapp Extentabs Quinidex Extentabs
	SA	Peritrate SA Tedral SA
	SR	PBZ-SR
(c)	Erosion core only	
	Dospan	Tenuate Dospan
	Ten-tab	Tepanil Ten-tab
	Timespan	Mestinon Timespan Roniacol Timespan
	Zero-order release	Zorprin
(d)	Pellets in capsules	
	Continuous action	Contac
	Controlled release	Novafed Capsules
	ProBeads	Theo-24
	S.A.	Sudafed S.A.
	Sequels	Artane Sequels Diamox Sequels Ferro-Sequels
	Spansule	Compazine Spansule Ornade Spansule Temaril Spansule
	-Span	Nico-Span
	span	Meprospan
	SR	Indocin SR

(*continued*)

Table 9 (*continued*)

	Designation	Typical product
	Tembids	Isordil Tembids Capsules
	Tempules	Nicobid
	Timesule	Isoclor
(e)	Pellets in tablets (or mixed granulations)	
	(None)	Naldecon
	-S	Bellergal-S Belladenal-S
	Sustained action	Nitroglyn Theo-Dur
	Tembids	Isordil Tembids Tablets
(f)	Leaching	
	Gradumets	Desoxyn Gradumet Fero-Gradumet Tral Gradumet
	SR	Procan SR
(g)	Ion exchange	
	Pennkinetic	Biphetamine Corsym (liquid) Delsym (liquid) Ionamin Tussionex (liquid)
(h)	Complexation	
	tan	Rynatan (tablets and suspension)
(i)	Microencapsulation	
	Extencaps	Micro-K Extencaps
	Plateau Caps	Duotrate Plateau Caps Nico-400 Nitro-Bid
	span	Cerespan Histaspan-D Nitrospan Capsules
	Sprinkle	Theo-Dur Sprinkle
	(None)	Measurin
(j)	Osmotic pump	
	Precision release	Acutrim
(k)	Gel-forming hydrocolloids	
	Hydrodynamically balanced system	Valrelease

to approach a constant value as closely as possible. Thus the geometric shape of the *S* compartment is chosen to provide the least possible decrease in surface area as the core undergoes erosion. For example, a cylinder having a large diameter/height ratio would present a constant surface as it dissolved, provided that the diameter remained relatively constant. The slow dissolution of a silver dollar, for example, might be expected to proceed with relatively constant surface, since the area would remain at $2\pi r^2$ (neglecting the edge), whereas a sphere would undergo a vast change in surface, since its area is $4\pi r^2$ and the radius would decrease significantly with dissolution.

PBZ-SR is an example of a compressed tablet surrounding an erosion core containing carnauba wax and stearyl alcohol. These are melted together with tripelennamine hydrochloride, granulated, and compressed to form the core. PBZ-SR taken every 8–12 hr replaces a normal regimen of 25–50 mg as tablets or an elixir taken every 4–6 hr.

Donnatal Extentabs have an outer colored pan coating containing the *DL* dose. The core is enteric coated and slowly dissolves in the intestines, releasing the equivalent of two additional doses. The total of three doses provides sustained effects for 10–12 hr.

Typical examples of laminated erosion-core tablets are Tedral SA and Peritrate SA. The 80-mg Peritrate SA contains 20 mg of pentaerythritol-tetranitrate in the *DL* layer and 60 mg in the *S* core. The core releases drug over an 8-hr period and the overall duration is listed as 12 hr since therapeutic blood levels are maintained for an additional 4-hr period after the core is expended. Tedral SA contains 90 mg of theophylline in each of the *DL* and *S* portions, 16 mg of ephedrine HCl in *DL* and 32 mg in *S*, and 25 mg of phenobarbital in *DL* only.

A number of sustained-release products are based on the erosion-core mechanism coupled with an initial dose.

c. Erosion Core Only. Many drugs may not require an initial dose. The therapeutic goal may be to maintain constant blood levels. In such cases a prolonged-action dosage form may be more appropriate than a sustained-release form. Typical examples are erosion-core tablets of an anorexic agent, such as Tenuate Dospan and Tepanil Ten-tab. The equivalent of three normal doses of the drug are contained within a uniform-release erosion core.

Another consideration in using prolonged-action medications is the fact that an initial dose may be required only when the patient first begins therapy and not accompanying each subsequent dose. One method used to achieve this is to use an erosion core without an initial dose. The dosage regimen may include several tablets to initiate therapy followed by a maintenance dose taken at fixed time intervals equal to the duration of the core.

d. Pellets in Capsules. The original sustained-release product was introduced on the market in October 1952 by Smith Kline & French Laboratories.

This Spansule consists of small, medicated pellets in a hard gelatin capsule. An average Spansule contains two to four times the normal single dose. The drug is contained within the pellets. There may be three to four different groups, each containing approximately 100 pellets. One group of pellets is left uncoated to act as the initial dose. A slowly permeable lipid membrane is used to coat the remaining groups. The rate of permeability is controlled by the thickness of the membrane, as well as its composition. The second group of pellets may be thinly coated, the third coated moderately coated, and the fourth coated to a thickness sufficient to last about 9 hr.

If each pellet in a group behaved exactly alike, the Spansule would release its drug like a repeat-action tablet. This is not the case. The drug-release pattern approaches that for a normal distribution within each group. For example, the mean value for a group may be 3 hr, but the pellets may be distributed over a range of, say, $\pm 30\%$. It is this distribution pattern that results in a sustained-release effect. As the release from pellets in each subsequent group overlaps, the sum total of the patterns approaches a constant. Thus release of drug is nearly continuous and dependent only on the rate of permeation of the pellets by moisture from the g.i. fluids.

It should be noted here that the Spansule does not really fit our model. One might picture the mechanism involved in these capsules by imagining a rubber stamp which will print a curve similar in shape to a normal distribution. If the stamp is used to print a series of such curves along the x axis of a piece of graph paper, it is possible to choose a constant time interval between the starting points so that the sum of the curves is nearly constant. Let us examine this analogy in the case of a Spansule. If there are four groups of pellets, we will need to stamp four times. Since the total blood level will be the sum of the effects of all pellets, all of the overlapped lines must be added. With proper spacing of the individual curves, the overall sum can be made to approach a constant value as a function of time.

Theo-24 capsules contain hundreds of coated beads of anhydrous theophylline. The coating and the large number of beads combine to provide a slow, continuous release of theophylline. Each bead has an expandable core designed to reduce the bead density on swelling to aid in prolonging the g.i. transit time. The multiplicity of beads, taken in the fasting state with water, tends to randomly spread the population throughout the g.i. tract over a 24-hr period.

For many patients optimum therapeutic results coincide with theophylline serum concentrations between 10 and 20 mg/liter. Theo-24 is designed to provide 24-hr theophylline therapy when administered once daily. However, strict attention must be paid to the relationship between the time of administration and meal times. Food can significantly increase theophylline absorption from Theo-24. One potential reason for this is the rapid dissolution of the coating on the beads as the pH exceeds 6. The pH of the small intestine

increases after a meal and may become as high as 8 [34]. When taken with food, the beads may not become sufficiently dispersed, so that a large number may simultaneously reach the intestine and release more than the intended amount. Food, especially fatty food, causes the pyloric sphincter to close. The time required for the stomach to empty is then highly variable. When it does empty, a large fraction of the administered dose may become available for rapid absorption. The release of more than the intended amount for a given time period from a controlled release device has been called dose dumping [34].

Both the absorption and the clearance of theophylline may be influenced by food, posture, and circadian rhythm. Theo-24 dosing following the evening meal has produced nighttime serum concentrations which are not similar to those following an identical dose during the waking hours. Theo-24 taken with a hearty breakfast produced peak levels approximately 2.3 times higher than those in the fasting state [34].

If once-daily doses are administered, it is recommended that Theo-24 be given in the morning followng an overnight fast and approximately 2 hr before eating.

e. Pellets in Tablets. The same principle used in the Spansules can be employed in tablets. Pellets are prepared in the manner previously described, mixed with appropriate diluents, and compressed into tablets. Bellergal-S and Belladenal-S are examples of this approach.

f. Leaching. Leaching is unusual in that the tablet shell excreted in the feces differs very little in appearance from the original tablet ingested by the patient. The shell is actually a plastic matrix that passes through the entire body intact. It may be likened to a plastic sponge which contains drug within the pores. As the tablet passes through the g.i. tract, the drug is leached out by the g.i. fluids at a rate that is relatively independent of pH, g.i. motility, and enzymes. Thus the sponge is excreted intact and depleted of its drug content.

Gradumet tablets use this principle. The initial dose is controlled by the geometry of the tablet. Since the channels open to the surface of the tablet, some drug comes into immediate contact with g.i. fluids; this dissolves at once and supplies an initial dose. The amount in this dose is dependent on surface area, which is controlled by the geometry of the tablet.

The design of a Gradumet is tailored to the specific drug to be used. The size of the channels, the ratio of drug to soluble and insoluble ingredients, the tablet geometry, and so on, must all be made compatible with the physicochemical properties of the drug, as well as its pharmacokinetic properties. This means that combining two drugs into a Gradumet presents a technological problem. One interesting solution is a laminated Gradumet, which is actually two independent Gradumets with a common interface. Thus a

pair of agents can be administered in combination yet the release mechanism can be tailored to the individual drugs.

g. Ion-Exchange Resins in Solids and Liquids. The ion-exchange principle involves the administration of salts of drugs with an ion-exchange polymer. This complex exchanges drug for ions as it passes through the g.i. tract. The rate of release is proportional to the concentration of the ions present in the g.i. tract. The contributions by H^+ and OH^- are negligible in g.i. fluids. The estimated total concentrations of Na^+, K^+, and Cl^- from published data are summarized in Table 10. Although some ions, such as bicarbonate, are not included in Table 10, one can see that the sum of the ions listed remains fairly constant throughout the g.i. tract. These concentrations would vary with changes in volume of g.i. fluids due to liquid intake. However, the constant-release principle is based upon a relatively constant exchange rate.

Pennkinetic combines ion exchange with a rate-limiting coating. The drug is complexed with either a cation- or anion-exchange polymer. Polyethylene glycol 4000 is applied to these loaded polymer matrix particles, which number more than 1×10^6 per capsule or teaspoonful. Ethyl cellulose is applied to provide a water-insoluble, permeable coating. An uncoated ion-exchange drug complex provides the initial dose. The mixture of coated and uncoated particles and the thickness of the coating determine the release rate. Ion exchange is required to displace the drug from the complex:

Cation exchange

$$[R - SO_3^- \cdots {}^+\text{drug}] \overset{X^+}{\rightleftarrows} R - SO_3^- X^+ + \text{drug}^+$$

Anion exchange

$$[R - N(CH_3)_3^+ \cdots {}^-\text{drug}] \overset{Y^-}{\rightleftarrows} R - N(CH_3)_3^+ Y^- + \text{drug}^-$$

The gradual release of drug from the coated matrix particles is controlled by the outward diffusion of free drug through the ethyl cellulose membrane.

Table 10 Concentration of Ions in the Gastrointestinal Tract

	Concentration (mg %)			
Ion	Gastic juice	Small intestine	Large intestine	Bile
Na^+	115	322	347	340
K^+	40	17	34	28
Cl^-	500	313	310	338
Sum	655	652	691	706

The relatively constant concentration of ions throughout the g.i. tract is responsible for constant exchange of drug from the polymer. Capsules have been made using phenylpropanolamine, codeine, pseudoephedrine, ephedrine, and chlorpheniramine. The approach is limited to drugs which are ionic.

Since ions are required to start this process, ion-free sustained-release liquid formulations can be formulated. This same principle has been used to formulate 12-hr oral liquid drug delivery systems for antitussives and decongestants. For example, the usual adult dose of Delsym (10 ml) contains dextromethorphan polistirex equivalent to 60 mg of the hydrobromide salt. The release pattern provides a loading dose and a controlled-release maintenance dose for a total period covering 12 hr.

h. Complexation. A once-significant compounding incompatibility occurred during the preparation of solutions of alkaloids in vehicles such as wild cherry syrup. Syrups that are high in tannis (wild cherry syrup was made from the bark) can result in precipitation of a drug–tannin complex of amine drugs. This principle is employed to produce long-acting oral dosage forms. These tablets contain a complex of the amine drug with tannic acid, $RCOO^{-}{}^{+}H_3N—R$.

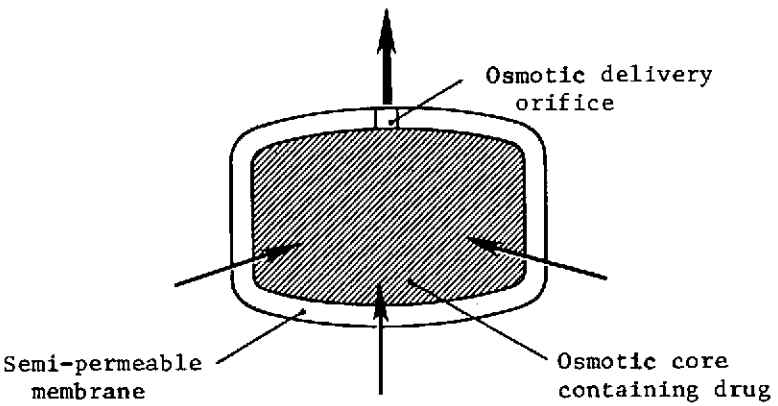
i. Microencapsulation. In the use of microencapsulation as a prolonged-release mechanism, drug powders (or in some cases particles) are covered with a thin coating that behaves like a dialysis membrane. The drug is released by diffusion through the membrane rather than by disintegration and dissolution. Gastrointestinal fluids diffuse through the membrane to form a saturated solution of drug within the sac or cell. Then the drug undergoes passive diffusion from this highly concentrated solution out through the membrane to the less concentrated g.i. fluids. The rate of release is governed by the diffusion properties of the drug with respect to the membrane. The microencapsulated drug can be incorporated into tablets or capsules. The release rate can be controlled by the size of the drug particles that are encapsulated, the surface area of the cells, and the permeability of the membrane coating. When powders are microencapsulated, the tablets appear similar to normal products.

Theo-Dur Sprinkle is a sustained-release microencapsulated anhydrous theophylline formulated for children or others who cannot swallow a tablet or capsule. The capsules are not completely filled and are meant to be opened and the entire contents sprinkled on a small amount of food just prior to ingestion. Subdividing the contents is not recommended. The microencapsulated contents should not be chewed or crushed. The polymer coating masks the bitter taste and provides a prolonged therapeutic duration. The dosing interval varies from 8 to 12 hr, owing to wide interpatient variability.

j. Osmotic Pump. The oral drug delivery system called OROS has the outward appearance of an ordinary tablet. It is capable, however, of delivering water-soluble drugs at a predetermined zero-order rate. The release of drug requires only the presence of water owing to its unique design.

The pump consists of a single core which contains the drug and an osmotic material. The core is surrounded by a semipermeable membrane with a minute hole which acts as a delivery orifice.

When a tablet is in contact with water, the core takes up water osmotically through the membrane. The rate is controlled by the permeability of the membrane and the formulation of the osmotic core. Since the internal volume is restricted to a constant value, the system pumps saturated solution of the osmotic principle out through the orifice. The delivery rate of the solution equals the rate of water uptake and will be constant, so long as excess solid is present within the core. During the passage through the core by this mechanism, the drug is dissolved into the water and is therefore pumped from the device at a constant rate.



One example is the product Acutrim, which provides 16 hr of relatively constant plasma phenylpropanolamine levels following a single dose. It is designed to be used as an all-day appetite suppressant.

k. Gel-Forming Hydrocolloids. Capsules are filled with a dry mixture of drug, fillers, and hydrocolloids. When the g.i. fluids permeate and dissolve the capsule shell, the outermost hydrocolloids swell to form a gelatinous mass which acts as a boundary layer, preventing further penetration. Initially only the outer portion forms a gel and the center remains dry. The layer gradually erodes, with subsequent formation of a new boundary layer. The process continuously releases drug as each gelatinous layer continues to erode and a new one forms.

The gelatinous mass formed on contact with gastric fluid has a specific gravity less than unity, which helps prolong gastric transit time. Gastric retention represents an advantage for prolonged-release dosage forms. The drug is then uniformly presented to the entire g.i. tract, thus circumventing potential bioavailability problems associated with an absorption window. In one report gel-forming capsules remained in the stomach for 3–6 hr. However, passage to the intestines is subject to physiological characteristics and will vary among individuals. On arrival in the intestines, the gelatinous mass will continue to release drug, independent of its location.

This mechanism is used in the product Valrelease (15-mg diazepam slow-release capsules), called a "hydrodynamically balanced system" (HBS). One 15-mg Valrelease capsule provides plasma diazepam concentrations equivalent to those from conventional 5-mg tablets given three times daily. Since the biological half-life of diazepam is 1–2 days, the goal of this controlled-release capsule is unique. By controlling the rate of release, C_{max} is decreased relative to that observed when 15 mg is administered as a single dose in tablets. Standard tablets dissolve within 15 min in vitro, whereas Valrelease dissolves gradually over an 8- to 12-hr period. This results in a smooth onset of action with a prolonged rate of release.

5. Drug Candidates for Long-Acting Oral Formulations

The goals for controlled release formulations vary from decreasing C_{max} to increasing the time between doses. The common goal for increased duration is twice a day or, when feasible, once a day. Several properties of the drug itself can preclude the achievement of a 12- to 24-hr oral prolonged-release dosage form. Some of the characteristics mitigating against success are the following:

1. Very short half-life and/or a relatively large single dose
2. Long half-life
3. Potent drug with a low margin of safety
4. Poorly soluble and/or poorly absorbed
5. Biological activity not a function of concentration in blood
6. Absorption primarily active through a "window"
7. Large first-pass metabolism

Successful dosage forms may be formulated for drugs which are nonideal with respect to a limited number of considerations. Theophylline is discussed

in detail in Chap. 8, Sec. III on clinical pharmacokinetics. Plasma theophylline concentrations are monitored in clinical use because of its narrow margin of safety, requiring maintenance between 10 and 20 μg/ml. It is marketed in long-acting oral dosage forms for 12- and 24-hr duration. This probably results from the fact that it is ideal with respect to the other characteristics in the list. It is soluble, well absorbed throughout the g.i. tract, has activity related to plasma concentration, has an appropriate biological half-life, and is not compromised by first-pass metabolism. Thus the preceding list is neither absolute nor complete but it will serve as a basis to discuss ideal criteria.

A drug with a very short half-life will require relatively rapid delivery together with a large dose in the sustained-release pool in comparison to the normal dose. If a drug has a half-life greater than 8 hr, there is no need for sustained release to achieve a 12-hr interval. A large dose, 1–2 g, for example, becomes impossible. Imagine a drug with a 1-hr half-life and a 1-g dose. The loading dose would be 1 g and the pool could be 8 g, for a grand total of 9 g to provide a 12-hr duration. ("Now open wide, Johnny, and get ready for a big swallow!")

The question of a potent drug with a low margin of safety in a long-acting form may be more controversial. In my opinion, it is not good practice to swallow five doses of a potent agent, especially if the margin of safety is relatively small. In spite of the fact that a well-designed, long-acting formulation should behave in a predictable manner, there is always a chance for the unexpected event in biological systems, and the potential for increased absorption is there.

The reasons for eliminating poorly absorbed drugs as candidates are twofold. Consider drugs such as hexamethonium and pentolinium. These are fairly potent agents and are extremely variable in their response upon oral administration. This is easily understood when considering that a patient is really swallowing 20 doses when a drug is only 5% absorbed. If, by some quirk of biological fate, the patient is able to absorb more on a given day, the potential for overdose is there. Now put such a drug in a sustained-release form. How much will be administered—80 doses? Second, a drug that is poorly absorbed because it does not pass the g.i. wall must accumulate in the g.i. tract. This means that a continuous-release dosage form will result in a pool of available but unabsorbed drug in solution in the g.i. tract. The controlled-release device is not in control.

What about the drug that is poorly absorbed because it is poorly soluble? Release from the dosage form must be the rate-limiting step. If the drug is poorly soluble, and thus poorly absorbed, then it is likely that dissolution of the drug itself is rate determining. The dosage form is therefore not governing

the absorption pattern but may be superfluous, as undissolved drug particles in the g.i. tract would behave independently of the formulation.

If the therapeutic activity of a drug is independent of its concentration, it is irrational to expend time, effort, and money in an attempt to maintain constant blood levels. Reserpine has a 15-min half-life yet its activity persists for as long as 48 hr [35]. Since reserpine may act by irreversibly inhibiting monamine oxidase, the duration may be related to the time of formation of new enzymes by the body. Thus the pharmacological activity is independent of the time course for drug in the blood. Pharmacokinetic parameters calculated from blood level data would not be therapeutically meaningful when applied to the development of a prolonged-release product.

An actively absorbed drug generally exhibits a preferential area of the g.i. tract for its absorption. If this is an enzyme transport process, this area will be located where the enzymes exist in greatest density. Prolonging the release of drug before reaching this site can increase the duration, since the arrival of drug in solution will be metered by the delivery system. Releasing drug after the formulation has passed by the site will decrease bioavailability in comparison to the normal case. This problem makes the chances for success very slim for any drug that is primarily absorbed through a window, unless gastric retention of the delivery device can be achieved.

Retarding the rate of absorption can increase the fraction metabolized for drugs susceptible to first-pass metabolism. Sustained-release aspirin has been shown to reduce the bioavailability of unmetabolized aspirin while total salicylate absorption is unchanged [8]. As shown in Fig. 18, the slower the presentation of a first-pass metabolism drug, the greater the loss to first-pass metabolism. This was also illustrated in reference to dose size in Fig. 6.

6. Evaluating Sustained-Release Products

Clinical evaluation of sustained-release products should include all of the statistical parameters normally encountered in a good experimental design. In addition, however, there are aspects unique to long-acting products. This is not always recognized in the literature, where it is easy to locate studies with conclusions that cannot be readily accepted in light of the experimental design.

The special characteristics of these dosage forms can present some unique problems in their clinical evaluation. They can also present practitioners with difficult decisions regarding the dosage form of choice. Each combination of dosage form, drug, and disease presents some unique considerations. Sustained-release dosage forms illustrate the problems involved in assessing the merits of special dosage forms.

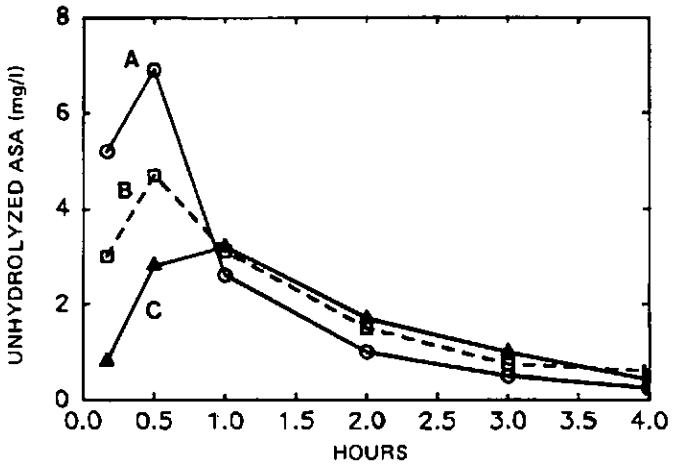


Fig. 18 Increasing the first-pass metabolism of aspirin (ASA) by retarding its absorption rate. The doses and total salicylate absorption from all three tablets are the same. The unmetabolized aspirin (ASA) is increased by rapid presentation of ASA: (A) buffered aspirin, (B) plain tablet, and (C) sustained-release tablet. (Data from Ref. 8.)

In most cases the drugs available in sustained-release or prolonged-release oral products are also available in traditional dosage forms. The claims are based not on the therapeutic entity but on the drug delivery system. This raises the question as to whether to use a normal dosage form or a sustained-release delivery system. The question can be divided into two parts: (1) Does the drug delivery system sustain plasma levels? (2) Are sustained plasma levels a clinical advantage?

Ideally the release pattern for a sustained-release preparation should be independent of pH, enzymes, agitation, and any other variables that might be encountered in the g.i. tract. This type of behavior can be tested in vitro, but negative results are more meaningful than positive ones. If the dosage form is unpredictable in vitro, then the in vivo behavior will not be more reliable. In vitro tests can be retrospectively correlated with blood level data for use in quality control.

Even clinical proof that sustained-release dosage forms produce the desired release patterns within the g.i. tract itself does not demonstrate that they will provide sustained therapeutic responses. The release of drug in the g.i. tract is not the final test for a constant absorption rate. Absorption of a given drug may vary as the dosage form travels down the g.i. tract. Thus x-ray or

gamma-scintigraphy studies commonly employed to follow the behavior of an ingested long-acting formulation can document only the release pattern. While this is certainly important, the rate and amount of absorption must be determined by other methods.

The most obvious measure of sustained release is the time course for drug in the blood. The formulation is designed to produce constant blood levels, and the level of success can be determined directly from blood or urine assays as a function of time. While this seems simple enough, there are some problems associated with the choice of a reference standard, in addition to the problems encountered in developing suitable analytical methods. It is common practice to compare a single sustained-release dose of the drug to the normal dosage regimen of the same drug. Many protocols attempt to demonstrate that blood levels from the sustained-release dosage form are equivalent to the usual dosage regimen. A typical study might prove that a single sustained-release tablet given once every 12 hr provides plasma levels that are equivalent or superior to those obtained from one regular tablet every 4 hr. This demonstrates that one sustained-release dose replaces three normal doses. However, it does not prove that the observation is due to the device. In the case of aspirin and meprobamate, a single dose in a non-sustained-release form, equivalent in size to the sustained-release product, provided similar results to the sustained-release dosage form [8,36].

Sustained-release devices normally contain several doses. Therefore there are two possible reasons for their prolonged plasma levels: One is the dosage form itself and the other is the larger dose. If the dosage form is the controlling factor, then plasma levels should be easily distinguishable from an equal dose in a regular dosage form. Hollister suggested that a study should include a single normal dose, the normal dosage regimen, the sustained-release form, and a single dose of drug equal to the amount in the sustained-release form. In his article "Measuring Measurin: Problems of Oral Prolonged-Action Medications" [8], Hollister demonstrated similar results from tablets and sustained-release tablets based on the *salicylate* time course in the blood following equal doses [37]. The reason for this may be due to the fact that salicylates easily saturate the enzyme system responsible for their metabolism. The apparent half-life of salicylic acid is dependent upon the dose, being roughly 2 hr at a 250-mg dose, 6 hr at a 1.3-g dose, and in overdoses of 10–20 g the apparent half-life has been reported to be approximately 20 hr. The rank order for peak *acetylsalicylic acid* plasma levels (at 30 min) was roughly 7, 4.5, 3 (in μg/ml) for buffered tablets, plain tablets, and sustained-release tablets, respectively. The terminal phase (which begins at approximately 1 hr) appeared similar for all three products with respect to acetylsalicylic acid (Fig. 18). Using this approach, Hollister demonstrated several cases where essentially equivalent blood level patterns were obtained with

a single dose of drug equal to that contained in the "long-acting" form [36]. It will not always be possible to administer such a large dose, but kinetics can be established as a function of dose and results representing the larger dose can be simulated.

There are two potential outcomes from these in vivo studies: One is that the sustained-release dosage form does prolong and maintain plasma levels compared to the normal dosage form; the other possibility is that it does not. Assuming that it does leads us to the next question: Is this a clinical advantage? The answer can only be determined by clinical studies. If the prolonged-action dosage form is advantageous, this should improve treatment of the disease when compared to the normal products.

While improvement in the disease state is the evidence for efficacy, quantitative measurements are often difficult. A clinical endpoint must first be established. Two types of data are encountered: *objective* and *subjective*. Objective data describe processes that can be measured by a prescribed procedure free of personal feeling, prejudice, or bias. The patient's height, weight, age, sex, and concentration of drug in blood or urine are examples of objective data. These involve prescribed tests yielding results which the observer *must* accept. One may not like the result found by stepping on a scale, but it cannot be arbitrarily lowered to suit the individual. In contrast, subjective data require the assignment of a rank or value based on a patient's response or on examination of the patient's condition by an observer. One example is the Clyde Mood Scale used to evaluate ataractics. Patients are asked to arrange cards with adjectives such as *hostile* to reflect their frame of mind. Results are scored to evaluate the effect of the drug on a patient's mood. In other situations an observer may examine the patient and assign a score that reflects improvement in the patient's condition. Obviously, objective data are more reliable than subjective data.

The study should be designed to remove bias. In spite of the fact that double-blind techniques are commonly employed, many such studies do not include a placebo or make any attempt to disguise the dosage forms. Sustained-release formulations are generally unique in appearance. The value of a double-blind study based on information collected by clinicians interviewing patients becomes questionable when the dosage forms have such distinguishing characteristics that a brief mention of it by the patient removes the blind.

An interesting study was carried out to test the efficacy of the double blind: 100 patients were given a drug by a group of interns and the results were determined subjectively. Excellent results were obtained in 61% of the cases. A known placebo was introduced and a 56% response was obtained. When the same tests were carried out using a double-blind technique with unknown placebo, only 38% excellent results were reported. How common

is the problem of experimental design affecting interpretation? An analysis of 100 consecutive articles in a group of medical journals revealed that 45 did not compare the treatment with control and an additional 18 had inadequate control, for a total of 63%.

If possible, the placebo should appear like the real thing. Sometimes it is not possible to use a placebo, as patients should not go untreated. Comparison with standard forms or other sustained-release products then becomes the only alternative. Elimination of the placebo should result in a crossover approach. A common error of general occurrence is to divide a group in two and treat each with a different drug without any crossover.

Optimally, the protocol should have three components: (1) the test drug itself, (2) the reference standard, and (3) the placebo. The reference standard should be the product which would be replaced in therapy by the new one, usually the current drug of choice. If the test drug is not superior, perhaps it is not needed. The reference standard tests the new drug. The placebo tests the study. If the study cannot adequately differentiate between the placebo and reference standard, then the methods are inadequate.

Bias is preconceived opinion; it produces a tendency toward a prejudiced result. Bias must be prevented from influencing the results of a clinical study. There are several types of bias which may enter a study and these are accommodated in the experimental design by three means: (1) avoidance (2) even distribution, and (3) measurement. A double-bind technique eliminates patient or observer bias, since the physician does not know what is being given and the patients do not know what they are receiving. This removes bias due to people. A physician may be very enthusiastic about the patient taking a new drug; conversely, if it is a placebo, a negative attitude can be transmitted to the patient. The patient may then respond to the influence of the physician. The dosage forms should be indistinguishable. It should not be possible to identify placebo or real drug by appearance.

Some bias cannot be avoided. When a drug is first administered, positive results may be favored owing to the initiation of treatment. The agent tested first may have an unfair advantage. To *evenly distribute* this bias throughout the measurements, a Latin square design may be used. A minimum of three groups will allow each agent to be administered first to one group.

The order of treatment and the passage of time may also be sources of bias. If the new agent is *A*, the reference standard *B*, and the placebo *C*, the Latin square order is represented by

A B C

B C A

C A B

Now all treatments have equal opportunity to be first, second, and third. Table 11 is an example of the Latin square design in the evaluation of a new anorectic agent *A*.

7. Rational Clinical Use of Sustained-Release Products

The rational use of sustained-release products is based upon an understanding of their construction and the principle by which they are intended to function. Those employing the erosion-core principle, for example, contain several doses and depend on the geometry of the intact core for their continuous release pattern. Anything that would destory this structure could result in an overdose. A markedly greater response was observed when tablets of the slow-release type were chewed by the patient before swallowing [38]. The report concurred with those of other investigators, who recommended chewing of the tablets as a routine procedure. In using sustained-release forms, it is good practice to avoid the introduction of new variables that may not have been present in the original evaluation. Thus beverages such as hot drinks that might soften fats or waxes, alcoholic beverages that might dissolve coatings, and so on, should be avoided. A worthwhile precaution would be to warn patients against the simultaneous ingestion of any foods or drugs that might affect the integrity of the dosage form with a resultant increase in the rate of drug release.

It is a frequent practice to administer sustained-release preparations or fractions of them to children. There are several factors that would raise doubt regarding the wisdom of this procedure. Children are not little adults. The dosage regimen for a child should be one that is specifically developed for that purpose, independently of the adult regimen and not calculated by applying some arbitrary equation to adjust the adult dose. It should be obvious that a given fraction, arrived at by any of the common pediatric

Table 11 Pretreatment Weights and Latin Square Design for the Evaluation of an Anorectic Agent

		Period			
Group	Number of patients	January through March	April through June	July through September	October through December
1	1–25	None	A	B	C
2	25–50	None	B	C	A
3	51–75	None	C	A	B

dosage equations, cannot be considered optimum for every drug when administered to a child. While this is a problem associated with pediatric posology in general, there are specific problems with respect to long-acting products.

The release pattern and the amount of drug in the slow-release compartment are directly related to the desired blood level and clearance values in adults. These are average values for an adult population. It is reasonable to expect that the clearance values and perhaps the desired blood level would be different for children. Clearance may be longer owing to underdeveloped enzyme systems, with a resultant decrease in metabolic rate or a more rapid one, as is the case with theophylline. It is not rational to administer either the whole or part of a long-acting adult dosage form to a child, especially since these forms will contain several doses.

There are additional problems associated with the administration of a fraction of a sustained-release dosage form, and these are related to the physical makeup of the formulations themselves. For example, how can one take one-half of the contents of a Spansule? Some physicians direct the parents to open the gelatin capsule and pour out one-half of the pellets. But which half do they obtain? Stratification of pellets in a mixture is a well-known "unmixing" problem to the pharmaceutical industry. A granulation may have to be remixed before tableting if it has been moved or stored long enough to result in different analyses at the top and bottom of the mixture. A Spansule contains several groups of pellets. One cannot expect to pour one-half of each group out into a spoon to get one-half of the release pattern on ingestion.

Erosion-type products may be broken or cut in half, but this also has its problems. Obviously, if an enteric coating or a time-lapse mechanism is present, it will be destroyed. Less obvious is the fact that one-half of the tablet has more than one-half of the surface area. The increase will vary with the geometry of the original tablet. The surface will be greater than half and thus the release rate will also be greater than half. The result would be blood levels that are greater than half and shorter in duration than the original tablet. The relative blood levels and duration can be calculated rather simply from the dimensions, as illustrated in the following problem.

Practice Problem 16

The relative dimensions as estimated with a ruler and the duration of action estimated from the manufacturer's product information are listed in Table 12 for several products.

Choose from the list of categories the appropriate descriptive phrase that best describes each product and then calculate what you would expect to be the relative blood level (%) and duration (hr) following administration of one-half of the dosage form:

Table 12 Duration of Action and Relative Dimensions for Several Products

Product	Duration (hr)	Relative dimensions[a]
Mestinon Timespan	~6	1 × 1 × 3
PBZ SR	8	Core diameter = 2, thickness = 1
Tenuate Dospan	12	3 × 5 × 12
Triaminic TR Tablets	8	Core diameter = 4, thickness = 1
Rynatan	12	1 × 2 × 5

[a]Goemetric formulas for areas: circle, πr^2; sphere, $4\pi r^2$; rectangle, length × width.

1. Erosion core only
2. Pan-coated erosion only
3. Press-coated erosion core
4. Repeat action
5. Laminated tablet/core
6. Spansule pellets in capsule
7. Enteric pellets in capsule
8. Spansule pellets in tablet
9. Leaching from plastic matrix
10. Polystyrene sulfonic acid resin
11. Tannic acid complex
12. Microencapsulation

(Hint: Use the relative rate and dosage form lifetime to estimate the answers.)

Practice Problem 17

a. Why are Gradumets containing two drugs formulated as two-layer tablets?
b. A patient complained to a physician that undisintegrated tablets (Gradumets) are appearing in the feces. The physician, in turn, asks the pharmacist if "old stock" was dispensed. What should the pharmacist answer?
c. What objection might be offered to the simultaneous ingestion of a Spansule along with hot tea, hot coffee, or a cathartic?
d. What objection can be raised to reducing an Extentab to a powder and administering it as a suspension in milk to a patient who has difficulty swallowing the tablet.

An excellent comprehensive review of the considerations regarding drug candidates and the theory and practice of sustaining mechanisms has been edited by Robinson [39]. This extensive multiauthor text includes detailed discussions on physical, chemical, and bioengineering approaches and the biological and drug-related constraints, as well as the pharmacokinetic theory, for dosage regimens.

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6

Dosage Regimens

I. INTRODUCTION

The development of an optimum dosage regimen, one which balances patient convenience with the proper body content of a drug, is an essential consideration for rational therapy with a drug product. The concept of achieving a certain desirable blood level following the administration of a single oral dose of a drug was considered in Chap. 5. However, few drugs are used in a single dose. Some examples of single-dosage drugs are headache remedies,

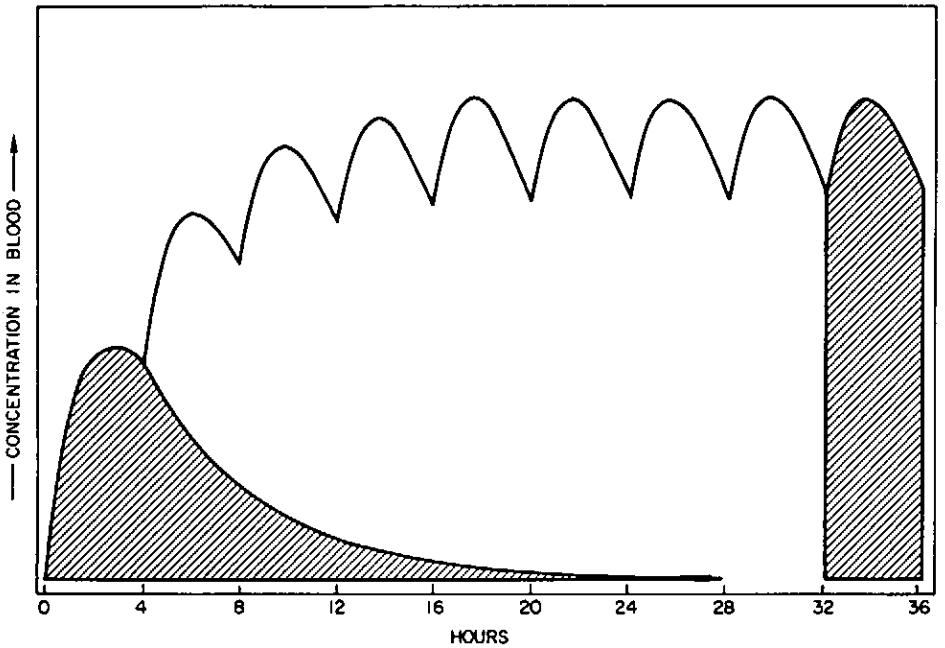

Fig. 1 An equal dose is administered orally every 4 hr. The absorption rate constant and bioavailable fraction f have been held constant. The total area under the curve (AUC) from $t = 0$ to $t = \infty$ following a single dose is equal to the AUC value between successive doses during the steady state.

digestive aids, antinauseants, laxatives, anthelmintics, and antacids, all of which may be used in one or two doses as the occasion arises. The large majority of drugs are administered repetitively, either on a maintenance regimen (as in cardiovascular diseases) or to the end of a prescribed course of therapy (as in treatment with an antibiotic). This type of therapy is illustrated in Fig. 1, which shows a blood level curve for a fixed oral dose repeated every 4 hr.

For many drugs a desirable minimum plasma concentration can be established. Kruger-Thiemer et al. [1–3] have stressed the clinical significance of maintaining constant minimum inhibitory blood concentrations for certain antimicrobial agents. For other agents, such as digoxin, theophylline, procainamide, and aminoglyosides, a narrow range of minimum and maximum blood concentrations can be defined. A multiple-dosage regimen can be calculated for either type of drug, that is, those that simply require a minimum or those which have a narrow margin of safety. The primary prerequisite for such calculations is that the desired therapeutic response must be related to a corresponding concentration of drug in blood.

The complexity of the equations employed for dosage regimen calculations is dependent upon the complexity of the pharmacokinetic model describing the situation. For example, a dosage regimen for a monoexponential disposition drug administered by repetitive rapid intravenous injections of equal doses is easily calculated. But a multiexponential disposition drug administered orally may become quite complex, and accurate assessments may require a value for the absorption rate constant k_a. Since values for k_a are often not readily obtainable, approximate methods have been devised for estimating dosage regimens. The present treatment will deal with the monoexponential (one-compartment) intravenous case; biexponential (two-compartment) intravenous case; biexponential oral administration, and model-independent estimates for drugs administered by intra- or extravascular routes. Literature references for more complex treatments will be cited.

Regardless of the route of administration or the complexity of the pharmacokinetics, there are only two parameters which can be adjusted in developing a regimen for a given drug: the size of the dose and the frequency of administration. The amount of a drug in the body at any given time will be a function of how much drug is administered and how often it is administered. If we know the mathematical relationship between the body content and the dose and frequency, we can estimate a regimen to maintain any desired body level. If a desirable therapeutic body content can be clinically defined, the optimum regimen can then be calculated to provide that level during repetitive multiple-dose therapy. The following sections are designed to illustrate this statement.

II. ACCUMULATION DURING REPETITIVE DOSING

A. Rapid Intravenous Injections

Accumulation is most simply considered for rapid intravenous injections of a dose of drug with monoexponential disposition administered at a fixed time interval τ. An ordinary first-order equation will describe the loss from the body following a rapid intravenous injection:

$$\ln A = \ln D - \lambda_z t \tag{1}$$

where D is the intravenous dose and A is the total amount remaining in the body. The equation may be rearranged to define the natural logarithm of the fraction of the dose remaining, $F = A/D$, as

$$\ln F = \ln\left(\frac{A}{D}\right) = -\lambda_Z t \tag{2}$$

which can be rearranged as

$$t_F = \frac{\ln F}{-\lambda_Z} \tag{3}$$

which includes the well-known half-life expression $t_{1/2} = 0.693/\lambda_Z$, when $F = 0.5$. Thus the time for the body content to reach any fraction of the administered dose t_F is the natural logarithm of that fraction divided by the negative value for λ_Z.

Consider the case where rapid equal intravenous doses of this drug are administered repetitively at a fixed interval, τ. For example, let us say that the doses are administered every time a half-life has elapsed. Then τ is equal to the biological half-life. Just prior to the second injection, one-half of the dose would remain in the body. Upon injection the body would contain 1.5

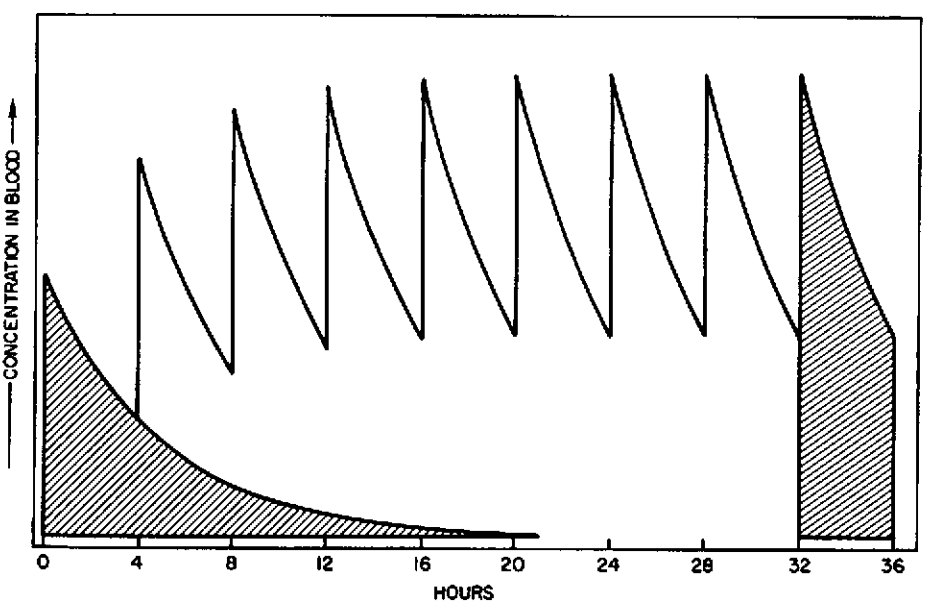

Fig. 2 An equal dose is administered by rapid intravenous injection every 4 hr. The total area under the curve (*AUC*) from $t = 0$ to ∞ following a single dose is equal to the *AUC* value between successive doses during the steady state.

Table 1 Fraction of the Dose in the Body Immediately Before and After Rapid Intravenous Administration where $\tau = t_F$ and Disposition is Monoexponential

Number of doses	$F = 0.50$		$F = 0.75$	
	Before dose	After dose	Before dose	After dose
1	0	1.00	0	1.00
2	0.50	1.50	0.75	1.75
3	0.75	1.75	1.313	2.313
4	0.875	1.875	1.734	2.734
5	0.938	1.938	2.050	3.050
6	0.969	1.969	2.228	3.288
7	0.984	1.984	2.466	3.466
8	0.992	1.992	2.600	3.600
9	0.996	1.996	2.700	3.700
10	0.998	1.998	2.775	3.775
∞	1.000	2.000	3.000	4.000

doses; before the third dose 0.75 doses remain; after the third dose 1.75 doses are present. The drug is accumulating within the patient. What does accumulation mean? After each subsequent dose there is more drug within the patient than after the previous dose. Therefore the administered dose is greater than the dose eliminated. But there is a limit. When the rate of drug supply becomes equal to its rate of loss, a steady state will be achieved. The time required to achieve the steady state will depend upon the $t_{1/2}$ value of the drug. The difference between the repetitive dosing and that of a zero-order constant-rate intravenous infusion is that the repetitive-dose steady state will fluctuate between a minimum and a maximum value as a function of time. This pattern (illustrated in Figs. 1 and 2) is shown quantitatively in Table 1 for the dosage intervals where $\tau = t_{1/2}$ and $\tau = t_{0.75}$. Once the body has reached the steady state, it is a necessary condition that the equivalent of a single dose be eliminated during each period of time equal to τ. This is implicit in the definition of steady state, which asserts simply that the dose administered is equal to that which has been eliminated. In Table 1 it is readily apparent that the difference between the body content before and after each dose approaches a constant value that is equal to a single dose. Thus during each dosage interval τ a single dose is eliminated and then replaced by the injected dose. The body content (amount A remaining in the body) before each subsequent dose will be called the minimum, so that

$$A_{\min\,(N)} = C_{\min\,(N)}\, V_Z \tag{4}$$

and the peak or maximum value

$$A_{\max\,(N)} = C_{\max\,(N)}\, V_Z \tag{5}$$

where N is the number of doses. If an infinite number ($N \rightarrow \infty$) of fixed doses are given at constant τ, the steady-state maxima ($A^{ss}_{\max}$ or $C^{ss}_{\max}$) and minima ($A^{ss}_{\min}$ or $C^{ss}_{\min}$) will approach constant values, as illustrated in Figs. 1 and 2 and Table 1.

Practice Problem 1

(a) A drug that is described by monoexponential disposition has a $t_{1/2}$ value of 6 hr. A 210 mg dose is administered by rapid intravenous injection every 12 hr. If V_Z is 40 liters, what values will be achieved for $C^{ss}_{\min}$ and $C^{ss}_{\max}$?
Answer: $C^{ss}_{\min} = 1.75$ mg/liter. $C^{ss}_{\max} = 7$ mg/liter.

(b) Construct a single figure showing three accumulation plots for the fraction of the dose in the body versus time in hours following rapid intravenous injections of a single drug with $t_{0.5} = 4$ hr when $F = 0.5$, $F = 0.75$ (data in Table 1), and $F = 0.25$—as in part (a)— and $\tau = t_F$. Note the steady-state maximum and minimum in each case and the time required to achieve the steady state.

Practice Problem 1 was designed to familiarize you with the kinetics of drug accumulation. The equations for quickly estimating $A^{ss}_{\max}$ and $A^{ss}_{\min}$ are quite simple and should become obvious upon examination of the time profile in your plot for part (b) of Practice Problem 1. Keep in mind that the dosage interval τ is defined as the time to reduce the body content to the fraction F; replacing t_F in Eq. 3 by τ provides the equation describing this:

$$\tau = \frac{\ln F}{-\lambda_Z} \tag{6}$$

We have observed that $A^{ss}_{\max}$ is always one dose larger than $A^{ss}_{\min}$. Your figure in part (b) of Practice Problem 1 should show that relative to a single dose $A^{ss}_{\max} = 4$ and $A^{ss}_{\min} = 3$ ($F = 0.75$), $A^{ss}_{\max} = 2$ and $A^{ss}_{\min} = 1$ ($F = 0.5$), and $A^{ss}_{\max} = 1.33$ and $A^{ss}_{\min} = 0.33$ ($F = 0.25$). The difference between $A^{ss}_{\max}$ and $A^{ss}_{\min}$ is always *one dose*, as you would expect for the steady state, where each subsequent dose replaces the one that has been lost. You should have no problem remembering this equation:

$$D = A^{ss}_{max} - A^{ss}_{min} \tag{7}$$

It is also a simple matter to calculate either A^{ss}_{max} or A^{ss}_{min} directly. The time of decrease from A^{ss}_{max} to A^{ss}_{min} is equal to the dosage interval τ. Since we have defined $\tau = t_F$ (Eq. 6), then, by definition, $A^{ss}_{min} = F(A^{ss}_{max})$. We know that one dose was lost during this time interval [Eq. (7)]; therefore, $D = (1 - F)A^{ss}_{max}$. This can also be derived by substituting $F(A^{ss}_{max})$ for A^{ss}_{min} in Eq. (7) and rearranging to obtain

$$A^{ss}_{max} = \frac{D}{1 - F} \tag{8}$$

The previous examples (Table 1 and Practice Problem 1) set $F = 0.75, 0.50$, and 0.25 and $\tau = t_F$. Equations (7) and (8) will provide the same steady-state approximations. Try them.

The estimation of C^{ss}_{min} and C^{ss}_{max} may be a practical problem in therapy or research. Equation (8) may be written in terms of the plasma concentration using the relationship $A = CV_Z$ to give

$$C^{ss}_{max} = \frac{C(0)}{1 - F} \tag{9}$$

and

$$C^{ss}_{min} = \frac{F^*C(0)}{1 - F} = FC^{ss}_{max} \tag{10}$$

where $C(0) = D/V_Z$ is the intercept value of the semilog plot following a single rapid intravenous injection of a monoexponential disposition drug.

B. Prediction of Multiple Dose Blood Levels from a Single-Dose Curve

1. Steady-State Blood Levels: Rapid Intravenous

If a fixed dose is repetitively administered at a constant dosage interval and all rate processes remain first order, then the results are additive as illustrated in Practice Problem 1. Under these conditions a single-dose equation may be converted to its corresponding multiple-dose equation by multiplying each term containing t in the exponent by the factor X, defined as

$$X = \frac{1 - e^{-Nk_i\tau}}{1 - e^{-k_i\tau}} \tag{11}$$

where k_i is the rate constant in the exponential term and N is the number of doses [4]. In the case of a rapid intravenous injection of a monoexponential drug where the single dose is described by

$$C = C(0)e^{-\lambda_z t} \tag{12}$$

where C is the plasma concentration at time t, the multiple-dose equation becomes

$$C_N = \frac{C(0)(1 - e^{-N\lambda_z\tau})e^{-\lambda_z t}}{1 - e^{-\lambda_z\tau}} \tag{13}$$

where the limits of time are $0 \leq t \leq \tau$. After $N \rightarrow \infty$ Eq. (13) approaches

$$C^{ss} = \frac{C(0)e^{-\lambda_z t}}{1 - e^{-\lambda_z\tau}} \tag{14}$$

From the antilog of Eq. (2) we see that F, the fraction remaining, equals $e^{-\lambda_z\tau}$, so that $1 - e^{-\lambda_z\tau} = 1 - F$, the fraction eliminated. The numerator of Eq. (14), $C(0)e^{-\lambda_z t}$, is the single-dose curve described by Eq. (12). Thus Eq. (14) states that the plasma steady-state concentration at a given time equals the single-dose concentration at the same time divided by $1 - F$. In these equations the measurement of time begins anew with each dose so that time falls within the limits $0 \leq t \leq \tau$.

Practice Problem 2

Figure 3 is an example of the plasma concentration time course for a monoexponential model drug following a single intravenous bolus injection. Assume that this dose is to be repeated every 12 hr. What steady-state time course would result?

Answer: At $t = 12$ hr, $N = 1$, the concentration in plasma is 2.8 mg %. Since the initial concentration is 8 mg %, $F = 2.8/8 = 0.35$. Therefore $C^{ss} = C/(1 - F) = 1.54C$. The steady-state plasma level curve may be predicted by multiplying each of the data points in Fig. 3a or b by the factor 1.54. Figure 4 shows the results where $0 \leq t \leq \tau$.

Any monoexponential curve may be converted to its steady-state time course by multiplying the data points or the line of best fit by the factor

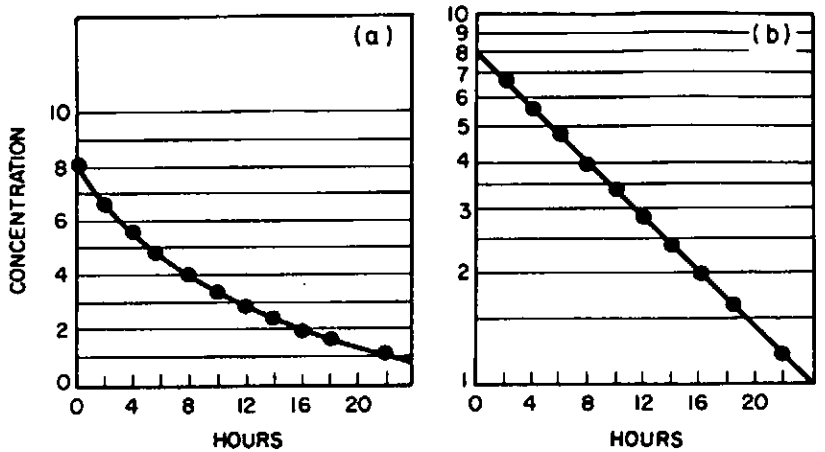

Fig. 3 (a) Concentration of drug in blood as a function of time (in hours) following a single rapid intravenous injection of a one-compartment model drug. (b) Semilog plot for the data in (a).

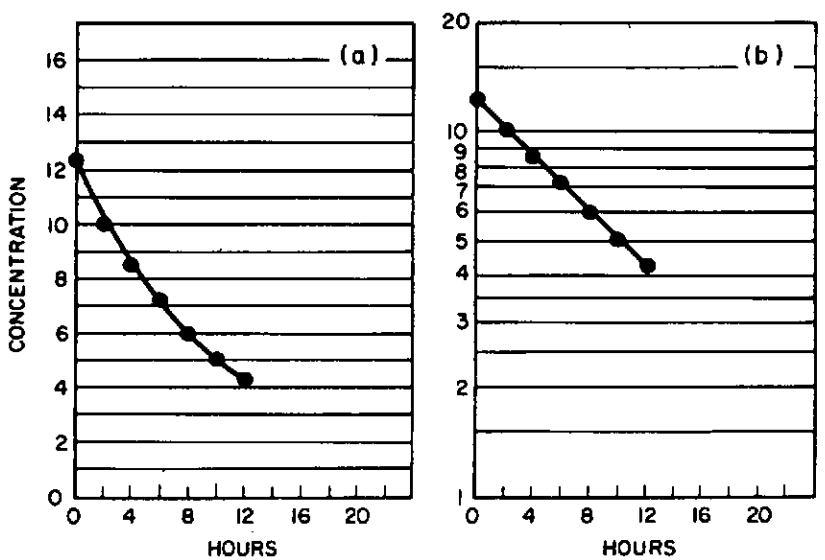

Fig. 4 (a) Predicted steady-state time course for the drug in Fig. 3 administered in equal doses every 12 hr by rapid intravenous injection. This plasma profile would be repeated following each steady-state dose as illustrated in Fig. 2. (b) Semilog plot for the data in (a).

$1/(1-F)$. The value for F, the fraction remaining, is based on the initial value or zero-time intercept for the curve. If a curve is made up of more than one exponential, each component may be converted individually and the results summed for the overall curve. This is illustrated using a biexponential disposition drug in Practice Problem 3.

Practice Problem 3

Figure 5 shows the feathered semilog plot for an intravenous bolus injection followed by biexponential disposition. Compare the steady-state time course that would result from repetitive equal doses administered every 24 hr to that which would result from administration every 6 hr.

Answer: The results are compared in Fig. 6a and b. The methods are discussed below.

Since disposition is biexponential, two exponential functions must be summed. When $\tau = 24$ hr, the value of F for the λ_Z line can be estimated in Fig. 6 as $F_Z = 1.6/7 = 0.23$. Thus the steady-state λ_Z line will be $1/(1-F_Z) = 1/0.77 = 1.30$ times the single-dose λ_Z line. The steady-state λ_Z intercept will be $1.30(7) = 9.10$ and the value at τ will be 2.08, as shown in Fig. 6a. The value of the λ_1 line at 24 hr cannot be read from Fig. 5. A rough estimate may be made by observing that this line passes through an entire log cycle (from $C = 2$ to $C = 0.2$) in 10 hr. Therefore in 24 hr C will be less than 1/10 of the value at 13 hr, or $C < 0.01$. Thus $F_1 < 0.01/2 = 0.005$ and $1/(1-F_1) < 1.005 \approx 1$. Since the conversion factor approaches unity, the λ_1 line will be the same in the steady state as it was following a single dose. The resulting steady-state blood level will be the sum of these two lines, as shown in Fig. 6a.

When $\tau = 6$ hr, the λ_Z line value for $F = 4.8/7 = 0.69$ and $1/(1-F_Z) = 3.2$. The steady-state λ_Z line will be 3.2 times higher than the single-dose line. The λ_1 line value for F is now significant, as the λ_1 value at 6 hr is 0.5, making $F_1 = 0.5/2 = 0.25$. Thus the steady-state λ_1 line is obtained by multiplying the single-dose λ_1 line by $1/(1-F_1) = 1/0.75 = 1.33$. The overall steady-state blood level curve will be the sum of these individual steady-state lines, as shown in Fig. 6b.

2. Steady-State Blood Levels: Oral

The process described above may be extended to any time profile that can be described by one or more exponentials. For example, blood concentration time courses following oral administration can often be described by an equation for the difference between two monoexponential terms.

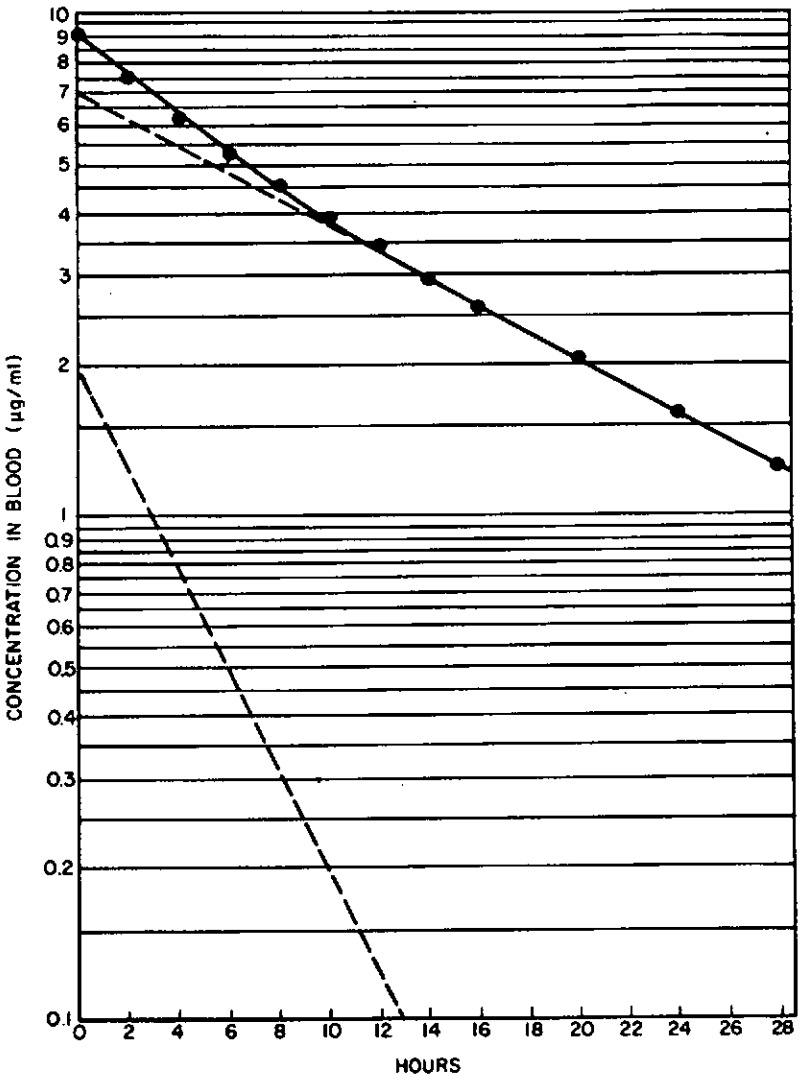

Fig. 5 Feathered semilog plot of data for the concentration of drug in blood as a function of time following a rapid intravenous injection.

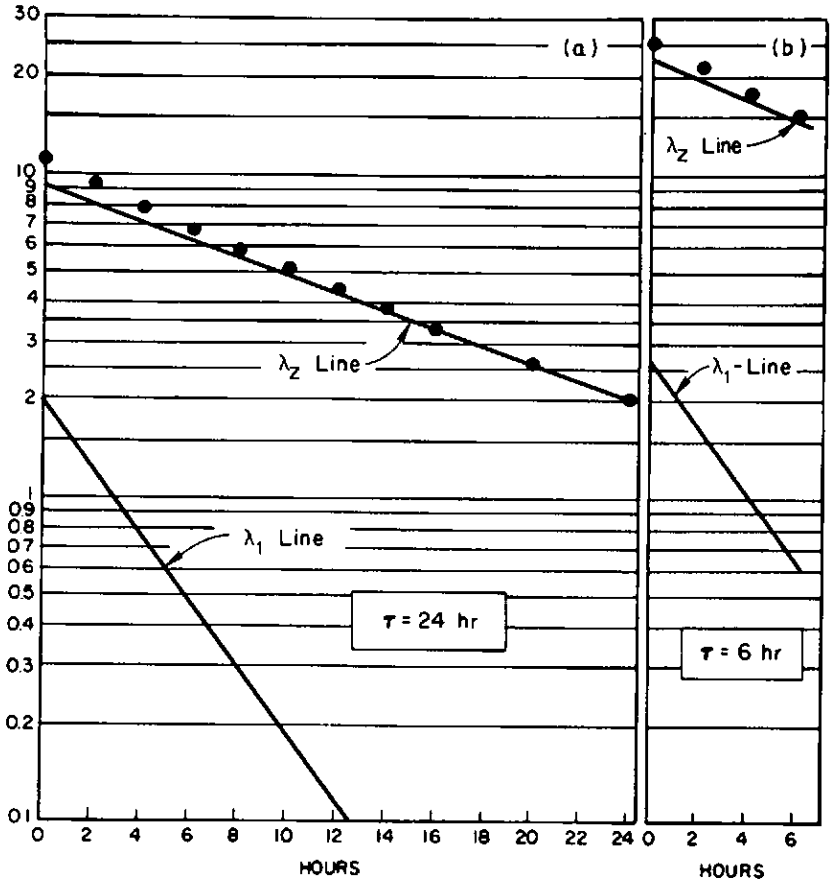

Fig. 6 (a) Semilog plots of the predicted steady-state λ_1 line, λ_Z line, and data points for the drug in Fig. 5 administered in equal doses every 24 hr by rapid intravenous injection. This plasma profile would be repeated after each steady-state dose given at $\tau = 24$ hr. (b) Semilog plots of the predicted steady-state λ_1 line, λ_Z line, and data points for the drug in Fig. 5 administered in equal doses every 6 hr by rapid intravenous injection. This plasma profile would be repeated after each steady-state dose given at $\tau = 6$ hr.

The equation describing this is of the form

$$C = C_i e^{-S_Z t} - C_i e^{-S_1 t} \tag{15}$$

where S_Z and S_1 are the negative slopes of the first-order plots for the terminal slopes (S_Z) and the feathered data (S_1) and C_i is the intercept. The smaller slope (S_Z) represents the rate-limiting step. This equation for monoexponential disposition with first-order absorption often describes biexponential

disposition with first-order absorption, since the rapid disposition phase is not easily seen unless absorption is extremely rapid. If the blood level curve following oral administration can be described by Eq. (15), the data may be feathered as shown in Fig. 7, provided that $S_1 \neq S_Z$. According to the flip-flop phenomenon, the S_Z term will reflect the slower of the competing processes, absorption or elimination [5]. It is not necessary to assign any physical meaning to the slopes in order to predict the steady state; it is only necessary that the plasma level time course can be described by the difference between a slow monoexponential term (the terminal slope) and a fast one (the feathered slope), as shown in Fig. 7 and described by Eq. (15).

Let us compare the steady-state blood level for the oral dose given in Fig. 7 repetitively dosed at $\tau = 12$ hr to the results when $\tau = 3$ hr. At $\tau = 12$ hr, F associated with the slower exponential (S_Z) is $F_Z = 2/8 = 0.25$ and $1/(1-F_Z) = 1.33$. For the faster exponential X will approach $1/(1-F_1) \approx 1$ as F_1 becomes insignificant in Fig. 7. The actual F_1 value may be calculated from $-\ln F_1 = S_1 t = 0.693(12)$ to give $F_1 = 0.00024$. Therefore the line associated with S_Z must be multiplied by 1.33 to obtain the steady-state line and the S_1 line remains constant. The actual blood level curve during each 12-hr dosage interval in the steady state will be the S_Z steady-state line minus the S_1 line.

At $\tau = 3$ hr the S_Z value for $F_Z = 5.6/8 = 0.7$ and $1/(1-F_Z) = 3.33$. The F_1 value for the S_1 line is $F_1 = 1/8 = 0.125$ and $1/(1-F_1) = 1.14$. Therefore at steady state the S_Z line will be 3.33 times its single-dose line, the S_1 line will be 1.14 times its single-dose line, and the blood level curve will be the S_Z steady-state line minus the S_1 steady-state line. Figure 8 illustrates these results for $\tau = 12$ hr and $\tau = 3$ hr.

One may also calculate any given data point in the steady state by this method. For example, the value for C at 3 hr in Fig. 7 appears to be the single-dose maximum value. It is simple to calculate the value at $t = 3$ hr in the steady state when $0 \leq t \leq \tau$. This may not be the steady-state maximum value; however, the calculation can be repeated on adjacent points to search for the steady-state maximum. For example, when $\tau = 12$ hr, the factor was calculated to be 1.33 for S_Z and 1 for S_1. Therefore at $\tau = 12$ hr, $C^{ss}(3\text{ hr})$ is 1.33 × (value in S_Z line) − (value in S_Z line) = 1.33 (5.6) − (1) = 6.45. The steady-state value for C^{ss} at $t = 3$ hr will be 6.45 when $\tau = 12$ hr. Similarly, one could calculate $C^{ss}_{\min}$ by adjusting the single-dose data point for C at $t = \tau$. This is simple at $\tau = 12$ hr, since the S_1 line is insignificant and $C^{ss}_{\min} = 2(1.33) = 2.66$.

Consider the case where the same drug is dosed at 3-hr intervals. Now the steady-state *minimum* ($C^{ss}_{\min}$) must occur at $t = 3$ hr (Fig. 8), which is the time of *maximum* concentration following a single dose (Fig. 7). This $C^{ss}_{\min}$ value may be calculated from the single-dose value of $C(3\text{ hr}) = 5.6$ using

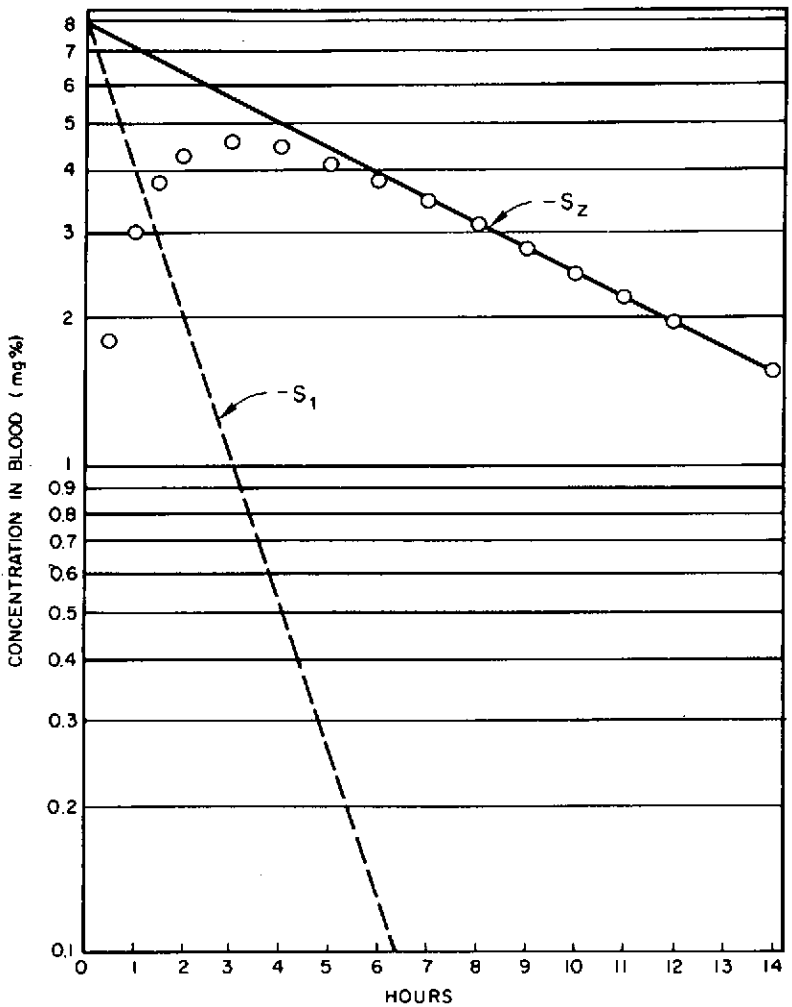

Fig. 7 Feathered semilog plot of data for the concentration of drug in blood as a function of time following oral administration when Eq. (15) describes the time course. Data such as this can result from first-order absorption of a one-compartment model drug or a two-compartment model drug with distribution being too rapid to observe by this route of administration. It is not necessary to know what the slow (S_2) and fast (S_1) slopes represent in order to predict the steady state.

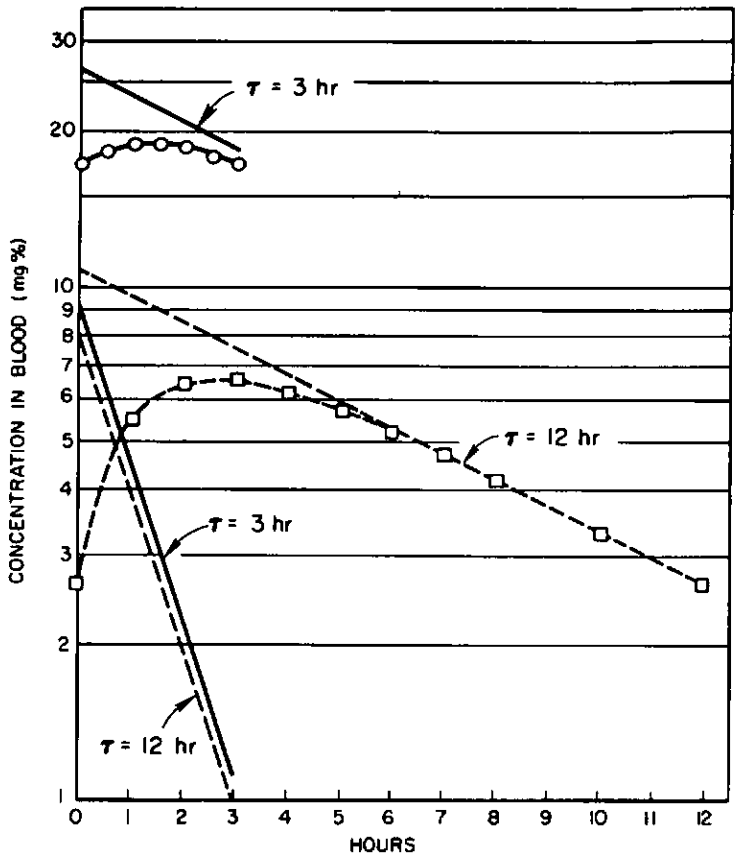

Fig. 8 Semilog plots of the two pairs of steady-state lines predicted from the S_1 and S_2 lines in Fig. 7 by assuming that equal oral doses are administered either every 3 hr (solid lines) or every 12 hr (dashed lines). Data points represent the absolute difference between the two solid lines (○) or the two dashed lines (□).

the factors calculated previously for the two reference lines as follows: C^{ss}_{min} = 3.33(5.6) − 1.14(1.0) = 17.51. As seen in Fig. 8, the steady-state C^{ss}_{min} value at τ = 3 hr is 17.51 mg %.

The preceding behavior is significant in deciding when to draw blood samples for monitoring steady-state drug plasma levels in dosage management in clinical pharmacokinetics. If the feathered line is significant relative to the steady-state calculations, then the time of the steady-state maximum (t^{ss}_{max}) is always less than that of a single dose (t_{max}). This can be seen by comparing the t^{ss}_{max} for τ = 3 hr in Fig. 8 to t_{max} in Fig. 7. If the S_1 line is

insignificant, then $t^{ss}_{max} \approx t_{max}$, as seen when t^{ss}_{max} at $\tau = 12$ hr in Fig. 8 is compared to t_{max} in Fig. 7. Thus the use of a single-dose t_{max} value to monitor C^{ss}_{max} in the steady state can lead to erroneous conclusions which may be avoided by examining the steady-state time course, as done in Fig. 8.

Practice Problem 4

A tablet containing 500 mg of drug was administered as a single oral dose to 10 normal adults. Blood samples were withdrawn as a function of time and the average results are given in Table 2.

(a) Predict the value for C^{ss}_{min} and the value for C^{ss} (1 hr) if a 200-mg dose is administered every 4 hr and blood levels are proportional to the dose.

(b) Predict the steady-state time course for the concentration of drug (C^{ss}) in the blood if a 500-mg dose is administered every 6 hr. What time course would result from 500 mg every 3 hr?

Answers: (a) The F_Z value associated with the terminal slope (S_Z) is $F_Z = 7.5/26 = 0.29$. Thus $1/(1-F_Z) = 1.4$ is the conversion factor for the curve associated with S_Z. The feathered plot for S_1 has a factor of $1/(1-F_1) \approx 1$. Therefore, at a 500-mg dose, $C^{ss}(1\text{ hr}) = 1.4(19) - 1(3.1) = 23.5$ mg %. The C^{ss}_{min} value would not be affected by the S_1 line, since its contribution is insignificant at $t = \tau = 4$ hr. Since the 4-hr data point is on the S_Z first-order plot, it can be used to calculate $C^{ss}_{min} = 1.4(7.5) = 10.5$ mg %. At a dose of 200 mg, $C^{ss}(1\text{ hr}) = 9.4$ mg % and $C^{ss}_{min} = 4.2$ mg %. (b) At $\tau = 6$ hr, $F_Z = 0.15$ and $F_1 \approx 0$. The steady-state values are therefore ($1.18 \times S_Z$ data) $-$ (S_1 data). For the time points in Table 2 the results are 0.5 hr, 17.4 mg %; 1.0 hr, 19.5 mg %; 1.5 hr, 18.2 mg %; 2.0 hr, 16.2 mg %; 3.0 hr, 12.0 mg %; 4.0 hr, 8.85 mg %; 5.0 hr, 6.37 mg %; 6.0 hr, 4.72 mg %.

At $\tau = 3$ hr, $F_Z = 0.39$ and F_1 remains neglible. Steady-state values are ($1.65 \times S_Z$ data) $-$ (S_1 data). Results are 0.5 hr, 27.9 mg %; 1.0 hr, 28.2 mg %; 1.5 hr, 25.9 mg %; 2.0 hr, 22.7 mg %; 3.0 hr, 16.8 mg %.

Table 2 Average Concentration of Drug in Blood Following Oral Administration of a 500-mg Tablet to 10 Normal Adults

t (hr)	Concentration (mg %)	t (hr)	Concentration (mg %)
0.5	13.4	4.0	7.5
1.0	16.1	5.0	5.4
1.5	15.4	6.0	4.0
2.0	13.7	7.0	2.9
3.0	10.2		

3. Predictions of Blood Levels After the Nth Dose

Equation (11) provided the basis for employing the factor $1/(1-F)$ to predict steady-state blood levels. The numerator approached unity, since $1-e^{-Nk_i\tau} \approx 1$ when $N \to \infty$. For the general case of dose N, Eq. (11) can be used in the same manner as previously employed. Since $e^{-k_i\tau} = F$, a monoexponential curve of rate constant k_i may be written

$$X = \frac{1-F^N}{1-F} \tag{16}$$

This is employed exactly as $1/(1-F)$ was used to predict steady-state values, but N (the number of doses administered) must be used to calculate $1-F^N$. The factor X is used to convert a single-dose plasma concentration to the corresponding value after N doses using F^N prior to the steady state. After the total elapsed time exceeds 4–5 half-lives, $1/(1-F)$ may be used.

Practice Problem 5
In each of the cases for Practice Problems 2–4, predict the drug time course in blood following the third dose.
Answer: In Practice Problem 2 the factor $(1-F^N)/(1-F) = (1 - 0.04)/(1 - 0.35) = 1.47$ is slightly less (4.5%) than the original value of 1.54. The points in Fig. 3 multiplied by 1.47 represent the profile following the third dose.

In Practice Problem 3 when $\tau = 24$ hr, F_Z then becomes $(1 - 0.012)/(1 - 0.23) = 1.28$ instead of 1.30, or 1.5% less. The time course for $N = 3$ will be 1.28 times the λ_Z line plus the λ_1 line which does not accumulate at $\tau = 24$ hr. At $\tau = 6$ hr the λ_Z line must be multiplied by $(1 - 0.33)/(1 - 0.69) = 2.16$, which is 32% less than the original 3.2 factor. The λ_1 line factor is $(1 - 0.016)/(1 - 0.25) = 1.31$, which is nearly the same as the previous 1.33. The overall blood level curve following the third dose will be the sum of $2.16 \times (\lambda_Z$ line) plus $1.33 \times (\lambda_1$ line).

In Practice Problem 4a the factor for the S_Z curve is $(1 - 0.024)/(1 - 0.29) = 1.36$ and that for S_1 remains ~1. Since the original S_Z factor was 1.40, the $N = 3$ value is 97% of that for the steady state; $C_{\min(3)} = 0.97C^{ss}_{\min} = 4.1$ mg %. The value for C at 1 hr is $= 1.36(7.6) - 1.24 = 9.1$ mg %.

In Practice Problem 4b at $\tau = 6$ hr the time course following $N = 3$ is the same as that given as the answer for $N = \infty$. For $\tau = 3$ hr values following dose 3 are 1.55 (S_Z data) − (S_1 data).

Practice Problem 6

Table 3 summarizes the concentration of drug in blood following a single rapid intravenous injection. Assume that only two additional doses are administered at intervals of 2 hr ($\tau = 2$ hr) for a total of $N = 3$. What is the concentration of drug in blood 8 hr after the first dose?

Answer: 1.08 mg %.

4. Degree of Accumulation

A variety of suggestions have been published regarding the calculations of accumulation of drug in a patient during repetitive multiple dosing. One simple and practical way is to calculate X in Eq. (16), which becomes $1/(1-F)$ in the steady state when $N = \infty$. If the single-dose curve is monoexponential (first order), then X will predict the increase in blood level of drug after dose N relative to the level when $N = 1$. That is, if the drug is administered at $\tau = t_{1/2}$, then $F = 0.5$ and $X = (1 - 0.5^N)/0.5$. In the steady state the blood levels will be 1/0.5, or twice that of $N = 1$. The accumulation is therefore twofold, or 200%, that of the single dose. By using the value for N in Eq. (16), one can calculate the accumulation following any specific dose in the regimen.

In cases that involve more than a single exponential, this approach can only be employed for those terminal exponential (i.e., Z slope) data which are not significantly influenced by the more rapid (or feathered) exponential. For example, the answer to Practice Problem 3 shows that at $\tau = 24$ hr the blood concentration data for the single dose at any time $t > 12$ hr can be

Table 3 Concentration of Drug in Blood Following a Rapid Intravenous Injection

t (hr)	Concentration (mg %)	t (hr)	Concentration (mg %)
1.0	0.82	6.0	0.34
2.0	0.70	7.0	0.28
3.0	0.59	8.0	0.24
4.0	0.49	10.0	0.17
5.0	0.41	12.0	0.12

used to predict the corresponding steady-state values using $X = 1.30$. The accumulation of the terminal phase is therefore 1.3-fold, or 130%, of the single dose.

This approach must be modified at $\tau = 6$ hr, where both the λ_1 and λ_Z lines contribute to the sum of the exponentials. The λ_Z line values were $F_Z = 4.8/7 = 0.69$ and $X = 1/(1-F_Z) = 3.2$. Those for the λ_1 line were $F_1 = 0.5/2 = 0.25$ and $X = 1/(1-F_1) = 1.33$. Therefore $C^{ss}_{min} = 3.2(4.8) + 1.33(0.5) = 16$ mg % at $\tau = 6$ hr, while $C(6\text{ hr}) = 4.8 + 0.5 = 5.3$ mg %. The degree of accumulation at C^{ss}_{min} is therefore three times that of a single dose. A similar treatment applied to C^{ss}_{max} results in a different value for X The value for the single dose is $C_{max} = 7 + 2 = 9$ mg %. At $\tau = 24$ hr, $C^{ss}_{max} = 1.30(7) + (2) = 11.1$ mg %. At $\tau = 6$ hr, $C^{ss}_{max} = 3.2(7) + 1.33(2) = 25$ mg %. Thus at $\tau = 24$ hr, C^{ss}_{min} shows 130% accumulation and C^{ss}_{max} shows 123%. At $\tau = 6$ hr, C^{ss}_{min} shows 300% accumulation and C^{ss}_{max} shows 278%. Using this approach on a monoexponential curve allows steady-state accumulation to be described by a single ratio, $X = 1/(1-F)$. However, if the curve is biexponential, only the terminal phase may be described by a single factor after the rapid-phase data become insignificant for those data points which lie on the terminal slope. When both phases contribute to the drug time course, it is necessary to specify the time at which the accumulation is considered, since, as just demonstrated, the factor can vary between two points, that is, C^{ss}_{max} and C^{ss}_{min}. The degree of accumulation may be considered following any number of doses by using $X = (1-F^N)/(1-F)$ as shown previously.

If we assume that the dosage interval τ corresponds to a time wherein the data points lie on the negative terminal slope, $(\text{slope})_Z$, we can define the *apparent* half-life as

$$t^*_{1/2} = 0.693/(\text{slope})_Z \tag{17}$$

The $t^*_{1/2}$ value will equal the biological half-life when $(\text{slope})_Z = \lambda_Z$. However, for an oral or intramuscular dose the value of $(\text{slope})_Z$ may represent rate-determining input in the case of a flip-flop situation [5,6]. As shown in Table 4, one can consider the effect of τ on F_Z and on the resultant accumulation X, assuming that τ is on the terminal log-linear phase. As F_Z approaches zero, the degree of accumulation, $1/(1-F)$, approaches unity, indicating that steady-state values are similar to those following a single dose. This is the mathematical limit as $\tau \to \infty$ and is therefore not of practical value. One must therefore decide what percent increase over the single dose can be regarded as insignificant. For many drugs a 10–15% increase may not be clinically significant. Table 4 shows that if $\tau \geq 3t^*_{1/2}$, then accumulation will be less than 15%. As a first approximation, a dosage interval that equals

Table 4 Degree of Accumulation During Repetitive-Dose Steady-State Relative to the Linear Terminal Phase Observed with a Single Dose

τ (number of apparent half-lives)[a]	F_Z^b	X $[1/(1 - F_Z)]$	Percent increase from single dose
0.5	0.707	3.41	241
1.0	0.50	2.00	100
1.5	0.35	1.55	55
2.0	0.25	1.33	33
2.5	0.177	1.21	21
3.0	0.125	1.14	14
3.5	0.088	1.10	10
4.0	0.063	1.07	7
∞	0	1.00	0

[a]See Eq. (17).
[b]Based on linear first-order plot of terminal phase.

or exceeds three times the apparent half-life will result in neglible accumulation of the drug relative to a single dose.

Practice Problem 7
What is the degree of accumulation at $t \geq 8$ hr for the drug shown in Fig. 7 if it is repetitively administered in the same dosage form, in the same dose size, and at $\tau = 12$ hr? (See Fig. 8 and discussion for steady-state curves.)
Answer: At $\tau = 12$ hr and $t \geq 8$ hr, $1/(1 - F_Z) = 1.33$. The terminal phase accumulation is 133%.

In Practice Problem 7 the degree of accumulation at $t \geq 8$ hr is constant at 133%. This is due to the fact that all of the data points at $t \geq 8$ hr are on the terminal log-linear phase of Fig. 7 and $\tau = 12$ hr lies on this line. If accumulation is evaluated in the biexponential portion, the degree will increase. For example, if we compare the peak values ($t_{max} = 3$ hr), the steady-state value $C^{ss}(3\text{ hr})$ is 1.44 times the single-dose value $C(3\text{ hr})$, or 144% accumulation.

If we consider $\tau = 3$ hr, both exponentials will contribute to every data point in the single-dose curve and its steady-state counterpart. The value for C^{ss}_{min} ($t = 3\text{ hr} = \tau$) in this case is roughly 3.9 times the $C(3\text{ hr})$ value. The t_{max} has shifted from ~ 3 hr ($N = 1$) to ~ 1.5 hr ($N = \infty$). The steady-state maximum value (C^{ss}_{max} at $t = 1.5$ hr) is roughly four times the single-dose C^1_{max} (at $t = 3$ hr). Thus the accumulation factor X is roughly 4, so that the steady-state curve is 400% of the single-dose curve when $\tau = 3$ hr.

The degree of accumulation has thus been shown to be inversely related to τ. At $\tau = 12$ hr the accumulation factor was approximately 1.4, while at $\tau = 3$ hr it was shown to be ~4.

Practice Problem 8
Table 5 shows the serum levels and duration of sterile ceftizoxime sodium following the intramuscular administration of 500-mg and 1.0-g doses to normal volunteers. If a 1-g dose were administered intramuscularly every 4 hr, what degree of accumulation would result in the steady state?
Answer: $X = 1.25$ (range of approximations, 1.2 to 1.3).

C. Average Steady-State Levels for Any Route and Model

The total area under the blood level curve following a single dose,

$$AUC = \int_0^\infty C\,dt$$

is equal to the area between successive doses during the multiple-dose steady state, wherein

$$AUC = \int_0^\tau C^{ss}\,dt \qquad 0 \leq t \leq \tau$$

This is illustrated by the shaded areas in Figs. 1 and 2. Thus for *any route and model* (assuming linear kinetics and elimination from the central compartment) the average steady-state plasma concentration (C_{av}^{ss}) during repetitive dosing at fixed time intervals may be predicted from single-dose data, since $C_{av}^{ss} = AUC/\tau$. The value for C_{av}^{ss} is therefore the average *area* between doses and *not* the average of $C_{max}^{ss} + C_{min}^{ss}$. Since $AUC = f(D)/CL = fD/\lambda_Z V_Z$, then substitution for AUC in $C_{av}^{ss} = AUC/\tau$ gives

Table 5 Serum Concentrations (μg/ml) After Intramuscular Administration

	Time (hr)					
Dose	½	1	2	4	6	8
500 mg	13.3	13.7	9.2	4.8	1.9	0.7
1.0 g	36.0	39.0	31.0	15.0	6.0	3.0

$$C_{av}^{ss} = \frac{f(DM)}{(CL)\tau} = \frac{f(DM)}{\lambda_Z V_Z \tau} = \frac{f(DM)(1.44)(t_{1/2})}{V_Z \tau} \tag{18}$$

where f is the bioavailable fraction of the maintenance dose DM. For an intravenous injection $f = 1$. Equation (18) was originally derived for a monoexponential (one-compartment) model [7] and later applied to multicompartmental models [8]. For monoexponential disposition, where the amount in the body equals CV_Z, the steady-state average amount may be calculated from

$$A_{av}^{ss} = C_{av}^{ss} V_Z \tag{19}$$

where the volume of distribution V_Z may be calculated by any of the standard methods. For drug disposition kinetics requiring more than one exponential the calculated value for V_Z may vary with the method employed. Since the values C_{av}^{ss} and A_{av}^{ss} are steady-state values, one would expect the steady-state estimate (i.e., V_{ss}) to provide the best C_{av}^{ss} estimates. If V_Z values are estimated following a single rapid intravenous dose, the resulting estimates for A_{av}^{ss} obtained from the product $A_{av}^{ss} V_Z$ may overestimate the actual amount in the body [9]. For example, it has been calculated that the percent error is 70% for penicillin G, 32% for lidocaine, 23% for ethchorvynol, but neglible for warfarin [9]. Thus for biexponential disposition the steady-state infusion value V_{ss} which will provide the correct relationship is

$$C_{av}^{ss} = \frac{A_{av}^{ss}}{V_{ss}} \tag{20}$$

Practice Problem 9

(a) If the desired average plasma level for a drug is 0.4 mg %, what dose should be given orally on a regimen of every 6 hr around the clock? The drug is 85% absorbed and the patient weighs 70 kg. The V_Z value is 140 liters and $t_{1/2}$ is 3.5 hr.

(b) If identical average plasma levels are to be maintained with a 500-mg. capsule, how often should it be administered?

Answer: (a) 783 mg; (b) 3.83 hr. $\simeq$ 4 hr.

Practice Problem 10

(a) If the AUC after a single 350-mg intravenous dose is 122 μg hr/ml, what C_{av}^{ss} value would result if this dose were repeated every 12 hr?

(b) A constant-rate intravenous infusion is to be used in place of the above repetitive dosage regimen. What infusion rate (in mg/hr) must be used

to produce a steady-state plasma concentration equal to that obtained by the repetitive dosage regimen?

Answers: (a) 10μg/ml; (b) 29 mg/hr. (Note: Any regimen providing the same hourly rate for fD/τ will produce the same C_{av}^{ss} value. Therefore 350 mg/12 hr = 29 mg/hr.)

Practice Problem 11

The data in Table 6 are to be used to answer the following questions.

(a) The usual adult oral dose is 500 mg every 6 hr. Predict the average steady-state plasma concentration C_{av}^{ss} (in μg/ml) that would be expected based on this study. Which subject would develop the highest C_{av}^{ss} value and what would it be?

(b) Subject 7 is to receive 500 mg every 6 hr. How long after starting the medication and following which dose should a blood sample be taken in order to determine the C_{min}^{ss} value in this patient?

Answer: (a) C_{av}^{ss} = 16.7 μg hr/ml based on the mean AUC and adjusted for dosage. Subject 5 would be highest at 22.7 μg h/ml. (b) Taken 36 hr after starting medication and following the sixth dose but before the seventh.

D. Repetitive Dosing for Minimum Effective Concentrations

1. Prediction of C_{min}^{ss} from Single-Dose Plots

Figure 8 illustrates how the choice of τ can influence the relative contribution of each exponential to the steady-state time course. If τ is sufficiently large, the value for C_{min}^{ss} can be calculated directly from the line representing the slower exponential (or rate-determining step). The minimum τ (τ_{min}) that will satisfy this condition may be estimated by inspection. If $\tau \geq t_Z$, where

Table 6 Pharmacokinetic Values Following a Single 400-mg Oral Dose of Metronidazole to Seven Normal Adults

	Subject							
	1	2	3	4	5	6	7	Mean
AUC (μg hr/ml)	70.5	90.8	56.2	67.7	109	74.6	91.4	80.0
$t_{1/2}$ (hr)	9.6	9.2	9.1	8.7	6.9	7.0	8.3	8.3
f	1.04	1.01	1.01	1.00	0.89	0.87	1.10	0.99

t_Z is the time at which the first data point C falls on the terminal log-linear plot, then the rapid exponential will be insignificant in the calculation of C^{ss}_{min} and $\tau_{min} \approx t_Z$. This is more easily visualized with graphic examples. In Fig. 5, τ_{min} is approximately 14 hr, since this is the time at which the first data point falls on the λ_Z line. Therefore, if $\tau \geq 14$ hr, then C^{ss}_{min} can be estimated from this reference line. We can test this method using Fig. 8. When $\tau = 24$ hr, $C^{ss}_{min} = 2$ μg/ml (Fig. 6a). Using the λ_Z line in Fig. 5 provides $X = 1/(1-0.23) = 1.3$, which predicts $C^{ss}_{min} = C(24\text{ hr})X = 1.6(1.3) = 2$ μg/ml. When $\tau < \tau_{min}$, both exponentials will contribute to C^{ss}_{min}. For example, at $\tau = 6$ hr (Fig. 6b), $C^{ss}_{min} = 16.1$ μg/ml, which is the sum of the contributions from the λ_Z line (15.46 μg/ml) and the λ_1 line (0.66 μg/ml). (The λ_1 line contribution is small even at $\tau = 6$ hr in this particular example, since at $t = 6$ hr in Fig. 5 the λ_1 line represents only 10% of the total. This is but one example and should not be misconstrued as the general case.)

Thus, if $\tau \geq \tau_{min}$, C^{ss}_{min} may be predicted from the λ_Z line of an intravenous biexponential semilog plot. This may be stated using equations as follows.

If the time course for drug concentration in blood can be described by

$$C = C_1 e^{-\lambda_1 t} + C_Z e^{-\lambda_Z t} \tag{21}$$

the steady-state equation may be written by applying Eq. (11) with $N = \infty$ to give

$$C^{ss} = \frac{C_1 e^{-\lambda_1 t}}{1 - e^{-\lambda_1 t}} + \frac{C_Z e^{-\lambda_Z t}}{1 - e^{-\lambda_Z t}} \tag{22}$$

Since C^{ss}_{min} occurs at $t = \tau$,

$$C^{ss}_{min} = \frac{C_1 F_1}{1 - F_1} + \frac{C_Z F_Z}{1 - F_Z} \tag{23}$$

where $F_1 = e^{-\lambda_1 \tau}$ and $F_Z = e^{-\lambda_Z \tau}$. When $C_1 e^{-\lambda_1 t}$ is insignificant, the data points in Eq. (21) may be described by $C \simeq C_Z e^{-\lambda_Z t}$, at which time the data appear to lie on the λ_Z line. The C^{ss}_{min} value in Eq. (23) then becomes $C_Z F_Z/(1 - F_Z)$. In the process described above we calculated F_Z from C_{min}/C_Z. Therefore $C_Z F_Z = C_{min}$, which is the data point on the single-dose curve at time τ. Substituting in Eq. (23), when $\tau > \tau_{min}$, so that $C_1 F_1/(1 - F_1)$ becomes insignificant gives

$$C_{\min}^{ss} \approx \frac{F_Z C_Z}{1 - F_Z} = \frac{C_{\min}}{1 - F_Z} \tag{24}$$

which is the equation describing the process used above to convert the single-dose data point in Fig. 5 to the $C_{\min}^{ss}$ value in Fig. 6a when $\tau = 24$ hr.

A similar approach can be used for the biexponential oral curve shown in Fig. 7, where $\tau_{\min} \approx 8$ hr. Figure 8 shows examples wherein $\tau_{\min} > \tau = 3$ hr and $\tau_{\min} < \tau = 12$ hr. The $C_{\min}^{ss}$ value of 17.51 at $\tau = 3$ hr is the difference between the slower exponential (S_Z) contribution (18.65 mg %) and the faster exponential (S_1) contribution (1.14 mg %). However, at $\tau = 24$ hr, $C_{\min}^{ss}$ is calculated directly from the S_Z line: $C_{\min}^{ss} = 2(1.33) = 2.66$ mg %. Equation (15) may be converted to the steady-state minimum using Eq. (11), as done above for Eq. (21), to give

$$C_{\min}^{ss} = \frac{F_Z C_i}{1 - F_Z} - \frac{F_1 C_i}{1 - F_1} \tag{25}$$

where $F_Z = e^{-S_Z \tau}$ and $F_1 = e^{-S_1 \tau}$. When $\tau > \tau_{\min}$ and $F_1 C_i/(1 - F_1)$ becomes insignificant, then

$$C_{\min}^{ss} \approx \frac{F_Z C_i}{1 - F_Z} = \frac{C_{\min}}{1 - F_Z} \tag{26}$$

Thus the line associated with the rate-determining exponential (S_Z in Fig. 7) can be used to calculate the steady-state minimum in the same way as the λ_Z line, since in both cases $C_{\min}^{ss} \approx C_{\min}/(1 - F_Z)$ when $\tau \geq \tau_{\min}$.

2. Calculating Dosage Regimens to Maintain Minimum Plasma Levels

In Sec. II.D.1 it was shown that $C_{\min}^{ss}$ can be estimated from the terminal log-linear plot provided that τ is equal to or greater than the time required for the single-dose semilog plot to become linear. When this condition is satisfied, the τ values will be based on the terminal or rate-determining slope. For monoexponential loss this will be the observed first-order rate constant, which is the negative slope of the entire plot. For a biexponential case it will be λ_Z. For an extravascular route described by two exponentials, it will be S_Z (Fig. 7). Thus we may define the dosing interval as $\tau = -\ln F_Z/(\text{slope})_Z$, where F_Z and $(\text{slope})_Z$ are the fraction remaining and the negative slope associated with the terminal log-linear plot, respectively. It is reasonable to assume that τ is normally sufficiently large to make $C_{\min}^{ss}$ primarily a function

of the Z line. That is, contrary to $\tau = 3$ hr in Fig. 8, the examples representing $\tau = 12$ hr (Fig. 8) and $\tau = 24$ hr (Practice Problem 3), wherein the rapid exponential is no longer significant, are considered more realistic. The validity of this assumption may be illustrated by the case where $\tau = 3$ hr. Examination of Figs. 7 and 8 will show that the 3-hr dosage interval is not rational. It is unlikely that one would choose to administer a dose at 3 hr when Fig. 7 clearly shows that blood levels following one dose persist at least 12 hr. Since blood levels are prolonged by the rate-determining exponential, it is reasonable to assume that the value normally chosen for τ will correspond to a time on the terminal log-linear plot.

We have seen from the previous discussion that it is relatively simple and practical to select a τ which will result in a C^{ss}_{min} value that may be safely predicted using only the terminal log-linear data line. A single equation, $C^{ss}_{min} \approx C_{min}/(1 - F_Z)$, may then be employed to calculate a dosage regimen to maintain a given value for the steady-state minimum. This may also be written as

$$C^{ss}_{min} = \frac{F_Z C_Z}{1 - F_Z} \tag{27}$$

where C_Z, the intercept of the terminal log-linear plot, was previously defined as C_Z (mono- and biexponential, rapid intravenous) and C_i (biexponential, oral). There are two variables which may be adjusted in developing a regimen with Eq. (27): the intercept, which is proportional to dose, and F, which is related to τ by Eq. (6). Thus the size of the dose and the dosage interval can be altered to design a convenient regimen to provide any desired minimum steady-state plasma concentration.

Although the values for D and τ may be altered, there will be an ideal combination if plasma levels are to be maintained within a narrow range. This is illustrated in Fig. 9, where the dose size is constant for all three cases, but the values for τ are altered. However, once the size of the dose is fixed, the ideal value for τ is also fixed, and vice versa. This can be illustrated with two examples taken from Schumacher [10]. In Practice Problem 12 the dose size is fixed and the interval must be calculated. In Practice Problem 13 the interval is fixed and the dose must therefore be adjusted.

Practice Problem 12: Calculation of the Dosage Interval to Maintain *MIC* with 500-mg Capsules of Tetracycline

A single oral dose of tetracycline (500-mg capsule) is found to give a linear terminal semilog plot for total drug in blood versus time. The equation for this line is $\ln C = \ln(3.9\ \mu g/ml) - (0.0729\ hr^{-1})\ (t)$. Calculate the dosage

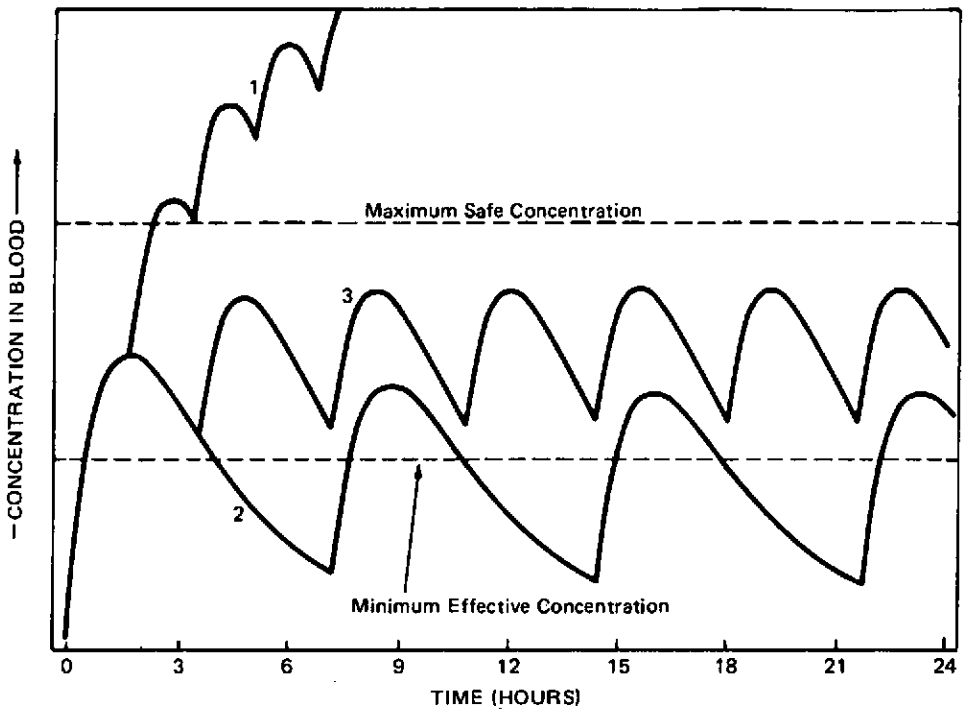

Fig. 9 The objective of the multiple-dosage regimen is to maintain the patient's blood level within the maximum and minimum concentrations shown. The dosage interval τ is too short in curve 1, too long in curve 2, and ideal in curve 3. The initial dose used for this simulation is 33% more than the maintenance dose.

interval that will provide an *MIC* of 0.8 μg/ml of free tetracycline if 50% of the drug in the blood is bound to serum protein.
Answer: 16.9 hr.

Practice Problem 13: Calculation of the Oral Dose of Tetracycline to Maintain *MIC* with a 12-hr Dosage Interval
In Practice Problem 12, 500-mg capsules were used to calculate a dosage interval. The regimen which resulted was one capsule every 16 or 17 hr. This is not a convenient interval; a regimen of morning and night (every 12 hr) would be more reasonable. Using the information in Practice Problem 12, calculate the dose to be administered every 12 hr.
Answer: 287 mg. (Hint: Assuming that blood levels are proportional to dose, calculate the value for C_Z when $\tau = 12$ hr and therefore $F_Z = 0.417$. The value for C_Z is 2.24, which is 57.4% of 3.90. Therefore the new dose is 57.4% of 500 mg.)

During the steady state a drug is administered on a fixed dose and dosage interval. The patient thereby maintains a relatively constant amount of the drug in the body. Practice Problem 13 demonstrates the manner in which the dose or time interval may be altered and still maintain the steady state. When the 12-hr interval was employed, a maintenance dose of 287 mg was sufficient; however, 500 mg was needed when the 17-hr interval was used. In the steady state a single dose of drug is eliminated during each τ interval and then replaced by the next dose. Therefore the difference between the minimum and maximum in the steady state is a single maintenance dose. This was illustrated in Table 1. The shorter the interval chosen for τ, the smaller the maintenance dose. This was just observed in the Practice Problems 12 and 13, where 287 mg replaced 500 mg. Thus the shorter the τ interval, the smoother the blood–time profile during steady state and the smaller the difference between C^{ss}_{min} and C^{ss}_{max}. This is an important consideration in developing a regimen for a drug with a narrow margin of safety.

Practice Problem 14

A 3-g intravenous dose of ticarcillin provided the serum levels as a function of time shown in Table 7.

(a) The *minimum inhibitory concentration* (*MIC*) for treating the detected strain of *Pseudomonas* is 60 μg/ml. What τ value is required to maintain this *MIC* value using the 3-g intravenous dose?

(b) What is the value of the area under the curve (*AUC*, in hr μg/ml) following the single 3-g dose and what is the total body clearance value CL (in ml/min)?

(c) What is the steady-state average drug plasma concentration for this regimen?

Answer: (a) A first-order plot is linear with $\lambda_Z = 0.655\ hr^{-1}$ and $C_Z = 206$ μg/ml. Using Eq. (27), where $C^{ss}_{min} = MIC = 60$ μg/ml and $C_Z = 206$, gives $F = 0.226$. Then $\tau = (-\ln F)/\lambda_Z = 2.3$ hr. (b) $AUC = 310$ hr μg/ml; $CL = 161$ ml/min. (c) $C^{ss}_{av} = 135$ μg/ml.

In Practice Problem 14 the τ value of 2.3 hr would not be convenient to use. If increased slightly to $\tau = 3$ hr, the regimen would be greatly simplified. But the dose size must be increased. This may be done by finding the new value for C_Z as follows: $-\ln F_Z = \lambda_Z \tau = 0.655(3) = 1.965$; $F_Z = 0.140$. Then $C_Z = C^{ss}_{min}(1 - F_Z)/F_Z = 368$ μg/ml. Since

Table 7 Ticarcillin Serum Levels Following a 3-g Intravenous Dose

Time (hr)	0.25	0.50	1.0	2.0	3.0	4.0	6.0
Serum level (μg/ml)	190	140	107	52.2	31.3	13.8	4.2

the intercept is proportional to the dose, D = (3 g) (368/206) = 5.36 g. The new regimen is therefore 5.36 g every 3 hr.

Practice Problem 15

A single dose study using 2 g of drug given orally to 19 normal subjects gave the mean free sulfamethoxazole plasma concentration data of Table 8.

(a) This drug is 70% protein bound in the blood. If the 2-g oral dose is given on a repetitive regimen, what τ value should be employed in order to maintain a total sulfamethoxazole steady-state minimum C^{ss}_{min} of 65 mg %?

(b) The usual maintenance dose is *1 g* every 8 hr for mild infections. What steady-state minimum free sulfamethoxizole plasma concentration C^{ss}_{min} will result from this regimen?

(c) If a regimen of 1 g every 8 hr is initiated at 7 A.M., what is the *earliest* time that a plasma sample may be taken to determine the patient's steady-state minimum value?

Table 8 Mean Concentration of Free Sulfamethoxazole Following Oral Administration of 2 g in Tablets to 19 Normal Adults

Time (hr)	1.5	3	6	9	12
Concentration (mg %)	8.38	12.08	9.82	7.9	6.45

Answer: (a) τ = 8 hr; (b) 10.05 mg %; (c) a sample should be taken at 11 P.M., after dose number 5 but before dose number 6.

Practice Problem 16

(a) A steady-state minimum serum level of carbenicillin is to be maintained at 34 μg/ml using a repetitive dosage regimen with the *maximum time between* doses. The route of administration and the dose size are to be chosen from Table 9. Calculate the dosage interval τ in hours.

Table 9 Average Carbenicillin Blood Levels in Normal Adults

Dosage (mg)	Route	Serum levels (μg/ml)						
		0.25 hr	0.5 hr	1 hr	2 hr	3 hr	4 hr	6 hr
500	Intramuscular	8	10	13	9.8	6.5	3.2	0
1000	Intramuscular	—	13	18	15	12	7.5	1.7
2000	Intramuscular	26	38	47	37	25	15	5.9
1000	Intravenous	71	45	31	14	8.2	3	0

(b) If the 2000-mg intramuscular dose is administered at 9 A.M., 1 P.M., 5 P.M., 9 P.M., 1 A.M., and so on, and continued around the clock, predict the C^{ss}_{min} value that will result.
Answer: (a) 2000 mg intramuscularly every 3 hr; (b) 17.6 μg/ml.

3. Calculating the Minimum Dosage Interval (τ_{min}) to Use the Monoexponential Approximation

It was demonstrated that Eq. (27) predicts C^{ss}_{min} if τ is sufficiently large ($\tau \geq \tau_{min}$) to be equal to or greater than the time required to reach the monoexponential phase of a semilogarithmic plot. This can be estimated by inspection by simply observing when the data points fall on the terminal log-linear plot. However, it was noted that at $\tau = 6$ hr the C^{ss}_{min} value in Fig. 6b could be approximated using only the λ_Z line, even though the estimated τ_{min} was 24 hr by inspection. Estimates obtained for τ_{min} by the method of inspection will ensure reliable predictions when using Eq. (27). They may, however, be larger than the actual minimum required for approximating monoexponential loss. The following equation may be employed to calculate the *minimum* time required, τ_{min}, to ensure that the contribution of the rapid exponential will not exceed some chosen percentage of the rate-determining exponential [Eq. (28) was adapted from Ref. 5]:

$$\tau_{min} = \frac{\ln(R/pct)}{\Delta} \tag{28}$$

where the value for *pct* is (percent chosen)/100, R is the rapid–slow intercept ratio, and Δ is the positive difference between the slopes. In the case of an oral dose, $R = 1$ (Fig. 7). For a biexponential intravenous case, R will generally not be unity. In the example shown in Fig. 5, $R = 0.29$. Equation (28) will predict the time after which the slow exponential alone will describe the phase occurring at $t > \tau_{min}$. Take, for example, a 5% contribution by the rapid exponential in the case of Figs. 5 and 7. For Fig. 5, $\tau_{min} = 10$ hr, and for Fig. 7, $\tau_{min} = 5$ hr. (The estimates by inspection were 14 and 8 hr.) Since the estimates using Eq. (28) are based on a single dose, the percent contribution would be even less during steady state, since the $1/(1-F)$ factor will always be greater for the slower exponential. This is due to the fact that F must be larger for the slower exponential, making its factor $1/(1-F_Z)$ greater, thus further reducing the percent contribution by the rapid exponential.

E. Calculation of the Loading Dose

In Fig. 1 a fixed dose was administered every 4 hr and roughly 16 hr was required to achieve the steady state. Contrast this to the time course of curve 3 in Fig. 9, where the steady state is practically attained with the first dose. The difference is the fact that a loading dose equal to 33% more than the maintenance dose was used in curve 3 of Fig. 9. Kruger-Thiemer [11] has pointed out that a nearly optimum regimen with little or no lag time results when the loading dose is twice that of the maintenance dose and $\tau = t_{1/2}$ (provided that absorption >> elimination). Thus, for a dosage regimen which accumulates drug, a loading dose can provide the shortest onset.

If a drug has a short half-life, a dosage regimen may not be designed to result in accumulation. The various penicillins, for example, have $t_{1/2}$ values of 0.5–1.0 hr. Oral penicillin tablets are generally administered every 4–6 hr. Assuming that absorption is relatively rapid and elimination is first-order, one would estimate that 94% of a dose is eliminated in 4 half-lives, or 2–4 hr. Thus administration of tablets every 4–6 hr will not result in significant accumulation, since each dose is administered to an empty patient. The time course of drug in the blood after each dose would therefore appear like a single-dose treatment.

For those drugs which do accumulate during a multiple-dose regimen, an onset period may be defined as the time required to reach the steady-state blood levels. As seen for the case of constant intravenous infusion, this onset is related to the $t_{1/2}$ of the drug. In other words, a drug with a long $t_{1/2}$ will have a longer onset than one with a shorter $t_{1/2}$ (all other parameters being equal). In Table 1, where $\tau = t_{1/2}$, one can observe that 94% of the steady-state minimum occurs just prior to $N = 5$, or 4τ, which is equal to 4 half-lives. Just prior to $N = 6$ (or 5 half-lives) 97% of the steady-state minimum is achieved. Thus a monoexponential intravenous repetitive-dose regimen will approach the steady-state minimum in 4–5 half-lives [12].

A biexponential drug may require even longer [13]. If one accepts that roughly 4 half-lives are required for accumulation, it follows that a drug with a 12-hr half-life will not reach steady state for 2.0 days. In such a case a loading dose may significantly improve therapy. Applying this estimate to a more extreme example, a 4-day regimen of a drug with a 24-hr half-life would not achieve the steady-state level during the course of therapy. The use of a sufficiently large initial dose will result in steady-state levels throughout the 4 days.

How does one calculate the initial dose, or loaing dose, DL? If $\tau \geq \tau_{min}$ or if the single-dose curve is monoexponential, DL may be calculated from the maintenance dose DM according to

$$DL = \frac{DM}{1 - F} \tag{29}$$

where the fraction remaining is related to the rate-determining step by $t_F = (-\ln F)/k_{(\text{slope})_Z}$. Thus the initial dose DL is calculated from the maintenance dose DM and the fraction F_Z. Equation (29) may be used for either the oral or intravenous route of administration, provided that the maintenance dose DM has been determined for the same route. This is the reason why Eq. (29) is identical to Eq. (9) for calculating $A^{ss}_{\max}$ by the intravenous route, where the bioavailability factor f is equal to 1. Thus for the intravenous case the loading dose is equal to $A^{ss}_{\max}$. For an extravascular route DM will generally be larger than $A^{ss}_{\max}$, since the bioavailability factor will be less than unity.

Practice Problem 17: Calculating the Loading Dose
Calculate a loading dose to be used for each of the maintenance regimens (doses and intervals) that you estimated in Practice Problems 9, 12, and 13.
Answer: (PP9a) 1.13 g; (PP9b) 940 mg; (PP12) 705 mg; (PP13) 492 mg.

Practice Problem 18
A drug having an apparent volume of distribution of 35 liters and a $t_{1/2}$ of 8 hr is administered by constant-rate intravenous infusion to provide a steady-state concentration of 6.2 μg/ml. The patient is to switch to oral administration of rapidly absorbed tablets with a bioavailability of 75% given every 8 hr. For the oral dosage regimen what is the maintenance dose DM and oral loading dose DL? What rapid intravenous loading dose would be appropriate to use with the intravenous infusion?
Answer: DM = 200 mg, DL = 400 mg; DL = 217 mg i.v.

It is important to distinguish between those factors controlling the onset of steady state and those controlling the resultant steady-state plasma levels. *Onset*, as defined above, refers to the time required to achieve steady state and is therefore a function of half-life—or apparent half-life, Eq. (17)—only. The *degree of accumulation* was previously defined as the quantitative relationship between the plasma level following a single dose (N = 1) and that following dose N. If $\tau > \tau_{\min}$ and the terminal log linear phase is considered, then the accumulation factor is $X = (1 - F_Z^N)/(1 - F_Z)$. The degree of accumulation in the steady state ($N = \infty$) was shown to depend on both τ and $t^*_{1/2}$ (see X values in Table 4). Thus onset depends only on $t^*_{1/2}$, whereas degree of accumulation is dependent on both $t^*_{1/2}$ and τ.

The amount of drug in the body at the steady state is dependent upon the bioavailable dose, the dosage interval, and $t_{1/2}$. The average steady-state plasma level C^{ss}_{av} has been defined by Eq. (18). This equation shows that C^{ss}_{av} will increase with increasing bioavailable dose fD and $t_{1/2}$ but will decrease with increasing τ. However, for any given $t_{1/2}$ only fD and τ will influence

C_{av}^{ss}. *Onset* will still require $4t_{1/2}$. (The onset time is mathematically $t = \infty$ but $4t_{1/2}$ will be considered a clinically acceptable approximation.)

Equation (18) may be rearranged to calculate the ratio of the average steady-state body drug content to the bioavailable dose as defined by the equation

$$\frac{A_{av}^{ss}}{f(DM)} = \frac{1.44t_{1/2}}{\tau} \tag{30}$$

Thus a drug that is completely absorbed ($f = 1$) will accumulate 1.44 times the dose if administered every half-life. If it is administered at intervals that are one-half of the value for the half-life, $\tau = 0.5t_{1/2}$, then 2.88 times the dose will accumulate. Thus we see that the average steady-state number of bioavailable doses which accumulate is directly proportional to $t_{1/2}$ and inversely proportional to the dosage interval. Equation (30) does *not* indicate the degree of accumulation. For example, when $\tau = t_{1/2}$, at $N = \infty$ Eq. (30) predicts $A_{av}^{ss}/f(DM) = 1.44$, while the accumulation relative to a single dose is $X = 1/(1 - F_Z) = 2$. The ratio $A_{av}^{ss}/f(DM)$ is not a measure of the degree of accumulation, since it does not compare steady-state results to those of a single dose. Therefore it will *not* be employed in this text when discussing accumulation. Equation (30) is included here to emphasize the fact that A_{av}^{ss} is proportional to $t_{1/2}/\tau$, whereas onset time remains a function of $t_{1/2}$.

One final complication which will be noted but not solved is the problem of calculating a dosage regimen when drugs are not administered at uniform

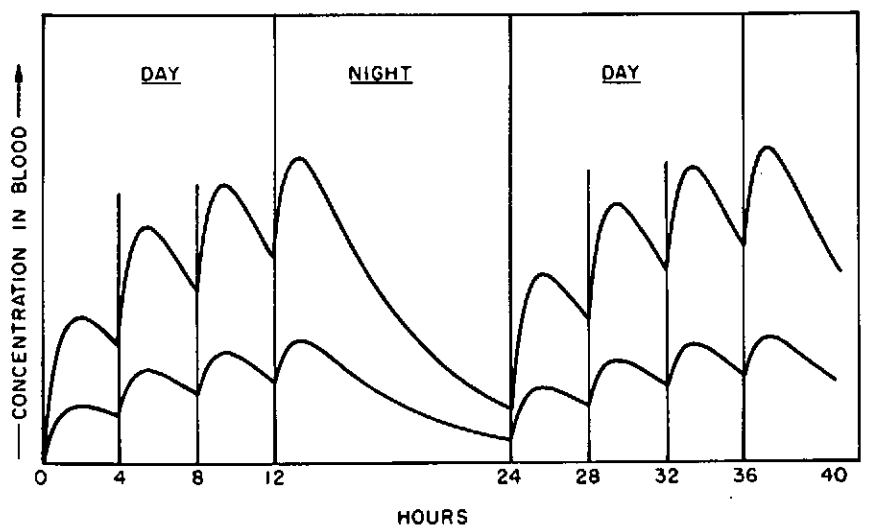

Fig. 10 A typical regimen of one tablet four times a day on a schedule of 10-2-6-10 or 9-1-5-9. Two different doses are illustrated over the first and second day of the regimen.

time intervals "around the clock." If the indicated dosage regimen for a drug is 4 times a day (q.i.d.), it is unlikely that it will be taken once every 6 hr. The most common definition found in hospital formularies for q.i.d. is either 10-2-6-10 or 9-1-5-9 [14]. Thus a 12-hr period follows the last dose each night. Figure 10 illustrates drug plasma–time profiles for this type of dosage regimen at two different doses. Methods have been devised for computerized calculations of plasma level time courses for such cases [14]. The steady-state drug plasma concentration time course can be generated graphically using the principle of superposition.

III. ADJUSTMENT OF DOSAGE REGIMEN IN RENAL FAILURE

A. Minimum and Maximum Desired Blood Levels

There are many specific examples of recommendations for adjustment of the dosage regimen for a patient experiencing renal failure. This precaution is of paramount importance in cases where the drug has a narrow margin of safety. Administration of such a drug on the normal or average schedule can result in higher levels of drug accumulation, with potential danger to the patient.

Two factors dictate the risk from drug accumulation due to renal failure. One is the acceptable range for the drug concentration in blood. Winek [15] has prepared a comprehensive list of values for the therapeutic range, the toxic level, and the lethal concentration of various compounds in blood. Some of these data are listed in Table 10 together with the ratios C_{max}/C_{min}, $C_{toxic}/\overline{C}$, and $C_{lethal}/\overline{C}$, $\overline{C}$ being the average of C_{max} and C_{min}. It is clear that useful drugs may have a very narrow range between the desired blood levels and those which can cause serious side effects. The second factor is whether or not renal failure will cause an increase in the blood level of the drug. A narrow range of safety together with increased accumulation due to renal failure mandate an adjustment of the dosage regimen.

B. Pharmacokinetic Basis for Renal Effects on Dosage Requirements

1. Clearance

The most reliable method for adjustment of a dosage regimen in the presence of renal failure is based on the principle that the total body clearance is the sum of the nonrenal and renal clearance values,

Table 10 Concentration of Drug in Blood (mg %, unless otherwise specified) Following Therapeutic Dosage (Therapeutic Range), Associated with Serious Toxic Symptoms (Toxic), and Reported or Judged Sufficient to Cause Death (Lethal)[a]

Drug	Therapeutic range	Toxic	Lethal	Ratios[b]		
				R_1	R_2	R_3
Acetaminophen	1–2	40	150	2	27	100
Acetohexamide	2.1–5.6	—	—	2.7	—	—
Amitriptyline	5–20 μg %	40 μg %	1.0–2.0 mg %	4	3	80
Barbiturates						
Phenobarbital	~1.0	4–6	8–15	—	4	8
Barbital	~1.0	6–8	10 and higher	—	6	10
Chloral hydrate	1.0	10	25	—	10	25
Chlordiazepozide	0.1–0.2	0.55	2	3	3	10
Chlorpromazine	0.05	0.1–0.2	0.3–1.2	—	2	6
Dextropropoxyphene	5–20 μg %	0.5–1 mg %	5.7 mg %	4	40	450
Diazepam	0.05–0.25	0.5–2.0	2.0	5	3	13
Ethchlorvynol	~0.5	2	15	—	4	30
Glutethimide	0.02	1–8	3–10	—	50	150
Lithium	0.42–0.83 (0.6–1.2 mEq/liter)	1.39 (2.0 mEq/liter)	1.39–3.47 (2.0–5.0 mEq/liter)	2	2	2
Meperidine	60–65 μg %	500 μg %	~3 mg %	1.1	8	48
Meprobamate	1	10	20	—	10	20
Methaqualone	0.5	1–3	3	—	2	6
Methyprylon	1.0	3–6	10	—	3	10
Paraldehyde	~5.0	20–40	50	—	4	10
Phenytoin	0.6–1.7	2–5	10	3	2	8
Salicylate (acetylsalicylic acid)	2–10	15–30	50	5	2	8

[a]Adapted from Ref. 15.

[b]$R_1 = (C_{max}/C_{min})_{therapeutic}$; $R_2 = C_{toxic}/\bar{C}_{normal}$; $R_3 = C_{lethal}/\bar{C}_{normal}$; where $\bar{C} = \frac{1}{2}(C_{max} + C_{min})$.

$$CL = CL_{NR} + CL_R \tag{31}$$

If the renal clearance value for the drug can be empirically related to glomerular filtration rate ($CL_R \propto GFR$), it is possible to rewrite Eq. (31) in terms of a kidney function test for GFR. Creatinine renal clearance (CL_{CR}) is a test

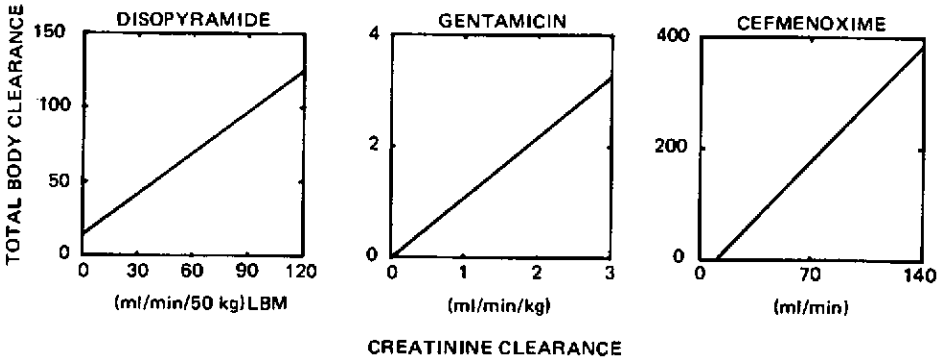

Fig. 11 Three examples of least-squares regression lines based on Eq. (32) for the clnically observed relationship between total body clearance of drug and creatinine renal clearance.

commonly employed to measure *GFR*. Thus if $CL_R \propto CL_{CR} = GFR$, then Eq. (31) may be written in terms of creatinine renal clearance,

$$CL = CL_{NR} + Q \times CL_{CR} \tag{32}$$

where Q is the observed proportionality constant as illustrated in Fig. 11. This relationship which is established through experimental observation can then be employed to predict the total renal clearance value for the drug in a patient whose creatinine clearance value is known. Once CL is estimated, the dosage can be reduced to compensate for reduced drug clearance if such adjustments are recommended for that drug. Calculations for the actual dosage adjustments are discussed later.

2. Overall Elimination Constant or Biological Half-Life

The use of observed clearance values CL versus observed GFR is the approach of choice, since the only assumption is that the patient will not differ widely from the population employed to define the empirical relationship. This assumption would be required of any method which employs a sample population to predict values for individuals in a larger population. The use of apparent total elimination rate constants λ_Z is further limited. While clearance values should be preferentially employed, λ_Z values may be employed in lieu of the availability of clearance data. Four assumptions must be met for the λ_Z (or $t_{1/2}$) method to be valid:

1. Rate constants for renal excretion (λ_R) and nonrenal drug loss (λ_{NR}) are first order.
2. The value for λ_{NR} remains constant.
3. The value for V_Z must also be constant, independent of renal function.
4. Renal excretion (not release from tissues) must be the rate-limiting step in drug elimination.

Under these conditions $CL = \lambda_Z V_Z$, $CL_{NR} = \lambda_{NR} V_Z$ and $CL_R = \lambda_R V_Z$, so that substitution into Eq. (31) yields

$$\lambda_Z V_Z = \lambda_{NR} V_Z + \lambda_R V_Z \tag{33}$$

This can be written to show the relationship between λ_Z and the renal clearance for the drug:

$$\lambda_Z = \lambda_{NR} + \frac{CL_R}{V_Z} \tag{34}$$

This may be related to *GFR* if $CL_R \propto CL_{CR}$,

$$\lambda_Z = \lambda_{NR} + K \times CL_{CR} \tag{35}$$

where K is the observed proportionality constant.

Equation (35), as well as Eq. (32), suggest three general classes of drugs as illustrated by Fig. 12, where the normal CL_{CR} value has been set at 120 ml/min. Figure 12a illustrates the effect of *GFR* on the λ_Z values for a drug that is eliminated only by renal excretion. Figure 12b shows the case where the drug is eliminated only by nonrenal routes. Figure 12c shows the dependence of λ_Z on CL_{CR} for a drug that is eliminated by both renal and nonrenal routes. In this example Fig. 12c has been constructed to represent a drug that is normally excreted 50% intact in the urine and 50% by other routes such as metabolism. This is reflected by the fact that the value for λ_Z at normal clearance (120 ml/min) is twice that at $CL_{CR} = 0$. Since λ_{NR} (the intercept at $CL_{CR} = 0$) is assumed to be constant, the normal λ_Z value is the sum of two equal values for λ_{NR} and λ_R. If the specific plot or equation, such as Fig. 12 or Eq. (35), is known for a drug, then the λ_Z value may be calculated for any given CL_{CR} value and the dosage regimen adjusted if necessary.

While the assumptions regarding Eq. (35) are commonly made, this is not the only approach used. Several studies simply define the empirical

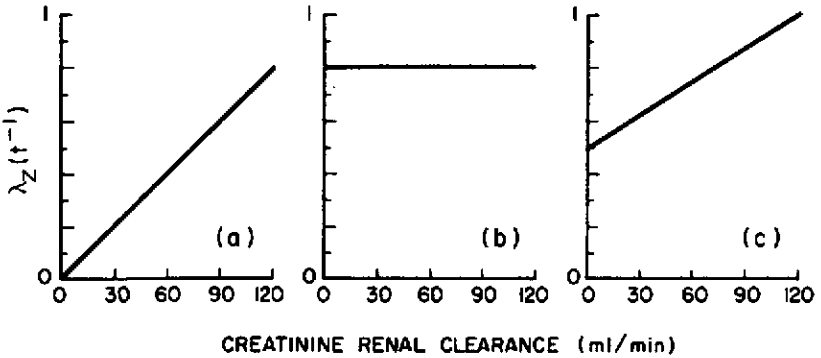

Fig. 12 Three hypothetical plots based on Eq. (35), which assumes a linear relationship between the overall drug elimination constant (λ_Z) and the glomerular filtration rate (*GFR*) as estimated from creatinine renal clearance (CL_{CR}): (a) negligible nonrenal elimination ($\lambda_{NR} = 0$) resulting in $\lambda_Z = 0$ when $GFR = 0$, (b) negligible renal excretion ($\lambda_R = 0$) so that λ_Z is represented by λ_{NR}, which is independent of *GFR*, and (c) $\lambda_R = \lambda_{NR}$, since $\lambda_Z = \lambda_{NR} + \lambda_R = 1$ at a normal *GFR* value (CL_{CR} = 120 ml/min) and $\lambda_Z = \lambda_{NR} = 0.5$ when $GFR = 0$.

relationship between the observed half-life for the drug (or the total elimination constant as defined by λ_Z) and the renal clearance value of creatinine or inulin. The resulting "calibration" plot, which may be curved, can then be used for the patient in renal failure whose clearance value for the test substance is known.

C. Individualization of Dosage Regimens

The adjustment of dosage for patients in renal failure may be deemed necessary when the increase in drug accumulation accompanying renal insufficiency is considered undesirable. One summary tabulates the effect of renal insufficiency on the behavior of 117 drugs in addition to reviewing the concepts and presenting specific recommendations for the dosage adjustment of 16 drugs [16]. Another containing more than 60 drugs lists the probable side effects in patients with renal failure and the recommended maintenance dosage intervals to avoid toxicities [16]. It contains a brief discussion of the use of creatinine clearance values in dosage adjustment and an excellent bibliography containing 78 references complete with titles. A number of investigators have recommended dosage adjustment based upon creatinine or inulin clearance values as an indicator of *GFR*. Notable among the drugs

used in these examples are cephalosporins, digoxin, aminoglycosides, and procainamide [17].

1. Clearance

The most frequently employed approach is to maintain the same average steady-state plasma concentration C_{av}^{ss} during renal insufficiency as that achieved with the usual dosage regimen and normal renal function. These adjustments are made using Eq. (18).

As discussed above, the pharmacokinetic parameter of choice is that of clearance, where

$$\underset{\text{To be kept normal}}{C_{av}^{ss}} = \underset{\text{Assumed constant}}{f} \times \underset{\text{Altered due to disease}}{\frac{1}{\text{CL}}} \times \underset{\text{Counteradjusted by regimen}}{\frac{DM}{\tau}} \tag{36}$$

The goal is to provide the renal failure patient with average steady-state plasma levels C_{av}^{ss} that are equal to those obtained in the patient with normal kidney function. It is assumed that the fraction absorbed remains constant. The clearance value for the drug in the renal failure patient must be calculated from a known relationship such as illustrated in Fig. 11. This requires a clinical study to establish the effect of renal insufficiency on the observed CL of the drug. Creatinine and inulin clearance tests are most frequently employed as a measure of renal function.

If the values for the renal failure patient are represented by CL',DM', and τ', then the adjustment is based on

$$C_{av}^{ss} = \frac{f(DM)}{(CL)\tau} = \frac{f(DM')}{(CL')\tau'} \tag{37}$$

The actual calculation is then made using

$$\frac{DM}{(CL)\tau} = \frac{DM'}{(CL')\tau'} \tag{38}$$

since f is constant. Since there are two unknowns, this may be written as

$$\frac{DM'}{\tau'} = \frac{(CL')(DM)}{(CL)\tau} \tag{39}$$

Thus any combination of DM'/τ' which satisfies Eq. (39) will provide the normal value for C_{av}^{ss}. Examination of Eq. (39) will demonstrate that this final calculation is one of common sense. A patient having difficulty excreting the drug would require a reduced drug intake. The reduction is related to the drug clearance. The normal dose size may be reduced in accordance with $DM' = (DM)(CL')/(CL)$. The normal τ may be increased; $\tau' = \tau(CL)/(CL')$. Both may be altered as shown in Eq. (39).

Practice Problem 19

An intravenous dose of 300 mg every 8 hr produces an average plasma steady-state concentration of 5.78 μg/ml in a patient of normal renal function where $CL = 108$ ml/min.

(a) Predict the C_{av}^{ss} value for this patient in the presence of renal failure wherein the CL' value is 23 ml/min if the normal dosage regimen is used.

(b) What adjusted dosage regimen will provide the normal C_{av}^{ss} value in this renal failure patient?

Answers: (a) Since the normal clearance value is 4.7 times higher than CL', then $(C_{av}^{ss})' = 4.7\ C_{av}^{ss} = 27$ μg/ml. (b) Eq. (39) results in $D'/\tau' = 8$ mg/hr, which will give $C_{av}^{ss} = 5.78$ μg/ml. Examples are 48 mg every 6 hr, 64 mg every 8 hr, and 96 mg every 12 hr.

Practice Problem 20

The total body clearance CL of disopyramide has been shown to be related to creatinine clearance (CL_{CR}) in a group of 30 patients where the least-squares regression line was $CL = 0.921CL_{CR} + 14.1$ (in ml/min). The usual dosage regimen is 150 mg every 6 hr. Capsules are available as 100 or 150 mg. Assuming normal $CL_{CR} = 120$ ml/min, recommend an adjusted dosage regimen to provide the normal C_{av}^{ss} value for a patient have a CL_{CR} value of 52 ml/min.

Answer: 100 mg every 8 hr or 150 mg every 12 hr.

In Practice Problem 19 any regimen where $DM'/\tau' = 8$ mg/hr will provide the same C_{av}^{ss} in the renal failure patient, but they will differ in C_{max}^{ss} and C_{min}^{ss} values. For a given patient the larger the dose size, the greater the fluctuation between C_{max}^{ss} and C_{min}^{ss}. In order to avoid high peaks, the adjustment may be made by reducing the dosage size rather than increasing τ. The flexibility in choosing individual values for the required DM'/τ' ratio

will be limited by available dosage form sizes and practical τ' values. There are no fixed rules for making these selections. When normal τ values are long, such as 1 day or 12 hr, they are generally not extended. Obviously, τ' values that do not conveniently fit a 24-hr time frame are impractical. In general, the final selection for D' and τ' is subject to the same considerations and limitations as a normal dosage regimen.

2. Overall Elimination Constant or Biological Half-Life

It may not be possible to find the required clearance data in the literature in order to apply Eq. (37). In many cases the dependency of λ_Z (or $t_{1/2}$) values on renal function are reported. These may be employed in lieu of the more reliable clearance data. The assumptions in employing λ_Z (or $t_{1/2}$), as listed previously, must be valid to use Eq. (18), as follows:

$$\underset{\substack{\uparrow \\ \text{To be kept} \\ \text{normal}}}{C_{av}^{ss}} = \underset{\substack{\uparrow \\ \text{Assumed} \\ \text{constant}}}{\frac{1.44f}{V_Z}} \times \underset{\substack{\uparrow \\ \text{Altered due} \\ \text{to disease}}}{t_{1/2}} \times \underset{\substack{\uparrow \\ \text{Counteradjusted} \\ \text{by regimen}}}{\frac{DM}{\tau}} \tag{40}$$

where $1/\lambda_Z = 1.44t_{1/2}$ derives from $t_{1/2} = 0.693/\lambda_Z$. Provided that V_Z remains constant and release from tissue is not rate limiting, $CL = \lambda_Z V_Z$ and Eq. (40) is equivalent to Eq. (36).

Therefore in this approach it is assumed that release from tissues is not rate limiting and that the fraction of absorbed drug and the volume of distribution remain constant. The biological half-life for the drug in the renal failure patient must be calculated from a known relationship, such as illustrated in Fig. 12a and c. This requires clinical data to establish the effect of renal insufficiency on the observed $t_{1/2}$ of the drug. Creatinine and inulin clearance tests are most frequently employed. It is necessary to study a wide range of renal insufficiency in order to clearly define the relationship between the observed λ_Z and CL_{CR}. In Practice Problem 21, an illustration of such a plot will be constructed from the data in Table 11. The value for $t_{1/2}$ in Eq. (40) will increase in renal failure for drugs behaving like those shown in Fig. 12a and c. If the patient cannot excrete the drug, the half-life will be longer and more drug will accumulate in the patient. The method for adjustment again resides in the final term of the equation (DM/τ), as discussed for Eq. (36). One can decrease the dose, increase τ, or both. The product $t_{1/2}(DM/\tau)$ must be kept constant:

$$t_{1/2}\frac{DM}{\tau} = t'_{1/2}\frac{DM'}{\tau'} \tag{41}$$

Therefore the adjusted dosage regimen may be calculated from

$$\frac{DM'}{\tau'} = \frac{t_{1/2}\,(DM)}{t'_{1/2}\,\tau} \tag{42}$$

Consider a drug with $V_Z = 140$ liter, $t_{1/2} = 3.5$ hr, $f = 0.85$, and a desired C_{av}^{ss} of 0.2 mg % that is normally administered every 6 hr. The dose may be calculated from Eq. (40) as $DM \approx 400$ mg. If the $t_{1/2}$ value is extended to 7 hr because of renal insufficiency, the regimen may be adjusted by decreasing DM/τ by half. The simplest adjustment would be to double τ ($\tau' = 12$ hr) or reduce the DM by half ($DM' = 200$ mg), since $t'_{1/2}/t_{1/2} = 2$. The original value for DM/τ was $400/6 = 66.7$. Any combination providing a D'/τ' ratio of 33.3 will maintain C_{av}^{ss} constant. Thus C_{av}^{ss} will be kept at 0.2 mg % by any of the following regimens: (1) 200 mg every 6 hr, (2) 400 mg every 12 hr, (3) 266 mg every 8 hr, and (4) 133 mg every 4 hr, and so on. Note, however, that the normal steady-state time *profile* cannot be duplicated in the renal patient. This is because of the change in $t_{1/2}$. The shape of a blood level curve will change when $t_{1/2}$ is changed. Dosage adjustment can maintain the normal C_{av}^{ss} value but not the normal time course. In the examples above, dosage regimen (1) will provide a $C_{\max}^{ss}$ value that is lower than normal, while the $C_{\min}^{ss}$ value will be higher than normal.

Practice Problem 21

An adult male patient normally taking a drug as a 50-mg dose every 8 hr is found to have a creatinine clearance value of 65 ml/min as a result of a renal complication. It is considered necessary to adjust the dosage of this drug for this patient. Tablets are available in 10-, 25-, and 50-mg doses. Recommend

Table 11 Relationship of Creatinine Clearance Values to Observed Elimination Rate Constants $\lambda_z = 0.693/t_{1/2}$ for Drug

CL_{CR} (ml/min)	λ_Z (hr^{-1})	CL_{CR} (ml/min)	λ_Z (hr^{-1})
10	0.033	50	0.049
22	0.037	69	0.058
33	0.044	86	0.069
40	0.048	128	0.084
50	0.053	132	0.089

an adjusted regimen using the data in Table 11 assuming that normal creatinine clearance is 128–132 ml/min in this study.
Answer: A plot of λ_Z versus CL_{CR} is linear with a slope of 0.000448 and an intercept of 0.0286. Therefore $\lambda_Z(65) = 0.058$ and the half-life is 12 hr. If a CL_{CR} of 128–132 ml/min is considered normal, than the normal $t_{1/2}$ is 8 hr and the $t_{1/2}$ has increased 1.5-fold. This can also be calculated directly from the values for λ_Z at 65 and 130 ml/min on the plot: 0.087/0.58 = 1.5. The adjusted dosage regimen may be 25 mg every 6 hr or 50 mg every 12 hr.

After therapy is initiated using an adjusted dosage regimen, the concentration of drug in the blood during steady state should be determined if possible and compared to the desired value. Further adjustment may then be made on an empirical basis.

3. A Method of Approximation by Dettli

Data for $t_{1/2}$ (or λ_Z) versus CL_{CR}, such as those given in Table 11, are not always available in the literature. Dettli [18,19] pointed out that the $t_{1/2}$ values are often reported in normal and anuric patients. He suggested an approximate method using these data when the calibration plots are not known. Assuming that Eq. (40) is applicable, the data for normal renal function, λ_Z, and for the absence of renal function, λ_{NR}, can be used to estimate the slopes and intercepts of plots such as those in Fig. 12a and c. Dettli has published several tables listing literature values for the elimination rate constants in normal and anuric patients. Some typical examples taken from Dettli [18,19] are listed in Table 12. The data are used in the manner described above. It is assumed that λ_Z is a linear function of creatinine renal clearance, as described by Eq. (35). Thus the value for the anuric patient represents the intercept value λ_{NR} in Fig. 12. The value for λ_Z in the presence of normal renal function is taken as that corresponding to 100 ml/min. With the use of 100 ml/min instead of 120 ml/min, no correction is necessary for minor changes in *GFR*.

Consider gentamicin, for example. Substitution of values from Table 12 into Eq. (35) yields $\lambda_Z(\text{calc}) = 0.006\ (\text{hr}^{-1}) + \text{slope}\ (\text{min/ml hr}) \times CL_{CR}$ (ml/min), where the slope = 0.003. What dosage adjustment must be made for a patient with a creatinine clearance value of 30 ml/min? The value for $\lambda_Z(30)$ may be calculated as $0.006 + 0.003(30) \approx 0.1\ \text{hr}^{-1}$. Since the normal value for λ_Z was $0.3\ \text{hr}^{-1}$, the $(t_{1/2})_{30} = 3(t_{1/2})_{\text{normal}}$. Therefore the adjusted dosing rate DM/τ must be decreased to one-third the normal dosage. The recommended dosage in the prescribing information for gentamicin at a

Table 12 Average Elimination Rate Constants[a] in Patients with Normal Renal Function, λ_z, and in Anuric Patients, λ_{NR}, as Reported by Dettli[b]

Drug	λ_{NR}	λ_Z	Drug	λ_{NR}	λ_Z
Ampicillin	0.06	0.6	Methicillin	0.17	1.4
Carbenicillin	0.06	0.6	α-Methyldopa	0.03 (?)	0.17
Cephacetril	0.03	0.7	Minocycline	0.05	0.06
Cephalexin	0.03	0.7	Nafcillin	0.5	1.2
Cephaloridine	0.03	0.4	Oxacillin	0.35	1.4
Cephalothin	0.06 (?)	1.4	Penicillin G	0.14	1.4
Cephazolin	0.02	0.35	Peruvoside[c]	0.24*	0.3*
Chloramphenicol	0.24	0.3	Polymyxin B	0.02	0.15
Chloretetracycline[c]	0.08	0.1	Practolol	0.01	0.07
Ciclacillin	0.1	1.0	Procainamide	0.007	0.21
Clindamycin	0.16	0.2	Rifampicin	0.25	0.25
Colistimethate	0.06	0.2	Rolitetracycline	0.02	0.06
Digitoxin	0.07*	0.1*	Sisomycin	0.0005	0.25
Digoxin	0.14*	0.45*	Streptomycin	0.01	0.25
α-Acetyldigoxin	0.21*	0.7*	Strophanthin G		
β-Methyldigoxin	0.13*	0.25*	(ouabain)[c]	0.3*	1.2*
Doxycycline	0.025	0.03	Strophanthin K[c]	0.25*	1.0*
Erythromycin	0.35	0.5	Sulfadiazine	0.03	0.07
5-Fluorocytosine	0.007	0.25	Sulfamethoxazole	0.06	0.07
Gentamicin	0.006	0.3	Sulfisomidine	0.01	0.12
Isoniazid (fast			Tetracycline	0.01	0.08
inactivators)	0.4	0.5	Thiamphenicol	0.02 (?)	0.25
Isoniazid (slow			Ticarcillin	0.06	0.6
inactivators)	0.13	0.25	Tobramycin	0.007	0.35
Kanamycin	0.01	0.35	Trimethoprim	0.03	0.06
Lidocaine	0.36	0.4	Vancomycin	0.004	0.12
Lincomycin	0.06	0.15			

[a]In hr^{-1} unless marked*, in which case the units are day^{-1}.
[b]Refs. 18 and 19.
[c]The clinical consequences of the formation of active metabolites in patients with renal disease remain to be determined.

creatinine clearance value of 30 ml/min is 30–35% of the normal dosage at the normal τ value of 8 hr [20], which agrees with the above approximation. This oversimplification is recommended as a first approximation when data are not available. In the case of gentamicin the problem of dosage individualization is really more complex and will be covered later as a special case.

Practice Problem 22

Answer the following questions using the data from Dettli given in Table 12.

(a) How would you classify chlortetracycline, lincomycin, and procainamide relative to Fig. 12?

(b) An adult patient normally receives digoxin, 0.25 mg/day, in a single dose. What regimen do you recommend if the patient experiences renal failure and the creatinine clearance value decreases to 40 ml/min?

Answer: (a) Chlortetracycline, Fig. 12b; lincomycin, Fig. 12c; and procainamide, Fig. 12a. (b) $\lambda_Z(40) = 0.14 + [(0.45-0.14)/100]40 = 0.27$ day^{-1}; $(t_{1/2})_{40} = 1.67t_{1/2}$. Since $\tau = 1$ day is both convenient and infrequent, it should be kept constant and the dosage size changed to 0.25 mg/ 1.66 = 0.15 mg. The recommended adjusted regimen is 0.15 mg/ 24 hr.

4. Further Approximations

The method of approximation of the dosage regimen was based on known data for λ_Z and λ_{NR} in the previous examples. This principle can be extended to cases where the only data available are the normal half-life value and the fraction of drug excreted intact in the urine. Equation (40) may again be employed as a *first approximation*. As always, it is necessary to monitor blood levels and correct the dosage empirically. The assumption is made that λ_{NR} is constant and may be calculated from λ_Z(1 − fraction excreted intact). The average normal creatinine renal clearance value for the patient's age and weight or the actual value for the patient before renal failure may be used. The following illustration is adapted from a literature response for drug information [21].

The drug ethambutol is normally administered once daily. If $t_{1/2} = 6.5$ hr, the expected accumulation would be insignificant. The steady-state degree of accumulation using this value would be 108% that of a single dose. (The apparent $t_{1/2}$ values during the 12 hr following oral administration to normal subjects has been estimated at 4.1 hr from tablets and 4.8 hr from solutions, with estimates increasing up to 10 hr when 24- and 72-hr data were included [22].) If renal failure prolonged $t_{1/2}$ sufficiently, then increased accumulation would occur. Since the usual dosage interval is so long (24 hr), it is more practical to correct the size of the maintenance dose rather than τ, as shown in Practice Problem 23.

Practice Problem 23

A 60-kg patient with a normal creatinine clearance value of 120 ml/min was taking 1.5 g of ethambutol in a single oral daily dose and underwent a kidney transplant. The creatinine clearance value decreased to 40 ml/min. Should the daily dosage of ethambutol be altered in order to maintain a body content

similar to that before the operation? Assume the half-life for this drug in this patient was 6.5 hr before the transplant and that 80% of the drug was excreted intact by the kidneys (normally).

Answer: The value for λ_Z (normal) is 0.107 hr^{-1}, and $\lambda_{NR} = 0.20(0.107) = 0.0214\ hr^{-1}$. Using Eq. (34), $\lambda_Z(40) = 0.0214 + [(0.107 - 0.0214)/120](40) = 0.0498\ hr^{-1}$. Thus $(t_{1/2})_{40} = 2.14t_{1/2}$, and the dose should be reduced to (1.5 g)/2.14 = 0.7 g every 24 hr.

IV. MULTIPLE DOSING OF CONSTANT-RATE INTRAVENOUS INFUSIONS

A. Accumulation of Drugs Exhibiting Monoexponential Disposition

Figure 13 illustrates the plasma concentration time course following two consecutive constant-rate (R_0) intravenous infusions, each given over the time period T, where $T = D/R_0$ is shorter than the time required to achieve steady state. The postinfusion time course can be described by

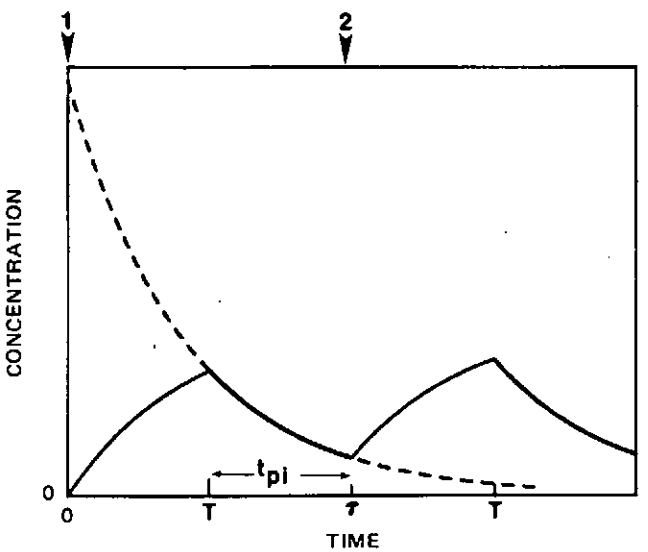

Fig. 13 The concentration of drug in plasma during consecutive constant-rate (R_0) intravenous infusions given τ hours apart over a period of time equal to $T = D/R_0$. The postinfusion time period is t_{pi}, where $t_{pi} = \tau - T$. Two doses are shown.

$$C = C(T)e^{-\lambda_z t_{pi}} \tag{43}$$

where t_{pi} is the time between τ and T and

$$C(T) = \frac{R_0}{CL}(1 - e^{-\lambda_z T}) \tag{44}$$

as indicated by the segment $T \rightarrow \tau$ of the solid curve of the larger monoexponential curve in Fig. 13. This is somewhat similar to the oral dose case, except that the infusion is completely stopped at T, so that the remaining curve represents drug disposition only. In the oral case the curve had to be feathered to separate the input and loss segments. The value of the monoexponential curve at time zero is

$$C(O) = C(T)e^{\lambda_z T} \tag{45}$$

so that the entire curve may be described by

$$C = C(O)e^{-\lambda_z t} \tag{46}$$

where $C(O)$ is defined by Eq. (45) and t is the time from zero to infinity. Therefore the fraction F remaining at time τ can be calculated from λ_Z by rearranging Eq. (46) and substituting τ for t to obtain

$$\frac{C_{\min}}{C(O)} = e^{-\lambda_z \tau} = F \tag{47}$$

The concentration at τ thus represents the minimum $C_{\min}$. The value for F can be employed in Eq. (16) to calculate X and make predictions regarding the reference curve described by Eq. (46). It must be remembered that the only segment of the plasma time course described by Eq. (46) is that from T to τ following each dose. Only these data are subject to predictions based on Eq. (16). Section IV.B illustrates the use of this approach.

B. Predictions of C_{max} and C_{min} Following Repetitive Constant-Rate Intravenous Infusions

As discussed in Sec. IV.A, the minimum concentration following each infusion will occur at time τ. Since the highest point following any given infusion will be just prior to stopping the infusion, the C_{max} value will be the concentration at time T, where $T = D/R_0$. Thus the two most critical values,

C_{max} and C_{min}, lie on the reference curve and can be manipulated in a manner similar to that following a rapid intravenous injection of a monoexponential drug.

This is illustrated in Fig. 14, which shows the time course following the first two doses on both a coordinate and a semilogarithmic plot. The fraction remaining at C_{min} can be calculated graphically from the reference line, $C_{min}/C(O)$, or from Eq. (47), where the value for λ_Z can be calculated from

$$\lambda_Z = \frac{\ln C_{max} - \ln C_{min}}{\tau - T} \tag{48}$$

The C_{min} value following any dose can be predicted by multiplying the C_{min} value when $N = 1$ by the factor X as defined in Eq. (16). This is true for predicting any value on the reference line between T and τ which includes C_{max}.

These predictions can be used in conjunction with a trial dose by intravenous infusion to individualize the required infusion rate to obtain desired values for C^{ss}_{max} and C^{ss}_{min} in a patient. The trial dose will be given over a fixed time period T and the postinfusion period can be used to calculate λ_Z. Because C^{ss}_{max}, C^{ss}_{min}, and T have been chosen, the τ value has been indirectly set. The postinfusion time t_{pi} can be calculated from the monoexponential equation describing the reference line. This line must decrease from C^{ss}_{max} to C^{ss}_{min} during the period t_{pi}, where $t_{pi} = \tau - T$. Therefore, from Eq. (48),

$$t_{pi} = \frac{\ln C^{ss}_{max} - \ln C^{ss}_{min}}{\lambda_Z} \tag{49}$$

and the τ value must be

$$\tau = T + t_{pi} \tag{50}$$

However, this sets only the ratio of $C^{ss}_{min}/C^{ss}_{max}$, and not the absolute values. The trial dose may produce values which are too high or too low relative to what is desired. Since the concentration at a fixed time is proportional to the rate of infusion, the desired valued for R_0 can be calculated from

$$R_0 \text{ (desired)} = \frac{C^{ss}_{max} \text{ (desired)}}{C^{ss}_{max} \text{ (trial)}} R_0 \text{ (test)} \tag{51}$$

where C^{ss}_{max} (desired) is the value to be achieved and C^{ss}_{max} (trial) is the value predicted if the trial dose were given every τ hours.

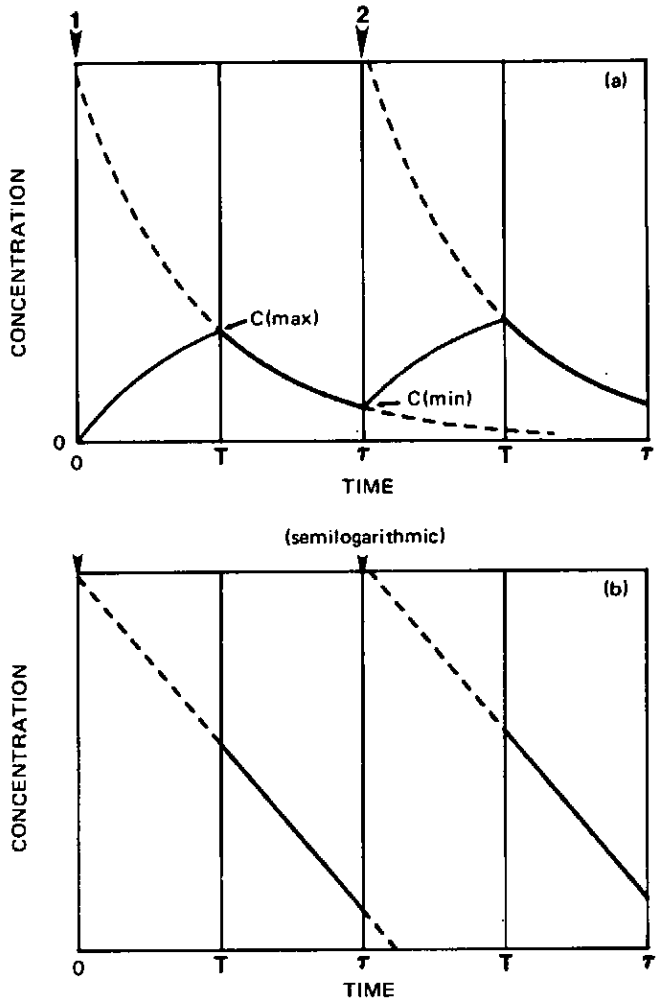

Fig. 14 Coordinate (a) and semilogarithmic (b) plots showing the segment of the concentration time course from T to τ which can be predicted from the $N = 1$ curve by using X [Eq. (16)].

This method includes the selection of an infusion period T and a trial infusion rate $R_0 = D/T$. The desired C^{ss}_{max} and C^{ss}_{min} ratio, then, sets the value for t_{pi}, which results in a fixed dosing interval of $\tau = T + t_{pi}$. Finally, the actual C^{ss}_{max} and C^{ss}_{min} values are achieved by modifying the trial value for R_0 based on what would result if the trial dosing rate were to be repeated at the interval that was calculated.

In all of the above calculations, several factors were controlled and these are summarized here for emphasis. Drug disposition was monoexponential. If a biexponential drug were used, the C_{min} values could be predicted if τ occurred during the terminal phase. The C_{max} values would require a more complex treatment. It is assumed that T occurs before steady state and that $\tau > T$. These limitations are likely to be the case in practice. This simplified discussion does not apply to $\tau < T$, which represents simultaneous rather than consecutive infusions.

For an application of this approach see Chap. 8, Sec. III.B.2 on the clinical pharmacokinetics of gentamicin.

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7

Pharmacokinetic Aspects of Structural Modifications in Drug Design and Therapy

I. INTRODUCTION

A. Typical Goals

In addition to pharmacological considerations, molecular modifications may be designed to alter selected pharmacokinetic properties of the parent drug. The derivative may be either a prodrug or an analog. In either case the primary goal is to improve specific pharmacokinetic processes without affecting any others. Absolute selectivity is unlikely, since each process is influenced by the physicochemical characteristics of the drug. In the end a compromise representing optimization of the overall pharmacokinetic pattern must be accepted.

The following represent typical pharmacokinetic goals:

1. Increased bioavailable fraction
2. Increased rate of bioavailability
3. Prolonged duration
4. Active-site enrichment
5. Decreased formation of toxic metabolites
6. Reduced peak plasma concentrations

Success in achieving these goals can be assessed by comparisons of appropriate pharmacokinetic properties of the derivative relative to the parent drug. Therapeutic success must combine both pharmacological and pharmacokinetic considerations in order to select derivatives with potential for clinical advantages. The differentiation between pharmacokinetic and pharmacological properties is delineated in the following section.

B. Pharmacokinetic Versus Pharmacological Properties

Consider Fig. 1, which represents substituent group effects in a series of molecules upon the "drug–receptor" interaction. Typically, assumptions are made regarding the interaction between the parent compound and the receptor. The basic assumptions are tested by molecular modifications. Unexpected results are explained by modifying the theory and occasionally by modifying the concept of the drug structure by arguing for a particular preferred conformation for that molecule only when it is in the vicinity of that receptor. Conclusions are often based upon dose–response curves, and the dose is assumed to be responsible for the magnitude of the response. It

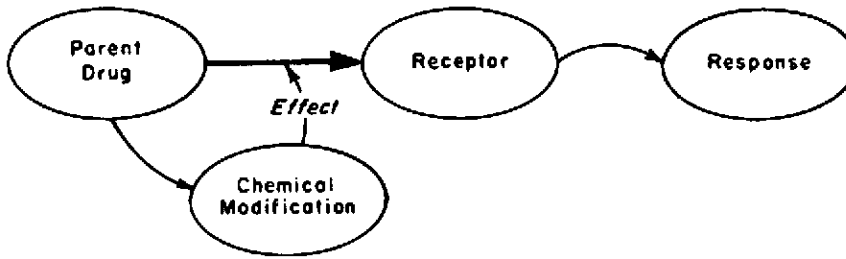


Fig. 1 Simplified model for considering the effect of various substituent groups on drug–receptor interaction.

is widely recognized that the time course for a drug at the receptor must be considered. The onset, duration, and intensity of effect may be considered as a function of at least two factors [1]:

1. Transport processes affecting the time course at the receptor site, delivery to and removal from the site (pharmacokinetics)
2. Interaction between drug and receptor after arrival at the site (pharmacology)

Figure 2 illustrates how modification of a parent structure can influence the drug time course at the receptor site. The following processes may be altered by changing a substituent group on a drug (D):

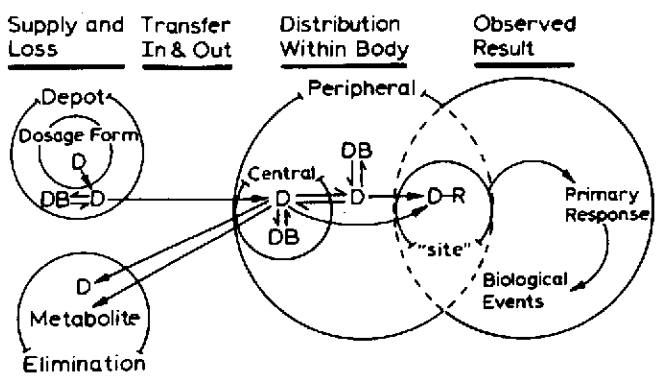


Fig. 2 Diagram of various rate processes which may be altered by chemical modification of a drug, thereby affecting the time course for drug at its site of action. The symbols and interactions are explained in the text.

1. Supply and loss
   a. Release from dosage form (rate and/or amount)
   b. Stability in depot
   c. Binding in depot (DB)
   d. Transfer from depot to central compartment (rate and/or amount)
   e. Elimination rate from central compartment
2. Distribution
   a. Binding in central compartment (DB)
   b. Binding in peripheral compartment (DB)
   c. Rate and volume of distribution
   d. Transfer to receptor site
3. Drug–receptor interaction

Consider the case where two "equipotent" drugs are admnistered but one results in a decreased biological response due to failure to reach the site. How many potential explanations for this can you identify in Fig. 2? (There are more than 10.)

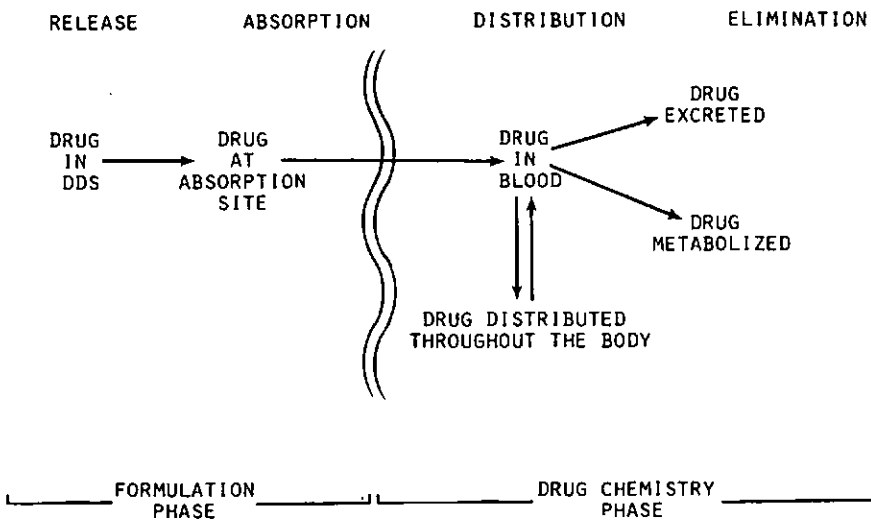
One obvious challenge in "optimizing" the above factors is locating the receptor site and defining an ideal time course for the drug–receptor interaction. An ideal drug should do the following:

1. Reach the site of action
2. Arrive rapidly in sufficient quantity
3. Remain at the site for a sufficient duration
4. Be excluded from other sites
5. Be removed from the site when appropriate

The most significant question ultimately is Does the alteration in pharmacokinetic behavior improve therapy with this drug? It is difficult to envision a model system that will lend itself to simple assessments of such questions.

C. Dosage Forms Versus Analogs: Plasma Concentration Time Courses

The interpretation of plasma drug concentration time-course data to compare analogs differs from that used to compare dosage forms (drug delivery systems). In both cases the pharmacokinetic events may be described by Scheme I.



Scheme I

1. Drug Delivery Systems

A study designed to compare two drug delivery systems (DDS) can be carried out by simple comparisons of their plasma drug concentration time courses using a crossover protocol. In such a study a single drug is being examined and only the DDS may differ. Thus in Scheme I only two parameters may be altered: the rate of release and the bioavailable fraction (f). If release from the DDS is rate determining, it will control the absorption rate. Thus the DDS may alter the bioavailable dose (fD) and/or the absorption rate constant (k_a). Since a single drug is employed and biological variability is evenly distributed by the experimental design, the remaining parameters are held constant (λ_Z, V_Z, CL, CL_R, λ_R, λ_{NR}, etc.). In such a case the dose-adjusted AUC values can be employed to calculate the bioavailability of the drug from one dosage form, DDS_1, relative to the other, DDS_2. The AUC ratio gives only the *relative* bioavailability, since absolute bioavailability from either DDS is not considered and in some cases may not be known:

$$\text{relative bioavailability} = \frac{AUC_1}{AUC_2} \tag{1}$$

This comparison is valid because total body clearance is held constant and AUC is normalized for any difference in dose. It is also necessary that AUC

values be linearly related to dose in the dose range of the study. Since total body clearance may be calculated from

$$CL = \frac{fD}{AUC} \tag{2}$$

then

$$\frac{AUC}{D} = \frac{f}{CL}$$

Thus the dose-adjusted AUC value for each DDS (AUC/D) is dependent upon the f value for that formulation, since CL is constant.

This comparison of the AUC values will provide the relative bioavailability of one DDS to another, but it does not consider any change in the shape of the plasma concentration time course. The second formulation effect, namely, absorption rate, can influence both the maximum plasma concentration C_{max} and the time t_{max} to achieve it. As the value for k_a is

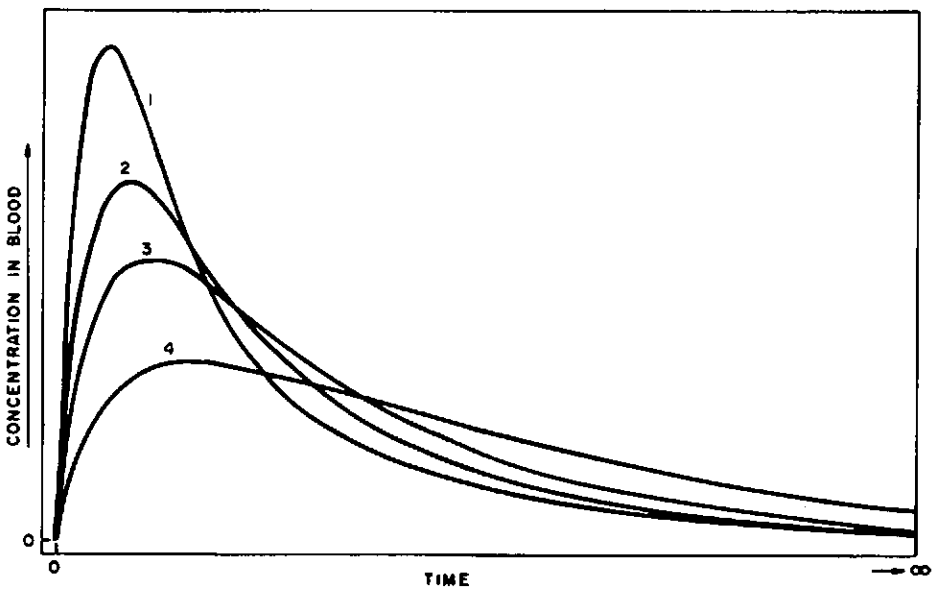


Fig. 3 The effect of the first-order rate constant for supply of drug to the blood. The relative values decrease from top to bottom: $k_a = 6$ (curve 1), $k_a = 3$ (curve 2), $k_a = 2$ (curve 3), and $k_a = 1$ (curve 4). All other parameters have been held constant.

increased and all other factors are held constant, the C_{max} value will increase proportionally and t_{max} will decrease (Fig. 3). By observation of C_{max} and t_{max} one can see that the order of rate of bioavailability from these formulations corresponds to curve 1 > curve 2 > curve 3 > curve 4. A quantitative rate assessment would require calculations for the k_a values. The AUC values could be employed to assess relative bioavailability.

It is also possible that only the bioavailable fraction f becomes altered by the DDS. In this case the t_{max} value will remain constant but the C_{max} values will be proportional to fD (Fig. 4). Since it is obvious in Fig. 4 that t_{max} (and therefore k_a) is constant, the C_{max} ratios may be used to compare the relative bioavailability associated with the time courses. For example, the observed C_{max} value for curve 1 is five times that for curve 5, so therefore the f for DDS_1 is five times that for DDS_5.

Figures 3 and 4 show curves where only k_a or f were varied but not both. Obviously a DDS can alter both k_a and f values. In this case Eq. (1) will still apply but the comparisons carried out on C_{max} values will no longer be valid. These rough C_{max} approximations are valid only when t_{max} is constant. The AUC values should be preferentially employed to the C_{max} approximations if AUC values are available.

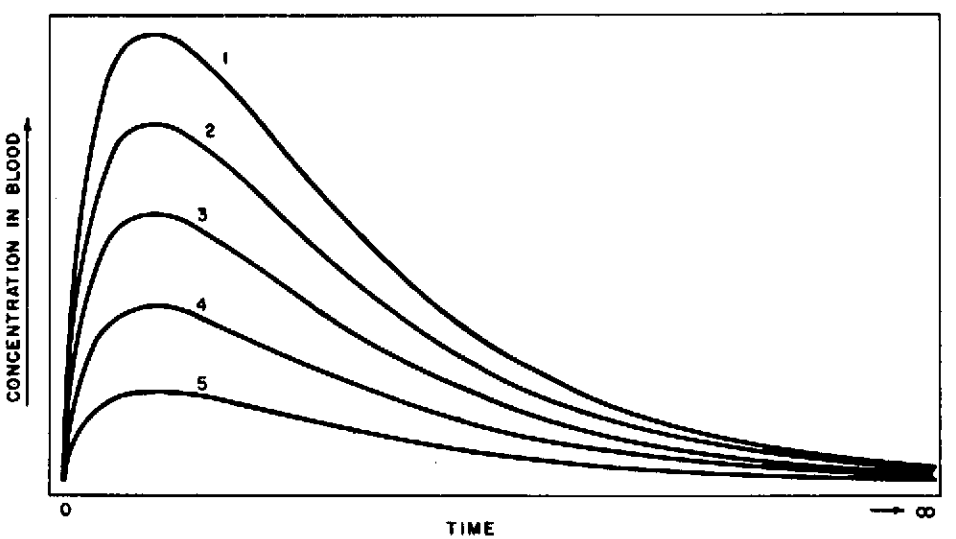


Fig. 4 Effect of the size of the bioavailable dose administered by an extravascular route. From top to bottom the relative dose is: 5(curve 1), 4(curve 2), 3(curve 3), 2(curve 4), and 1(curve 5). All other parameters have been held constant.

Sample Problem 1

While testing a new drug, a pharmacologist administered equal doses both intramuscularly and subcutaneously to some test animals. The ED_{50} for the intramuscular route was found to be about 25% lower. A study using the same experimental conditions produced the blood curves shown in Fig. 5. Offer an explanation for the observed difference in ED_{50}.

Solution: Both curves are for the same drug; therefore drug disposition is held constant. The peak time is the same in both cases, indicating that k_a is the same for both routes. However, the areas under the curves appear different. Because k_a remains constant, we can use peak height to estimate relative areas. Subcutaneous administration shows 25% less area under the curve, indicating 25% less drug absorbed. Therefore the change in amount absorbed will explain the difference in ED_{50}.

Practice Problem 1

Capsules of the amorphous and crystalline forms of a new drug were administered to healthy volunteers in a crossover study. Nearly all of those receiving the amorphous form showed some toxicity, while those who received equal doses of the crystals had no side effects. In both cases all of the administered drug was recovered in the urine. Using the blood level curves shown in Fig. 6, explain the results.

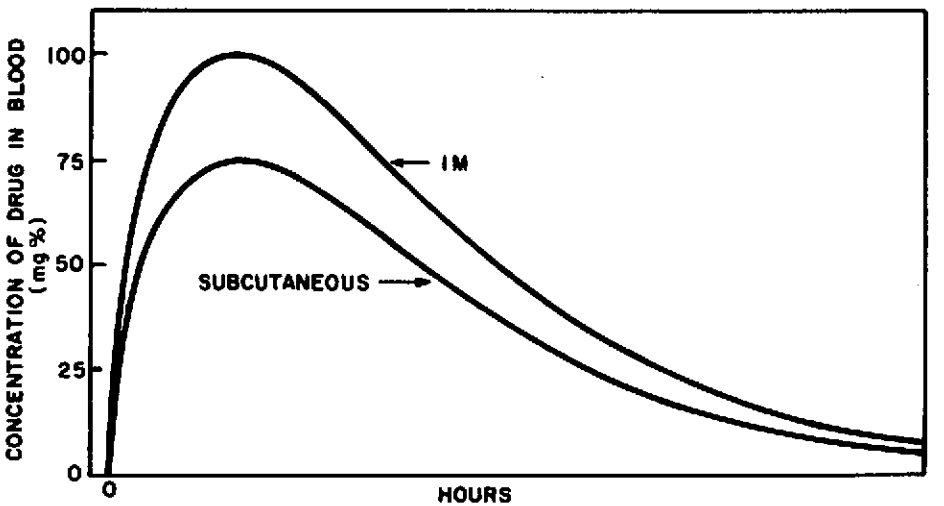


Fig. 5 Time course for drug in the blood following the administration of equal doses by two different routes, as described in Sample Problem 1.

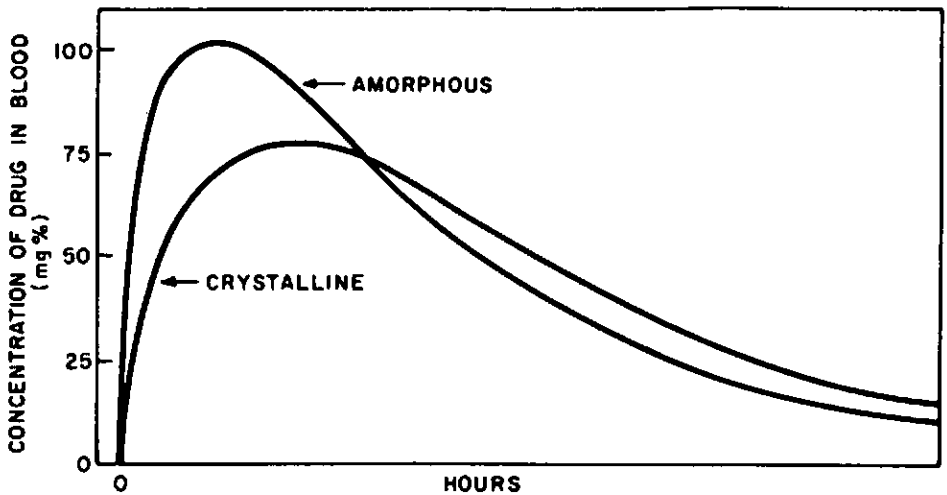


Fig. 6 Time course for drug in the blood following equal oral doses administered as the amorphous and crystalline forms, as described in Practice Problem 1.

Answer: The amorphous form dissolves more rapidly, leading to a larger k_a. An increase in k_a increases the peak height and decreases the peak time, as observed in Fig. 6. This increase in peak height accounts for the toxic symptoms, even though the same amount of drug was absorbed in each case.

2. Analogs

The comparison of a series of analogs is totally different from that described previously for dosage forms. In this case all of the analogs must be administered in exactly the same manner and in the same formulation. The potential influence of the formulation on the results is therefore held constant for all of the analogs. These drugs are generally administered in solution or in a rapidly releasing DDS. Since each derivative is a unique chemical entity, all of the factors in the drug chemistry phase are subject to change, namely, f, k_a, λ_Z (λ_R, λ_{NR}), V_Z, and $CL(CL_R, CL_{NR})$. As a result, none of the previous approaches used to compare different dosage forms of one drug are valid. For example, Eq. (1) requires constant CL. The rough interpretations made from the shapes of the curves require that only absorption can change, that is, f and/or k_a. In the comparison of analogs the potential pharmacokinetic changes are absorption, distribution, and elimination.

How, then, can drug derivatives be evaluated to assess the effect of the modification on bioavailability? The bioavailable fractions must be determined and used to calculate the effect. Absolute bioavailability must be employed to calculate relative bioavailability from the ratio

$$\text{relative bioavailability} = \frac{f_{\text{analog}}}{f_{\text{drug}}} \tag{4}$$

The relative shapes of the curves themselves cannot be interpreted. For example, it would be necessary to calculate the values for k_a in order to compare the rates of absorption. The reason for this is illustrated in Fig. 7, where only the elimination rates differ for the four curves. These curves could represent four analogs which differ only in elimination. They appear to show a decrease in bioavailable fraction ($DDS_1 > DDS_2 > DDS_3 > DDS_4$), with an increase in the relative absorption rates using t_{max} as a guide. In truth, they all have the same values for f and k_a. This chemical modification changed

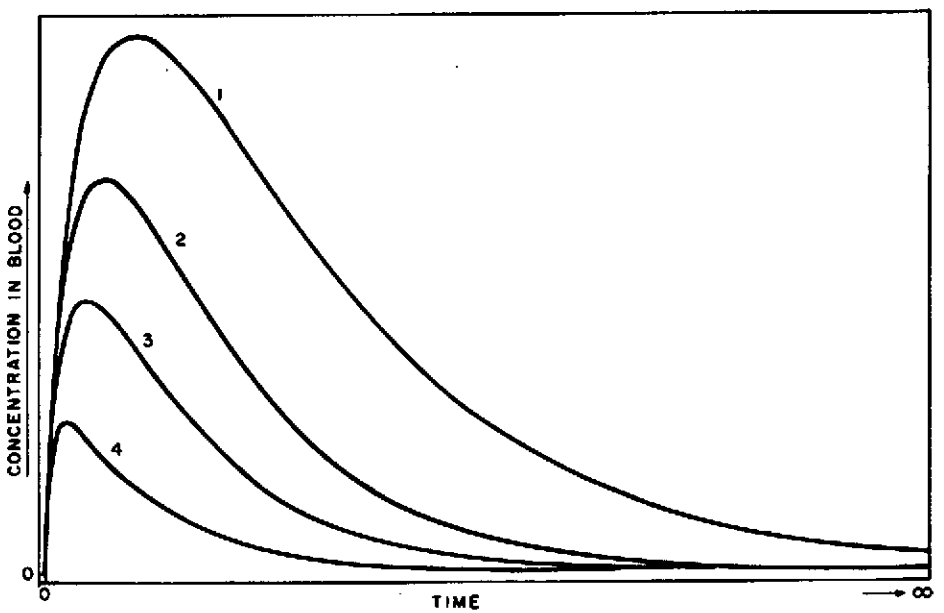


Fig. 7 Effect of increasing the elimination rate constant. The relative elimination rates (from top to bottom) are 1 (curve 1), 2 (curve 2), 4 (curve 3), and 10 (curve 4). All other parameters have been held constant.

only elimination (or biological half-lives, since $t_{1/2} = 0.693/\lambda_Z$) in this example. Thus the faster the rate of elimination from the body, the smaller the AUC value, as can readily be observed by comparing curve 1 to curve 4.

In summary, drug analogs can be compared using Eq. (4), which is based on their individual absolute bioavailable fractions, which are calculated by comparing AUC values following extravascular doses to those obtained from intravenous administration. Any further comparisons must be based on calculations for their individual pharmacokinetic parameters, as discussed in Sec. II.A.2 on penicillins.

In each of the following problems choose the statement which is most appropriate to the situation. The answers are provided following Practice Problem 6.

Practice Problem 2

Which one of the following is most likely to be influenced by the formulation and processing of the drug delivery system?

(a) The distribution of drug between blood and tissues
(b) The rate constant for urinary excretion
(c) The biological half-life of the drug
(d) The amount and/or rate of drug absorbed from the site of administration
(e) The binding of drug to plasma protein

Practice Problem 3

Figure 8 represents blood levels from two different generic brands of the same drug administered orally in equal doses. Assume the study is conducted in normal healthy volunteers and properly designed.

(a) The bioavailable dose of brand 1 is larger but the rate constant for absorption is greater from brand 2.
(b) Since the peak heights are equal, the bioavailable doses are equal.
(c) The bioavailable dose is greater from brand 2 but brand 1 has a faster absorption rate constant.
(d) Brands 1 and 2 are bioequivalent.
(e) Both the absorption rate constant and the bioavailable dose are greater from brand 2.

Practice Problem 4

The blood levels in Fig. 9 were obtained when two products containing the same drug were administered to normal healthy volunteers in a crossover study.

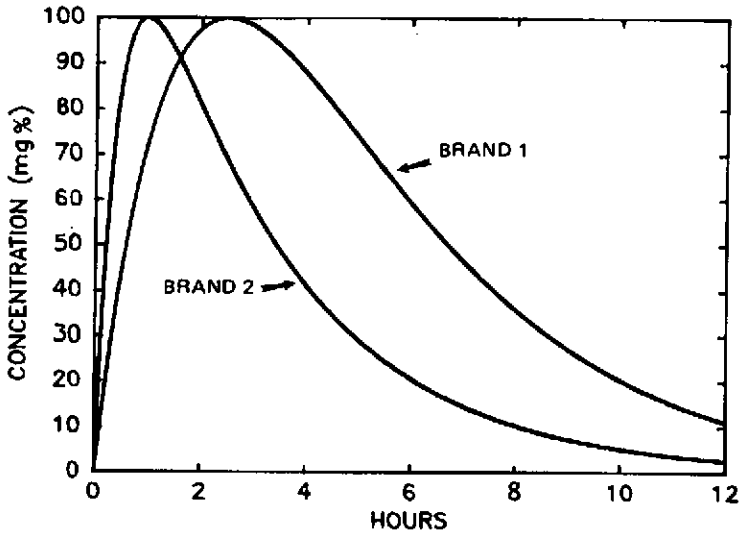


Fig. 8 Concentration of drug in blood following equal doses of two different brands of the same drug.

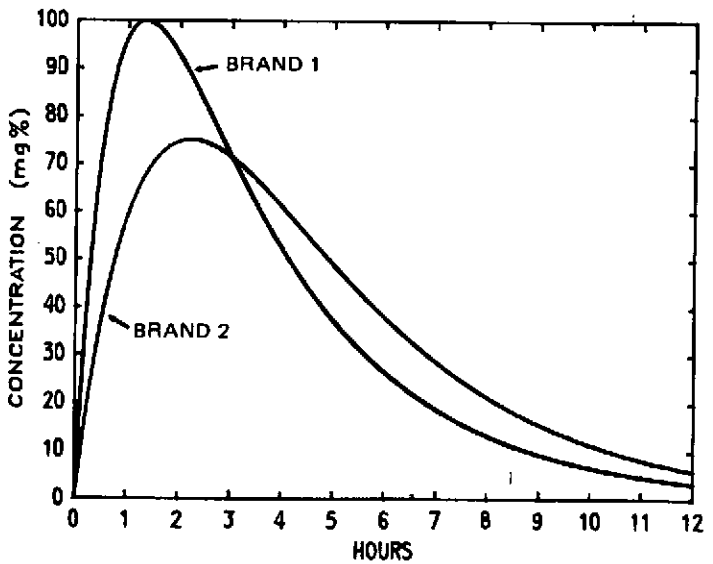


Fig. 9 Concentration of drug in blood following equal doses of two different brands of the same drug.

(a) A total of 33% more drug is absorbed from product 1 as compared to product 2.
(b) A total of 25% more drug is absorbed from product 1 as compared to product 2.
(c) The rate constant for absorption from product 1 is greater than the rate constant for absorption from product 2.
(d) Both the rate constant for absorption and the total amount of drug are greater for product 1.
(e) The rate constant for absorption is greater for product 2 but the total amount of drug absorbed is greater from product 1.

Practice Problem 5

The blood levels in Fig. 10 were obtained when equal doses of two formulations of the same drug were administered to normal, healthy volunteers in a crossover study.

(a) Peak plasma levels cannot be compared, since formulations and manufacturing methods vary.

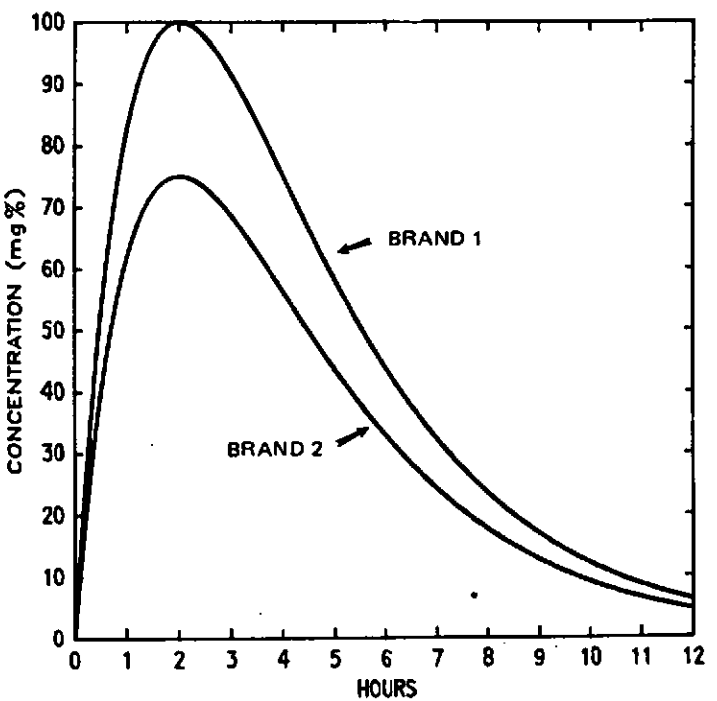


Fig. 10 Concentration of drug in the blood following equal doses of two different brands of the same drug.

(b) The rate constant for absorption from brand 1 is greater than the rate constant for absorption from brand 2.
(c) Both the rate constant for absorption and the total amount of drug absorbed are greater for brand 1.
(d) The rate constant for absorption is greater for brand 2 but the total amount of drug absorbed is greater from brand 1.
(e) None of the above are true statements.

Practice Problem 6

The average serum level time courses in Fig. 11 were obtained following 500-mg oral doses of dicloxacillin (curve A) and cloxacillin (curve B).

(a) The amount of cloxacillin absorbed is approximately 60% that of dicloxacillin, based on peak height comparison.
(b) The absorption rate constants are approximately equal for both drugs.
(c) Both the absorption rate constant and the bioavailable dose are greater for dicloxacillin.

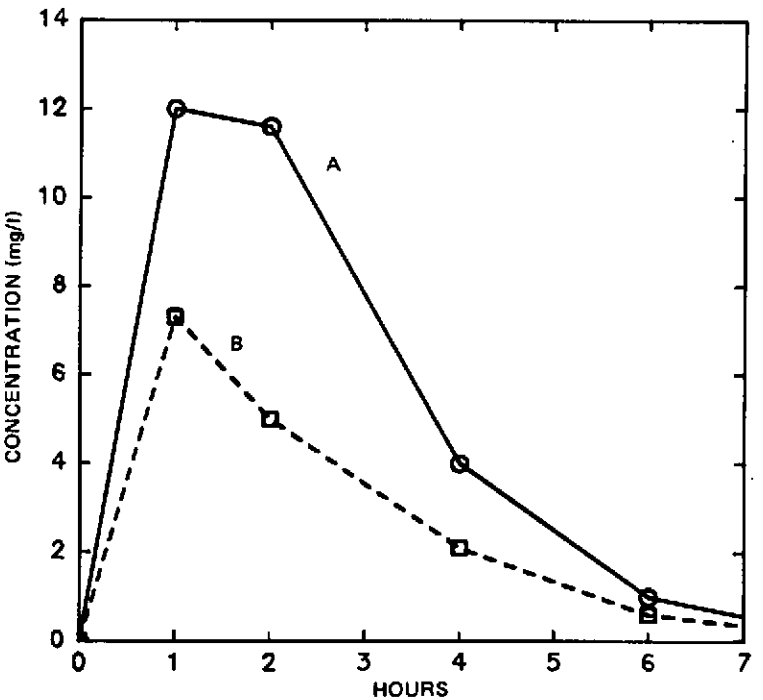


Fig. 11 Concentration of drug in serum following equal doses of dicloxacillin (curve A) and cloxacillin (curve B).

(d) The absorption rate is greater for cloxacillin but the bioavailable dose is larger for dicloxacillin.
(e) Dicloxacillin is absorbed to a much greater extent but the percentage increase cannot be assessed from the data.
(f) None of the above conclusions can be drawn.
Answers: 2 (d), 3 (a), 4 (c), 5 (e), 6 (f).

II. ANTIMICROBIAL AGENTS

A. Systemic Antibiotics

1. Goals for Derivative Formation

Some of the goals in improving the clinical effectiveness of known systemic antibiotic agents are the following:

1. Increasing the amount and/or rate of oral absorption
2. Increasing the distribution of the drug
3. Increasing the biological half-life
4. Decreasing the binding to food and/or plasma proteins
5. Decreasing the minimum inhibitory concentration (*MIC*)

Increased rates of oral absorption have been obtained by using salt forms of the parent drug such as potassium salts of penicillins or sodium salts of sulfonamides. Penicillin absorption has been improved by increasing gastric stability through molecular modification. Altering the oil–water partition coefficient through ester prodrug formation has resulted in the improved oral absorption of erythromycin, lincomycin, and ampicillin. Molecular modification of tetracyclines has resulted in increased tissue distribution.

The significance of tissue distribution of antimicrobial agents has been emphasized by several authors. Spitzy and Hitzenberger [2] stated that "bacteria germinate more frequently in the tissues than in blood," while Pratt [3] stated that "bacteria are more common in other tissues than blood." Several authors stress the importance of tissue concentrations [4–7]. Fabre et al. [7] stated that antibiotic effectiveness depends upon penetration into tissues, and particularly inflamed tissues. Thus, if binding values were equal, an antibiotic with greater tissue distribution would appear to reach the site of action with better efficiency.

The development of a β-lactamase-resistant penicillin has resulted in increased biological half-life and higher postdistribution body levels. Both penicillins and tetracyclines serve as examples where attempts to increase half-life and reduce binding to food and/or plasma proteins have been achieved.

2. Penicillins

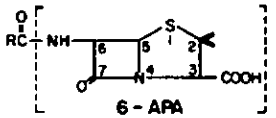
a. Structural Requirements and Ideal Properties. The penicillin molecule has two parts: the 6-aminopenicillanic acid nucleus and various side chains (R) attached through an amide linkage (Table 1). Rupture of the β-lactam ring at any point results in loss of activity [8,9]. The presence of the free carboxyl group and sulfur atom are also necessary [8–10]. The side chain can vary widely and appears to control the relative potency and the pharmacokinetics of various derivatives. An ideal penicillin would be stable toward acids and β-lactamases, well absorbed and distributed, less bound to plasma proteins, and have a broad spectrum and high antibacterial activity. In terms of pharmacokinetic parameters, it should possess a large f value, a long $t_{1/2}$, and a large V_Z.

b. Effect of Molecular Modification on Gastric Stability and Dissolution Rate. Schwartz and Buckwalter [11] have discussed the gastric stability of penicillins as a primary factor in determining bioavailability. Penicillin G and methicillin are very unstable in acid, having half-lives of 3.5 and 2.3 min, respectively, at pH 1.3, 35°C. On the other hand, ampicillin has a half-life of 660 min under the same conditions. The dramatic change in $t_{1/2}$ appears to be due to electronic effects of the protonated amine in acidic solution. In general, an electron-withdrawing group attached to the α-carbon inhibits cleavage of the β-lactam ring. The inhibition diminishes when the electron-withdrawing group is present elsewhere in the side chain.

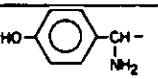
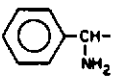
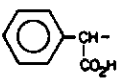
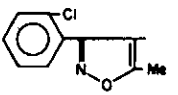
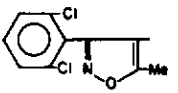
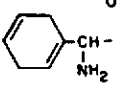
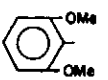
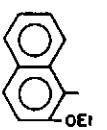
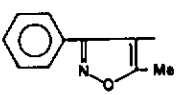
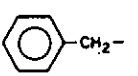
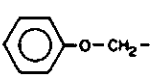
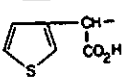
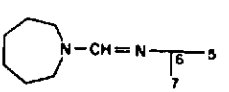
The dissolution rate and rate of oral absorption of penicillins have been increased by forming the potassium salt of the carboxylic acid, such as in potassium penicillin G and V. Highly insoluble salts are formed with amines such as procaine and *N,N'*-dibenzylethylenediamine, which dissolve very slowly. These salts are injected intramuscularly, and they form a slowly released depot of the drug, thus extending the duration of plasma levels. Prodrugs are discussed in a later section.

c. Pharmacokinetic Analysis of Structural Changes. Two misinterpretations are commonly found in comparisons of drug analogs. First, pharmacokinetic data are directly compared as evidence of relative bioavailability. This error is made by comparing their blood level time courses, the area under the

Table 1 Structures of Some Common Penicillins



6 - APA

Name	*R*
Amoxicillin	
Ampicillin	
Carbenicillin	
Cloxacillin	
Dicloxacillin	
Epicillin	
Methicillin	
Nafcillin	
Oxacillin	
Penicillin G	
Penicillin V	
Ticarcillin	
Mecillinam	

curve (*AUC*) values, or the relative amount of drug excreted intact in the urine. The second error is the failure to recognize the potential for changes in pharmacokinetic patterns as the amount of absorbed drug is increased. Nonlinear kinetics can result in incorrect quantitative comparisons although the rank order may remain the same.

Direct comparison of blood levels of chemical analogs fails to take into account that three pharmacokinetic consequences can result from molecular modification:

1. Changing the absorption
2. Changing the distribution
3. Changing the elimination

In order to assess minor differences in structurally related drugs, it is necessary to consider all three of these aspects. The assessment of the effect of molecular modification of the penicillin side chain may be illustrated by considering the isoxazolyl penicillins, which are closely related derivatives with varied pharmacokinetic behavior. They differ in structure only in the number of chlorine atoms present on the benzene ring in the side chain (see

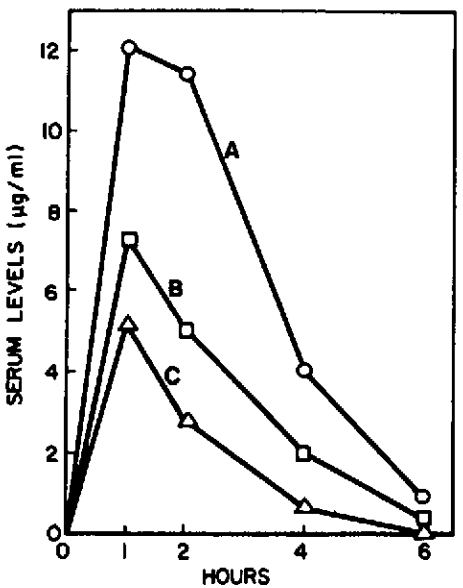


Fig. 12 Average serum levels following 500-mg oral doses of dicloxacillin (A), cloxacillin (B), and oxacillin (C). (Drawn from data in Ref. 12.)

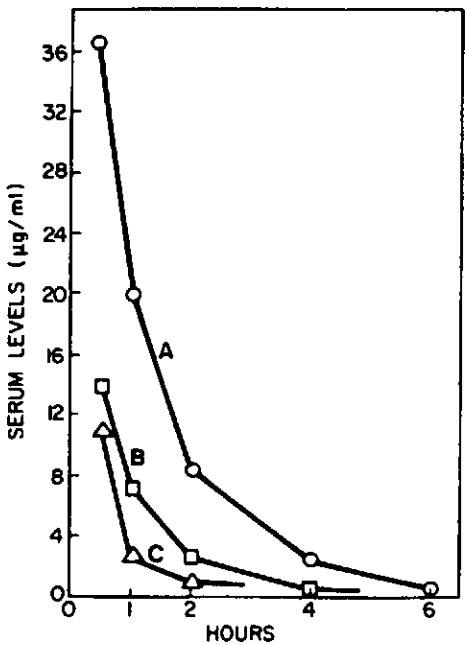


Fig. 13 Average serum levels following 500-mg I.V. doses of dicloxacillin (curve A), cloxacillin (curve B), and oxacillin (curve C). (Drawn from data in Ref. 12.)

Table 1). The time course for each of these analogs in blood has been studied by Modr and Dvoracek [12]. Figure 12 shows the comparison following the oral administration of 500 mg of dicloxacillin, cloxacillin, and oxacillin. The direct comparison of these curves would lead to the erroneous conclusion that absorption was increased by the addition of each chlorine atom. But if one examines these same three drugs given by rapid intravenous injection, it is apparent that the same relative order exists with the serum level of dicloxacillin dramatically higher than that of cloxacillin, which is somewhat higher than that of oxacillin (Fig. 13). Therefore it is obvious that absorption cannot be the sole cause for observed differences in the plasma time profiles. When the AUC values for the oral rpute were compared with those for the intravenous route according to equation

$$f = \text{fraction absorbed} = \frac{AUC_{\text{oral}}}{AUC_{iv}} \tag{5}$$

results showed that all three drugs were absorbed by approximately 74% ($\pm 6\%$). Thus oral absorption is not the primary reason for the drastic

difference in the blood level time profiles; therefore distribution and/or elimination must be considered.

Sample Problem 2

Rosenblatt et al. [13] compared dicloxacillin, cloxacillin, and oxacillin by constant intravenous infusion (250 mg/hr). The results are shown in Fig. 14. The authors reported $t_{1/2}$ values of 0.71 hr for dicloxacillin, 0.42 hr for cloxacillin, and 0.38 hr for oxacillin.

(a) Explain the differences in steady-state plasma levels.

Solution: The values for λ_Z and V_Z calculated from $\lambda_Z = 0.0693/t_{1/2}$ and $V_Z = k_0/\lambda_Z C^{ss}$ are given in Table 2.

It can be seen that cloxacillin and oxacillin have similar values for their elimination rate constants but differ in their volumes of distribution. The primary reason for higher blood levels of cloxacillin during the steady state,

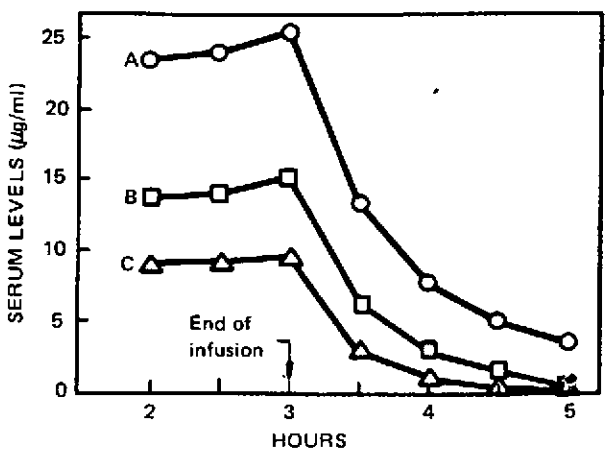


Fig. 14 Averate serum levels following intravenous infusions at 250 mg/hr for dicloxacillin (curve A), cloxacillin (curve B), and oxacillin (curve C). (Drawn from data in Ref. 13.)

Table 2 Steady-State Plasma Levels Obtained During Intravenous Infusion at 250 mg/hr

Penicillin	C^{ss} (mg/liter)	λ_Z (hr^{-1})	V_Z (liters)
Oxacillin	9.7	1.82	14
Cloxacillin	15.0	1.65	10
Dicloxacillin	25.0	0.98	10

as compared to oxacillin, is therefore the value for V_Z. Conversely, dicloxacillin and cloxacillin have similar distribution volumes. The primary difference in this case is that dicloxacillin has a smaller elimination rate constant than cloxacillin and therefore achieves higher blood levels. By comparing both the elimination rate constants and the volumes of distribution during steady state we can observe in more detail the effect of the chlorine atoms on these penicillins.

(b) Rosenblatt et al. [13] also showed that the urinary excretion of intact penicillin (as a percentage of the intravenous dose) was 56, 62, and 73% for oxacillin, cloxacillin, and dicloxacillin, respectively. Predict the steady-state C^{ss} values that would result from the 250-mg/hr infusion in the absence of renal function.
Solution: Assuming that $\lambda = \lambda_R + \lambda_{NR}$, then λ_{NR} (in hr^{-1}) = 0.44 (1.80) = 0.80 (oxacillin), λ_{NR} = 0.038(1.65) = 0.63 (cloxacillin), and λ_{NR} = 0.27(0.98) = 0.26 (dicloxacillin). The resulting C^{ss} values would be 22 mg/liter for oxacillin, 39 mg/liter for cloxacillin, and 93 mg/liter for dicloxacillin.

Sample Problem 3

The observed steady-state plasma levels and half-life values for various penicillins following intravenous infusions of 500 mg/hr are given in Table 3.

(a) What rank order would be predicted solely on the basis of elimination?
Solution: Based solely on elimination, the penicillin with the longest half-life would be predicted to have the highest plasma concentration. Therefore the rank order would be carbenicillin > ampicillin > dicloxacillin > penicillin G > nafcillin > cloxacillin > oxacillin.

Table 3 Observed Steady-State Plasma Concentrations for Various Penicillins Following Intravenous Infusions of 500 mg/hr

Penicillin	C^{ss} (mg/liter)	$t_{1/2}$ (hr)
Carbenicillin	73	1.00
Dicloxicillin	51	0.71
Cloxacillin	30	0.42
Ampicillin	29	0.98
Oxacillin	19	0.39
Nafcillin	18	0.55
Penicillin G	16	0.61

(b) Another parameter must be considered in order to predict the observed steady-state plasma levels correctly. Calculate the value of this parameter for each penicillin.
Solution: The value of V_Z must also be considered when predicting the observed steady-state plasma concentrations. The value of V_Z for each penicillin can be calculated using the equation

$$V_Z = \frac{R_0}{\lambda_Z C^{ss}} \tag{6}$$

The values of some selected pharmacokinetic parameters are given in Table 4. These parameters are the ones used most often to make comparisons between analogs. These parameters also can be used to calculate other parameters of interest, as discussed. Nauta and Mattie [18] examined dicloxacillin and cloxacillin at higher dosage levels and showed that increasing the dose of dicloxacillin gave higher AUC values and lower urinary recovery. For example, the AUC following a 1-g intravenous dose was 114 mg hr/liter, while it was 310 mg hr/liter after a 2-g intravenous dose. The fraction recovered in the urine was 0.726 for the 1-g dose and 0.592 for the 2-g dose. The fraction

Table 4 Values for Selected Pharmacokinetic Parameters for Several Penicillins[a]

Penicillin	$t_{1/2}$(hr)	V_Z (liters)	CL_R (ml/min)[b]
Amoxicillin	1.0	28.7	(332)[c]
Ampicillin	1.0, 0.8	22, 20, 25, 30	283, 210,[c] 312
Carbenicillin	1.0	10	86
Cloxacillin	0.42, 0.6	10, 11, 23	162, 287
Dicloxacillin	0.88, 0.71, 0.7	13, 10, 9.4, 16	88, 162, 130
Methicillin	0.43	22	350
Nafcillin	0.55	21	160[c]
Oxacillin	0.7, 0.38, 0.40	27, 14, 13, 15, 26	
Penicillin G	0.70, 0.5, 0.84–0.93[d], 0.6–0.99,[e] 0.54, 0.65, 0.78	26, 22, 37–47,[d] 35	433, 386, [c] 340–480,[d] 393
Penicillin V	0.53, 0.43, 0.52,	51, 54	393

[a]The values were taken from Ref. 12–17 or calculated from data contained therein.
[b]Renal clearance value.
[c]Total body clearance.
[d]Variation due to ambulatory versus bed-rest values.
[e]Variation due to the size of the dose.

absorbed orally, f, was calculated with the AUC values, Eq. (5), and from the ratio of drug excreted in the urine after oral administration relative to intravenous administration. The answers obviously do not agree. The value for f is 0.63 (urine) and 0.73 (AUC) for 1 g and 0.74 (urine) and 0.53 (AUC) for 2 g. In view of the dose effects, it is likely that the f values are incorrect. If the intravenous dose is doubled (from 1 to 2 g), the AUC increases by a factor of 2.7 (from 114 to 310). Since the observed oral AUC for 2 g is 0.53 (310) = 164 mg hr/liter, it can be seen to be larger than that expected from intravenous administration of 1 g, 114 mg hr/liter. Therefore the conclusion that $f = 0.53$ is doubtful.

This problem must be taken into account in comparisons of analogs. If one is to use the equations for linear kinetics, such as Eq. (1), it is necessary to demonstrate the validity of the assumptions. The values for the AUC (or for the fraction excreted in the urine) must be a linear function of the intravenous doses and the oral values for AUC (or for fraction excreted) must fall within the calibration range if simple comparisons are to be made. Many examples of failure to demonstrate linearity may be found in the literature. In some instances the fraction excreted in the urine is seen to decrease with increased dosage within the same article where comparisons of plasma AUC values are used directly for bioavailability. Apparent structural effects may be due to the misuse of pharmacokinetic equations.

Several investigators have reported direct comparisons of amoxicillin plasma level data to those of ampicillin after oral administration. The AUC values for amoxicillin were in excess of 50% more than those for ampicillin. This would indicate an increase in bioavailability of roughly $f_{amox} > 1.5 f_{amp}$. However, it is fortuitous that this estimate is so close to the value found using Eq. (5). The reason for this agreement lies in the fact that the clearance values for the drugs are very similar. The effect of this coincidence can be appreciated by examining the equations for AUC:

$$AUC_{iv} = \int_0^\infty C\,dt = \frac{C_1}{\lambda_1} + \frac{C_Z}{\lambda_Z} \tag{7}$$

where C is the plasma concentration associated with the equation

$$C = C_1 e^{-\lambda_1 t} + C_Z e^{-\lambda_Z t} \tag{8}$$

The AUC value associated with this equation is related to the total body clearance value by

$$AUC_{iv} = \frac{D}{CL} \tag{9}$$

A similar equation can be derived for oral administration, wherein

$$AUC_{\text{oral}} = \frac{fD}{CL} \tag{10}$$

Thus the area under the plasma concentration curve is proportional to fD and inversely related to clearance.

Therefore two drugs with equal values for CL could be compared using Eq. (1) even though their disposition kinetics are dissimilar. Substitution from Eq. (10) into Eq. (1) provides

$$\text{relative bioavailability} = \left(\frac{f_1 D}{CL}\right)_1 \div \left(\frac{f_2 D}{CL}\right)_2 \tag{11}$$

which reduces to

$$\text{relative bioavailability} = \frac{f_1}{f_2} \tag{12}$$

when the dose and clearance values are held constant. This explains why the comparison of amoxicillin and ampicillin AUC values provided good estimates for their relative bioavailability. Although their disposition kinetics are quite different, their total body clearance values are similar, with ampicillin reported at 335 ml/min [19] and amoxicillin at 332 ml/min as calculated from the reported mean weight, 74.5 kg, and the CL value of 0.264 liter/kg hr [20].

Ampicillin, epicillin, and amoxicillin have similar antibacterial spectra and MIC values. The nearly complete oral absorption of amoxicillin is generally regarded as advantageous relative to ampicillin. A triple crossover study of 500-mg oral doses of amoxicillin, ampicillin, and epicillin demonstrated a significant sequence effect on ampicillin peak levels, which were 6.4 μg/ml if epicillin was taken the previous week and 2.7 μg/ml when ampicillin was first [21]. Total 24-hr urinary recoveries and apparent $t_{1/2}$ estimates were amoxicillin, 57%, 1 hr; ampicillin, 50%, 1.3 hr; and epicillin, 23%, 1.4 hr. Mean renal clearance values CL_R were similar being 278, 268, and 208 ml/min for amoxicillin, ampicillin, and epicillin, respectively. Reported comparisons of serum levels may not be appropriate to the epicillin case,

since its lower urinary recovery and roughly equal CL_R imply that its total body clearance CL may not be similar [Eqs. (6) and (7)].

Ticarcillin, like carbenicillin, is not orally absorbed as one would expect with the additional carboxylic acid substituent. (For a discussion of the oral prodrug carbenicillin indanyl sodium, see Sec. III.) Ticarcillin has been shown to be two to four times as active against *Pseudomonas* strains and has been compared kinetically to carbenicillin. Following intravenous administration to healthy adults, the CL values were identical in the steady-state determinations (134 ml/min) while the 5-min infusion resulted in 154 ml/min for ticarcillin and 132 ml/min for carbenicillin. Half-lives and CL_R values were similar. Urinary recovery (24 hr) and percent binding in serum were 86 and 65% for ticarcillin and 99 and 50% for carbenicillin. The similarity in average serum time profiles following 5 min, 30 min, and 2.75 hr (with loading dose) is remarkable [22].

Mecillinam is also limited to parenteral use, showing a maximum urinary excretion of 5% following oral administration [23]. Its prodrug, pivmecillinam, is discussed later.

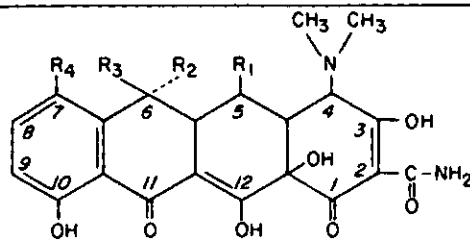
3. Tetracyclines

a. Structural Requirements and Ideal Properties. Since the isolation in 1947 of the first known member of the tetracycline family, many semisynthetic derivatives have been prepared and their properties extensively studied. Typical structures are shown in Table 5.

In general, molecular modifications of the basic tetracycline structure have reflected attempts to improve absorption, decrease binding to plasma proteins, improve distribution to the tissues, and decrease minimum inhibitory concentrations. These attempts are examples of research directed toward preparation of an ideal tetracycline. The ideal tetracycline is one which would be rapidly and completely absorbed, only slightly bound to plasma protein, distributed throughout the proper tissues, of long duration, and of high intrinsic antimicrobial activity. In terms of pharmacokinetic parameters, an ideal tetracycline might therefore have a large V_Z and long $t_{1/2}$.

b. Absorption and Distribution. The tetracycline molecule has pK_a values of 3.3, 7.7, and 9.5 [24] associated with the tricarbonylmethane, phenyldiketone, and dimethylamino groups, respectively, and thus will be ionized over the entire pH range that a molecule would encounter after oral administration. This fact, coupled with the tendency of tetracyclines to form complexes with substances in the stomach, implies that their oral absorption might be slow and incomplete. Oral administration of tetracycline HCl with 200 ml

Table 5 Structures of Various Tetracyclines



Name	R_1	R_2	R_3	R_4
Tetracycline	H	OH	CH_3	H
Chlortetracycline	H	OH	CH_3	Cl
Demethylchlortetracycline	H	OH	H	Cl
Oxytetracycline	OH	OH	CH_3	H
Methacycline	OH	$=CH_2$	—	H
Minocycline	H	H	H	$-N(CH_3)_2$
Doxycycline	OH	H	CH_3	H

of water containing 2.0 g of $NaHCO_3$ resulted in a 50% decrease in absorption relative to that in the absence of $NaHCO_3$ [25]. When the tetracycline was dissolved prior to administration, no differences were observed.

There is some indication that lipid solubility plays a major role in the distribution of tetracyclines and that serum protein binding may be less of a factor. Tetracyclines permeate both extra- and intracellular fluid, and calculated values of V_Z in humans exceed the volume of total body water. In a comparison of four tetracyclines in dogs, no linear relationships could be found between partition coefficient (PC) or log PC and any of the nine concentration gradients determined between tissues or body fluids and blood [26]. An inverse relationship was observed between lipid solubility and both urinary excretion and absolute renal extraction.

c. Binding to Dairy Products and Various Divalent or Trivalent Cations. It became apparent soon after the introduction of chlortetracycline in 1948 that concomitant administration of aluminum hydroxide gel resulted in decreased biological activity for the antibiotic. Decreased gastrointestinal absorption due to complexation with divalent and trivalent cations, such as calcium, magnesium, aluminum, and so on, indicates that the coadministration of milk or antacids in order to diminish the potential side effects of anorexia, nausea, and vomiting must be avoided. The data of Scheiner and Altemeir [27] demonstrate the dramatic sensitivity of dimethylchlortetracycline to complexation with heavy metals. Relative to equal doses in the fasting

state, only 13% oral absorption takes place when the antibiotic is administered with 8 oz of milk, and 22% with 20 ml of aluminum hydroxide gel. Thus the development of tetracyclines with a lesser tendency toward complexation became a clinically significant research goal. However, since the sites considered most likely to be the site of complexation [28–30] are also necessary for antimicrobial activity, any direct molecular modification of these sites in order to reduce complexation is precluded. Modifications can be made only in positions such as 5–9, where the substituents may exert either electronic or steric effects on binding.

Some measure of success has been obtained with newer tetracyclines. Doxycycline oral absorption is markedly less sensitive to food and homogenized milk. This is illustrated in Sample Problem 4.

Sample Problem 4

Rosenblatt et al. [31] studied the effect of diet on the oral bioavailability of doxycycline and demethylchlortetracycline. Some of the results are illustrated in Fig. 15. The reported maximum plasma value (or peak height) and the time at which it occurred (t_{max}) for each of these eight curves is given in Table 6.

(a) Summarize the effects of (1) food, (2) skim milk, and (3) whole milk and food on the bioavailability of these two antibiotics and include a rough estimate on the percent reduction of oral absorption in each case.
Solution: The peak height may be used for a rough estimate provided that the k_a is relatively constant as indicated by the constancy of the t_{max} values (see Chap. 5). The t_{max} values for demethylchlortetracycline are constant at 4 hr. The estimates are therefore (1) 108/1.98 = 54%

Table 6 Values[a] for Peak Plasma Levels (C_{max}) and Their Times of Occurrence (t_{max}) Following Single Oral Doses of 300 mg of Demethylchlortetracycline or 100 mg of Doxycycline to Healthy Volunteers in a Crossover Study

	Fasting		Nondairy food		Skim milk		Whole milk and food	
Drug	C_{max} (μg/ml)	t_{max} (hr)	C_{max} (μg/ml)	t_{max} (hr)	C_{max} (μg/ml)	t_{max} (hr)	C_{max} (μg/ml)	t_{max} (hr)
Doxycycline	1.79	2	1.76	4	1.45	2	1.18	4
Demethylchlortetracycline	1.98	4	1.08	4	0.59	4	0.71	4

[a]From Ref. 31.

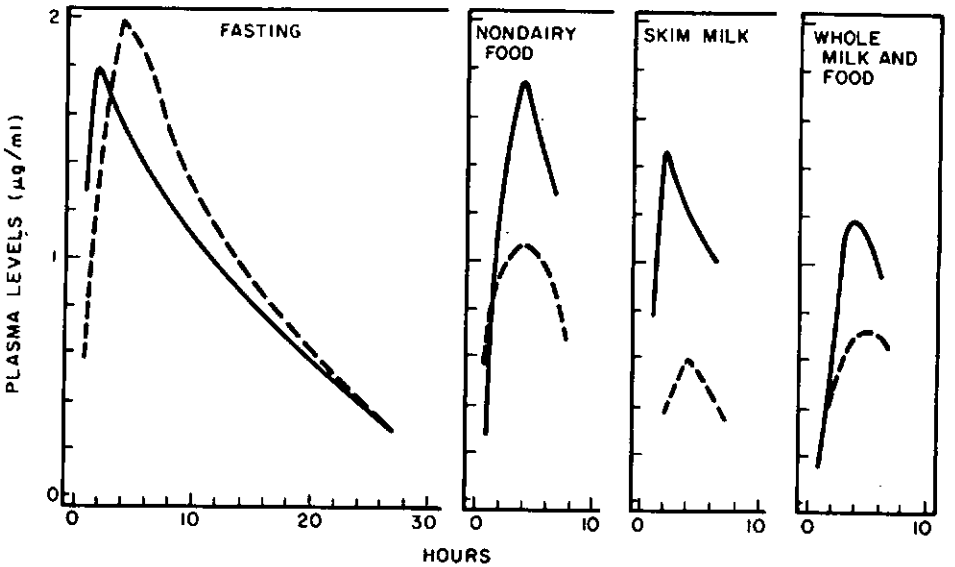


Fig. 15 The data of Rosenblatt et al. [31] have been used to construct these curves representing the time course in blood following single oral doses of 100 mg of doxycycline (solid line) or 300 mg of demethylchlortetracycline (dashed line).

(or 46% reduction), (2) 59/1.98 = 30% (70% reduction), and (3) 71/1.98 = 36% (64% reduction).

The t_{max} values for doxycycline are given as 2 and 4 hr. Therefore (1) food appears to have delayed absorption but provided the same peak value; (2) for skim milk 145/1.79 = 81% (19% reduction); and (3) for food and whole milk, again absorption appears to be delayed. Since food and food with whole milk both have a t_{max} value of 4 hr, the effect of whole milk can be estimated from 118/1.75 = 67% (33% reduction).

(b) How do these results compare with those calculated from the data of Scheiner and Altemeir [27]?
Solution: See Practice Problem 10 in Chap. 5.

(c) Figure 15 shows fairly similar time profiles for the two tetracyclines in the fasting state for doses of 300 and 100 mg. What conclusions can be made regarding the oral absorption of demethylchlortetracycline relative to doxycycline?
Solution: None; additional information is required because these are two different chemical entities.

(d) Product information supplied with doxycycline hyclate for injection indicates that 40% of the dose is excreted by the kidney within 72 hr after administration to individuals with normal renal function. Rosenblatt et al. [31] recovered 45.4 mg during 72 hr following oral ingestion of 100 mg by normal volunteers (creatinine clearance roughly 130 ml/min). What percent of the orally administered dose was absorbed in the study of Rosenblatt et al.?
Solution: It was apparently 100% absorbed, since urinary recovery of 45.4 mg exceeds the value calculated based on the 40% figure (or 40% of 100 mg = 40 mg).

Thus doxycycline absorption has been shown to be less sensitive to skim milk, food, and homogenized milk when compared to demethylchlortetracycline. However, ingestion of antacids containing divalent or trivalent cations resulted in negligible absorption for both drugs. In another study food was shown to reduce tetracycline plasma levels by 50% and doxycycline levels by 20% when compared to the fasting state [32]. The formulations provided blood levels similar to those of solutions for both drugs when compared in the fasting state.

d. Effect of Binding on Distribution and Elimination. A number of excellent reviews which discuss the binding of antibiotics [33] and other agents [34,35] have been published. In spite of widespread attention, the clinical significance of tissue and protein binding in relation to therapeutic efficacy remains unclear for many antibiotics. Readily reversible binding by serum or tissues may serve as a pool of active drug to prolong therapeutic levels [5]. For example, the antibacterial activity of three long-acting sulfonamides may be independent of their protein binding, but this binding may determine their duration [36]. Research indicates that penicillins bound to protein lose their activity. It has been stated [5] that absorption, distribution, and inactivation may be more important than binding in determining penicillin therapy, presumably because of reversibility. Other data [37] emphasize the decrease in availability of penicillins due to inactivation by protein binding. The *MIC* values of eight penicillins in human serum are the same as in broth when corrected for the bound fraction. Methicillin was least active where there was no binding. In serum, where it was bound to a lesser extent than other penicillins, it required the lowest total concentration of drug to kill 99% of the inoculum and acted more rapidly than the other penicillins.

Some of the confusion regarding the significance of the percent of protein binding is due to the lack of appreciation for the meaning of this value. Literature values for the percent of protein bound generally refer to in vitro

values determined in blood; they do not refer to the percent of total drug bound in the body. It is therefore possible to have a drug with a high percent bound which results in a large free fraction of total body content. Without this consideration it would seem that tissue distribution would always decrease with increasing serum binding as a result of the inability of the potein-bound form to diffuse. Data exist [15,37] which do not support this hypothesis in the case of penicillins. Similar values of V_Z were obtained for four penicillins whose percent binding in plasma varied from 22 to 94% [15]. The fraction of the dose distributed throughout the body was similar for all five penicillins studied [15].

Reversibility is another key factor. It has been noted and documented by authors of seemingly opposing views that reversible binding can serve to prolong drug action [5,37], whereas irreversible binding removes the drug from the biophase. The clinical significance of drug binding is probably dependent upon the strength of binding, and it has been calculated that protein binding will affect drug distribution only if the binding constant exceeds 10^4 [38].

The renal clearance of tetracyclines decreases with increasing protein binding [7]. Urinary clearance is greater for oxytetracycline (73% free) and least for doxycycline (18% free). Chlortetracycline and minocycline are exceptions, since they are excreted mainly in bile. The $t_{1/2}$ appears to be related to protein binding only for those drugs that are primarily cleared by glomerular filtration. A drug that is excreted by tubular secretion does not appear to be influenced by protein binding. Penicillins that have high clearance values (reflecting tubular secretion) have half-lives which are relatively insensitive to protein binding. Data suggest that tetracyclines are primarily excreted by glomerular filtration rather than by tubular secretion, although the lack of precise serum protein binding measurements makes it difficult to calculate the individual contributions. Tetracyclines tend to accumulate during renal insufficiency, with chlortetracycline, minocycline, and doxycycline being exceptions. Fabre et al. [7] reported that doxycycline clearance decreased during renal insufficiency without a concurrent increase in hepatic excretion despite a relatively constant $t_{1/2}$ in normal and anuric patients. Studies [39] of the extent of metabolic degradation of doxycycline in humans and dogs indicate that more than 90% of the intact drug was recovered from the urine and feces in both species. Thus the extraction of intact doxycycline in feces appeared to compensate for decreased renal clearance in uremic patients. The urinary recovery of minocycline was only 6–9% following intravenous injections [40]. The lack of sensitivity to renal failure was apparent when the biological $t_{1/2}$ of minocycline did not vary statistically in patients with CL_{CR} values of 3.9, 26.2, and 93.9 ml/min [41].

e. Tetracycline Half-Lives. The extension of biological half-life to increase duration and decrease the frequency of administration has been a major research goal. Chlortetracycline first appeared in 1948 with a reported $t_{1/2}$ of 5.6 hr and a recommended dosage interval of 6 hr. Oxytetracycline and tetracycline were introduced soon after with reported half-lives of 8.2 and 9.2 hr, respectively. In 1958 demethylchlortetracycline ($t_{1/2}$, 11.8 hr) and methacycline were introduced as useful on a 12-hr regimen. Doxycycline ($t_{1/2}$, 18–22 hr) marked a new stage in this evolution, with the advent of once-a-day therapy, and minocycline is roughly equal in $t_{1/2}$ (Table 7).

It has been suggested that the increased $t_{1/2}$ values following multiple dosing might be due to a failure to obtain an accurate assessment of the terminal slope following a single oral dose [43]. Inclusion of part of the absorption or distribution phase could tend to make the $t_{1/2}$ appear smaller with a single dose, whereas this problem is decreased during the steady state, where plasma concentrations are higher.

4. Aminoglycoside Antibiotics

a. Introduction and Ideal Properties. The first aminoglycoside antibiotic to be used clinically was streptomycin, which was isolated in 1944. This group has since gained in clinical significance. Gentamicin was commercially introduced in the United States in 1969, tobramycin in 1975, and most recently amikacin. These additions show a broad spectrum of activity against both gram-positive and gram-negative pathogens, with some being very active against *Pseudomonas aeruginosa*. Hospital-acquired ("nosocomial") infections

Table 7 Apparent Biological $t_{1/2}$ Values for Tetracyclines[a]

Antibiotic	Single dose	Multiple doses	Steady state
Tetracycline	6.3, 5.6–9.3, 8.2, 8.0, 7.2, 7.3	10,[b] 9.5, 11	10.8
Demethylchlortetracycline	9.0, 6.3–13.3, 12.6, 10, 11, 12.7	14.7,[b] 14.7, 15	13.6
Methacycline	7.0, 14.3, 8.5, 9.6, 7.7	11.0,[b] 10.5, 11.5	14.3
Minocycline	16	19	—
Doxycycline	8.3, 11.7, 15, 15.1	14.5,[b] 22	16.6

[a]From Ref. 42, except for minocycline [41].
[b]Values determined on days 4 and 5 of a multiple-dose regimen.

of resistant strains of Enterobacteriacea often respond to aminoglycoside therapy. Potent bactericidal action against gram-negative bacilli has resulted in the widespread use of aminoglycosides in the treatment of coliform bacteria. In the treatment of infections which are resistant to antibiotics in general, the aminoglycosides may often be regarded as life saving [44].

Aminoglycoside antibiotics are not sufficiently absorbed to be used orally for systemic infections. They are thus administered parenterally, which, together with their ototoxicity and nephrotoxicity, somewhat limits their use. In spite of these disadvantages, aminoglycosides have gained a prominent role in combating serious infections caused by organisms that are resistant to other antibiotics.

Gentamicin respresents the reference standard against which improvement in aminoglycoside chemotherapy is measured. As clinical usage has become more prevalent, bacterial resistance has developed. The major research goals in this area have been to overcome the development of resistance and to decrease toxicity. While accumulation in tissues and tissue fluids has been implicated in ototoxicity and nephrotoxicity, it has become clear that intrinsic toxicity also differs among aminoglycosides. Netilmicin appears to be less oto- and nephrotoxic than gentamicin or tobramycin in spite of its high tissue accumulation [45].

Aminoglycosides are excreted intact in the urine. They are neither metabolized nor eliminated in the bile. Renal excretion is attributed to glomerular filtration with variable tubular reabsorption [46–52]. The elimination of aminoglycosides is significantly altered by renal failure, making the adjustment of dosage necessary in order to decrease the known potential for toxicity. There are numerous dosage nomograms based on glomerular filtration rate as estimated by creatinine renal clearance values. These provide a basis for a trial dose which can then be used to individualize the patient's dosage regimen.

b. Tissue Accumulation and Serum Pharmacokinetics. The time course for an aminoglycoside concentration in plasma following an intravenous dose is probably best described by a triexponential equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_Z e^{-\lambda_Z t} \tag{13}$$

During the initial phase ($t_{1/2} < 30$ min), rapid distribution to highly perfused organs and extracellular water occurs. The λ_2 phase, which is most readily apparent, has a half-life of 2–3 hr. During the time period corresponding to this phase a large fraction of the administered dose can be recovered intact in the urine. The third, very slow λ_Z phase therefore occurs at very low plasma concentrations. This prolonged terminal phase has a highly variable

Table 8 Comparison of the Predominant Log-Linear Slope for the Decay of Aminoglycoside Serum Levels During the Period 1–10 hr Following Intravenous Administration

Drug	Number of compartments	Reference symbol	CL_{CR} (ml/min)	Percent recovered in urine/time (hr)	Rate constant (hr^{-1})	Half-life (hr)	Reference
Amikacin	1	$t_{0.5}$	—	—	—	~3	62
Amikacin	1	$t_{0.5}$	120	94%/24 hr	0.31	2.3	63
Gentamicin	2	α	50–75	Complete[a]	0.21	3.3	49
Gentamicin	1	$t_{0.5}$	Normal	85%/24 hr	0.35[b]	2.0[b]	52
Gentamicin	2	β	Normal	69%/24 hr	0.43[c]	1.6[c]	61
Gentamicin	1	$t_{0.5}$	Normal	—	0.27	2.6	64
Kanamycin	1	$t_{0.5}$	119	94%/24 hr	0.34	2.1	63
Kanamycin	1	$t_{0.5}$	>90	—	0.31	2.3	65
Kanamycin	1	k_D	Normal	81%/24 hr	0.3[b]	2.4[b]	66

Netilmicin	1	$t_{0.5}$	Normal	87%/24 hr	~0.37	~1.9	52
Netilmicin	1	$t_{0.5}$	Normal	45%/6 hr	~0.3	~2.2	67
Netilmicin	2	β	Normal	90%/24 hr	0.31	2.3	68
Netilmicin	1	$t_{0.5}$	>90	complete/8 hr	0.22	3.2	69
Netilmicin	2	β	Normal	45%/24 hr	0.21	3.3	70
Netilmicin	2	β	>92	76%/24 hr	0.29	2.4	51
Netilmicin	3	β	Normal	~75%/24 hr	0.35	2.0	57
Sisomicin	3	β	Normal	~75%/24 hr	0.36	1.9	
Sisomicin	2	β	Normal	40%/24 hr	0.27	2.6	72
Sisomicin	2	β	Normal	55%/8 hr	0.43[d]	1.6[d]	71
Sisomicin	2	β	Normal	77%/24 hr	0.34[c]	2.0[c]	61
Tobramycin	2	α	76–150	Complete[a]	0.25	2.8	50
Tobramycin	2	β	Normal	74%/24 hr	0.35[c]	2.0[c]	61

[a]Studies carried out over a sufficiently long period to recover all of the dose.
[b]Based on terminal slope following intramuscular administration.
[c]Taken from terminal slopes of figures in Ref. 61; $t_{0.5}$ values calculated from reported microconstants: gentamicin, 2.3 hr; sisomicin, 6.1 hr; and tobramycin, 4.8 hr.
[d]Calculated from reported k_{12}, k_{21}, and k_2 values; reported β value is 0.87 hr^{-1}.

half-life of approximately 1–20 days and is thought to be due to slow release of a small fraction of the dose from tissue-binding sites [53–61]. Because of the great difference in rates of these phases and the low terminal concentrations, aminoglycosides have been described by mono-, bi-, and triexponential equations. The equation chosen may be attributed to the sampling period used in the study. Monoexponential disposition was observed in those studies which sampled between 1 and 24 hr. Biexponential disposition was found with early sampling continuing for 24 hr or sampling from 2 hr to 1 month. Table 8 shows that good agreement exists for the λ_2 half-life, as evidenced by comparison of the reported slopes for the common time period of 1–10 hr.

The significance of each exponential to steady-state plasma concentrations may be estimated in the following way. Since the average steady-state concentration C_{av}^{ss} is defined as AUC/τ, the percentage contribution of each phase to the total AUC will provide its contribution to C_{av}^{ss}. For triexponential disposition the total AUC may be calculated from

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} + \frac{C_Z}{\lambda_Z} \tag{14}$$

The percentage contributions for each term, based on reported values for sisomicin and netilmicin, are (approximately) 18, 72, and 11%, respectively. The λ_2 phase is thus the predominant term in defining aminoglycoside plasma concentrations.

The biological half-lives of aminoglycoside antibiotics are commonly reported as 2–3 hr in patients with normal renal function [44]. These values ae based on plasma concentration data for a 24-hr period following a single dose. Although the aminoglycosides are neither metabolized nor excreted in the bile, urinary recovery in 24-hr collections is incomplete even with normal renal function. Serum and urine levels are detectable for weeks after termination of drug administration [53–56]. The reported extended terminal phase $t_{1/2}$ values are 37 hr for netilmicin [57], 17 hr for sisomicin [57], 1–28 days for gentamicin [52,53,56], and 1.5–18 days for tobramycin [50,58].

Studies undertaken specifically to examine the "washout" period following gentamicin and tobramycin multiple-dose therapy [49,50,55] determined serum levels and urinary excretion for as long as 20 days. A radioimmunoassay (RIA), reportedly sensitive to 0.03 μg/ml [55], was used to supplement the usual microbiological assay. The λ_Z phase appeared more than 24 hr after the final dose, when serum levels were typically below 0.5 μg/ml. The apparent λ_Z half-lives were varied, with a maximum value of 29 days for 47 patients on gentamicin [55] and 18 days for tobramycin [50].

Both tobramycin [50] and gentamicin [49,55] doses were completely recovered in the urine when patients were available for long-term studies. Postmortem tissue analyses were performed as follows: gentamicin, six patients [55] and one patient [49]; tobramycin, four patients [50], where the antibiotic was recovered from several tissues and fluids. Edwards et al. [59] had previously measured high kidney concentrations of gentamicin or amikacin in 9 out of 10 patients who died during aminoglycoside therapy. It thus appears that the λ_Z phase observed during washout periods is due to release from tissues. This is further evidenced by the observation that the λ_Z values were not related to renal function, whereas the λ_2 slopes are correlated with creatinine clearance values.

The terminal phase showed extreme intersubject variability, as might be expected for release from aminoglycoside bound to tissue. The reported averages (and ranges) are gentamicin, 112 hr (27–693 hr) in 47 patients [55], and tobramycin 146 hr (33–428 hr) in 35 patients [50]. This slow release would not be expected to be dependent on renal function, since diffusion from the tissues rather than glomerular filtration has become rate determining. Approximately 1 day after withdrawal of the aminoglycoside was required before the slower phase was observed. By this time 80–90% of the dose was recovered in the urine and the serum levels were extremely low [49,50,60,61], representing only a small fraction of the maximum value.

The λ_Z' phase contributes very little to the serum levels during the normal course of therapy, which is 7–10 days. The accumulation due to this phase may be within the normal assay and/or biological variability. The resulting tissue accumulation may be clinically significant and should be cause for some concern, especially in long-term therapy. An increase in C_{min} values after 24 hr of repetitive-dose therapy has been cited as an early warning for predisposition to nephrotoxicity. Most clinical estimates employ monoexponential disposition as a simplifying approximation. Accumulation due to the third phase (λ_Z) will be exceedingly slow and will therefore increase in significance as the treatment period is extended. The following problem is designed to illustrate how incorrectly assuming that the data are monoexponential will lead to minimal errors in predicting the plasma levels following the final dose ($N = 21$) in a 7-day treatment.

Sample Problem 5

The data in Table 9 represent serum gentamicin levels for a patient receiving a single 80-mg intravenous dose.

(a) If the patient receives 80 mg every 8 hr for 7 days, how will the final plasma profile compare to that observed in Table 2?

Solution: A semilog plot of the data appears linear with negative slope of 0.170 hr^{-1} and intercept 5 μg/ml. At $\tau = 8$ hr the value for the

Table 9 Concentration of Gentamicin in Serum Following the Intravenous Injection of 80 mg[a]

Time (hr)	Concentration (μg/ml)	Time (hr)	Concentration (μg/ml)
1	4.21	4	2.53
2	3.55	6	1.80
3	3.00	8	1.28

[a]Data are based on the pharmacokinetic constants for patient 1 in Ref. 49.

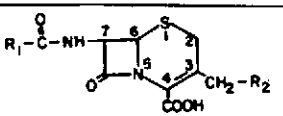
fraction remaining (F) is 0.256 and $X = (1-F^N)/(1-F) = 1.344$, where $N = 21$. Thus $C_{max(21)} = 1.344\ (5) = 6.72$ μg/ml and $C_{min(21)} = 1.344\ (1.28) = 1.72$ μg/ml, where $C_{max} = 5$ μg/ml and $C_{min} = 1.28$ μg/ml following dose 1.

(b) The same patient was treated for 7 days and a sensitive radioimmunoassay was employed to determine serum levels for an additional 9 days. The curve was found to be biphasic, with the λ_Z phase appearing roughly 24 hr after the last dose. This was not observed in solving part (a), since the final data point was 8 hr. The data given in Table 2 may be described as $C = C_1e^{-\lambda_1 t} + C_Ze^{-\lambda_Z t}$, where C is the plasma concentration (μg/ml) and the reported values for this patient are $C_1 = 4.97$ μg/ml, $\lambda_1 = 0.172\ hr^{-1}$, $C_Z = 0.03$ μg/ml, and $\lambda_Z = 0.008\ hr^{-1}$ [49]. Calculate the $C_{max(21)}$ and $C_{min(21)}$ values and compare them to those predicted in part (a), where monoexponential disposition was assumed. *Solution*: At $\tau = 8$ hr the fraction of the λ_1 curve remaining is $e^{-\lambda_1\tau} = e^{-1.376} = 0.253 = F_1$. For the λ_Z curve $F_Z = e^{-\lambda_Z\tau}\ e^{-0.064} = 0.938$. Thus $X_1 = (1-F_1^N)/(1-F_1) = 1.338$ and $X_Z = (1-F_Z^N)/(1-F_Z) = 0.739/0.0620 = 11.92$. The maximum will be $C_{max(21)} = C_1X_1 + C_ZX_Z = 4.97(1.338) + 0.03(11.92) = 7.00$ μg/ml. The 6.72 μg/ml estimated in part (a) is 4% less. The minimum value will be $C_{min(21)} = C_1F_1X_1 + C_ZF_ZX_Z = 4.97(0.253)(1.338) + 0.03(0.938)(11.92) = 2.02$ μg/ml, making the estimate in part (a) 15% less. It is easily appreciated how these small errors are readily obscured by patient and assay variability in clinical practice.

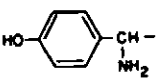
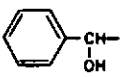
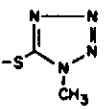
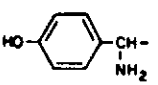
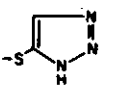
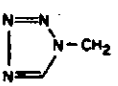
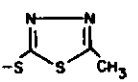
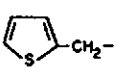
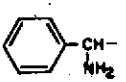
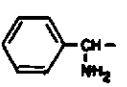
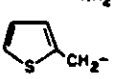
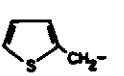
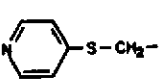
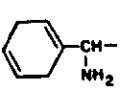
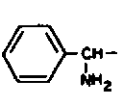
5. Cephalosporins

a. Structural Requirements and Ideal Properties. Cephalosporin research began as early as 1945, but not until 1964 did these antibiotics gain clinical recognition. Three distinct chemical structures were originally isolated from the

Table 10 Structures of Some Common Cephalosporins



7-ACA: $R_1 = H$, $R_2 = -OCOCH_3$

Name	R_1	R_2
Cefadroxil		-H
Cefamandole		
Cefatrizine		
Cefazolin		
Cefoxitin		$-OCONH_2$ 
Cephalexin		-H
Cephaloglycin		$-OCOCH_3$
Cephaloridine		
Cephalothin		$-OCOCH_3$
Cephapirin		$OCOCH_3$
Cephraidine		-H
Cefaclor		

Cephalosporium fungus. One of the first was cephalosporin C, which, although active, was never clinically useful. The hydrolysis of cephalosporin C provided the initial source for 7-aminocephalosporanic acid (7-ACA; shown in Table 10), which served as the nucleus for the production of semisynthetics such as cephalothin, cephaloridine, and cephaloglycine. Thousands of semisynthetic analogs have since been reported involving alteration of the C7 amide substituent or displacement of the acetoxy function at the C3 methylene position. Some common examples are shown in Table 10. The nomenclature has been simplified by assigning the name cephem to the bicyclic nucleus including the β-lactam ring oxygen. When the double bond occurs between C2 and C3, it is called 2-cephen or Δ^2-cephem and these compounds are inactive.

Much of the cephalosporin chemistry and structural requirements for antimicrobial activity resembles that of the penicillins and has been thoroughly reviewed [6,73]. An intact β-lactam ring is essential for activity [8] and derivative formation of the free carboxyl group results in complete loss or significant decrease in activity [8]. Although cephalosporins are more acid stable than penicillins and are resistant to penicillin β-lactmase, they share a similar history with regard to developmental problems. Oral absorption of early analogs was not sufficient for systemic use, thus limiting several to parenteral administration, including cefazolin, cephaloridine, cephalothin, and cephapirin. A brief summary of the outstanding features of the available cephalosporins was published in 1976 [74]. As for the penicillins, the storage of aqueous solutions is a problem owing to chemical degradation. Cephaloridine and cefazolin are considered the least painful on intramuscular injection. Although cephalosporins are penicillinase resistant, their widespread use has resulted in cephalosporin-resistant bacteria which do produce β-lactam-hydrolyzing enzymes. Partial cross-allergenicity with penicillins appears to occur. Cephalosporins should be administered cautiously to penicillin-sensitive patients. There have been instances in which patients react to both drug classes, including anaphylaxis following parenteral use. The goals of molecular modification of cephalosporins have included the following:

1. Increased acid stability
2. Improved oral absorption
3. Increased activity against resistant strains (particularly those producing destructive enzymes)
4. Decreased pain on injection
5. Decreased allergenicity
6. Prolonged biological half-life

Considerable success has been realized and selected examples are reviewed in the following section.

b. Pharmacokinetics. An extensive and excellent review of cephalosporin pharmacokinetics together with some reworking of literature data appeared in 1975 [75]. Kinetic studies for all of the analogs in Table 10 except cefamandole, cefatrizine, and cefaclor were included. Some of the significant pharmacokinetic information from several sources is summarized in Table 11. A few of the derivatives have achieved some increase in the biological half-life values: cephanone (2.8 hr; withdrawn from clinical trial), cefazolin (1.7 hr), and cephacetrile (1.3 hr). The rest fall roughly in the range of 30 min to 1 hr, as seen for the penicillins (Table 4). As for the penicillins, this short half-life precludes significant accumulation during the usual dosage regimen with normal kidney function. Several cephalosporins are eliminated by renal tubular secretion as evidenced by high renal clearance values (Table 11: cephradine, 367 ml/min; cephalothin, 274 ml/min; cephalexin, 252 ml/min; cephacetrile, 235 ml/min), whereas cephanone (47 ml/min) and cefazolin (64 ml/min) appear to undergo tubular reabsorption. In general, the cephalosporins are excreted intact in the urine, with little, if any, evidence for metabolism. Two notable exceptions are cephapirin (43%) [76] and cephalothin (33%)[75], both of which are rapidly deacetylated. Since urinary excretion is the primary route for cephalosporin elimination, it may become necessary to adjust the dosage regimen during renal failure. Among cephalosporins in current use, the prescribing information for cefazolin, cephalothin, and cephaloridine includes dosage adjustments based on creatinine clearance values, whereas that for cephradine provides guidelines when $CL_{CR} <$ 20 ml/min. Cephaloglycin, cephalexin, and cephapirin dosage instructions suggest caution in the presence of severe renal impairment. The use of nomograms for the adjustment of cefaclor dosage in renal failure was shown to make little difference, since the dosage interval (τ = 6 hr) is roughly three times the maximum half-life values of 2–3 hr observed in anephric patients ($CL_{CR} \approx 0$ ml/min) [77]. For most cephalosporins the short half-life in normal renal function (~1 hr) relative to the long dose interval ($\tau \approx$ 6–12 hr) obviates the need for adjustment in moderate renal failure.

Cephalexin and cephradine appear to be completely bioavailable by the oral route and are employed clinically as oral dosage forms. Cefaclor, cephaloglycin, cefadroxil, and cefatrizine are also administered orally. When examined against cephalexin, 70% of the oral cefaclor dose was recovered in the urine, as compared to 96% for cephalexin [78]. The 12-hour urinary recovery of cefatrizine was 35% orally and 45% intramuscularly as compared with 68 and 74% for cephalexin [79]. The total cumulative urinary excretion values of cefadroxil and cephalexin were statistically equivalent with a mean of 88%, whereas cephradine recovery was complete following oral doses of

Table 11 Average Reported Values for Biological Half-Lives, Percent Excreted Unchanged in Urine, Renal Clearance Values, and Oral Absorption for Cephalosporins in Adults with Normal Renal Function

Cephalosporin	Terminal $t_{1/2}$ (hr)	Percent dose recovered in urine	CL_R (ml/min)	Oral absorption	References
Cefaclor[a]	0.67–1.0; 0.58	50–70 in 8 hr; 70	—	Good[b]	78, 82
Cefadroxil[a]	1.3	88, 93	—	~Complete[b]	80, 89
Cefamandole	0.86; 0.87; 1.7; 0.57; 0.5	47–61, 80, ~100	234, 257	Poor	83–85, 90, 91
Cefatrizine	1.1	45 (i.m.)	—	~78% (?)[c]	79
Cefazolin	1.9; 1.8; 1.4	89; 100; 76	64	Poor	75, 86, 88
Cefonicid	4.5	99	—	Poor	84
Cefoperazone	2.0	20–30	—	Poor	84
Ceforanide	2.9	78–95	—	Poor	84
Cefotaxime	1.0	50–60	—	Poor	84
Cefoxitin	0.67	90–100	—	Poor	75
Ceftizoxime	1.7	99	—	Poor	84
Cefuroxime	1.3	90	—	Poor	84
Cephacetrile	1.3; 1.3	88; 60–100	235	Poor	75
Cephalexin	0.80[a]; 0.76; 0.61; 0.94	96[a] 96; 87; 80–100	252	~Complete	75, 78, 87, 88
Cephaloglycin	—	18–25	—	~27%[c]	75
Cephaloridine	0.6–1.5; 1.4; 1.1	85	125	Poor	75, 87, 88
Cephalothin	0.56; 0.63; 0.47; 0.65; 0.34	52, 64, 38	274	Poor	75, 83, 86–88
Cephapirin	0.71, 0.72, 0.36	41, 48	—	Poor	75, 76, 83
Cephradine	0.76; 0.61[a]	79–100	367	~Complete	75, 80
Moxalactam	1.9	60–90	—	Poor	84

[a]Following oral administration.
[b]Assuming that the percent excreted in urine following oral administration represents a minimum value for absorption.
[c]Estimated by a comparison of urinary excretion following oral administration to that following intramuscular administration.

250–500 mg in fasting subjects [80]. These studies, as well as many others, compare the blood level time profiles of the test cephalosporins to a reference standard such as that of cephalexin. As discussed previously, the direct comparison of blood levels for different chemical entities can lead to erroneous conclusions. Measurements of cephaloglycin blood levels have been complicated by the formation of the active deacetylated metabolite. A comparison of peak heights after oral and intramuscular administration concluded only 25% oral absorption [75]. As with many newer antibiotics, the necessary intravenous studies to establish a linear relationship between the AUC and the dose for the assessment of absolute bioavailability, Eq. (5), are often lacking.

c. Clinical Use. An in vitro study compared four oral cephalosporins (cefaclor, cefatrizine, cephalexin, and cephradine) to penicillin V, ampicillin, carbenicillin, oxacillin, clindamycin, and tetracycline on more than 30 organisms in 342 respiratory, skin, soft tissue, and urinary isolates [81]. Against *Staphylococcus aureus* and streptococci (other than enterococci) cefatrizine was the most active cephalosporin, but was less active than penicillin V, ampicillin, oxacillin, and clindamycin. It was also the most active cephalosporin against anaerobes (other than *Bacteroides fragilis*), where it was similar to oxacillin but less active than penicillin V, ampicillin, and clindamycin, which was the most active and the only antibiotic active against *B. fragilis*. Tetracycline was more active than cefaclor, which was similar in activity to ampicillin and greater in activity than other cephalosporins, penicillin V, and clindamycin against *Hemophilus influenzae*. The rank order for percentages of strains susceptible to cephalosporins among *Escherichia coli, Klebsiella* (where cephalosporins were more active than penicillin V, ampicillin, carbenicillin, and tetracycline), and *Proteus mirabilis* was cefaclor > cefatrizine > cephalexin > cephradine. These in vitro studies provide information for potential effectiveness without the many complications which accompany clinical use. They do not predict optimum therapy, which provides adequate drug concentrations at the site of the pathogen without producing serious side effects.

The 1975 review [75] provided several critical recommendations regarding cephalosporin use. Noting that cephalosporin popularity stems mainly from its broad spectrum, high safety, and low frequency of cross-sensitivity with penicillins, it was stated that other antibiotics are generally preferable once the bacteria are identified. This conclusion was based on either greater activity or reduced likelihood of suprainfection. Cephalosporins were thought to have the advantage against *Klebsiella* based on activity in the case of penicillins and toxicity in the case of aminoglycosides. That review recommends

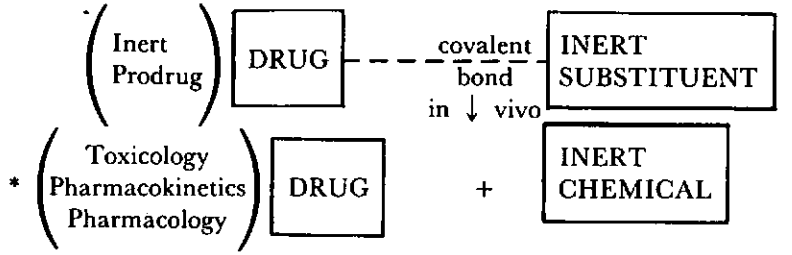
penicillin G for group A streptococcus, non-penicillinase-producing staphylococci, "pneumococcus," and anaerobic streptococci; ampicillin for *Hemophilus*; and oxacillin for penicillinase-producing *S. aureus*. Of the cephalosporins reviewed, cefazolin was recommended for parenteral use and cephaloridine was criticized owing to significant nephrotoxicity. Cephalexin and cephradine were considered similar in oral use and superior to cephaloglycin, which is not absorbed as well. Less expensive oral antibiotics were considered better choices, except for either the follow-up of initial cephalosporin therapy or urinary tract infections where patients are penicillin hypersensitive or organisms are resistant to other antibiotics. Cefaclor, cefamandole, and cefadroxil were not included in the review.

d. Third-Generation Cephalosporins. Cephalosporins for parenteral use may be classified according to their activity against gram-negative organisms. They are categorized as first, second, or third generation, in increasing order of activity. Those with the highest activity, third-generation cephalosporins, include cefoperazone, cefotaxime, ceftizoxime, and moxalactam. Moxalactam is unique in that it has an oxygen atom in place of the sulfur in position 1 in the 7-ACA nucleus. None of these are absorbed sufficiently for oral use; they are limited to intramuscular and intravenous administration. Cefoperazone has an average half-life of 2 hr and is generally given every 12 hr. It is primarily excreted in the bile and therefore does not result in extraordinary accumulation during renal failure. It can, however, show two- to fourfold increases in half-life during biliary obstruction or hepatic disease. The other three drugs are excreted primarily by the kidneys, and lower doses are indicated during impaired renal function. Ceftizoxime and moxalactam are normally dosed at 8- to 12-hr intervals, whereas cefotaxime has the shortest half-life and is administered at 6- to 8-hr intervals. Probenecid extends the duration of cefotaxime and ceftizoxime by competing for tubular secretion. Moxalactam is not affected, since its tubular secretion is insignificant.

III. PHARMACOKINETICS OF PRODRUGS

A. Introduction

There is no universally accepted definition for a prodrug. Within this text it will be defined as an inactive drug precurser formed by covalently bonding a drug to an inert chemical by a linkage which may be broken (by any mechanism, but usually in vivo) to provide the drug (Scheme II).



* (exception: irreversible site delivery)

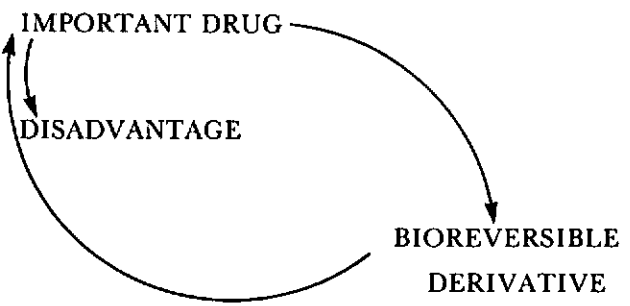
Scheme II

This definition differs from some others, which have done the following:

1. included poorly soluble salts or complexes
2. not ruled out prodrug activity
3. limited the reversal mechanism to metabolism
4. included formation of active metabolites from compounds thought to be drugs.

Other terms used interchangeably with prodrugs include *reversible* or *bio-reversible derivatives* and *latentiated drugs*. While definitions are arbitrary, and to some degree irrelevant, it is important to realize that prodrugs are assumed to be inactive throughout this discussion.

A prodrug candidate is typically a clinically significant drug having a major disadvantage which may be circumvented through the formation of a reversible derivative. The application is thus limited to those molecules which can form reversible derivatives wherein the derivatives will improve upon the drug problem yet give rise to the original drug for its ultimate therapeutic effect (Scheme III).



Scheme III

B. Goals

1. Formulation and Pharmacokinetic Problems

The parent-drug disadvantages which may be overcome by the prodrug approach can be classified as pharmaceutical or pharmacokinetic problems. Typical examples are as follows:

1. Pharmaceutical
   a. Unpleasant taste
   b. Pain on injection
   c. Poor solubility
   d. Instability
   e. Slow dissolution rate
2. Pharmacokinetic
   a. Poor bioavailability
   b. Short duration
   c. High first-pass metabolism
   d. Toxicity or side effects
   e. Nonspecificity

Some examples of prodrugs and the reasons for chemical modification of the parent drugs are given in Table 12.

2. Conversion Site

One goal that is common to all prodrugs is that the prodrug should be quantitatively converted to drug after the specific problem has been overcome (Scheme IV).

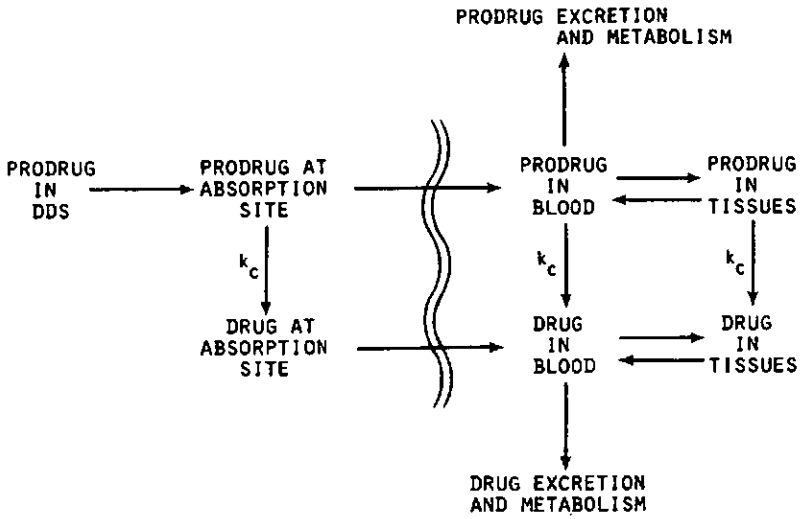
$$\overbrace{\left[\begin{array}{c}\text{AFTER COMPLETION} \\ \text{OF TASK}\end{array}\right] \xrightarrow[\text{conversion}]{\text{Complete}} [\text{DRUG}]}^{\text{COMMON GOAL}}$$

Scheme IV

The site for this conversion will therefore depend upon the specific goal for the prodrug. Scheme V is a generalized representation of the rate processes which can occur following the administration of a prodrug in a dosage form.

Table 12 Examples of Prodrugs and the Reasons for Their Development

Parent drug	Prodrug	Goal of modification
Amoxicillin	Sarmoxicillin	Increase distribution
Ampicillin	Bacampicillin, Pivampicillin, Talampicillin	Bioavailability
Ampicillin	Hetacillin	Stability
N-t-Butylarterenol	Bitolterol	Delivery to lungs
Carbenicillin	Carfecillin, carindacillin	Bioavailability
Chloramphenicol	Palmitate ester	Improve taste
Chloramphenicol	Succinate ester	Water soluble
Clindamycin	Palmitate ester	Improve taste
Clindamycin	2'-Phosphate ester	Decrease pain on injection
Cytarabine	Cytarabine 5'-adamantoate	Extend duration
	Cyclocytidine	Extend duration
Cefamandole	Nafate ester	Stability
Corticosteroids	21-Succinate esters, 21-phosphate esters	Water soluble
Cycloserine	Pentizidone	Stability
Diethylstilbesterol	Fosfestrol	Decrease gastric distress
Dinoprostone	Phenyl esters	Stability
Dopamine	L-Dopa	Delivery to brain
Epinephrine	Dipivefrin	Corneal penetration
Erythromycin	Estolate, ethylsuccinate	Gastric stability
Estradiol	Cypionate	Extend duration
Etilefrine	Stearate ester	Bioavailability
Fluphenazine	Decanoate, Enanthate	Long-acting depot injections
Formaldehyde	Methenamine	Urinary tract delivery
Mecillinam	Bacmecillinam Pivmecillinam	Bioavailability
Metronidazole	Amino acid esters	Water soluble
Naloxone	Mono- and disulfate esters	Extend duration
Salicylic acid	Salsalate	Gastrointestinal tolerance and bioavailability
Sulfisoxazole	Acetyl ester	Improve taste
Testosterone	Propionate	Extend duration
Thiamine	Tetrahydrofurfuryl disulfide	Extend duration; delivery to red blood cells
Triamcinolone	Acetonide	Increased topical activity
Triamcinolone	Diacetate	Improve taste

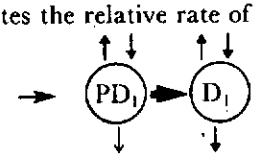


Scheme V

Conversion may occur at the site of administration, within the blood, and at some extravascular site. In some instances conversion may begin within the formulation itself. For each prodrug goal one conversion site and rate are ideal. The resultant pharmacokinetic requirements and their assessment are discussed in the following sections.

C. Bioavailability

A prodrug designed to improve drug bioavailability may achieve this goal by having a larger prodrug bioavailable fraction f_{pd} than that of the original drug (f_d) and/or a faster absorption rate constant k_a'. Ideally, the prodrug should be absorbed quickly and, having arrived in the blood, undergo even more rapid conversion to drug. The significant rate processes in Scheme V can be isolated in the simplified illustration shown in Scheme VI. The relative size of the arrows indicates the relative rate of the process.



Scheme VI

The prodrug should be completely absorbed intact, since conversion to drug at the site can revert to the original bioavailability problem associated with

the drug. The subsequent conversion to drug in blood should be rapid, while elimination and metabolism of prodrug should be minimized, since prodrug lost to non-drug-forming processes will reduce the bioavailability of drug. The distribution of intact prodrug throughout the remainder of the body is also counterproductive. If prodrug is immediately converted to drug in the blood, then the pharmacology, toxicology, and disposition kinetics are those of the original drug. If the prodrug is distributed throughout the body, then these properties must be assessed for the prodrug itself. Also, the possibility of new biological effects resulting from delivery of drug to new regions of the body must be then considered.

In summary, prodrug absorption should be complete and rapid and its conversion in blood instantaneous if the goal is to improve drug bioavailability. Examples of the resultant time courses are shown in Fig. 16.

1. Evaluation

Since the molecular weight of a prodrug will be greater than that of the drug, the dose and concentration units should be expressed on a molar basis rather than on a mass basis. An alternative approach to normalizing the data is to express dose and concentration in terms of parent-drug equivalents.

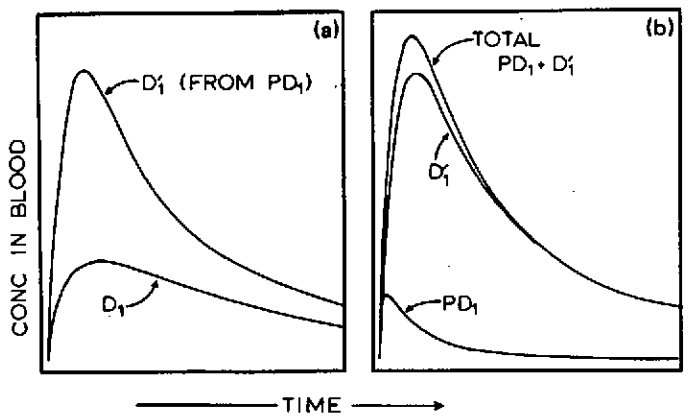


Fig. 16 (a) Molar concentration time course for drug in blood following the extravascular administration of either drug itself (curve D_1) or an equimolar dose of its prodrug (curve D_1'), which is described by Scheme V, where $f' = 2f$, $k_a' = k_a$, and the prodrug conversion constant is 12 times greater than its absorption constant. (b) As shown in Scheme V, the blood contains both prodrug (PD_1) and drug (D_1') following the administration of prodrug. Because conversion in blood is relatively fast, the curve for the total ($PD_1 + D_1'$) is only slightly higher than the D_1' curve and prodrug time course is minimal.

Unlike the evaluation of analogs, prodrug evaluation is based upon the parent drug itself. In this respect, a prodrug is a drug delivery system, albeit the basis is chemistry rather than formulation. As long as the time course for a drug comprises the data, the performance of an extravascular dose of a prodrug can be evaluated in the same manner as that of a DDS, The bioavailability of drug from prodrug, relative to that from an equivalent dose of parent drug, can be evaluated using the following form of Eq. (1):

$$\text{relative bioavailability} = \frac{AUC_{pd}}{AUC} \tag{15}$$

In this case both AUC values refer to the area under the concentration time course for the drug itself, but the numerator represents that observed following administration of the prodrug. The route of administration, the formulation, and the dose must be the same for both drug and prodrug if the influence of prodrug is to be assessed. Comparisons of C_{max} and t_{max} values, the shapes of the curves, the apparent absorption rate constants, and the durations can all be made directly from the concentration time course data for parent drug. In summary, any data interpretation method that is valid for drug delivery systems is also valid for drug concentration data following prodrug administration.

In contrast to formulations, the bioavailability of drug from administered prodrug must be evaluated regardless of the route of prodrug administration. This is because even an intravenous dose of prodrug may provide a bioavailable fraction of drug that is less than unity if some prodrug is lost to competing non-drug-producing processes. The bioavailable fraction of drug following prodrug administration (f_{pd}) may be calculated from

$$f_{pd} = \frac{AUC_{pd}}{AUC_{iv}} \tag{16}$$

where both AUC values are dose-adjusted areas under the concentration time course for drug itself following prodrug administration by any route (numerator) and intravenous administration of the parent drug. The assumption of linear pharmacokinetics is implicit.

Chloramphenicol sodium succinate is a water-soluble prodrug for intravenous administration. It provides one example wherein the bioavailability of drug is incomplete following intravenous administration of the prodrug. In one study of 12 patients aged 2.5 months to 20 years the mean bioavailable fraction of chloramphenicol following intravenous administration of the succinate prodrug was 0.69 (SD = 0.13) [92]. Another study using eight adult

patients reported that 26.0% ($SD = 7.0$) of the dose was recovered as unhydrolyzed prodrug in the urine [93]. A third study in 18 children reported that 36% of the prodrug dose was collected in the urine and higher relative bioavailability was observed using the oral palmitate prodrug than from intravenous succinate [94]. These observations emphasize the need to evaluate the bioavailability of drug even when the prodrug is administered intravenously. In the case of chloramphenicol succinate the conversion to chloramphenicol is generally incomplete and intact prodrug is excreted in the urine.

2. Assay Specificity

The evaluation of prodrug performance requires an assay that is specific for the drug. The most common problem has been that of the conversion or partial conversion of prodrug to drug during the storage and assay procedures following blood sampling. Since the conversion of prodrug is an expected result of the experiment, this additional conversion may go undetected. Since intact prodrug and drug will each have a unique concentration time course, data which include drug and some of the prodrug can result in misinterpretation of the results. For example, the limits for the bioavailable fraction of drug from a dose of prodrug are $0 \leq f_{pd} \leq 1$. Circulating prodrug and a nonspecific assay provided higher AUC values following the intravenous administration of the prodrug hetacillin than those following intravenous administration of the parent drug ampicillin. The result was later attributed to conversion during the microbiological assay procedure [19,95,96].

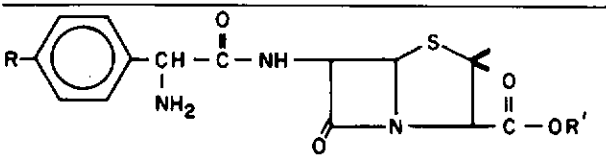
The degree to which results may be influenced by this problem will depend upon the conversion rate during the assay and the amount of intact prodrug in the original sample. Those prodrugs which convert rapidly on arrival in the blood should not present a problem. Prodrugs which circulate intact are, by contrast, amenable to postsampling conversion. These two cases are therefore discussed separately.

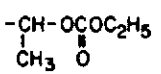
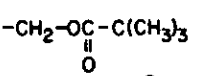
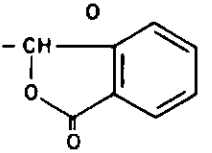
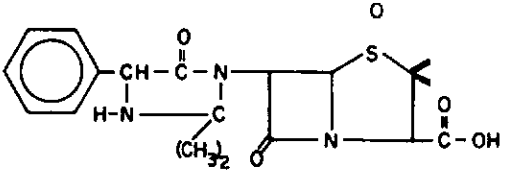
a. Rapid Prodrug Conversion. The degree of error in an assay which converts some fraction of prodrug to drug will be related to the prodrug available for postsampling conversion. If intact prodrug does not exist in the sampled blood, then no conversion can occur during the assay. Figure 16b illustrates the concentration time course for prodrug, drug, and the total using an example wherein the conversion rate constant in blood is 12 times the prodrug absorption rate constant. If all of the prodrug were converted during the assay, the degree of error would be reflected by comparing the curve for total ($PD_1 + D_1'$) to that for drug alone (D_1'). This error, while small, has been intentionally kept large enough to make a visible difference in Fig. 16b.

If the ratio of the conversion to the absorption rate were increased to 20 or more, the curves would appear identical. This illustrates the fact that prodrugs which rapidly convert to drugs in vivo are least likely to present problems due to postsampling conversion.

Of the ampicillin prodrugs in Table 13, only hetacillin has been found to circulate intact (Fig. 17). However, its conversion is so rapid ($t_{1/2}$ for conversion is 11 min [19]) that the observed difference between a nonspecific assay and a specific assay [96] is not dramatic. This small difference did cause early investigators to erroneously conclude that parenteral doses of hetacillin provided greater *AUC* values than ampicillin itself. Simple alkyl and aryl esters of penicillins are somewhat resistant to hydrolysis by human blood or tissues. Conversely, rapid conversion with little or no evidence for circulating intact prodrug has been reported for pivampicillin [97,98],

Table 13 Structures for Ampicillin, Its Analog Amoxicillin, and Some of Its Prodrugs



	R	R′
Ampicillin	-H	-H
Amoxicillin	-OH	-H
Bacampicillin	-H	
Pivampicillin	-H	
Talampicillin	-H	
Hetacillin		

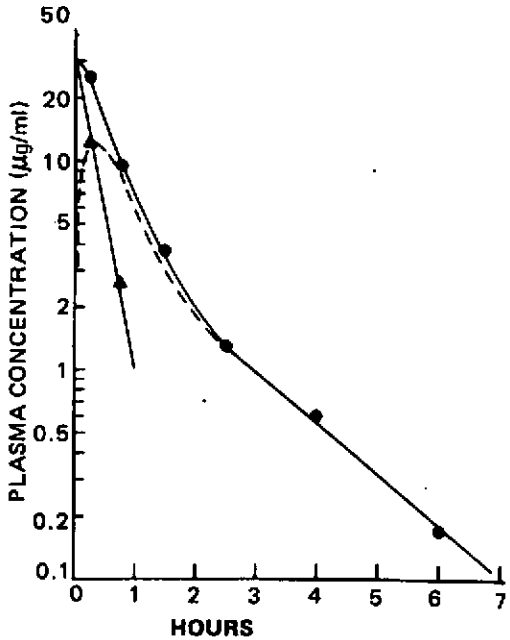


Fig. 17 Data of Jusko and Lewis [19] were used to construct these semilog plots showing the time course for hetacillin (▲), ampicillin (---), and the sum of both (●) following the intravenous administration of the prodrug hetacillin.

bacampicillin [99–101], and talampicillin [102–104] (Table 13). Each of these has achieved increased oral absorption followed by rapid bioreversal.

Ehrnebo et al. [105] have reported the f_{pd} for ampicillin from bacampicillin to be 0.83 and that from pivampicillin to be 0.89 with nearly complete conversion in vivo. Loo et al. [97] have shown that the percent of ampicillin absorbed from the oral administration of pivampicillin is roughly 82%, as opposed to 49 and 53%, respectively, for the trihydrate and anhydrous forms of ampicillin. While the conversion rate was not reported in that study, pivampicillin has been shown to have a half-life of 5 min in whole blood [106]. The suggestion that formaldehyde release during pivampicillin reversal may cause side effects prompted the synthesis of lactonyl esters such as talampicillin [103,107]. Mean ampicillin plasma levels during the first 6 hr following talampicillin oral administration in humans were approximately six times higher at 20 min and equivalent at 4 hr when compared with ampicillin itself [103]. Another study reported that the AUC values in humans roughly doubled following talampicillin administration as compared to ampicillin and the C_{max} value (at $t_{max} \approx$ 1 hr for both) was 2.6 times higher [104].

Hydrolysis in human blood was complete in less than 2 min in both studies [103,104]. This rapid conversion in vitro is qualitative proof that circulating prodrug is unlikely. However, the half-life obtained in whole blood cannot be extrapolated to the half-life for conversion in clinical use. There are many factors which prevent the use of in vitro data to quantitatively predict in vivo conversion rates. Two opposing influences are a first-pass effect, which would be expected to increase the rate of conversion, and distribution of prodrug into nonmetabolizing tissues, which would decrease the rate of conversion.

Bacampicillin was reported to be 40% better absorbed than ampicillin based on a comparison of both the *AUC* values and urinary excretion data following oral administration [100]. In another study relative *AUC* values following the oral administration of equimolar doses were reported to be 1 for ampicillin, 1.5 for bacampicillin, and 1.5 for pivampicillin [108]. Bergan [109] has reported the f_{pd} value for oral bacampicillin as 0.87, with no detectable prodrug in serum.

When a prodrug is rapidly converted to drug, the pharmacokinetic parameters estimated from plasma data should agreed with those for the drug itself. If agreement is lacking, this may be evidence for circulating prodrug and lack of assay specificity. This had led to some confusion in the comparison of prodrugs. Bacampicillin has shown increased ampicillin levels in several organs and in tissue cage transudates [100]. This has been attributed to higher levels of ampicillin in plasma, since no bacampicillin has been found in the circulation. This interpretation is most likely correct in spite of the fact that organ- (or transudate) to-plasma ratios were not the same following the administration of drug and drug from administered prodrug. It is important to realize that rapidly converting prodrugs can only alter the input function of the drug and not the pharmacokinetic parameters associated with equivalent plasma levels of the drug itself. This was confirmed by Tan and Salstrom [110], who showed that while ampicillin serum levels were higher from oral bacampicillin than from ampicillin itself, the time-dependent ratios of interstitial fluid concentration to serum concentration were equal.

Mecillinam (see Table 1) is poorly absorbed when administered orally. The prodrug pivmecillinam (pivaloylmethyl ester) appears to show satisfactory oral absorption in human volunteers [23] and in both young volunteers and elderly patients [111]. The mecillinam *AUC* values following the oral administration of 400 mg of pivmecillinam HCl in solutions, capsules, or tablets were roughly 45% of the *AUC* values following either intravenous or intramuscular administration of 400 mg of mecillinam. The *AUC* values following oral doses of 200, 400, and 800 mg of prodrug were proportional to dose, but the percent of the dose excreted in the urine as mecillinam decreased with increasing dose (51, 46, and 32%). A 400-mg oral dose of

pivmecillinam HCl tablets provided mecillinam AUC values equal to that of a 200-mg intramuscular injection of mecillinam, but urinary recovery was only 39% of the dose for the tablets as compared to 58% for the injection [23]. Correcting for the increased molecular weight of the prodrug as compared to the drug would increase all of the above reported values, which were expressed as a percent of the dose of pivmecillinam. There is some evidence that the serum half-life of mecillinam, following 400-mg oral doses of pivmecillinam, was increased in patients over 65 years of age with normal renal function ($t_{1/2}$ = 4 hr) compared with that of young (<30 years) volunteers ($t_{1/2}$ = 0.9 hr) [111]. The prodrug bacmecillinam has been found to increase the mecillinam AUC values relative to the oral administration of drug itself [112].

b. Prodrug Conversion Rates Which Result in Circulating Prodrug. When conversion is not sufficiently rapid to prevent the circulation of intact prodrug, misinterpretation can result when assays are not sufficiently specific. Figure 18 is an illustration of a prodrug whose absorption rate constant is 2.7 times

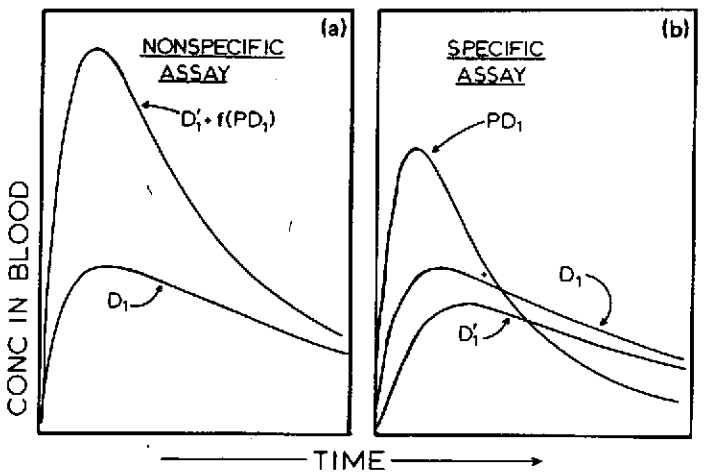


Fig. 18 (a) The molar concentration time course for drug in blood following the extravascular administration of drug itself (curve D_1) and data using a nonspecific assay following an equimolar dose of its prodrug. The assay measures both the drug from the prodrug (D_1') and a fraction of the circulating prodrug (PD_1). Without a knowledge of this error, it would appear that the prodrug has greatly increased bioavailability. (b) The prodrug data in (a) have been analyzed by an assay that can differentiate drug (D_1') from prodrug (PD_1). Administration of prodrug has reduced the bioavailability of the drug (D_1') relative to an equimolar dose of the drug itself (D_1).

that of the original drug but whose bioavailability is only 0.8 times that of the original drug. Contrary to the case of Fig. 16, the conversion of prodrug to drug in the plasma is slower than its absorption. In this case the conversion constant has been set at 75% of the value of the absorption constant. Figure 18a illustrates a comparison of plasma levels where the assay method is not specific. Here the analytical method detects not only free drug but also some fraction of the prodrug. This case can occur with antibiotic prodrugs using microbiological assays. For example, an ester prodrug might hydrolyze in the culture media and liberate free drug during the assay. Figure 18a might be misinterpreted as an example of a dramatic increase of bioavailability of drug by use of the prodrug. The same data are examined using a specific assay in Fig. 18b. It can now be seen that the actual effect of the prodrug is to decrease the bioavailability of the drug. Thus the prodrug has interfered with delivery of the drug rather than improved it.

One example illustrating this problem of assay nonspecificity in the presence of circulating prodrug is that of orally administered erythromycin estolate. While these data do not show a reversal of the order of magnitude in Fig. 18, they do show the importance of assay specificity when intact prodrug is present in plasma. The dashed line in Fig. 19 compares erythromycin estolate plasma levels to those obtained from the salt erythromycin stearate [113]. This assay was not completely specific for free drug alone. Some of the estolate apparently hydrolyzed during the culture workup. The solid line shows the same set of data where a specific assay was designed to differentiate between total erythromycin as estolate and as free drug [114]. It can be seen that the free drug levels from the estolate is still higher than the free drug levels from the stearate. However, the degree of difference is not nearly as pronounced as would appear from the original curve (dashed line).

Welling et al. [115] have reported higher erythromycin levels from the stearate salt than from the estolate prodrug. DiSanto et al. [116] found no difference in erythromycin plasma concentrations on repetitive dosing of either the estolate prodrug or enteric-coated erythromycin base. While the estolate is absorbed to a greater extent, its partial conversion to drug has been estimated at approximately 16–27% [116].

The prodrug erythromycin ethylsuccinate (EES) is also well absorbed but incompletely converted. Like the estolate, EES absorption is not reduced by coadministration with food, which has been observed for both erythromycin free base and stearate. However, total erythromycin plasma levels (drug plus prodrug) following EES oral administration have been found to contain only 30% erythromycin [117], which is slightly higher than that reported for the estolate [116]. A comparison between 250 mg of erythromycin base in enteric-coated encapsulated pellets and 400 mg of erythromycin as the EES prodrug both given every 6 hr to 24 subjects showed

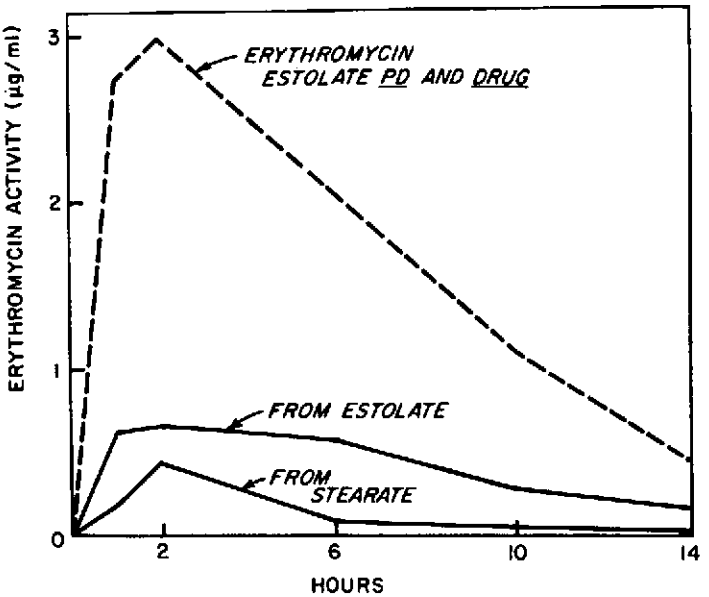


Fig. 19 Erythromycin activity in blood as a function of time following the oral administration of either the estolate prodrug or the stearate salt. The assay used for the dashed line was nonspecific with regard to drug and prodrug. The solid lines represent an assay that was specific for erythromycin. Data are averages for 10 nonfasting human subjects after the fifth dose (250 mg) as given in Ref. 113.

strikingly higher drug levels from the pellets. The free-base levels from the pellets produced C_{max} levels 5–22 times higher and AUC values 5–28 times higher than those from EES [117]. The mean plasma concentrations for the prodrug EES and for erythromycin from EES and from the pellets following the first and ninth doses are shown in Fig. 20. (See Practice Problem 9, Chap. 5.)

D. Prolonged Duration

In theory, the duration of drug in plasma may be increased by controlling the rate of either of the following two precursor steps (Scheme VII):

1. The rate of input (or absorption) of prodrug from the site of administration to the blood
2. The subsequent conversion of prodrug to drug in the blood

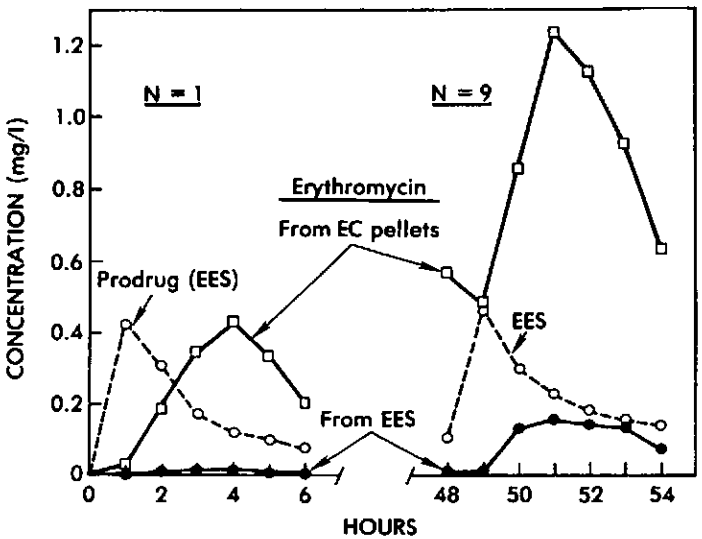
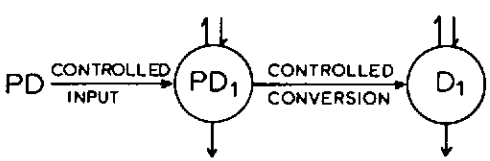
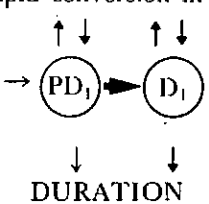


Fig. 20 Average concentrations in 24 subjects taking 250 mg of erythromycin in enteric-coated encapsulated pellets or 400 mg of erythromycin as the prodrug erythromycin ethylsuccinate every 6 hr: (○) intact prodrug (EES), (●) free erythromycin from EES, and (□) erythromycin from the pellets. (Data from Ref. 117.)



Scheme VII

However, the rate-determining conversion of prodrug is less practical owing to the problem of the elimination of circulating prodrug to non-drug-producing processes. In contrast, depot injections with rate-limited release from the injection site followed by rapid conversion in the blood have proven very effective (Scheme VIII).



Scheme VIII

1. Depot Injections

Scheme VIII illustrates the relative magnitude of the rate constants for a prodrug designed to prolong duration by rate-determining release from the injection site. The release from the site should be slow, while conversion in blood should be very rapid. The duration of drug concentration in blood would thus be a function of the prodrug absorption rate constant. Competing loss to non-drug-producing processes should be very slow so that conversion to drug can predominate.

Prodrugs of fluphenazine provide outstanding examples of prolongation using rate-determining depot release. The observed half-life for the loss of fluphenazine following oral or intramuscular administration has been reported at 15 hr [118]. Intramuscular injection of the enanthate prodrug provides a terminal slope which is due to rate-limiting absorption with an average apparent half-life of 3.5 days, while that for the decanoate prodrug is 8 days. The apparent absorption rate constant k_a' is only 8–18% of the elimination rate constant for fluphenazine (Table 14). This may be termed intentional flip-flop, wherein the duration of drug in plasma reflects its slow release from the muscle [119–121]. This dramatic increase in duration is reflected by the dosage interval for the drug relative to that for the prodrugs. A typical oral dosage regimen for the hydrochloride is 1–20 mg/day, while that for the prodrugs is 25 mg every 2 weeks (enanthate) or every 3–4 weeks (decanoate).

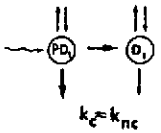
2. Rate-Limiting Conversion

Rate-limiting conversion suffers the disadvantage of having to compete with loss of prodrug to other processes such as excretion and metabolism.

Table 14 Kinetics of Fluphenazine in Humans[a]

		Half-Life		
Form	Route	λ_z (hours)	k_a' (days)	k_a'/λ_z
Dihydrochloride	Intramuscular, oral	15	—	—
Enanthate	Intramuscular	15	3.5	0.18
Decanoate	Intramuscular	—	8.0	0.08

[a]Data from Ref. 118.



Scheme IX

This is illustrated in Scheme IX, which represents an intravenous dose of prodrug, where large arrows are used to emphasize that the rate constant for conversion (k_c) is close to the value for loss of prodrug to nonconversion processes (k_{nc}), regardless of their absolute values. In this case the absorbed prodrug must act as a depot while it is simultaneously lost during the process. However, it may still prolong the blood level of the drug. Figure 21 illustrates the slight prolongation of cytarabine (ara-C) levels when the prodrug cyclocytidine (cyclo-C) is given by rapid intravenous injection. The extension of ara-C levels in this case is possible owing to the extremely rapid metabolism of ara-C itself, which makes it very sensitive to a rate-limiting input process, even when that process is short lived [122].

E. Stability

1. Gastrointestinal

All penicillins are subject to hydrolysis of the β-lactam in stomach acid. The degree of instability varies for the penicillin analogs, but intact β-lactam is required for activity.

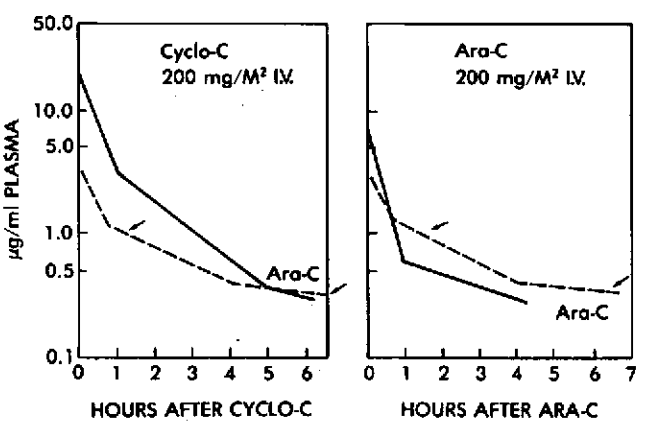


Fig. 21 (a) Plasma concentrations of cyclocytidine (cyclo-C) and cytarabine (ara-C) following an intravenous dose of the prodrug cyclo-C. (b) Concentrations of ara-C following an intravenous dose of ara-C. The dashed line in (b) is the ara-C time course from (a) included for comparison [122].

Carbenicillin is a penicillin that is limited to parenteral use owing to poor bioavailability. This is presumably due to its low lipid solubility (it is a dicarboxylic acid) and its acid instability. At pH 3 and 35°C it has a half-life of approximately 30 min [123]. Esterification has been used to prepare prodrugs which are more lipophilic and acid stable, thereby decreasing degradation while enhancing absorption. Two successful prodrugs are carindacillin (the α-indanol ester) and carfecillin (the α-phenyl ester). The indanol ester of carbenicillin was stable when incubated in simulated gastric juice at pH 2.0 and 37°C for 1 hr, while under these same conditions carbenicillin was almost totally destroyed. Both prodrugs have half-life values (at 35°C) of ~10 hr at pH 3 and ~8 hr at pH 7. At pH ≥ 7 the primary route of prodrug loss is conversion to drug [123,124]. Thus conversion of these prodrugs probably begins in the intestines, where carbenicillin is relatively stable ($t_{1/2} \cong 300$ hr at pH 7), and is completed in the blood. While 500-mg oral doses of carbenicillin gave no detectable concentrations in blood or urine, both prodrugs provide carbenicillin C_{max} values of 7 μg/ml, 34% carbenicillin recovery in 6-hr urine, and no intact prodrug in blood or urine [125]. In experimental urinary tract infections the effectiveness of oral carindacillin was generally as good or better than that of parenteral carbenicillin. The oral prodrug is useful only in urinary tract infections, since it has been shown that systemic levels of carbenicillin from the oral prodrug are suboptimal [126].

Conversion of prodrug in the intestines is also a useful mechanism for bypassing problems other than stomach instability. It could also apply to poorly soluble drugs, drugs with taste or odor problems, those which upset the stomach, or those which are unstable on storage. Since conversion occurs prior to absorption, the pharmacokinetics are not complicated by the presence of circulating prodrug. Evaluation methods are identical to those employed for comparison of drug bioavailability from various dosage forms. Since prodrug is not absorbed, the pharmacokinetics describe only the drug without the problem of assay specificity. The prodrug would affect only the rate of absorption or the fraction of drug absorbed. Direct comparisons of plasma levels of drug from various prodrugs can be made without misinterpretation. In the case of a solubility problem reversal of prodrug to drug in the intestine might be based on either enzymatic or hydrolytic reversal immediately after dissolution.

2. Shelf-Life

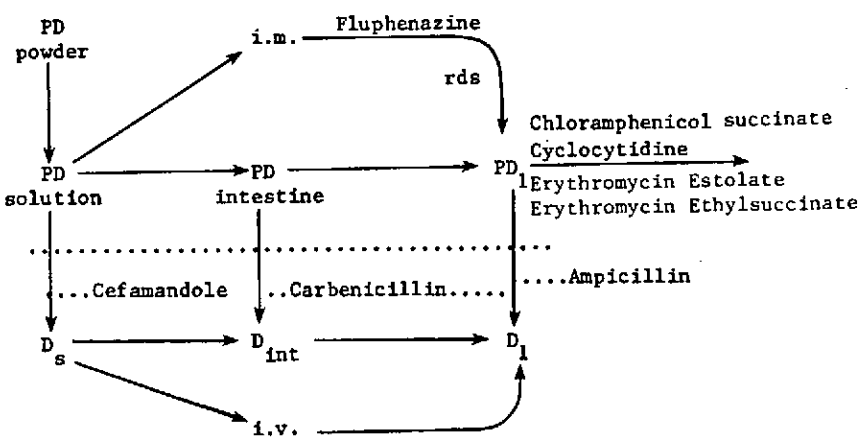
The shelf-life of a drug may be increased by prodrug formation for storage as a dry powder or as a solution. That of a solution is more difficult to achieve, since the prodrug must resist conversion on storage but convert in

vivo. This requires a starting mechanism sometimes referred to as a "trigger." The trigger may be based on the presence of enzymes in the body or on a difference between the pH of the formulation and the body fluids [127].

In the storage of a dry powder the conversion may begin upon reconstitution, provided that the drug is stable in the solvent. Cefamandole nafate provides a good example of this approach. The dry powder shelf-life of cefamandole has been increased by formation of the nafate ester prodrug. When pure prodrug itself was administered parenterally, approximately 41% of the dose of intact prodrug appeared in the urine [128]; however, when the commercial prodrug was reconstituted and used, only 14% intact prodrug appeared in the urine. This was attributed to conversion in the intravenous solution which was buffered by the Na_2CO_3 in the commercial powder. Thus the combination of conversion in vitro followed by in vivo conversion results in an overall total conversion of roughly 86%.

F. Summary

Scheme X summarizes the conversion sites and rate-limiting steps for some of the examples which were discussed. Once the prodrug task is complete, it is important for the prodrug to quantitatively convert to the drug. The site where this may occur, and therefore the methods used to evaluate success, depend upon the specific task of the prodrug. Cefamandole nafate conversion



Scheme X

begins in the intravenous solution to produce drug in solution (D_s) and the remaining prodrug converts to form drug in the blood (D_1). The carbenicillin esters may begin to form drug in the intestine (D_{int}), with completion in the blood. Ampicillin esters (bacampacillin, pivampicillin, and talampicillin) rapidly hydrolyze to form drug in the blood, whereas chloramphenicol succinate, cyclocytidine, erythromycin estolate, and erythromycin ethylsuccinate are partly excreted intact, since conversion is not sufficiently rapid to prevent their loss. Fluphenazine enanthate and decanoate prolong drug levels owing to the rate-limiting input of prodrug into blood (PD_1) followed by rapid conversion to form the drug (D_1).

The pharmacokinetic equations describing prodrug and drug concentration time courses in plasma will vary with the goal of the prodrug. The general equations and the simplified approximations which accompany each goal have been derived and the applications discussed in Ref. 129.

In each of the following problems choose the statement which is most appropriate. Answers are given after Practice Problem 11.

Practice Problem 7

The following data were obtained by administering the equivalent of 250 mg of erythromycin every 6 hr as described in Table 15. Which conclusion agrees best with these data?

Table 15 Erythromycin Plasma Concentrations from the Oral Administration of 250 mg every 6 hr as the Estolate Prodrug of Enteric-Coated Base[a]

Number of hours	Erythromycin estolate		Enteric-coated erythromycin
	Total erythromycin	Erythromycin free base	Erythromycin free base
0	0.0	0.0	0.0
3	4.4	0.7	1.2
6	1.1	0.3	0.3
9	4.5	1.2	1.2
12	3.2	0.4	0.4
48	4.0	0.6	0.7
51	4.6	1.0	1.5
54	2.6	0.7	0.5[1]

[a]Based on data in Ref. 116.

(a) Steady-state erythromycin blood levels are three to eight times higher from the estolate than from the free base.
(b) Steady-state erythromycin blood levels are three to eight times higher from the estolate than from enteric-coated erythromycin tablets.
(c) Enteric-coating erythromycin estolate appears to decrease its bioavailability.
(d) Steady-state erythromycin blood levels from enteric-coated erythromycin are similar to those from the estolate.
(e) These blood level data cannot be compared because the estolate assay is nonspecific.

Practice Problem 8

Figure 22 and Table 16 summarize mean serum concentrations of effective substance in a Latin-square design using fasting volunteers.

(a) Ampicillin trihydrate is absorbed 1.33 times better than the sodium salt. No comparisons can be made regarding the other compounds, since they are chemically different.

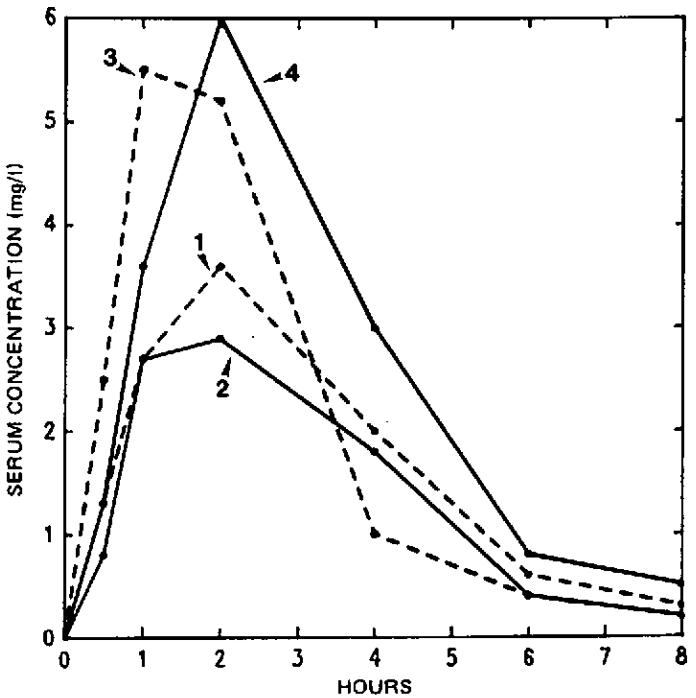


Fig. 22 Average serum concentrations of drug in 13 fasting volunteers after oral dose providing 500 mg of the active agent as (1) ampicillin trihydrate, (2) ampicillin sodium, (3) pivampicillin, and (4) amoxycillin.

Table 16

Compound	*AUC*/*AUC* (ampicillin trihydrate)
Ampicillin trihydrate	1.00
Ampicillin sodium	0.75
Pivampicillin	1.80
Amoxycillin	1.90

(b) The bioavailability of these compounds relative to that of ampicillin sodium is as follows:

Ampicillin trihydrate, 1.3 times
Pivampicillin, 2.4 times
Amoxycillin, 2.5 times

(c) Amoxycillin is 2.5 times more bioavailable than ampicillin sodium, while ampicillin trihydrate is 1.3 times more bioavailable. Pivampicillin cannot be compared, since its peak occurs earlier than that of the others.

(d) The bioavailability of ampicillin trihydrate is 1.3 times that of ampicillin sodium, while that for pivampicillin is 2.4 times higher. Amoxycillin cannot be compared, since it is not an ampicillin prodrug.

(e) No conclusions can be drawn from the data.

Practice Problem 9

Examine the following excerpts from product descriptions.

"AMOXIL (amoxicillin). Capsules and for Oral Suspension.
Description: AMOXIL (amoxicillin) is a semisynthetic antibiotic, an analog of ampicillin, with a broad-spectrum of bactericidal activity"

Flavored Granules CLEOCIN PEDIATRIC (Clindamycin Palmitate HCl for Oral Solution, N.F.)"

"ERYTHROCIN ETHYL SUCCINATE Chewable Tablets (erythromycin ethylsuccinate tablets, U.S.P.)
Description: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics."

"Sterile Solution CLEOCIN PHOSPHATE (Clindamycin Phosphate Injection, N.F.) For Intramuscular and Intravenous Use"

"ERYTHROCIN LACTOBIONATE-I.V. (erythromycin lactobionate for injection, U.S.P.)
Description: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics."

"ERYTHROCIN STEARATE (erythromycin stearate tablets, U.S.P.) Filmtab Tablets.
Description: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids."

Which of the above are *not* prodrugs?
(a) Amoxil, erythromycin stearate, and erythromycin lactobionate
(b) Clindamycin palmitate *only*
(c) Clindamycin phosphate *only*
(d) Erythromycin lactobionate and amoxil *only*
(e) Erythromycin ethyl succinate (EES) *only*

Practice Problem 10
Which of the following s best described as a prodrug which provides rapid and complete conversion in vivo?
(a) Chloramphenicol succinate
(b) Erythromycin estolate
(c) Cyclocytidine
(d) Bacampicillin
(e) Cefamandole nafate

Practice Problem 11
Figure 23 and the accompanying data compare a suspension of ampicillin to that of pivampicillin. Read each of the choices and select the *most accurate statement* for the data.
(a) The curves cannot be compared without using reference curves obtained by rapid intravenous injections.
(b) Peak heights demonstrate that pivampicillin is absorbed 1.84 times more than ampicillin.
(c) Ampicillin is absorbed 57% as much as pivampicillin.
(d) The slow conversion of pivampicillin to ampicillin makes the comparison of the serum time profiles unreliable.
(e) Comparisons cannot be made since doses are not adjusted for the differences in molecular weight between ampicillin and pivampicillin.
Answers: 7 (d), 8 (b), 9 (a), 10 (d), 11 (c).

IV. STEREOISOMERS

Stereoselectivity of biologically active agents is well known in pharmacology. Stereoisomers, such as enantiomers, are distinctively different chemical entities that may be separated by chromatography and which can differ in binding,

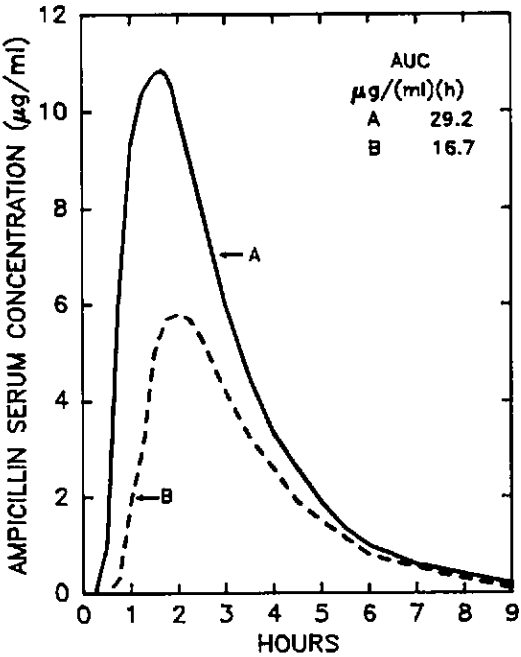


Fig. 23 Average ampicillin serum levels following a single oral dose of 16.7 mg of ampicillin per kilogram as a suspension of pivampicillin (curve A) and ampicillin (curve B) and the corresponding *AUC* values.

metabolism, distribution, and receptor interactions [130–132]. It has been estimated that as much as 90% of the β-adrenergic agents, antiepileptics, and oral anticoagulents are racemic mixtures, whereas about 50% of the antidepressants and antihistamines are so described [132]. In general, 10–15% of all drugs are racemic mixtures [132].

While natural products are commonly found in one optically active form, organic synthesis generally results in a mixture containing 50% of each isomer. Since each isomer is a unique chemical structure which can differ in so many ways from its enantiomer, the pharmacokinetic behavior of each must be independently assessed. This requires specific analytical methodology for each isomer. Failure to resolve the two forms in the assay will provide meaningless data. Such data for the racemic mixture would represent the sum of two independent plasma time courses superimposed one on the other. Unless it is known that both isomers are identical in every aspect, an unlikely prospect, the pharmacokinetics of a racemic mixture, without independent assays for each isomer, is unjustified. The publication of such studies

has led Ariëns to refer to these works as "sophisticated nonsense in pharmacokinetics" [132].

While stereoselective aspects of receptor interactions and pharmacological response have received significant attention, the pharmacokinetic differences have, in comparison, been nearly ignored. Significant differences have been observed in clearance values, distribution, protein binding, and metabolism for those isomers which have been examined. Some examples of biological half-life values in humans are given in Table 17.

The misinterpretation of plasma drug concentration time course data by analysis of the total racemic mixture may be thought of as a hybrid error combining the popular errors in analog comparisons with that of nonspecificity in prodrug analysis. The lack of an appreciation for pharmacokinetic differences arising from minor molecular modifications has led to invalid direct comparisons between structural analogs. The failure to recognize that racemates are mixtures of two different chemical entities is yet another ramification of that original basic misconception. The analysis of both drug and prodrug in blood samples has led to erroneous pharmacokinetic conclusions based on an invalid plasma concentration time course which combines the drug and prodrug time courses into a meaningless composite profile. So, too, the pharmacokinetics of racemic mixtures merges two unique sets of data, one for each isomer, into an uninterpretable amalgam. The further derivation of pharmacokinetic parameters from such data is best described as "sophisticated nonsense" [132].

Table 17 Examples of Differences in Reported Biological Half-Life Values for Isomers

Drug	Approximate biological half-life (hr)	Reference
R(−)-Disopyramide	3.7	133
S(+)-Disopyramide	4.6	133
(+)-Hexobarbital	4.6	134
(−)-Hexobarbital	1:4	134
R Warfarin	37–89	135
S Warfarin	21–43	135
d-Propranolol	2.0	136
l-Propranolol	3.2	136

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8

Pharmacokinetic Applications in Clinical Practice

I. INTRODUCTION

A. Applications of Pharmacokinetic Research

Both the methodology and published results of pharmacokinetic research hold potential for the improvement of three areas of drug therapy:

1. Product design and evaluation
2. Drug design and evaluation
3. Clinical practice

The practicality of pharmacokinetic research was initially realized in the area of product design and evaluation. Here optimum bioavailability has become a well-recognized goal for quality products. Specialized products, such as sustained release dosage forms, illustrate how the application of kinetic principles can improve the clinical efficacy of a known drug. Progress in the application of biopharmaceutics to product development is reviewed in Chap. 5.

Chemical modification of drugs has been successfully employed to improve pharmacokinetic properties and, in turn, efficacy. Kinetic considerations play a major role in determining the relative potency and effectiveness of structural analogs. Pharmacokinetic aspects of drug design and evaluation are reviewed in Chap. 7.

This chapter provides an overview of the contributions of pharmacokinetics to the improvement of drug therapy at the clinical level. The degree of success achieved in therapy with any drug is measured by the degree to which the observed results approach the expected results. Given that a good choice of drug has been made, the observed results may fall short of the expected results for a number of reasons:

1. Drug–drug interactions
2. Drug–food interactions
3. Improper dosage regimen
4. Improper product use
5. Inappropriate route of administration
6. Poor formulation
7. Toxicity

Pharmacokinetics provides the foundation for two elements which can be significant in clinical practice:

1. Product evaluation
2. Rational choice and use of drug products

A single drug may be available in several doasge forms from many manufacturers. What type of information is necessary to evaluate product efficacy? Once a drug and its dosage form have been chosen, it must then be rationally used. This includes establishing the correct mode of administration, avoiding drug and food interactions, and adjusting the dosage regimen. The influence of biopharmaceutics and pharmacokinetics in achieving clinical success is the subject of this chapter.

B. Drug Product Selection

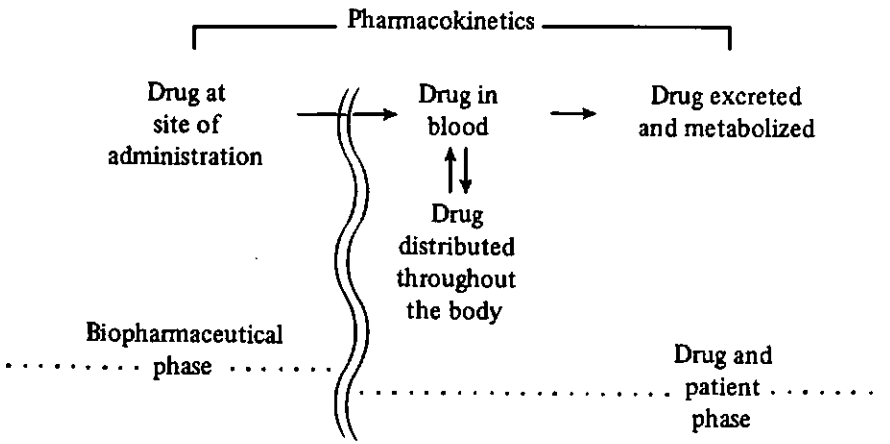
It is well recognized that the route of administration and the formulation can affect drug bioavailability. *Bioavailability* refers to both the amount of drug absorbed and its rate of absorption, whereas *bioavailable dose* refers only to the amount absorbed. It is therefore possible to have drug products that are absorbed to the same extent (have equivalent bioavailable doses) but which provide different therapeutic results because of differences in their rates of absorption. The areas under the plasma level time profiles (AUC) are indicative only of the *amount* absorbed when comparing products containing a *single* drug. Conversely, the onset and the height of the plasma curve at its peak are affected by both the amount and the rate. As discussed in Chap. 5, there are many reasons why the dosage form can alter the time course for drug in the blood. Since the *bioavailable dose* does not take into account the shape of the profile, *bioequivalency* provides a more rigorous test for product comparison.

An acceptable product should be either superior or bioequivalent to the reference product. But what is the reference product? The answer is not simple. It is often the first marketed product (sometimes called the innovator's product) containing that particular drug. This is especially evident in literature comparing antibiotic products. An example may be found in Practice Problem 11, Chap. 5, where comparison to the original product A resulted in the recall of over 200 million capsules of nonbioequivalent formulations. However, the original or first-marketed dosage form cannot be categorically assumed to have the ideal plasma profile.

One definition for the optimum bioavailability pattern is that which provides the longest duration per unit mass [1]. If the minimum effective

concentration (*MEC*) is known, then the optimum formulation would be that which exceeded this value for the longest duration of time without the sacrifice of bioavailable fraction or side effects. Comparisons based on duration are more difficult (if not impossible) when *MEC* values are not known. The criteria for optimum profiles may change with the drug and/or disease in question. While it is generally agreed that the efficacy of an antimicrobial agent depends upon its ability to reach a given area of inflammation, it is often debated as to whether high peak or extended effective levels are more desirable. High peak blood levels may aid diffusion into relatively avascular areas, such as in the treatment of pneumococcal meningitis with penicillin [2]. In gonorrhea sustained high concentrations are required to destory relatively insensitive organisms [2]. It is not yet clear as to how the mechanism of bacterial kill may alter the optimum time course for antibiotic therapy. For drugs wherein blood levels are not related to the clinical response the ideal pattern must be determined using clinical endpoints. This is not to say that bioavailability is no longer important, since absorption is still prerequisite to reaching the site of action.

When two products exceed the MEC for equal duration but differ significantly in f value, the one with the greater bioavailable fraction should be considered superior. In the author's opinion the argument that both will work is not sufficient for clinical equivalence. The product that is less bioavailable will be more variable in performance and will therefore have a greater risk. The one which exceeds the MEC to a greater extent and has the larger f value will be more predictable and more likely to successfully withstand some negative effect on its absorption. If side effects due to high plasma levels are a consideration, then a smaller dose of a more bioavailable product is still better than a large dose of a poorly absorbed product.



Scheme I

Scheme I reviews the rate processes involved in biopharmaceutics and pharmacokinetics. Biopharmaceutics includes all of the processes leading up to the arrival of drug in the bloodstream. The *biopharmaceutical phase* may be influenced by the manufacturing methods of the dosage form, the foods eaten by the patient, the route of administration, the effect of the disease state on the absorption process, the age of the patient, and the chemistry of the drug. The fate of the absorbed drug is determined by the *drug and patient phase*. For example, a patient in renal failure may elicit a reduction in the elimination of certain drugs that are excreted in the urine. Pharmacokinetics includes all of the rate processes, namely, absorption, distribution, metabolism, and excretion. Molecular modification may affect any or all of the processes. Thus selection of a particular analog or prodrug for clinical use should include pharmacokinetic considerations. Clinical results are best assured when the predictability of the processes in Scheme I is at its maximum. It is the responsibility of the clinician to pursue this goal.

II. PHARMACOKINETIC DRUG INTERACTIONS

Drug interactions may be classified under two categories:

1. Pharmacological interactions
2. Pharmacokinetic interactions

The number and types of pharmacological reactions are both numerous and diverse. In general, they are learned through experience and are often difficult to predict. The multiplicity of pharmacological interactions which have been

Table 1 Pharmacokinetic Drug Interactions

Absorption
Stability
Complexation
Dissolution
Physiology
Elimination
Excretion
Metabolism
Distribution
Binding

observed and their ever-increasing numbers make this problem best controlled by the aid of computers. In such an approach the patient's individual drug therapy is entered into the computer, which could then warn of drug interactions and suggest alternatives based on a vast memory of stored information. It is impossible for any member of the health team to be responsible for memorizing all of the possible pharmacological drug–drug interactions and to effectively deal with this problem. Conversely, to some degree pharmacokinetic drug interactions can be predicted from a knowledge of the physical chemistry of the drugs and the interplay of the physicochemical characteristics with the pharmacokinetic behavior. Table 1 lists the three primary mechanisms by which pharmacokinetic drug interactions might be expected to alter an otherwise successful course of therapy.

In simple terms, one drug may decrease the absorption of a second drug. One drug may change the distribution pattern of a second drug. Finally, a drug may alter the elimination of a second drug in such a way as to increase or decrease its biological half-life, depending on the circumstances. Theoretical [3] and clinical [4,5] aspects have been reviewed.

A. Oral Absorption

The absorption of a drug may be altered by other drugs or foods in four ways. Drugs which are unstable may be caused to undergo increased degradation. Some drugs may undergo complexation (as with heavy metals) and may not be well absorbed. A drug may fail to undergo dissolution owing to the ingestion of food or other drug substances. The gastrointestinal physiology may be altered such as to interfere with an active absorption process or alter gastrointestinal motility.

In addition to drug interactions, absorption may be altered owing to disease states or physiological changes accompanying aging. Nimmo [6] has discussed the factors which can alter gastric emptying and their potential influence on the absorption of orally administered drugs. Parsons [7] has reviewed the effects of gastrointestinal diseases on bioavailability, with particular emphasis on malabsorption syndromes. Welling [8] has reviewed the influence of food on the gastrointestinal absorption of drugs. A few examples are discussed here to illustrate the concepts.

1. Instability

Consider the problem of acid instability, as in the case of penicillins, erythromycin, cephalosporins, and so on, where the stomach represents a prime area for drug degradation. Drugs which undergo hydrolysis in the stomach

have a decreased possibility for absorption. Since this degradation is acid catalyzed, the pH of the stomach can influence the degree of hydrolysis. Stomach pH varies from roughly 1 to 3.5 and the pH of the duodenum is 5–6. Since stomach emptying is delayed by food ingestion, taking medications at meal times traps the drug in a more acidic environment relative to the intestines. Table 3, Chap. 5, summarizes the half-lives for some of the common penicillins in an acid pH at 35°C. Methicillin, with a half-life of 2.3 min, is so unstable in the gastrointestinal tract as to be suitable for use only by the parenteral route. More recent penicillins (such as oxacillin, penicillin V, amoxicillin, and ampicillin) have increased stability in stomach acid. In spite of this, it has been observed that penicillins in general are better absorbed on a fasting stomach than they are just after meals. For optimum oral penicillin therapy one should always be advised to take penicillins at least 30 min before or 2 hr after mealtime.

The effect of food on erythromycin absorption has been somewhat varied. In the case of those dosage forms which readily present erythromycin base to stomach fluids, there is usually a decrease in bioavailability with meals. Suspension dosage forms, coated tablets, and prodrugs all appear less sensitive to this effect. The effect of food on the bioavailability of the ethyl succinate or the estolate is probably clinically insignificant.

2. Complexation

The tetracyclines provide the most well-known example for decreased absorption due to complexation. This problem has been widely publicized and it is known that all tetracyclines undergo such complexation with a resultant decrease in oral absorption in the presence of aluminum, calcium, and magnesium. This complexation is known to yield inactive species which are unable to penetrate biological membranes. In the case of demeclocyclin it has been shown that only 13% is absorbed when taken with 8 oz of whole milk as compared to the amount absorbed with an equal dose taken after 7 hr of fasting (Practice Problem 10, Chap. 5). On coadministration with 20 ml of aluminum hydroxide gel, only 22% was absorbed compared to the fasting state. Doxycycline has been shown to be less sensitive than demeclocyclin to nondairy foods and to skim milk. While doxycycline absorption is decreased somewhat in the presence of whole milk, it appears to be the least sensitive tetracycline in current clinical use. However, all tetracyclines (including doxycycline) undergo decreased bioavailability with the simultaneous ingestion of antacids containing divalent or trivalent cations. When doxycycline was administered orally with aluminum hydroxide gel, observed plasma concentrations were reduced to 10% of normal (see Chap. 7). Rational oral tetracycline therapy should include precautions against the concomitant

administration of dairy products or aluminum-, magnesium-, or calcium-containing antacid preparations. Certainly the patient cannot be expected to realize this without being counseled by the clinician.

3. Dissolution Rate

As might be expected, the dissolution of poorly soluble drugs is often rate limiting in the absorption process. It is therefore important to keep those factors in mind which govern dissolution rates (see Chap. 5).

With weak base drugs, which require protonation for good dissolution characteristics, the bioavailability may be decreased if the stomach is buffered to an alkaline pH. This phenomenon has also been observed in the case of tetracycline, which behaves as a zwitterion [9]. Tetracycline hydrochloride capsules resulted in decreased oral absorption when administered with an aqeuous solution of sodium bicarbonate. Since the hydrochloride salt of tetracycline is meant to aid in the dissolution rate, it might have been anticipated that coadministration with sodium bicarbonate would tend to neutralize the acid salt and either decrease dissolution rate or precipitate tetracycline which had dissolved in the stomach.

A logical extension of this observation is the hypothesis that achlorhydria accompanying disease states, aging, or certain drug therapy might also reduce the bioavailability of tetracycline. The most widely used trade name capsules were compared to solutions in normal volunteers and elderly achlorhydric patients [10]. The capsules were also administered to the normal subjects with concurrent administration of sodium bicarbonate solution. Contrary to the results of the previous study [9], neither alkalinization nor achlorhydria decreased absorption, which was equivalent for both the capsules and the solutions [10]. Since the products which had previously been shown to be decreased by sodium bicarbonate were only 61.5% as bioavailable as the capsules used in the latter study, it was suggested that the pH effect was significant only to a product with less than optimum dissolution characteristics. If the formulation is sufficiently rapid in its dissolution pattern, the increase in stomach pH may not significantly inhibit its dissolution.

This supports the suggestion made earlier, in Sec. I. B on drug product selection. A product that achieves therapeutic blood levels but which has decreased bioavailability will have an increased risk in clinical use, where less than ideal circumstances may further compromise its potential.

4. Physiology

More complex phenomena include the alteration of gastrointestinal absorption due to changes in active mechanisms for absorption (enzyme transport systems) or in gastrointestinal motility. One rather complex example involves

phenytoin (diphenylhydantoin) and folic acid. It has been reported that phenytoin inhibits folic acid absorption. A patient on phenytoin therapy may therefore experience folic acid deficiency. One such patient, who was adequately controlled for 18 months without a seizure, was given 5 mg of folic acid in addition to the regular dosage for phenytoin and phenobarbital. Although no significant effect was observed on the phenobarbital plasma levels, the phenytoin level fell and the patient experienced the first grand mal seizure in 18 months. When the phenytoin dose was doubled, the plasma level soared from 5 to 80 μg/ml, with severe intoxication. However, when the folic acid dose was reduced to 2 mg and the phenytoin dosage returned to 300 mg daily, the patient again showed normal plasma levels of phenytoin without side effects [11]. Admittedly, such complicated interactions are unfortunately learned from experience. However, the potential exists for drugs that are actively absorbed to interfere with other compounds which can compete for the same enzyme systems. Individualization of phenytoin dosage is complicated by other factors and is covered separately in this chapter.

Drugs which show "site-specific" absorption may be influenced by gastrointestinal motility, which can determine the time available for absorption. Digoxin appears to be best absorbed from the upper intestine. Higher steady-state plasma levels of digoxin have been reported after treatment with propantheline, presumably owing to increased residence time in the upper intestine. Conversely, propantheline has been reported to decrease the plasma concentrations obtained with paracetamol.

B. Elimination

The second category of pharmacokinetic-based drug interactions is that of alteration of elimination. This may be considered in terms of drugs which influence *excretion* by the kidneys or *metabolic* processes. At this time the first is better understood and more easily predicted. Drugs that are eliminated solely by glomerular filtration tend to show less interpatient variation in elimination half-life than those which are wholly metabolized. The adjustment of dosage in renal failure by considering glomerular filtration rate (GFR) has further reduced interpatient variability. Attempts to accommodate changes in liver function based on clinical tests have not been successful.

How can one look at drugs from the standpoint of relative *susceptibility* to drug–drug interaction due to changes in renal excretion? Basically, two considerations have to be brought into this question: the percent of elimination of a drug attributed to the kidney, and the mechanism by which the kidney excretes drug.

1. Renal Excretion

a. Glomerular Filtration. Chapter 4 provides a discussion of renal clearance. If we consider the mechanisms by which the kidney eliminates drugs, we can roughly categorize compounds according to their renal clearance values. Table 2 presents typical normal renal clearance values. The elimination of compounds by glomerular filtration can be reduced by plasma protein binding. The biological half-lives for sulfonamides, for example, have been shown to be correlated with the degree of plasma protein binding. However, compounds which undergo active tubular secretion (such as penicillins with renal clearance values in the range of 200–500 ml/min) are not affected by the percentage which is plasma protein bound. In fact, all penicillins have half-lives in the range of 30 min to 1 hr, regardless of the wide range of their protein binding, from 20% to greater than 90%. The effect that the displacement of one protein-bound drug by another has on renal clearance and duration is therefore somewhat predictable.

b. Tubular Resorption. Renal clearance values significantly less than 120 ml/min indicate tubular resorption (or reabsorption). Tubular reabsorption of drugs is a passive process. Figure 1 illustrates tubular reabsorption of acidic and basic drugs. The concepts are analogous to those of the pH partition considerations in gastrointestinal absorption. A neutral species is preferentially reabsorbed in comparison to a charged form. For a weak acid drug passive reabsorption would be increased if the urine were acidic enough to cause an increase in the concentration of neutral species. This would result in increased biological half-life. Notable examples are sulfonamides and salicylates. The effect is opposite with weakly basic drugs. Here the uncharged species is formed in alkaline urine and its reabsorption would be expected to increase. Amphetamines have been shown to be reabsorbed when alkaline urine increases the concentration of the noncharged base species.

Tetracyclines are zwitterions which are generally thought to have their maximum lipid solubility at their isoelectric points. Doxycycline has an isoelectric point of 5.6, which is presumably its pH of maximum tubular reabsorption. Thus alkalinization of the urine (mean pH range 7.4–8.0) decreased

Table 2 Renal Clearance[a]

Glomerular filtration	120–130
Tubular resorption	<120
Tubular secretion	>>130

[a]Average values (ml/min) based on $CL_R \times 1.73$ per surface area (in m^2).

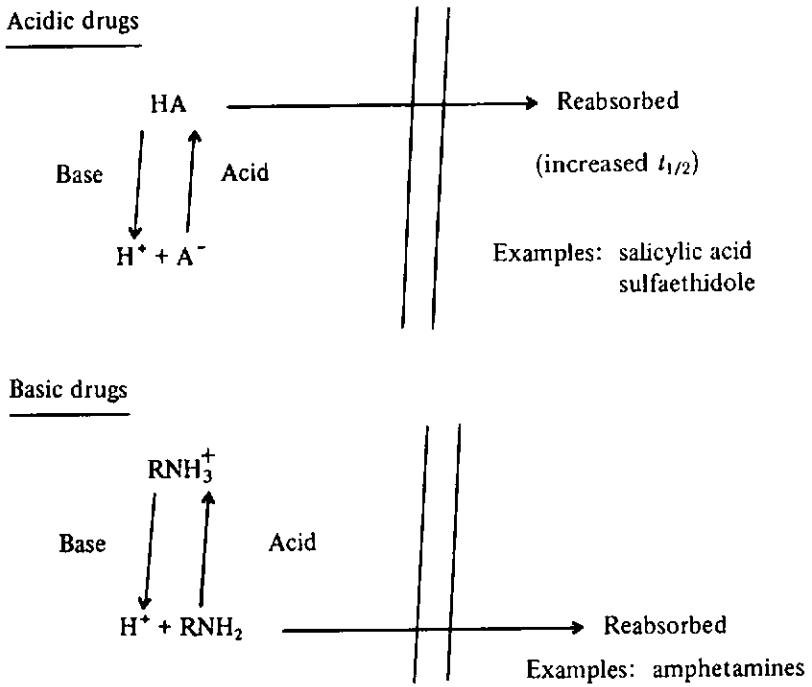


Fig. 1 Passive tubular reabsorption of acidic and basic drugs in the kidney.

the apparent $t_{1/2}$ of doxycycline from 13 hr in the control group (mean pH range 5.3–6.3) to 9 hr following the administration of a single oral dose of 200 mg. During multiple-dose steady state the apparent $t_{1/2}$ decreased from 17 hr in the control (pH 5.6–6.7) to 12 hr in the alkaline urine (pH 7.7–8.4) [12].

The narcotic analgesic methadone is an amine base of pK_a 8.62. Lowering the urinary pH should therefore increase the formation of the charged protonated species and promote renal excretion. A study of 12 male patients attributed nearly a threefold increase in renal clearance to decreased urinary pH [13]. This was accompanied by a reduction in the excretion ratio of metabolite to intact methadone.

Urinary pH is often controlled in the clinic for a variety of therapeutic reasons. Typical compounds which are used are shown in Table 3. In addition to the desired therapeutic effect of controlling urinary pH, the half-life of drugs which have been administered to the patient may be altered.For example, the half-life of salicylic acid may be increased by acidifying the urine with oral doses of NH_4Cl. Conversely, alkalinization of the urine with

Table 3 Control of Urinary pH

Acid (daily)	Alkaline (daily)
NH_4Cl (8–12 g)	Na_2HPO_4 (2 g)
Methionine (8–12 g)	$NaHCO_3$ (12–24 g)
Ascorbic Acid (2 g)	Acetazolamide (0.5–1.5 g)

sodium bicarbonate will decrease the half-life of salicylic acid. It has been demonstrated that adjustment of the pH of the urine during sulfonamide excretion can change the half-life from 11 hr at a urinary pH of roughly 5 to only 4 hr after alkalinization of the urine to a pH of roughly 7.5 [14]. The half-life of dl-amphetamine is roughly 4 hr at pH 5.3 (NH_4Cl) and 13 hr at pH 7.8 ($NaHCO_3$) [15].

It is also possible to inadvertently increase urinary pH by the repetitive administration of oral antacids. Although the potential for pH variation in the distal tubules ranges from pH 4.5 to 8.0, the observed increase due to antacid was only about 1 pH unit. A suspension of magnesium and aluminum hydroxides was the most effective of those tested in increasing the pH of the urine [16]. Similar results were obtained with either 15 or 30 ml of suspension given four times daily (8-1-6-11), which increased the average pH (seven normal subjects) from ~5.8 to approximately 6.2–6.9. Although the change in pH is small, it could significantly change ionization if the pK_a of the drug is in the range 5–7.

It is easily recognized that two types of therapeutic problems can result from unexpected changes in drug reabsorption. If the half-life of a drug is decreased, then its duration of action may decrease and therapeutic failure may result. Since the dosage regimen has been based on the normal or average half-life, it can be inadequate for the patient experiencing an increased rate of elimination due to alteration of urinary pH. Conversely, an increase in half-life could result in the undesirable accumulation of drug, with resultant toxicity or side effects.

c. Tubular Secretion. The kidneys are able to actively secrete many organic carboxylic acids by a somewhat nonspecific active tubular secretion process. A drug which is normally secreted in this fashion can accumulate when coadministered with a second drug competing for the same mechanism. Renal clearance tests such as p-aminohippuric acid (PAH) may be altered by such drugs if the sum of their concentrations in the plasma is sufficient to exceed the capacity for the system.

An interesting example of a toxic drug interaction of this type has been reported in the literature. The antidiabetic agent acetohexamide is converted

in the body to hydroxyhexamide, which is an active metabolite. Phenylbutazone, given concurrently with the parent drug, competes with hydroxyhexamide for tubular secretion. Although the half-life of acetohexamide remains constant, phenylbutazone was shown to increase the half-life of hydroxyhexamide from 5 to 22 hr [17]. In the presence of phenylbutazone the hypoglycemia following administration of acetohexamide is therefore greatly prolonged owing to the inability of the body to eliminate the active metabolite hydroxyhexamide.

The intentional interference with penicillin tubular secretion by coadministration of probenecid has long been recognized as a means of increasing the duration of penicillin body levels.

2. Metabolism

Alteration of drug metabolism may either increase or decrease the biological half-life, depending on the mechanism. Certain drugs are enzyme inducers, which can result in increased metabolism of other drugs; conversely, a drug may inhibit enzymatic activity, with the opposite result. These are difficult to predict a priori, but once observed appear to be rather general.

a. Enzyme Induction. Several drugs are known enzyme inducers [4,18]. Rifampicin, glutethimide, phenytoin, and nearly all barbiturates are known to increase the rate of drug metabolism in humans. The effect of barbiturates on oral anticoagulant plasma levels is of particular clinical significance. Phenobarbital induces the metabolic rate of coumarin anticoagulants, phenytoin, antipyrine, desmethylimipramine, and others. Pretreatment of either a mother or her newborn with phenobarbital leads to a significant reduction of diazepam half-life in the newborn from 35 to 15 hr. Antipyrine is often used in humans as a model for metabolic hydroxylation kinetics; however, it has not been successful as a means to predict an individual's ability to metabolize other drugs.

b. Enzyme Inhibition or Competition. Agents which either compete with a drug for an enzyme system or inhibit the enzyme activity can produce an increase in the duration of drug. Competition for the glucuronidation pathways appears to be responsible for extended half-lives of both drugs when paracetamol and salicylates are administered together. Tolbutamide elimination is reduced in the presence of concomitant therapy with dicoumarol, phenylbutazone, sulfaphenazole, or phenyramidol, presumably owing in part to the inhibition of oxidation to hydroxytolbutamide. Sulfaphenazole has been reported to increase the tolbutamide half-life from roughly 4–8 to 24–70 hr. The clinical pharmacokinetics of phenytoin are discussed in a later section, where it is shown that nonlinear kinetics are observed at therapeutic

Table 4 Reported Changes in Biological Half-Lives of Drugs Observed After Initiating Therapy with a Second Agent[a]

Agent causing interaction	Drug affected	Half-life (hr)		Reason
		Before	After	
Rifampicin	Tolbutamide	6.0	2.8	Induction
	Hexobarbital	5.2	2.8	Induction
	Digitoxin	288	76	Induction
Phenobarbital	Antipyrine	17	9	Induction
Dicoumarol	Tolbutamide	5	17	Inhibition
	Phenytoin[b]	9	40	Inhibition
Phenylbutazone	Phenytoin[b]	14	22	Inhibition
	Tolbutamide	4.5	10	Inhibition
Sulfaphenazole	Tolbutamide	4	27	Inhibition[c]
Sulfadimethoxine	Tolbutamide	5	2.8	Displacement from plasma protein

[a]From Refs. 4 and 18.
[b]Apparent values, since the kinetics are nonlinear (see Sec. III.B.1).
[c]Also increases free tolbutamide in vitro.

dosage levels. Although the half-life is dose dependent, the apparent phenytoin half-life has been observed to increase from roughly 9 to 30 hr on coadministration of dicoumarol. Table 4 summarizes a few of the reported changes in $t_{1/2}$ attributed to drug interactions.

c. Dosage Adjustment in Drug Interactions. Theoretically it might be possible to adjust the dosage regimen in order to accommodate drug–drug interactions which change the biological half-lives of the drugs. Adjustment of dosage regimen during renal impairment is becoming commonplace. However, there is little information on half-lives of drugs during combined therapy and no procedure for accommodating intersubject variability. It would be safest to avoid the coadministration of drugs which can be expected to alter drug elimination, especially if one has a low margin of safety.

C. Distribution

1. Binding

The potential for changes in pharmacokinetics by alteration in plasma and tissue protein binding due to age, disease, or displacement by other agents is widely recognized. Two excellent reviews summarize a great cross section

of the literature [19,20]. The displacement of one protein-bound drug by another can increase the body levels of free drug, resulting in increased biological activity, distribution into tissues, and in some instances elimination. The clinical significance and the prediction and management of these phenomena have not been systematically developed.

There is a common misconception that drugs which have a high degree of binding to plasma proteins are therefore amenable to displacement by other drugs, which will result in increased free-drug levels. While such drugs may be displaced, the plasma level need not rise. The meaning of the data generally used to describe the protein binding of drugs is not always understood. If a drug is said to be 98% protein bound, this does not mean that 98% of the drug in the body is protein bound; it means that 98% of the drug contained in the blood is protein bound and 2% is free. Since free drug undergoes distribution throughout the rest of the body (Fig. 2), the fraction of total drug which is protein bound is dependent on the total volume in which the free drug is distributed. If the volume of distribution is small, then a large fraction of the drug may be stored on plasma protein. Displacement of this drug from the protein might be expected to increase the concentration of the free drug which must be distributed between blood and tissue. However, if the volume of distribution is exceedingly large so that the total drug stored on the protein is a very small fraction of drug in the

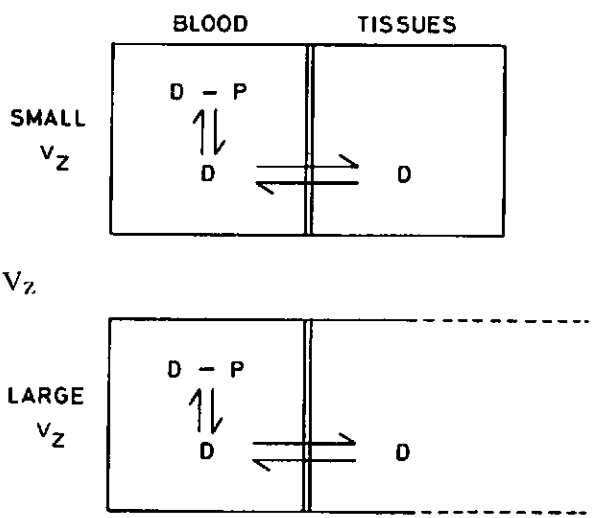


Fig. 2 Equilibria between plasma protein-bound drug (D-P) and free drug (D) where the volume of distribution of D is small and where it is large.

body, then displacement of the drug from the protein would not notably increase the concentration of free drug. In other words, if free drug must be distributed over a very large volume, then any increase that one might observe in the blood due to displacement from plasma protein would be diluted to the point where it would have no clinical significance.

Several orally active anticoagulants apparently fulfill the criteria required to present a danger due to displacement from plasma protein. These criteria are the following:

1. A high percentage bound
2. A small volume of distribution

One such example which is well known is that of warfarin. It has been shown that the concomitant administration of warfarin and phenylbutazone can result in increased loss of warfarin from plasma. This reduced half-life is presumably due to the increased access to metabolic destruction of warfarin resulting from the displacement of bound warfarin to form free warfarin. As would be expected, this increase in free warfarin in the blood caused not only an increased rate of loss but also an increase in pharmacological activity. The peak prothrombin time was increased from roughly 25 to 50 sec. Thus the duration of warfarin in circulating plasma decreased while prothrombin time was seen to roughly double. It is easily appreciated that a patient who was normally well controlled by warfarin may suddenly be out of control upon administration of phenylbutazone.

It has been emphasized that this displacement of bound warfarin by phenylbutazone is probably an oversimplification of the clinical situation [5]. Warfarin in clinical use is a mixture of R(+) and S(−) enantiomers. These two forms differ in pharmacokinetic behavior, potency, and biotransformation [21]. Phenylbutazone and metronidazole increase the hypothrombinemic activity of S(−) but not R(+) warfarin. It has been suggested that the potential for drug interactions might be reduced if R(+)-warfarin replaced the commonly used racemic mixture in therapy.

Patients receiving anticoagulants should be carefully and continuously checked so that any change in prothrombin time can be rapidly diagnosed. Many drugs have been observed to cause such interactions with coumarin anticoagulants. Among those reported are chloral hydrate, several analgetics, barbiturates, several diuretics, and some antibiotics. It is well known that both sulfonamide drugs and vitamin K are able to interact at plasma protein-binding sites with the subsequent release of bilirubin. This effect was originally discovered in a clinical trial comparing tetracycline and penicillin–sulfonamide mixture in the treatment of premature infants. The higher rate

of kernicterus found in the sulfonamide–penicillin treatment led to the realization that displaced bilirubin in the premature infant passed into the brain, causing kernicterus, which is often fatal.

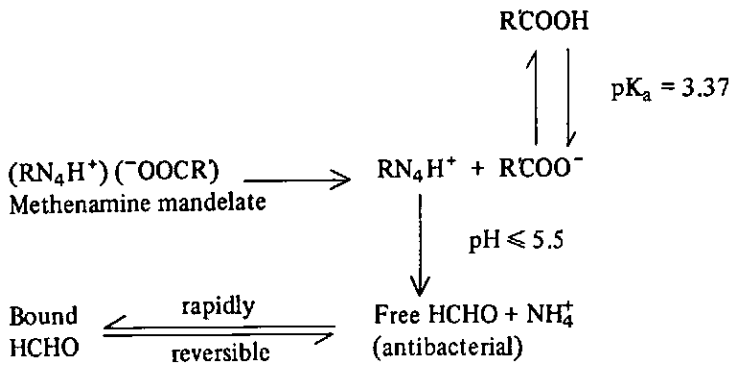
D. Improper Product Use

The pharmacist often takes for granted an understanding of drug products, which is unique in the health professions. The pharmacist is the single health professional who studies (in detail) drug products, the physical chemistry of drugs, and biopharmaceutics. One cannot expect patients or professionals to rationally make use of drug products without regard for their design. A simple example is the grinding of sustained-release or enteric-coated products into a powder to be administered in food or drink for patients who have difficulty in swallowing. While the long-acting form may produce an overdose, the enteric-coated form may fail to produce adequate blood levels or may cause gastric side effects. The following example is taken from a clinical practice experience.

Methenamine mandelate is a urinary tract anti-infective agent. The usual dose is 250 mg to 1.0 g taken two to four times a day. If methenamine itself is administered orally, 10–30% may be degradated in the stomach. This degradation is responsible for its mechanism of action in urine. Methenamine may be considered a prodrug. Methenamine itself is not a drug, but in the presence of acid it is converted to the antibacterial agent formaldehyde. Since the stomach is acid, orally administered methenamine may be prematurely converted to formaldehyde.

The use of methenamine mandelate in an enteric-coated preparation is an attempt to prevent premature conversion. Upon reaching the intestine, the enteric coating is removed and methenamine undergoes dissolution. Since the intestinal tract is not sufficiently acidic to convert the methenamine to formaldehyde, the absorption of the prodrug follows. A pH of 5.5 or less is required for the conversion of methenamine to formaldehyde. Upon arriving in the blood, methenamine is in an environment at pH of 7.4, which is insufficient acidity for conversion and it is highly cleared into the urine. Scheme II represents conversion of methanamine into formaldehyde in the urine. This rate of conversion is proportional to hydrogen ion concentration. If the pH is less than 5.5, sufficient formaldehyde may be formed for antibacterial treatment. This should be ensured by the administration of a urinary acidifier (Table 3). Table 5 represents some selected aspects of a patient's medication record. It can be seen that the patient was receiving sodium bicarbonate to aid in uric acid excretion. However, the sodium bicarbonate

simultaneously aided uric acid excretion while preventing conversion of the methenamine to the active antibacterial agent formaldehyde.



Scheme II

Lack of success in treating the urinary tract infection with mandelamine led to the use of furadantin. When furadantin failed to help, macrodantin (which is a form of furadantin) was employed.

This well illustrates the potential significance of knowledge that the pharmacist often takes for granted. The study of drug products is unique to pharmacy. It would have been a simple matter for the pharmacist to predict the failure of methenamine by considering the chemistry required for it to be effective. In addition, the choice of furadantin under conditions of alkaline pH was not rational (Table 6); neither was the change from furadantin to macrodantin, since it is macrocrystals of the same drug.

Table 5 Selected Excerpts from a Patient's Medication Record[a]

	Days						
Drug	1–2	3–14	15–18	19–23	24	25–26	27–33
Sodium bicarbonate (i.v.)	X						
Allopurinol (300 mg/day)	X	X	X	X	X	X	X
Sodium bicarbonate (p.o. 6 g/day)			X	X	X	X	X
Mandelamine (2 g/day)				X	X		
Furadantin (400 mg/day)					X	X	
Macrodantin (400 mg/day)							X

[a]The author is indebted to Dr. James Visconti for suggesting this example and for supplying the necessary information.

Table 6 Optimum pH for Urinary Tract Anti-Infective Agents

Acid	Alkaline	Other
Tetracyclines	Erythromycin	Sufonamides (close to the pK_a)
Nitrofurantoin	Streptomycin	Penicillins (literature is contradictory)
Mandelamine	Kanamycin	Nalidixic acid (no pH adjustment needed)
Carbenicillin	Gentamicin	Chloramphenicol (not affected)
	Polymyxin B and E	Cephaloridine, cephalexin, cephalothin (pH 6–8)

E. Summary

The clinical use of drugs generally varies widely from the carefully controlled studies employed to establish the average dosage regimen. Many complicating factors can alter the pharmacokinetic behavior of a given drug in a particular patient. Some factors which can influence the biological half-life of drugs together with some examples are listed in Table 7. If the normal regimen is employed when the half-life is significantly altered in the patient, the plasma concentrations will be abnormally high or low. For many drugs this may not be important; however, the outcome could be extremely serious. If the half-life is increased, the plasma concentration will be higher than normal and the patient could be at risk for increased toxicity. Conversely,

Table 7 Summary of Pharmacokinetic Factors Influencing the Biological Half-Life Values for Selected Drugs

Factors	Biological $t_{1/2}$[a] (hr)	
Age	≤ 20 yr	31–64 yr
Gentamicin	1	3
Metabolism: Tolbutamide	Before	After
Induction (Rifampicin)	6	3
Inhibition (Phenylbutazone)	6	10
Genetics: Acetylators	Slow	Fast
Isoniazid	3	1
Renal excretion	Without	With
Hydroxyhexamide secretion by phenylbutazone	5	22
Sulfaethidole resorption by alkalinity	11	4
Renal Insufficiency: gentamicin	2	100

[a]Potential consequences: increased $t_{1/2}$, toxicity; $t_{1/2}$, therapeutic failure.

a short half-life would eliminate drug more rapidly than expected, providing concentrations which may be too low to be effective. In some cases the control of plasma concentration is so necessary and difficult that the patient's blood must be assayed for drug content and the dosage adjusted to achieve the desired result. This process, called monitoring of drug plasma levels, is the subject of Sect. III.

III. CLINICAL PHARMACOKINETICS

A. Introduction

By necessity, drug therapy represents a gamble wherein optimization of the benefit-to-risk ratio is the reward. What we refer to as our knowledge of drug action is really a statement based on population averages. The normal dosage regimen and its expected results are generally a statistical best guess which we term "usual dosage" and "actions and adverse reactions." Clinicians recognize that each individual patient is different and the practice of medicine attempts to anticipate and avoid "nonaverage" complications or to adjust therapy based on observations made a posteriori.

Individual patients can be expected to differ with respect to both drug disposition (pharmacokinetics) and drug sensitivity (pharmacology). Many factors are potentially capable of influencing the drug–patient interaction, including age, sex, disease state, weight, personal habits such as smoking, other drugs, and foods. Obviously the modification of drug therapy based on the quantitative prediction of these effects for every drug is not possible, nor is it always necessary. However, there are a growing number of drugs for which consideration of the overriding characteristics of the drug–patient interaction can increase the likelihood of a more favorable benefit-to-risk ratio. This section will present five drugs selected to illustrate the clinical use of pharmacokinetics in improving the prospects for successful drug therapy. Individual pharmacokinetic variations may occur in absorption, distribution, excretion, and metabolism. These may be affected by disease, age, drugs, and so on. The use of kinetic methods to counteract these influences by individualization of drug therapy is called clinical pharmacokinetics.

Reviews on pharmacokinetics in the aged [22,23] and two published symposia, *Clinical Pharmacokinetics* [24] and *The Effect of Disease States on Drug Pharmacokinetics* [25], contain excellent examples together with an abundance of literature references. Although it is not reviewed here, it should be kept in mind that pharmacological response is also potentially affected by these same factors.

The safe and effective management of drug therapy in individual patients represents one of the most dramatic means by which pharmacokinetics has contributed to improved medial practice. While the dosage regimens for many drugs can be adjusted safely using symptomatic endpoints, there are important agents for which this is not ideal. Some agents require individual blood level determinations and adjustment of the dosage schedule to "titrate" the patient with the drug. Typical drug characteristics calling for this approach are (1) the drug is critically needed, (2) the response is better related to plasma concentration than to drug dosage, (3) a narrow range exists between the minimum required blood level and that which is likely to produce adverse effects, and (4) wide variability occurs in interpatient blood levels resulting from identical dosage regimens. An effective course of therapy with such an agent thus necessitates the determination of the dosage regimen required to provide the desired blood levels for each individual patient.

There has been a great deal of research on the problem of individual dosage regimens. The number of publications and dosage nomograms is too large to allow citation. One should also realize that it is a dynamic area. The future will bring further refinements. Today's "state of the art" with regard to a given drug therapy is just that. Therefore the selected drugs which follow are presented to illustrate the *concepts* involved in the individualization of dosage and not to recommend treatments, since tomorrow's answer may be different. The problems presented by each of these examples differ and therefore their clinical solutions differ as well. In each case the author's goal is to define the problem and to review the kinetic approaches to its solution.

B. Selected Problems in Clinical Pharmacokinetics

1. Phenytoin

Phenytoin (diphenyhydantoin) is one of the most widely used anticonvulsants. The control of seizures is more reliably correlated with anticonvulsant plasma levels than with dose. Average dosage regimens do not take into account individual patient variability. Plasma level monitoring of anticonvulsant drugs is widely recognized as the recommended approach to establishing the optimum dosage regimen for each patient. The range of optimal plasma concentrations has been established for several anticonvulsant drugs (Table 8).

The clinical evaluation of phenytoin pharmacokinetics has been extensively reported and references may be found in the reviews [26–29]. The

Table 8 Optimum Therapeutic Plasma Levels for Anticonvulsant Drugs[a]

Drug	Range (amount/ml)
Carbamazepine	4–10; 6–12 μg
Clonazepam	~30–60; 15–50 ng
Ethosuximide	40–80; 40–110 μg
Diazepam	>400–500; >600 ng
N-Desmethylmethsuximide[b]	10–40 μg
Phenobarbital	10–30; 10–25 μg
Phenytoin	10–20 μg
Primidone	5–10 μg
Valproic acid	~60–80; >50 μg

[a]As reviewed in Refs. 26 and 27.
[b]Active metabolite of methsuximide.

problems associated with individual patient variation in phenytoin plasma levels has made this research necessary.

Individual patient variability in phenytoin plasma concentration may be attributed to one or more of several reasons:

1. Nonlinear kinetics
2. Bioavailability
3. Drug interactions
4. Noncompliance

a. Nonlinear Kinetics. Less than 2% of the administered dose is excreted as intact phenytoin in the urine. The primary metabolite, parahydroxyphenylphenyhydantoin (HPPH), accounts for 70–80% of the dose [30]. In most patients phenytoin elimination is nonlinear following therapeutic doses owing to partial saturation of the p-hydroxylation metabolic pathway. A dose of 300 mg given once daily is often recommended for adequate seizure control with minimum side effects. While this was found to provide a mean of 10.8 μg/ml in 38 patients, the range was roughly 1–53 μg/ml [28]. A dose of 400 mg daily showed a mean nearly twice as high (18 μg/ml, 19 patients) and a similar wide range. This is due to the fact that the therapeutic range (10–20 μg/ml) approaches the maximum rate at which phenytoin can be eliminated [30]. Thus minor changes in dosage (or enzyme activity) can show dramatic effects on steady-state phenytoin levels. Since the therapeutic range is close to that for both toxicity and saturation, the resulting wide

variability indicates the need for individual patient dosage adjustment and plasma monitoring of drug concentration.

b. Bioavailability. Phenytoin is a cyclic imide of $pK_a \approx 9$ that is practically insoluble in water. The sodium salt dissolves to the extent of 1 g in 66 ml of water, but the solution is turbid until the pH is adjusted to >11.7. Thus the drug presents a solubility problem at physiological pH. It is mainly absorbed from the proximal portion of the small intestine, where the rate is slow and variable, with t_{max} values varying from 4 to 24 hr [29]. In a single-dose study of 100-mg capsules containing phenytoin sodium the elimination phase was apparently first order, thus allowing the comparison of *AUC* values, which varied from 92 to 131% of the innovator's product [31]. These results are surprisingly uniform when compared to previous reports of bioavailability from tablets, which varied from 20 to 90% [29]. Phenytoin is completely absorbed from most products currently available.

Steady-state phenytoin blood levels are significantly affected by absorption rates. Differences in manufacturing processes for various dosage forms can alter dissolution and absorption rates. Most capsules of phenytoin sodium should be administered several times a day, with the possible exception of Dilantin sodium, which might be given once a day owing to its slow release characteristics [32,33]. Differences in bioavailability characteristics do not appear to be due to faulty manufacturing processes but seem, instead, to be a problem inherent to phenytoin dosage forms. In general, the behavior of a single product from a single source appears consistent. Thus a patient whose dosage has been adjusted to provide suitable plasma levels should not be switched to alternate dosage forms or brands without reestablishing the optimum dosage regimen.

c. Drug Interactions. A great number of pharmacokinetic drug interactions involving phenytoin may be found in the literature. Only a few have been shown to be clinically significant [27]. Some of these have been reviewed in Sect. II. B, on pharmacokinetic drug interactions, and additional references are given elsewhere [27,28]. It should be kept in mind that drugs may elevate or depress phenytoin levels and some of the variability reported in patients may be attributed to differences in their drug therapy.

d. Compliance. Compliance, while always a problem, is especially difficult when patients do not understand the prophylactic nature of the treatment. Absence of seizures often provides a basis for noncompliance in the patient's mind. This is a well-documented problem with phenytoin.

Results reported by Lund [29] are typical, showing that 52% of 276 patients had levels below 10 μg/ml at prescribed doses of 5.6 ± 1.8 (SD)

mg/kg per day. Only 36.6% had values in the 10.0–20 μg/ml range, while 11.6% (35 patients) were higher than 20 μg/ml and 6 of these patients had side effects (nystagmus, ataxia, or somnolence). Compliance was tested in low plasma level patients, one of which had reported a seizure. Drug administration was supervised over a 7-day period and an increase of 25% or more in the plasma concentration was taken as evidence for previous lack of compliance. Of the 48 patients tested, 16 showed a positive test and admitted to noncompliance.

e. Dosage Adjustment with Nonlinear Kinetics. Phenytoin elimination can be described by Michaelis–Menten kinetics, where the elimination rate V (in mg/kg per day) may be defined

$$V = \frac{V_{\max} C}{K_m + C} \tag{1}$$

where $V_{\max}$ is the maximum rate and K_m is numerically equal to that value for C which provides $V = \frac{1}{2} V_{\max}$. During multiple-dose steady state the dose administered is equal to the amount eliminated during each dosage interval τ. It follows that the daily drug intake must equal the daily output. If R is defined as the daily administration rate (mg/kg per day or mg/day), then at steady state

$$R = \frac{V_{\max} C_{av}^{ss}}{K_m + C_{av}^{ss}} \tag{2}$$

which may be written

$$RK_m + RC_{av}^{ss} = V_{\max} C_{av}^{ss} \tag{3}$$

Dividing by C_{av}^{ss} and rearranging provides

$$R = V_{\max} - \frac{K_m R}{C_{av}^{ss}} \tag{4}$$

Thus a plot of daily dosing rate R versus R/C_{av}^{ss} has an intercept of $V_{\max}$ and a negative slope K_m.

Practice Problem 1
The steady-state data in Table 9 were obtained from a single patient as a function of the total daily dose of phenytoin given approximately every 8 hr. Estimate the value for K_m (in mg/liter) and V_{max} (in mg/day) for this patient.
Answer: A plot of R versus R/C_{av}^{ss} is linear with negative slope $K_m = 11.4$ mg/liter and intercept $V_{max} = 935$ mg/day.

The approach used in Practice Problem 1 can be applied to the adjustment of dose for an individual patient. If the C_{av}^{ss} values associated with two dosing rates (R) are known for a patient, then V_{max} and K_m may be estimated and R can be calculated for the desired C_{av}^{ss} using Eq. (4). If additional sets of C_{av}^{ss} and R values are obtained in the process of adjusting the dose for that patient, then the line of best fit for a plot based on Eq. (4) can be used to graphically to redetermine the V_{max}, K_m, and finally the new dosage rate to obtain a desired steady-state plasma level.

Practice Problem 2
Using the figure constructed for Practice Problem 1, predict the dose required to provide a steady-state plasma level of 12 mg/liter.
Answer: Substitution for C_{av}^{ss}, V_{max}, and K_m in Eq. (4) provides an R value of 480 mg/day.

A similar approach has been reported by Ludden et al. [34] based on Eq. (4) where a linear plot of R versus R/C_{av}^{ss} has an intercept V_{max} and a negative slope K_m. Therapy is initiated at a dosage rate R of 3–4 mg/kg per day using phenytoin sodium (for phenytoin use $R/1.09$). In accordance with Mawer et al. [35], dosage may be increased by increments of 50–100 mg/day if the average steady-state plasma levels are less than 6 mg/liter. If the

Table 9 Average Phenytoin Steady-State Plasma Levels C_{av}^{ss} as a Function of the Total Daily Dose in a Single Patient (90 kg)

Dose (mg/day)	C_{av}^{ss} (mg/liter)
90	1.20
210	3.36
300	5.41
390	8.13
540	15.4
600	20.3

levels exceed this value, then more conservative increments of 25–50 mg/day are suggested. Once two pairs of R and C_{av}^{ss} values are available, a two-point plot based on Eq. (4) may be used to estimate V_{max}, K_m, and, if necessary, the third dosage rate. As additional data become available, the assessment of V_{max} and K_m may be done on a statistical basis.

Practice Problem 3

A trial dosage regimen of 250 mg/day of phenytoin is found to produce a C_{av}^{ss} value of 4.16 mg/liter. The dose is increased to 350 mg/day and the resultant C_{av}^{ss} value is 6.82 mg/liter. Using the method of Ludden et al. [34], estimate V_{max} and K_m by making a two-point plot based on Eq. (4). Recommend a dose rate to provide a C_{av}^{ss} value of 12 mg/liter in this patient.

Answer: These data represent the patient in Practice Problems 1 and 2. The best estimates are V_{max} = 935 mg/day, K_m = 11.4 mg/liter, and R = 480 mg/day.

f. Constructing a Linear Dosage Nomogram with Nonlinear Kinetics. A nomogram may be defined as a graph that, by using a straight edge, allows the estimation of a dependent variable from the known values for two or more independent variables. It has the advantage of providing a rapid estimate without solving complex equations. If the equations for a system are solved once and represented in an effective nomogram, it should be possible to make future estimates without the need for repeatedly solving the equations. Phenytoin dosage adjustment provides an excellent example wherein nonlinear pharmacokinetics makes simple dosage adjustment decisions difficult, especially since K_m and/or V_{max} may vary. It would be convenient to construct a nomogram which would use the known values for the two independent variables (daily dose and observed plasma concentration) to determine what adjustment, if any, should be made in order to obtain the desired plasma concentration.

The following approach, taken from Martin et al. [30], illustrates how a convenient nomogram was developed and employed. The experimental values are for normal volunteers taking a suspension of phenytoin as the free acid. The resulting nomogram provided satisfactory estimates when applied to literature data. The extent of utility of this specific nomogram is not the reason for its inclusion here; rather, the method of construction of this linear dosage nomogram for nonlinear kinetics is considered a useful technique.

The method of Ludden et al. [34] allowed the calculation of the third dose based on the results for the first and second estimates. But how can one estimate the second dosage adjustment, given nonlinear kinetics, when the first dosage schedule (R) chosen for a patient does not provide the desired concentration? One approach is by use of the nomogram suggested by Martin et al. [30].

The recommended test dose is 4.3 mg/kg per day given in two or more divided doses. (A minimum of two doses per day is recommended [30].) If the average values apply to the patient, then the C_{av}^{ss} value will be approximately 8.2 mg/liter, as shown by the reference line in Fig. 3. The adjusted dosage to achieve a therapeutic level may then be taken directly from this reference line. For example, a dose of 5.8 mg/kg per day would be required to achieve 15 mg/liter. Once two doses are tried and their resulting C_{av}^{ss} values are known, the patient's K_m and V_{max} may be estimated. Further adjustments, if necessary, can be made using Eq. (2).

If the first C_{av}^{ss} is not on the reference line, then K_m and/or V_{max} may be different for that patient. The additional lines in Fig. 3 represent other estimates for K_m and V_{max}. The mathematical technique by which the additional lines were calculated is complex. It involves an acceptable fit to this single observation so that the new K_m and V_{max} estimates are jointly a minimum scaled distance from the original population averages. The lines represent a statistical best estimate for that individual based on the single data point and a knowledge of the population values. The use of the nomogram is simple. (Figure 3 has been constructed from values in the original report. For the complete nomogram see Ref. 30.) The line which is closest to the observed C_{av}^{ss} value at a given dose is used to make an estimate of the adjusted dose for the desired C_{av}^{ss}.

Practice Problem 4

A 4-ml dose of phenytoin suspension (125 mg of phenytoin acid per 5 ml) is administered to a 70-kg patient every 8 hr and the resultant steady-state plasma level was found to be 4.1 mg/liter. Using the portion of the dosage nomogram of Martin et al. [30] reconstructed in Fig. 3, recommend a regimen to provide a C_{av}^{ss} of 11 mg/liter.

Answer:The total daily dose being given is 3 (100 mg/70 kg) or 4.3 mg/kg per day. After locating the appropriate line in Fig. 3, one can estimate that a dose rate of 7.1 mg/kg per day or 497 mg/day would provide the desired C_{av}^{ss}. The recommended second trial dose rate would be 5 ml every 6 hr or 10 ml every 12 hr. Once this dose is given and the resultant C_{av}^{ss} determined, a final adjustment (if necessary) may be made by estimating K_m and V_{max} for this patient and using Eq. (2) (or the graphical approach shown in Practice Problem 2).

2. Gentamicin

a. Therapeutic and Toxic Plasma Levels. Survival rates for patients with nosocomial infections caused by gram-negative organisms are significantly improved by aminoglycoside therapy. This success is realized in spite of their

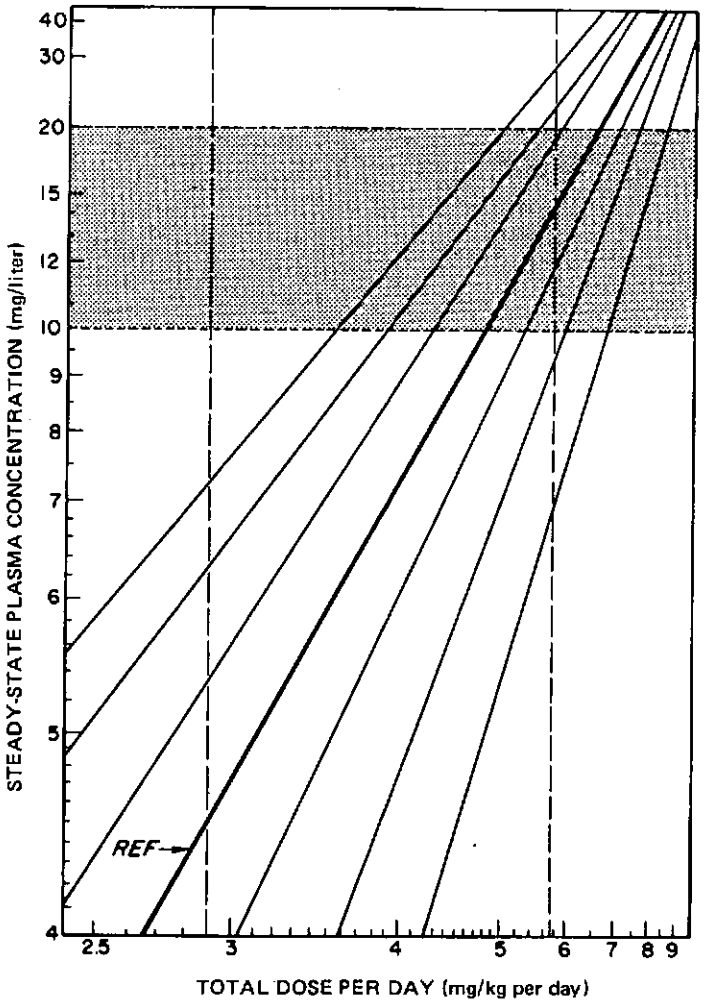


Fig. 3 The reference line was drawn using V_{max} = 10.3 mg/kg per day and K_m = 11.5 mg/liter [30] in Eq. (4). If a trial dose of 4.3 mg/kg per day of phenytoin (in two or more doses) provides a C_{av}^{ss} near this line (~8.2 mg/liter), then the reference line may be used to predict the corrected dosing rate (R) to achieve the therapeutic range (shaded). If the trial dose provides a C_{av}^{ss} closer to one of the other lines, then that line should be used. The additional lines have been constructed by estimating the V_{max} and K_m values used in the nomogram of Martin et al.; for the complete nomogram see Ref. 30. The region of applicability for the initial dose is shown by the two broken, horizontal lines.

known oto- and nephrotoxicity. While there is general agreement that a narrow margin exists between therapeutic and toxic blood levels, the optimum therapeutic range is uncertain. In addition to variations in bacterial sensitivity which alter the minimum effective concentration of antibiotic required for various infections, there is also the difficulty of relating plasma concentration to potential for toxicity.

Controversy exists regarding the feasibility of assigning therapeutic and toxic plasma concentrations to the aminoglycosides. Variability exists both in bacterial resistance and patient sensitivity. Among the high-risk patients are the elderly, the dehydrated and those with renal damage. Guidelines for plasma concentrations are summarized in Table 10 [36–49].

The therapeutic peak levels for gentamicin may be regarded as 5–10 μg/ml. Peak levels above 12–15 μg/ml and prolonged maintenance of trough (or nadir) levels above 2 μg/ml have been associated with an increased incidence of toxicity [36,37]. Goodman et al. [38] reported that a gentamicin nadir level greater than 4 μg/ml was the only variable among those tested that was correlated significantly with nephrotoxicity. Treatment failures may be due to either resistant organisms or subtherapeutic serum levels. Serum concentrations following calculated doses are highly unpredictable, even when creatinine renal clearance values are used as a guide. The $t_{1/2}$ values show wide intersubject variation, even with normal renal function. While dosage adjustment based on creatinine clearance values has undoubtedly reduced the incidence of toxicity, it has not provided a reliable means for predicting gentamicin plasma levels.

b. The Need for Monitoring. The narrow therapeutic index and wide patient variability make plasma level monitoring a necessity in aminoglycoside antibiotic therapy. A large number of dosage adjustment calculations and nomograms have been suggested. One proposal for gentamicin dosage based on the pharmacokinetic analysis of the drug in each individual patient [40] cited 11 earlier methods, 9 of which had previously been critically reviewed [41].

Table 10 Approximate Therapeutic and Toxic Plasma Concentrations

	C^{ss}_{max} (μg/ml)		C^{ss}_{min} μg(ml)	
Aminoglycoside	Therapeutic	Toxic	Therapeutic	Toxic
Amikacin	20–28	>32	<8	>10
Gentamicin	5–10	>12	<1	>2
Tobramycin	5–10	>12	<1	>2
Netilmicin	6–10	>16	<2	>4
Sisomicin	4–12			

The earlier methods were based on the relationship between gentamicin half-life and either creatinine renal clearance or creatinine plasma concentrations, assuming monoexponential drug disposition. These recommendations have been beneficial but not ideal; the predictability of gentamicin plasma levels was improved but still uncertain.

The mean values for aminoglycoside half-lives are generally reported as 2–3 hr and the volume of distribution as 0.2–0.3 liters/kg. However, they are influenced by the age and disease state of the patient and are subject to a high degree of variability. The distribution volumes have been reported to vary 12-fold for gentamicin, 6-fold for tobramycin, and 4-fold for amikacin. In a study of burn patients a dose of 5 mg/kg per day was found to be subtherapeutic (peak concentrations < 4 mg/liter) [43] owing to decreased $t_{1/2}$ values. The $t_{1/2}$ values in the younger patients ($\leq$20 years) were significantly shorter than those in the older patients (31–64 years), with means and standard deviations of 1.1 ± 0.44 hr and 3.3 ± 1.1 hr, respectively. The average doses required to obtain similar peaks were 12.8 mg/kg per day for 7.6 mg/liter (younger) and 7.2 mg/kg per day for 7.7 mg/liter (older). No renal toxicity or ototoxicity was observed. These studies suggest that burn patients may require an increased dosage of gentamicin and that the measurement of serum gentamicin levels is required to individualize the regimen, since additional factors, such as age, are also significant [42,43].

It has been suggested that, since aminoglycosides are primarily distributed throughout extracellular fluid, dosing on a body weight basis can result in overdoses in obesity. Hull and Sarubbi [44] have published an improved method for gentamicin dosage adjustment based on lean body weight and renal function. Bryan [45] criticized the approach, arguing that while the dose size has been corrected for distribution, the dosage interval, which is dependent on both renal clearance and distribution, has been corrected for only renal function. A small patient would tend to be underdosed and a large patient overdosed. Spyker and Guerrant [46] reach a similar conclusion and advocate the use of a "corrected creatinine clearance" to account for the fact that a single clearance value may be operating on different V_Z values. Thus, if the initial concentration and creatinine clearance values are equal, the fraction of drug cleared per dosing interval will increase as V_Z decreases. Hull and Sarubbi [47] applied this recommendation retrospectively and found that ignoring this resulted in an overprediction of 0.7 μg/ml at 40 kg and an underprediction of 1.2 μg/ml at 95 kg. The clinical significance was questionable.

The determination of the optimum basis for body weight has also caused debate [48]. Tobramycin concentration was 28% higher and gentamicin was 22% greater in obese subjects given doses equal to those of normal volunteers [49]. The adjustment of V_Z based on ideal weight plus 40% of excess

weight provided values similar to those for the normals. It was suggested that this reflects some distribution into adipose tissue.

Dosing weight is normally estimated from the ideal body weight (IBW) and actual body height and weight (ABW) of the patient as follows:

$$\text{Males:} \quad \text{IBW} = 50 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft} \tag{5}$$

$$\text{Females:} \quad \text{IBW} = 45.5 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft} \tag{6}$$

$$\text{Dosing weight} = \text{IBW} + 0.4\,(\text{ABW} - \text{IBW}) \tag{7}$$

There is general agreement that maintenance doses should be based on IBW and renal function. There is controversy regarding the appropriate body weight to use for the loading dose. An argument in favor of using larger loading doses based on actual body weight is that higher concentrations, albeit transient, will guard against subtherapeutic levels during the critical early period.

The reduced dose during renal insufficiency may be approximated from

$$\text{adjusted dose} \cong \text{dose}\,\frac{CL_{CR}}{100} \tag{8}$$

where the creatinine clearance value is in milliliters per minute. Prescribing information will commonly supply a nomogram that is specific for the aminoglycoside. These vary slightly from this approximation. Creatinine clearance values may be roughly approximated from creatinine serum concentration C_{CR} as follows:

$$\text{Males:} \quad CL_{CR} = \frac{[140 - \text{age (yr)}][\text{weight (kg)}]}{72\ C_{CR}\ (\text{mg \%})} \tag{9}$$

$$\text{Females:} \quad CL_{CR} = 0.85\ CL_{CR}\ (\text{males}) \tag{10}$$

c. Individualized Dosage Regimens. Although the plasma concentration requirements may differ, the pharmacokinetic approach to aminoglycoside dosage control is similar for all the antibiotics in this group. Gentamicin will serve as the example for the group, since it has been most extensively used.

Since creatine renal clearance values do not result in reliable dosage adjustments, it has been suggested that the drug itself be used to calibrate the patient [40,42]. In this method an initial dose must be administered in order to determine the gentamicin time course and calculate subsequent doses. The test dose and subsequent doses are given by constant-rate infusion over a 1-hr period and a minimum of three blood samples are analyzed

during the postinfusion phase, usually 30 min after termination and 1 and 3 hr later. In renal failure the creatinine clearance or creatinine plasma values may be used a priori to estimate the $t_{1/2}$ and adjust the sampling time. The three or more data points are fitted by nonlinear regression to a simple monoexponential function, $C = C_{max}e^{-\lambda_2 t}$, where t is the time since cessation of the infusion. The initial rapid distribution (λ_1) is ignored together with the slow terminal (λ_Z) tissue release phase. The basis of the method is illustrated in Sample Problem 1 and the approach using three blood samples is shown in Practice Problem 5.

Sample Problem 1

An 80-kg adult male with normal renal function is given a 1-mg/kg test dose of gentamicin as a constant-rate infusion over a 1-hr period. A semilogarithmic plot of the resulting gentamicin plasma concentration time course is shown in Fig. 4. Recommend a dosage interval and an infusion rate to achieve a steady-state maximum of 6 μg/ml and a minimum of 1 μg/ml using a 1-hr infusion period T for each dose.

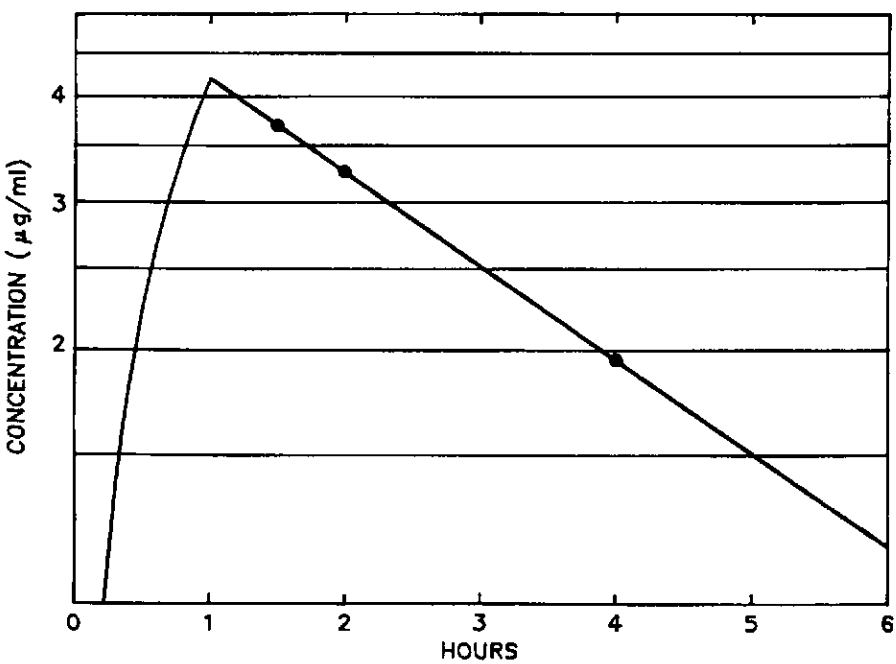


Fig. 4 Gentamicin plasma concentration from 1-mg/kg constant-rate infusion.

Solution: The apparent elimination rate constant λ_2 for this patient is 0.256 hr^{-1}. Thus the postinfusion period t_{pi} may be calculated from

$$t_{pi} = \frac{1}{\lambda_2}\left[-\ln\left(\frac{C^{ss}_{min}}{C^{ss}_{max}}\right)\right] = \frac{1}{0.256}\left[-\ln\left(\frac{1}{6}\right)\right] = 7 \text{ hr}$$

Therefore $\tau = T + t_{pi} = 8$ hr.

The degree of accumulation may be calculated from

$$X = \frac{1}{1-e^{-\lambda_2 \tau}} = \frac{1}{1-0.129} = 1.15$$

Therefore the test infusion rate would provide a steady-state maximum of

$$C^{ss}_{max} = C_{max} X = 4.2\ (1.15) = 4.83\ \mu g/ml$$

The adjusted infusion rate is

$$R_0 \text{ (desired)} = [R_0 \text{ (test)}] \frac{C^{ss}_{max} \text{ (desired)}}{C^{ss}_{max} \text{ (test)}}$$

$$= [80 \text{ mg/hr}]\left(\frac{6}{4.83}\right) = 99 \text{ mg/hr}$$

The individualized regimen would be an infusion rate R_0 of 100 mg/hr for 1 hr repeated every 8 hr.

Practice Problem 5

A 70-kg adult with normal renal function receives a test dose of 2 mg/kg of netilmicin infused at a constant rate over a 1-hr period. Three netilmicin serum concentrations were determined after termination of the infusion with the following results:

Time (hr):	1.5	2.0	4.0
C (μg/ml):	5.2	4.5	2.6

Recommend a dosage interval and an infusion rate to provide a steady-state maximum of 8 μg/ml and a minimum of 1 μg/ml.

Answer: The value for λ_2 is 0.276 and the calculated value for C_{max} (at 1 hr for the test dose) is 5.95 μg/ml. Thus $t_{pi} = -\ln 0.125/\lambda_2 = 7.5$ hr and $\tau =$

8.5 hr, which will be changed to 8 hr for practical reasons. Thus $X = 1.12$ and C^{ss}_{max} (test) = 6.66. The final regimen is $R_0 = 168$ mg/hr given over a 1-hr period every 8 hr.

The approach shown above is one of direct use of the first dose profile without calculating the volume of distribution. The same result may be obtained by calculating the apparent volume of distribution or the total body clearance for the individual patient and using this value to calculate the adjusted infusion rate. The τ value is calculated as done above and the same results are obtained by either approach. Clearance may be estimated by rearranging the postinfusion equation

$$C = \frac{(1 - e^{-\lambda_2 t})R_0}{CL} \tag{11}$$

and solving for CL at a specific time such as T when $C = C_{max}$:

$$CL = \frac{(1 - e^{-\lambda_2 T})R_0}{C_{max}} \tag{12}$$

The values for R_0, λ_2, T, and C_{max} are all obtained from the test dose. Equation (12) may be rewritten as the multiple-dose steady-state equation for C^{ss}_{max} as follows:

$$C^{ss}_{max} = \frac{R_0(1 - e^{-\lambda_2 T})}{CL(1 - F)} \tag{13}$$

where $F = e^{-\lambda_2 \tau}$. The infusion rate required to provide the desired C^{ss}_{max} can be calculated by rearranging Eq. (13) to give

$$R_0 = \frac{C^{ss}_{max}\ CL\ (1 - F)}{1 - e^{-\lambda_2 T}} \tag{14}$$

Practice Problem 6 illustrates the use of these equations.

Practice Problem 6

Using the data in Sample Problem 1, calculate the value for CL and use this value to find the adjusted infusion rate required to provide C^{ss}_{max} value of 6 and a C^{ss}_{min} value of 1 on a repetitive 1-hr infusion regimen.

Answer: The values are $\tau = 8$ hr, $CL = 4.3$ liter/hr, and $R_0 = 100$ mg/hr.

This method was assessed in burn patients [42,43] and in surgical, medical, obstetric, and gynecological patients receiving gentamicin for gram-negative infections [40]. In the latter study desired peak and nadir levels ranged from 6 to 10 and 0.5 to 2 μg/ml, depending on the diagnosis and clinical condition. To assess the predictability of the method, 63 pairs of peak and nadir levels were determined at least five half-lives after the regimen was initiated. A total of 60% of the C^{ss}_{max} values and 56% of the C^{ss}_{min} values were within 1 μg/ml of those predicted. Some bias was observed in the results, in that predicted steady-state nadir values tended to be lower than observed. Patients with serum creatinine values below 1.2 mg % had $t_{1/2}$ and total body clearance (CL) values (means: $t_{1/2}$ = 2.25 hr; CL = 0.082 liter/hr per kilogram) significantly different from those with levels above 1.2 mg % (means: 5.3 hr and 0.21 liter/hr per kilogram). Distribution volumes were similar (means: 0.22 and 0.21 liter/kg). The variability in distribution, $t_{1/2}$, and CL values was significant, even with normal renal function. Although the maximum recommended dose is considered to be 5 mg/kg per day for life-threatening infections in patients with normal renal function, the average doses for patients under 40 years of age was 6.78 mg/kg per day. Those with serum creatinine levels less than 1.2 mg % required 6.14 mg/kg per day.

A biexponential equation has been shown to be more predicative in fitting long-term postinfusion data. Although the difference may be clinically insignificant, determination of postdistribution increase in minimum levels is suggested as a means of detecting tissue accumulation.

The methods outlined by Sawchuk et al. [40,42] use the individual patient as his or her own control. They argue that, with proper management, the time required to evaluate the patient's individual pharmacokinetic parameters using a test dose can be less than that required to determine creatinine clearance. This also has the advantage of representing a direct determination of CL and $t_{1/2}$ for that patient.

3. Lidocaine

a. Pharmacokinetics and Actions. The clinical pharmacokinetics of lidocaine has been reviewed [50,51]. Rowland [50] has recommended an approach to dosage adjustment of lidocaine based on the clinical endpoint of suppression of arrhythmias. The following discussion is based on those recommendations.

Lidocaine is widely employed for treating ventricular arrhythmias accompanying myocardial infarction and heart surgery. Lidocaine is not administered orally owing to extensive "first-pass" metabolism. Following intravenous injections, only a small percentage of intact lidocaine (3–10%) can be recovered from the urine. It is recommended that an intravenous bolus *not* be administered faster than 1 mg/kg per minute. Lidocaine is rapidly

taken up by highly perfused organs, such as heart, brain, lungs, liver, and kidney, leaving only an estimated 15% of the dose in the blood [50]. A biphasic time course follows, with the distribution phase lasting approximately 30 min, $t_{1/2}(\lambda_1) \approx 4$ min, and an elimination half-life $t_{1/2}(\lambda_Z)$ of roughly 1.6 hr. Up to 30% of the administration dose may be eliminated during the distribution phase. Total body clearance CL is roughly 10 ml/kg per minute.

Lidocaine undergoes successive N-de-ethylation to form monoethylglycinexylidide (MEGX), which approximates lidocaine in half-life and potency. This is further metabolized to glycinexylidide (GX), with decreased antiarrhythmic effect but an increased $t_{1/2}$ of 10 hr, making its contribution to toxicity likely owing to its accumulation.

The onset of antiarrhythmic and central nervous effects following intravenous bolus is 1–2 min. The maximum rate of injection should *not* exceed 1 mg/kg per minute for safety [50]. The majority of patients respond to 1.2–6.9 μg/ml blood (or plasma) levels. Normally plasma levels are linear with dose and show an initial level of 2 μg/ml per dose of 1 mg/kg. Duration is often 20–30 min and effects are minimal below 1.2 μg/ml. Toxicity (usually central nervous depression, hypotension, convulsions) generally occurs above 6 μg/ml. However, the MEC must be determined for each patient and levels in excess of 6 μg/ml have been reportedly required to suppress premature ventricular beats in some patients while central nervous symptoms have been observed within the range of 1.2–6.0 μg/ml in some cases.

b. Dosage Regimen Adjustment. It is only practical to monitor plasma levels during extended treatment to check predictions or to distinguish between low levels and refractory patients. Rowland [50] has pointed out that the emergency use of lidocaine does not provide time for dose adjustments based on plasma assays and has recommended the following method based on clinical response.

Since onset is immediate, the dosage adjustment period begins with the very first dose and does not refer only to the steady state, as was the case with previous discussions in Chap. 6. An intravenous bolus of 1 mg/kg (infused no faster than 1 mg/kg per minute) is often used as an initial dose. If suppression is achieved, then the dose is repeated each time arrhythmias return. In this regimen the value for τ increases with each succeeding dose as the tissue levels increase until the steady state is achieved. It is only in the steady state that the duration following each dose will become uniform.

If the first dose fails to achieve acceptable results, a dose of 0.5 mg/kg every 5 min up to three times should be administered until suppression is achieved. After the third dose the total administered is 2.5 μg/kg, which, if given as a bolus, would provide an initial level of 5 μg/ml. If one neglects the fact that levels would be lower owing to elimination and distribution, the lack of suppression at this dose suggests a refractory patient and the

potential for toxicity. An alternative agent might be considered in this event.

If suppression is achieved at 1 mg/kg followed by 0.5 mg/kg (every 5 min up to three doses), then the observed duration may be used to estimate how high the plasma levels are above the MEC. If duration is 15 min, then plasma levels are sufficiently high and an infusion rate may be calculated based on the plasma level expected from a bolus of the total administered lidocaine. If duration is short, such as 5 min, then another bolus of 0.5 kg/mg is recommended and the contribution of this dose to the expected plasma level should be included in the infusion rate calculation. The infusion is then started to maintain this estimated blood level.

An infusion steady state will require approximately four half-lives, or 6 hr. During the first hour the rapid decline following the initial loading doses may not be offset by the slow infusion and symptom breakthrough may occur. A single 0.5-mg/kg bolus is recommended while maintaining the infusion rate.

If arrhythmias reappear during a stabilized infusion, then a 0.5-mg/kg bolus is recommended together with an increase in infusion rate. A transient duration following this supplemental bolus suggests that the infusion is too slow and should be increased by an increment of 10–15 μg/kg per minute. A relatively long duration indicates that a smaller increase in infusion would be appropriate. As the need for lidocaine decreases, the infusion rate should be slowly reduced in increments of 10 μg/kg per minute, since the time to achieve a new steady-state plateau is also four half-lives. If arrhythmias reappears, a 0.5-mg/kg bolus should be given and the duration again used to estimate the relationship of plasma levels to MEC. Loss of control within an hour suggests returning to the previous rate, whereas control lasting several hours implies that the adjusted rate is adequate. During steady state each increase of 10 μg/kg per minute of constant-rate infusion increases the plasma level by approximately 1 μg/ml.

During congestive heart failure the lidocaine clearance is reduced. In the range of cardiac output (CO) equal to 35–90 ml/kg per minute the clearance may be approximated by

$$CL \text{ (ml/min per kg)} \simeq 0.14\text{CO} - 1.7 \tag{15}$$

The recommended procedure is similar to that previously described, except that the *CL* value used to calculate the infusion rate is estimated from Eq. (15).

Practice Problem 7

A 60-kg patient is given an initial dose of 1 mg/kg by intravenous bolus (at 1 mg/kg per minute), which fails to suppress arrhythmias. A second bolus of 0.5 mg/kg is given with adequate results for 15 min.

(a) Recommend an infusion rate for this patient.
Answer: The initial plasma concentration estimate is 3 μg/ml. The infusion rate R_0 is C_0CL = 30 μg/min per kg = 1800 μg/min.

(b) After 30 min the arrhythmias are found to return. Recommend a course of action.
Answer: A single dose of 0.5 mg/kg (30 mg) is given while maintaining the infusion. If the relief is transient, the infusion rate should be increased.

(c) If a 70-kg patient suffered from congestive heart failure and had a cardiac output of 40 ml/kg per minute, how would this change the estimates in part (a), assuming the same history regarding the bolus doses?
Answer: The estimated clearance, Eq. (15) is $CL = 0.14(40) - 1.7 =$ 3.9 ml/min per kilogram. Therefore R_0 = (3μg/ml)(3.9 ml/min per kg) = 12 μg/kg per minute or 840 μg/min.

4. Theophylline

Theophylline was isolated in 1885 and first introduced as a diuretic near the turn of the century. Its value in treating bronchial asthma has been recognized since at least 1941 [Lamson and Bacon, *J. Am. Med. Assoc., 116*:915 (1941)]. In the United States alone nearly 9 million people are asthmatics [52]. Theophylline overdosage can result in anorexia, headache, nausea,diarrhea, vomiting, seizures, and cardiac arrhythmias [52–54]. Deaths have generally been preceded by seizures wherein high blood levels (a mean of 54 μg/ml in one study [54]) have been reported. No serious adverse effects were reported when patients averaged less than 20 μg/ml [54]. The degree of toxicity in 17 patients with elevated blood levels was reported as mild at 28 μg/ml (averages), potentially serious at 41 μg/ml, and severe at 47 μg/ml. However, in one report seven out of eight deaths occurred without apparent adverse effects prior to the seizure [54]. A great deal of clinical research has been directed toward effective and safe theophylline dosage regimens. Only in recent years has theophylline therapy become dependent on pharmacokinetic management. The reports on which the following section is based are cited in the Refs. 52–56. Although progress has been made, it is likely that further refinements will become available.

a. Why Monitor? Theophylline pharmacokinetics are well behaved with the exception of the intersubject variability in biological half-life. This is somewhat surprising, since its pharmacokinetics are generally linear in adults within the dosage ranges encountered in therapy. It might be anticipated that genetic factors would play an important role, since only 7% of the intravenous dose is excreted intact in the urine. In general, highly metabolized drugs appear predisposed toward wide $t_{1/2}$ variation. In addition, age,

weight, diet, disease, and cigarette smoking can influence theophylline elimination.

The exact mechanisms and enzymes by which the liver metabolizes theophylline are not known. Since cigarette smoking increases elimination, cytochrome P_{448}, which can be induced by substances in the smoke, has been implicated. The proposed metabolic products are 3-methylxanthine (36%), 1,3-dimethyluric acid (40%), and 1-methyluric acid (17%), the remaining 7% being excreted as theophylline.

The effective plasma concentration range for theophylline is rather narrow. Although improvement in pulmonary function was reported at blood levels of 5, 10, and 20 μg/ml, it is generally agreed that 10–20 μg/ml is the desirable range. Despite considerable variation in the individual tolerance to theophylline, steady-state minimum levels above 20 μg/ml are generally associated with adverse effects and those below 5 μg/ml are considered subtherapeutic.

That theophylline toxicity and efficacy are related to serum levels, the low therapeutic index, and the high degree of interpatient half-life variability all combine to make individual patient blood level monitoring a necessity.

b. Pharmacokinetics. Theophylline blood levels following intravenous injections have been described by a two-compartment open model. The λ_1 phase is completed within roughly 30 min and is very rapid relative to the λ_Z phase, which has an average $t_{1/2}$ of 5–6 hr. Typical reported ratios for λ_1/λ_Z (average values) vary from 24 to 46. Therefore for most clinical decisions theophylline may be regarded practically as monoexponential disposition. Although Michaelis–Menten kinetics might be expected, dose-dependent kinetics have not been reported in adults in the usual dosage range. In children, where the $t_{1/2}$ value is reduced to an average of 3–4 hr, steady-state levels as a function of infusion rate were characteristic of saturation kinetics [57].

In spite of normally linear kinetics, the $t_{1/2}$ varies from roughly 3.0 to 20.7 hr (usually stated 3–10 hr) in healthy adults and 1.4–7.9 in asthmatic children [53]. In premature primary apnea a range of 12.6–29 hr has been reported [53]. The $t_{1/2}$ was decreased in adults who smoked (from roughly 7 to 4 hr) and increased in the case of liver disease. Reduced clearance and increased toxicity have been reported in congestive heart failure. Mean half-life values increased slightly in obese patients while V_Z was not altered when based on total body weight (TBW) [58], making TBW more useful than ideal weight for calculating loading doses. Mean values for CL increased from 52 ml/kg per hour in nonsmokers to 74 ml/kg per hour in either marihuana or tobacco smokers [59].

In contrast to elimination, the absorption and distribution parameters are relatively stable. Theophylline is quickly and nearly completely absorbed (>90%) from solutions and rapid-release tablets. Plasma peak concentrations

are reached within 1–2 hr and absorption is generally predictable. Displacement problems are not considered significant, since only 55–63% is plasma protein bound in the therapeutic range [52]. The apparent volume of distribution is approximately 0.5 liter/kg and is relatively constant in comparison to the $t_{1/2}$ values. Since the λ_1/λ_Z ratios are so large, there is no significant difference between V_Z and V_{ss}.

Thus absorption is dependable, V_Z is relatively constant, and displacement from bound protein is insignificant, whereas $t_{1/2}$ is extremely variable and the steady-state desirable range is narrow.

c. Dosage Regimen Complications. In addition to genetic factors, the plasma clearance of theophylline is altered by age, obesity, hepatic cirrhosis, congestive heart failure, cigarette and marihuana smoking, troleandomycin, erythromycin, and possibly other dietary, disease, and drug influences [53]. In comparison, V_Z is relatively constant, with an average of roughly 0.5 liter/kg and a range of 0.3–0.7 liter/kg. Since absorption is rapid and complete, the loading dose equation for intravenous administration, $DL = CV_Z$, is useful for either route [54]. This equation is generally employed without individualization. In contrast, the initial estimation of maintenance dose is dependent on $t_{1/2}$, making it nearly impossible to proceed with certainty. Hendeles et al. [54] have stated that "variability in plasma clearance among patients is so great that no constant infusion can be recommended that can reasonably predict both optimum therapeutic efficacy and safety." Literature recommendations do not always agree on the details of approaching this problem [60]. There is general agreement on dosage philosophy: Cautiously attempt to steady-state the patient without exceeding 20 μg/ml by using average values for guidelines. The plasma theophylline levels must then be determined and the dose adjusted accordingly.

Determination of steady-state plasma values is a good example of differences among recommendations. Levy [52] emphasized that the shape of the plasma concentration curve between doses makes single time point determinations risky. He recommended taking four to six samples followed by the calculation $C_{av}^{ss} = AUC/\text{dose}$. He noted that the use of saliva samples in place of plasma represents a potential solution to the problems of pain and trauma associated with multiple blood sampling during a short (typically 6 hr) dosage interval. Hendeles et al. [54] recommended the determination of C_{max}^{ss}, assuming t_{max} values of 2 hr (solutions and rapid tablets) and 4 hr (prolonged release tablets) after 3 days or more of a stable regimen. They criticize the use of only C_{min}^{ss} values using the following example. Suppose $C_{max}^{ss} = 18$ μg/ml and $C_{min}^{ss} = 8$ μg/ml and the patient experiences symptom breakthrough near the end of each dosage interval. Since $C_{min}^{ss} < 10$ μg/ml, one might be tempted to increase the dosage. Realizing that C_{max}^{ss} is nearly 20 μg/ml, it would be better to keep the total daily dose constant but decrease the dosing

interval and dose size. This would increase C^{ss}_{min} and decrease C^{ss}_{max}. According to Ogilvie [53], C^{ss}_{min} is the single most useful value if only one sample is to be taken, since it is known to occur at $t = \tau$, whereas t_{max} is variable. The divergence in opinion reflects the problem of obtaining the best appraisal of the patient's situation with the minimum pain and cost. It is well accepted that initial doses should be low and the increases small to reduce patient risk. The adjustment of dosage with a knowledge of an adult patient's steady-state values is done by simple proportion, assuming linear kinetics, and has been discussed in Chap 6. The process requires added caution in children, where nonlinear kinetics have been reported [57]. The difficult question is how to begin when interpatient $t_{1/2}$ values are so variable. The recommendations as reviewed by Hendeles et al. [54], which illustrate one rational approach to the problem, will be discussed.

d. Loading Dose. The average Vd of 0.5 liter/kg allows one to estimate that each 1-mg/kg dose results in a 2-μg/ml increase in plasma concentration using $DL = CV_Z$. To avoid overestimates due to V_Z values that are smaller than average, it is recommended that 10–15 μg/ml be used as the target value. In patients having no residual theophylline levels prior to initiating therapy, the loading dose based on this range would be 5–7.5 mg/kg. This can be administered as an oral solution, as uncoated tablets, or as a 30-min infusion of aminophylline wherein the dosage must be adjusted for theophylline content. (Each 100 mg of aminophylline contains 78–86 mg of theophylline.) If the treatment is an emergency and the patient has been taking theophylline previously, it is recommended that the initial plasma level be rapidly determined and the dose be calculated to make up the difference. If this is not possible, then a reduced dose should be estimated (e.g., 2.5 mg/kg).

e. Maintenance Dose. The initial estimation of a maintenance dosage regimen represents a best guess in consideration of all possible factors followed by cautious drug administration and finally correction of the regimen based on plasma theophylline levels. An early estimate which was often reviewed recommended 0.9 mg/kg per hour of aminophylline (approximately 0.75 mg/kg per hour of theophylline) as a constant infusion to provide 10 μg/ml. With the equation $C^{ss} = R_0/\lambda_Z V_Z$ the $t_{1/2}$ value which corresponds to this estimate is roughly 4.6 hr. Since this $t_{1/2}$ value is near the lower end of the adult range, the input rate would tend to be high for many patients. This recommendation was found to be more likely to produce an average of 20 μg/ml in hospitalized adults and some of those above the average approached the seizure range [54]. Using average doses corresponding to 0.7 mg/kg per hour of theophylline resulted in 20 of 49 patients exceeding 20 μg/ml and 17 patients experiencing various degrees of toxicity [54].

The initial estimated infusion rate following the loading dose must be modified to include those factors which influence $t_{1/2}$ [53,54]. Examples in mg/kg per hour are 0.85 for children less than 9 years, 0.75 for children over 9 years, 0.75 for smoking adults, 0.5 for nonsmoking adults, 0.3 for cardiac decompensation, and 0.1 for liver dysfunction and cardiac decompensation [54].

The loading dose and infusion rates discussed above are only first approximations. The resulting blood levels must be determined and the dosage adjusted for each patient. Hendeles et al. [54] have suggested that samples be drawn just prior to and 4–8 hr after beginning the maintenance infusion. The concentrations are then compared to determine the direction taken by the serum concentrations and their values relative to the therapeutic range. Empirical adjustments followed by repeated serum measurements are employed to achieve the final steady-state desired values. An alternative approach is to employ a conservative infusion rate over a 24-hr period and determine the resulting plasma concentration, which should begin to approach the steady-state value for most patients. Adjustments are then made and plasma concentrations monitored until a satisfactory stable condition is achieved. When the emergency has passed, the satisfactory infusion rate can then be converted to an oral maintenance dose regimen.

f. Oral Administration. In order to minimize patient intolerance, it is recommended that the dosage be slowly increased, with a minimum of 3 days between each adjustment [54]..The initial dose should be 16 mg/kg per day up to a maximum of 400 mg/day. If tolerated, this is to be increased slowly up to the average, which is 900 mg/day for adults. For children the averages are age dependent: 24 mg/kg per day under 9 years, 20 mg/kg per day for ages 9–12, and 18 mg/kg per day for ages 12–16. It is estimated that 10–20% of the patients will be at risk of toxicity owing to peak levels exceeding 20 μg/ml when using the average dosage regimens. Plasma monitoring and adjustment of dose (if indicated) are therefore appropriate. It is cautioned that small increments in dosage changes are prudent, especially in children, where dose-dependent elimination has been implicated [57]. Determination of plasma levels during the process of attaining steady state will help avoid the potential for high levels due to a patient being at the long end of the half-life range.

g. Dosage Forms. The wide variety of dosage forms containing various amounts of theophylline has contributed to the confusion surrounding dosage calculations. Kern and Lipman [55a] have listed more than 50 theophylline products, including the chemical analog dyphylline [7-(2,3-dihydroxypropyl)theophylline], which is not a theophylline salt and whose theophylline reference point has been challenged [55b]. Some typical examples of products

and their approximate theophylline contents are aminophylline (theophylline ethylenediamine) 85%; theophylline sodium glycinate 50%; oxtriphylline (choline theophyllinate) 65%; theophylline ethanolamine 75%; and theophylline as the monohydrate 91%.

There appears to be little difference in the oral bioavailability of various dosage forms with the exception of the longer duration in the case of sustained-release products. While sustained-release oral dosage forms appear to be generally well absorbed (there are notable exceptions), their absorption rate characteristics vary widely. Some of these products show very slow drug input rates. Such products are not interchangeable with the normal rapidly bioavailable tablets without careful monitoring of the patient and the readjustment of the dosage regimen. The same degree of caution should be exercised in interchanging sustained-release products, since bioequivalency cannot be assumed owing to the wide variability in release rates. A well-designed sustained-release product can afford a clinical advantage. One study documents the maintenance of therapeutic blood levels, with a peak–trough difference of 5 μg/ml, by administration of sustained-release oral tablets every 12 hr [60]. For the interested reader, that report also provides an excellent bibliography on the biopharmaceutics of theophylline sustained-release products.

When parenteral use is indicated, the intravenous route is preferred over the intramuscular route, which is painful. Rectal solutions are well absorbed, but suppositories appear to be absorbed slowly, erratically, and with irritation.

5. Digoxin

a. Introduction. In 1785 William Withering published "An Account of the Foxglove and Some of Its Medical Uses; With Practical Remarks on Dropsy, and Other Diseases." In it he commented, "For the last two years I have not had occasion to alter the modes of management; but I am still far from thinking them perfect" [61]. After two centuries of use, management of safe and effective therapy with digitalis alkaloids has remained difficult and imperfect. Digoxin, discovered in 1930, is no exception, in spite of the fact that it has been subjected to the most extensive clinical pharmacokinetic research. The safety and efficacy of digoxin therapy have increased decidedly since the importance of renal function in digoxin dosing became evident in 1964 and since the significance of digoxin bioavailability became recognized in 1971. In 1967 Jelliffe published a mathematical approach to digitalis kinetics in patients with normal and impaired renal function [62]. In spite of the limited clinical pharmacokinetic data at that time, this work led to reduced digitalis toxicity when the physician's dosage recommendations were

kinetic based. Although the pharmacokinetic parameters used for that nomogram are no longer regarded as dependable, the results were encouraging. In one report the incidence of toxicity was reduced from 35 to 12% [63].

These reports did much to foster the philosophy of individualization of dosage and of monitoring patient drug levels. Digoxin served as a case in point in the widespread acceptance of the role of clinical pharmacokinetics in therapy. Ironically, today there is less agreement on dosage recommendations for digoxin than for many other drugs wherein plasma monitoring and/or individualization of dosage is practiced. This is due to the fact that increased research has shown that patient variability is increasingly unmanageable. Published opinions vary from the position that plasma monitoring will never be successful to claiming that it is already successful and future research will make it even more so [64].

The variability in patient response to digoxin therapy may be ascribed to a combination of factors which fall into the following three categories:

1. Relationship of pharmacodynamics to pharmacokinetics
2. Absorption
3. Disposition

These are discussed next.

b. Pharmacokinetics and Pharmacodynamics. Following intravenous injection the serum digoxin concentration time course may be described by a biexponential equation, although a triexponential equation has also been reported. The time course for digoxin pharmacological response implies that the first exponential is associated with delivery from the blood to the site of action (Table 11). This rapid phase lasts 6–8 hr with a half-life of approximately 40 min. Following this initial distribution, the response has been shown to be correlated with digoxin plasma concentrations.

In spite of this correlation, the plasma concentrations required for similar responses vary widely between patients. Some patients elicit toxic manifestations at low or what are considered therapeutic plasma concentrations;

Table 11 Approximate Times for Onset and Peak of Digoxin Cardiac Activity

Route	Time of onset (hr)	Time of peak activity (hr)
Oral	0.5–2.0	2–6
Intramuscular	0.5–2.0	2–6
Intravenous	0.1–0.5	1–4

conversely, others show suboptimal responses at what are considered toxic levels. An absolute standard for a therapeutic window for the overall population cannot be defined. In general, approximately 67% of adults considered to be adequately digitalized will have digoxin serum levels in the range of 0.8–2.0 ng/ml. Approximately 67% of those adults presenting symptoms of digoxin toxicity will have concentrations exceeding 2.0 ng/ml. Although infrequent, some patients cannot tolerate concentrations even lower than 0.8 ng/ml.

Monitoring steady-state digoxin levels can be combined with clinical observations to identify patients who are either ultrasensitive or resistant to digoxin. While such monitoring can help decrease toxicity, it cannot be preventative. The uncertainty with regard to ideal digoxin plasma levels makes concentration-based predictions unreliable. Most patients exhibit a satisfactory inotropic effect at steady-state digoxin levels of 0.7–1.5 ng/ml [65]. Toxicity, especially life-threatening arrhythmias, are most likely at levels exceeding 3 ng/ml. But there is an undefined range, from 1.5 to 3 ng/ml, regarding potential toxicity. In a study of 109 patients treated with digitalis preparations, 16 patients developed arrhythmias potentially due to digitalis intoxication; when subjected to further testing, 5 were nontoxic and showed levels under 1.6 ng/ml. The remaining 11 patients all exceeded 1.6 ng/ml and were categorized as either definitely or possibly toxic [66].

An isolated digoxin serum concentration is not a sufficiently reliable basis to warrant the decision to increase or decrease the dose; clinical responses must be taken into account. When a discrepancy exists between the response and the established serum concentrations, several factors should be considered:

1. The analytical procedure
2. Sampling time
3. Compliance
4. The possibility that the digitalis glycoside administered was not digoxin
5. Pharmacological interactions which alter patient sensitivity to digoxin

Only after excluding these as possibilities should the conclusion be made that the patient falls outside the normal expectations for digoxin response or disposition.

In the presence of hypokalemia, digoxin toxicity may occur despite serum concentrations in the target range. Potassium depletion sensitizes the myocardium to digoxin. Potassium-depleting diuretics, corticosteroids, or amphotericin B can therefore predispose the patient to digoxin toxicity. Low magnesium levels can also result in digoxin toxicity.

Calcium causes cardiac contractility and excitability similar to that caused by digoxin. Hypercalcemia, especially from rapid intravenous injection, can

produce serious arrhythmias in digitalized patients. Conversely, low calcium levels can eliminate expected digoxin response. Serum calcium should be normal for digoxin therapy. In addition, disease states can increase (i.e., severe pulmonary disease) or decrease (i.e., hyperthyroidism) individual sensitivity to digoxin.

c. Absorption. Digoxin administered orally in solution is passively absorbed primarily in the small intestine. When digoxin is administered in tablets, absorption may continue in the lower intestine. Table 12 compares the absolute bioavailability from digoxin dosage forms. When oral dosage forms are taken after meals, the absorption rate may decrease but the total bioavailable dose is relatively constant. However, food high in bran fiber may reduce the amount absorbed.

Historically, digoxin tablet bioavailability represents one of the landmarks in recognition of the significance of formulation in clinical success. Just as success in digoxin dosage adjustment provided a major incentive for clinical pharmacokinetics, so did the variability in bioavailability from oral tablets cause unprecedented interest in generic bioequivalency. This is understandable, because the risk involved is high. A patient who is underdigitalized may die from the disease; overdosage may result in death from the drug. The range between these limits is narrow. It has been estimated that a 50% difference in bioavailability can make a well-digitalized patient either toxic or nontreated [67].

In 1971 Lindenbaum et al. [68] provided the basis for international concern when they discovered significant differences in bioavailability from different products, with peak levels from one tablet being seven times those from tablets of another manufacturer. Dissolution rate has been shown to be a key factor in controlling the absorption of digoxin from tablets [67,69]. Rapidly dissolving tablets approach the absorption obtained from an elixir. In one review the range of percentage absorbed and their dissolution rates for commercial tablets was from 38% (with 44% dissolution in 2 hr) to more than 90% (with more than 90% dissolution in 2 hr). Since 1973 (beginning with the U.S. Pharmacopeia) offical compendia have required dissolution rates aimed at producing a tablet bioavailability equivalent to that of the elixir. The most rigorous test appears to be the Dutch Pharmacopeia (a

Table 12 Absolute Bioavailable Fraction f of Digoxin Dosage Forms

Intravenous	Intramuscular	Elixir	Tablets	Solution-filled capsules
1.0	0.7–0.85	0.7–0.85	0.6–0.8	0.9–1.0

minimum of 90% dissolution in 1 hr), whereas the British Pharmacopeia requires 75% (1975) and the U.S. Pharmacopeia 65% (1975) [67]. Current U.S. Food and Drug Administration requirements for digoxin dissolution rate are 65–90% in 1 hr but not more than 90% in 15 min. Results show that these marketed products have clinically satisfactory bioavailability and variations in absorption are primarily due to patient factors [69].

Normally, 25–40% of a digoxin dose is excreted as metabolites formed primarily by hepatic hydroxylation. In approximately 10% of the patients given digoxin, 40% or more of the digoxin may be excreted as cardioinactive metabolites having reduction of the lactone ring formed by gut flora in the lower intestines. In these patients the formation of digoxin reduction products (DRP) is increased by formulations which allow unabsorbed digoxin to reach the lower intestines (slow-dissolving tablet > elixir > intravenous). Digoxin solution in soft gelatin capsules has been shown to be rapidly and nearly completely ($f = 0.9$–1.0) bioavailable. Consequently, the mean percent of DRP excreted by 22 subjects known to produce significant amounts was lower for the capsules (24%) than for rapidly dissolving tablets (41%) and less for the capsule in every subject. The mean urinary excretion of digoxin itself was 43% higher for the capsules and higher than from the tablets in each of the 22 subjects [70].

Both erythromycin and tetracycline were found to decrease gut bacterial metabolism of digoxin, resulting in increased digoxin serum concentrations in those patients who produced DRP on tablet regimens. This effect would be expected to decrease with the capsules or elixir. Because the solution-filled capsules provide nearly complete absorption, the oral doses are only 80% those of other extravascular dosage forms. These rapidly absorbed capsules also produce higher peaks. Until these are shown to be insignificant, it is recommended that capsules be taken twice a day in reduced doses rather than the larger dose once daily.

Coadministration of a number of agents has been shown to reduce the bioavailable dose of digoxin. Kaolin–pectin mixture causes a 40% reduction, while kaolin–pectin concentrated mixture reduces absorption by 62%. The concentrated product produced no effect when given 2 hr after digoxin, and a 20% reduction given 2 hr before. Antacids such as magnesium hydroxide, aluminum hydroxide, and magnesium trisilicate reduce bioavailability by approximately 30%. Other interfering drugs include cholestyramine (-20% to -30%), sulfasalazine (-18%), and paraminosalicylic acid (-20%).

Diphenoxylate with atropine products can increase digoxin bioavailability by approximately 20% by reducing gastrointestinal motility. Absorption from tablets was decreased in patients receiving metoclopramide (which increases motility) and increased with propantheline (which reduces motility) [69]. The reduction may be due to reduced time for dissolution, since

these tablets were slow to dissolve and the effect was not seen with the elixir or rapidly dissolving tablets. Another comparison showed that liquid-filled capsules were unaffected by meclopramide, while rapidly dissolving tablets showed a 24% reduction in AUC values [71].

The effect of various malabsorption syndromes on digoxin bioavailability is a subject of some controversy. Jejunoileal bypass for morbid obesity severely limited absorption surface and decreased fat absorption, but digoxin bioavailability from rapidly dissolving tablets was 87% of that prior to surgery [63]. Intrasubject variation in bioavailability is well recognized and appears to be an additional problem to that of dosage form effects [67]. While intersubject variation was partially connected to the dosage form, some subjects showed reduced absorption ability even with rapidly dissolving tablets [67].

d. Digoxin Disposition and Plasma Sampling. It has been practical to describe the digoxin plasma concentration time course following intravenous administration using a biexponential equation. While early plasma levels do not reflect the concentration of digoxin at the site of action, the concentrations during the terminal phase are correlated with pharmacological response. These levels are linearly related to dose within a given patient. Ideally, plasma samples to monitor steady-state concentrations should be taken just before the next dose. Minimally, they should be taken 6–8 hr after the last dose to allow adequate time to reach the terminal phase.

Digoxin has a biological half-life of 1.5–2.0 days in patients with normal renal function. In anuric patients this is prolonged to 4–6 days. This extension would be even longer but it is somewhat offset by a reduction in the apparent volume of distribution.

Digoxin is cleared from plasma by both renal excretion and metabolism to less cardioactive metabolites. In the absence of congestive heart failure the total body clearance has been estimated from

$$CL_{dig}\ (\text{ml/min}) = 57\ \text{ml/min} + 1.02CL_{CR} \tag{16}$$

for a 70-kg (1.73 m^2) patient [72]. In the presence of congestive heart failure the following estimate was suggested:

$$CL_{DIG}\ (\text{ml/min}) = 23\ \text{ml/min} + 0.88\ CL_{CR} \tag{17}$$

Renal clearance of digoxin is proportional to glomerular filtration rate. Both verapamil and quinidine cause an increase in serum digoxin concentrations through a reduction in digoxin clearance and, for quinidine, a decrease in distribution volume. By using the total body clearance value for dosage

adjustment, one can simultaneously compensate for changes in both half-life and apparent volume of distribution.

There exists a wide and unpredictable variation in steady-state distribution volume (V_{ss}) among both normal and renal failure patients. The range in normal adults has been reported as 430–630 liters [73] and 580–777 liters [74]. In a single study of only seven azotemic patients, the V_{ss} range was 195–489 liters/1.72 m^2 [75]. Half-life values in these patients ranged from 36 to 125 hr, whereas values for normal patients had means of 44 hr [74] (range 33–52 hr) and 45 hr [76] based on the terminal slopes of bi- [74] and triexponential [76] models, respectively. Thus the normal and renal failure half-life ranges overlap.

e. Individualized Dosage Regimens. In spite of the role that digoxin itself has played in bringing about widespread interest in drug plasma monitoring and bioequivalency, uncertainty remains regarding the optimum approach to digitalization of a patient. One difficulty is that of variabilty in the therapeutic drug plasma concentration. This necessitates careful individualization to establish the optimum steady-state plasma levels based on clinical evaluations. The adjustment of steady-state levels can be done empirically using the equation

$$C_{av}^{ss} = \frac{f(DM)}{\tau\ CL_{dig}} \tag{18}$$

where $f(DM)$ is the bioavailable maintenance dose, τ is the dosage interval, and CL_{dig} is the total body clearance.

For a given product, patient, and route of administration the C_{av}^{ss} values can be expected to be linearly related to the maintenance dose as shown by Eq. (18). Variability in the kinetic patterns for products obtained from various manufacturers makes it unwise to change brands for a given patient.

Since both the half-life and volume of distribution vary with normal patients and those with renal failure, the use of total body clearance is recommended over half-life estimates. The original nomogram by Jelliffe used an average $t_{1/2}$ value of 4.46 days for anephric patients. Ranges of 2.2–4.9 days (four patients) and 1.5–5.2 days (seven patients) have been reported [75]. Correction for $t_{1/2}$ alone is insufficient, since V_{ss} varies widely in renal failure.

Digoxin serum concentrations are not significantly changed by high fat tissue weight. Digitalization is therefore based on lean (ideal) body weight. Rapid digitalization in patients with heart failure and normal sinus rhythm is often achieved with a peak digoxin body content of 8–12 μg/kg. In renal insufficiency this is reduced to 6–10 μg/kg. The loading dose should be given as half the total followed by additional fractions every 4–8 hr (intravenously)

or 6–8 hr (oral), with assessment of response prior to each additional dose. Once the patient is digitalized, the maintenance dose may be calculated to replace the digoxin body content lost each day. The percent lost may be estimated from the fraction F remaining using

$$\text{percent loss} = 100(1-F) \tag{19}$$

The value for the fraction remaining may be estimated from $e^{-\lambda_Z \tau}$ where λ_Z is approximately 0.693/(1.8 days) with normal renal function. The percent daily loss, 100% $(1-F)$ when $\tau = 24$, can also be estimated from

$$\text{percent daily loss} = 14 + \frac{CL_{CR}}{5} \tag{20}$$

Gradual digitalization may be achieved by using the maintenance dose calculated on the assumption that peak body stores of digoxin will be 10 μg/kg. Since the steady state requires four half-lives, digitalization will require 6–8 days with normal renal function.

Practice Problem 8

Assume that the biological half-life for digoxin is 2 days in a patient who is taking tablets once daily. What percentage decrease would a plasma sample taken at 24 hr show relative to the concentration of a sample taken 8 hr after the dose?

Answer: $\lambda_Z = 0.693/48 \text{ hr} = 0.0144 \text{ hr}^{-1}$; $F = e^{-\lambda_Z t} = 0.89$ (8 hr); 0.71 (24 hr). The 24-hr concentration will be 20% less. For example, if the 8-hr concentration were 1.5 ng/ml, then the 24-hr concentration would be 1.2 ng/ml, which is not a significant difference for monitoring digoxin levels.

Practice Problem 9

(a) A patient with normal renal function shows symptoms of possible digoxin toxicity. The digoxin serum concentration is found to be 4.2 ng/ml. If the biological half-life for digoxin is assumed to be 1.8 days, how long will it take for the digoxin concentration to decrease to 1.3 ng/ml if digoxin dosage is stopped?

Answer: The fraction F remaining is $1.3/4.2 = 0.31$; $t_F = -\ln F/\lambda_Z = 3$ days.

(b) If a plasma sample taken after 3 days is found to be 2 ng/ml, estimate the biological half-life for digoxin in this patient and the predicted total time to decrease to 1.3 ng/ml.

Answer: $\lambda_Z = -\ln F/t_F = 0.74/3 \text{ days} = 0.247 \text{ days}^{-1}$, $t_{1/2} = 2.8$ days; $t_F = -\ln 0.31/0.247 \text{ days}^{-1} = 4.7$ days.

Practice Problem 10

A 58-year-old adult male, 5 ft 9 in. tall and weighing 185 lbs, is to be placed on oral digoxin tablets once daily for congestive heart failure. The following problems are meant to compare dosages calculated by alternative methods.

(a) The loading dose DL may be calculated from the general rule of 8–12 μg/kg as the recommended peak body stores or from the target serum concentration of 0.8–2.0 ng/ml. Compare these two calculations for DL values using ideal body weight, a bioavailable fraction of 0.7 for the tablets, a digoxin serum level of 1.5 ng/ml, an apparent volume of distribution of 7.3 liters/kg, and average peak body stores.
Answer: IBW_M = 50 kg + 2.3 kg for every inch over 5 ft = 70.7 kg; DL (at 10 μg/kg) = (10 mg/kg)(70.7 kg)/0.7 = 1010 μg = 1.0 mg; DL (for 1.5 ng/ml) = (7.3 liters/kg)(70.7 kg)(1.5 μg/liter)/0.7 = 1106 μg = 1.1 mg.

(b) The maintenance dose DM may be calculated from the general rule to replace peak body stores with percent daily loss = 14 + $CL_{CR}/5$ or from the steady-state equation [Eq. (18)], where total body clearance is estimated from Eq. (16) or (17) and the target digoxin serum level is employed. Compare the calculated DM values for this patient in congestive heart failure, assuming a creatinine clearance value of 100 ml/min and a C_{av}^{ss} target of 1.5 ng/ml.
Answer: Percent daily loss = 34%; DM = 0.34 *DL* = 343 μg = 0.34 mg; CL_{dig} = 23 ml/min + 0.88CL_{CR} = 111 ml/min; $DM = C_{av}^{ss}\, CL_{dig}\, \tau/f$ = (1.5 μg/liter)(6.66 liters/hr) = (1.5 μg/liter)(6.66 liter/hr)(24 hr)/0.7 = 342 μg = 0.34 mg.

(c) Assume that this patient is stabilized on a regimen of one 0.25-mg and one 0.125-mg digoxin tablet daily. If the patient develops a renal problem and the serum creatinine level C_{CR} is 2 mg/dl, compare the estimates for maintenance dose DM using Eq. (9) to estimate CL_{CR} to that using the following equation:
Answer: CL_{CR} = [98 − 0.8 (age − 20)]/C_{CR} = 33.8 ml/min. Eq. (9): CL_{CR} = (140 − age)(weight)/C_{CR} (72) = 47.9 ml/min. The estimates for CL_{dig} are therefore 53 and 65 ml/min. Since the previous estimate was 111 ml/min, the DM values are 0.18 and 0.22 mg/day.

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Appendix

LIST OF SYMBOLS OF GENERAL OCCURRENCE

A	amount of drug in the body at any time
A_e	amount of drug excreted unchanged in the urine
AUC	area under plasma concentration-time curve from zero to infinity
C	drug concentration in plasma at any time
$C(0)$	initial (fictive) plasma drug concentration following rapid intravenous injection
C_{max}	maximum (peak) plasma drug concentration after single dose administration
C^{ss}	steady-state drug concentration in plasma during constant rate drug delivery
C^{ss}_{av}	average steady-state drug concentration in plasma during multiple dosing
C^{ss}_{max}	maximum (peak) steady-state drug concentration in plasma during each multiple dosing interval
C^{ss}_{min}	minimum steady-state drug concentration in plasma during each multiple dosing interval
CL	total body clearance of drug from plasma
CL_H	hepatic clearance of drug from plasma
CL_{int}	intrinsic hepatic clearance of free (unbound) drug in plasma
CL_{NR}	nonrenal clearance of drug from plasma
CL_R	renal clearance of drug from plasma
CL_{CR}	creatinine clearance
D	dose
DL	loading dose in repetitive dosing or constant-rate infusion
DM	maintenance dose in repetitive dosing

f	fraction of administered dose systemically available; the bioavailable fraction
f_e	fraction of bioavailable dose excreted in the urine
k	first-order rate constant
k_a	apparent first-order absorption rate constant
K_m	Michaelis-Menten constant
k_o	zero-order rate constant, used to describe constant-rate sustained-release drug delivery
λ_i	exponent of the ith exponential term of a polyexponential equation
λ_1	largest apparent first-order rate constant in a polyexponential disposition equation
λ_Z	smallest apparent first-order rate constant in a polyexponential disposition equation. The terminal ln-linear negative slope following intravenous dosing
Q_H	liver blood flow
Q_R	renal blood flow
R_o	constant (zero-order) infusion rate
S_Z	terminal negative ln-linear slope following extravascular administration and so indicated when the true pharmacokinetic meaning of the slope is not certain (See also $t^*_{1/2}$.)
T	duration of constant-rate infusion or other zero-order drug delivery
t_{max}	time to reach peak or maximum concentration following extravascular drug administration
t_{pi}	time elapsed since end of a constant-rate infusion
$t_{1/2}$	elimination half-life associated with negative terminal slope ($-\lambda_Z$) ln-linear plot following intraveneous administration
$t^*_{1/2}$	apparent half-life associated with a ln-linear terminal phase following extravascular administration when true meaning of the slope is not known (see also S_Z)
τ	dosing interval in repetitive dosing
V_c	pharmacokinetic volume of central or plasma compartment
V_Z	apparent volume of distribution during terminal (λ_Z) phase
V_{ss}	volume of distribution at steady state
V_{max}	apparent maximum rate of metabolism in nonlinear pharmacokinetics described by the Michaelis-Menten equation

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A

D

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S