Clinical Pharmacokinetics:

Concepts and Applications

Malcolm Rowland, Ph.D.

Thomas N. Tozer, Ph.D.

Clinical Pharmacokinetics:

Concepts and Applications

Malcolm Rowland, Ph.D.
Department of Pharmacy
University of Manchester
Manchester, England

Thomas N. Tozer, Ph.D.
School of Pharmacy
University of California
San Francisco, California

LEA & FEBIGER PHILADELPHIA
1980

Library of Congress Cataloging in Publication Data

Rowland, Malcolm.
Clinical pharmacokinetics.

Bibliography: p.
Includes index,
1. Pharmacokinetics. 2. Chemotherapy.
I. Tozer, Thomas N., joint author. II. Title.
[DNLM: 1. Drug therapy. 2. Kinetics.
3. Pharmacology. QV38.3 R883c]
RM301.5.R68 1980 615'.7 79-10735
ISBN 0-8121-0681-4

Published in Great Britain by Henry Kimpton Publishers, London
Printed in the United States of America
Print Number 3 2 1

preface

FOR EIGHT years we jointly shared responsibility for teaching basic courses in pharmacokinetics at the University of California. The students were from a variety of persuasions, including professional students in pharmacy, clinical pharmacology fellows, and graduate academic students. Their feedback on the courses resulted in our making a dramatic shift in the way we presented the material. Over the years the emphasis shifted from kinetics and modeling to providing a conceptual base for applying pharmacokinetics to rational drug therapy. We firmly believe that the reoriented content of these courses goes much further in relating to the needs of students and of practitioners of pharmacotherapeutics. One of the major difficulties in teaching the subject has been the lack of a book that teaches the application of pharmacokinetics in drug therapy. This deficiency prompted the writing of this book.

The title of the book was chosen because it emphasizes the bedside application of pharmacokinetics. The book, in fact, is a primer on pharmacokinetics with clinical applications. It should be useful to any student, practitioner, or researcher who is interested or engaged in the development, evaluation, or use of drugs in man. It is an introductory text and therefore presumes that the reader has had little or no experience or knowledge in the area. Previous exposure to certain aspects of physiology and pharmacology would be helpful, but is not essential. Some knowledge of calculus is also desirable.

In our experience, the average student has felt very uncomfortable with kinetic principles and mathematics. Indeed, in many cases there is a strong mental block. Our desire is to teach the application of pharmacokinetics in therapeutics. We believe we are achieving this goal by applying the essential concepts through problem solving with only the essence of required mathematics. This approach is a theme throughout the book. In this respect this book is a programmed learning text. Every attempt is made at the beginning of each chapter to present objectives that identify the more important points to be learned. To further aid in the learning process, examples are worked out in detail in the text. At the end of many chapters there are two kinds of problems. The first is study problems, which allow the reader to test his grasp of the material in the chapter. The second kind is unifying problems, which build upon the material of previous chapters. For the interested reader there is a list of suggested further reading located at the back of the book.

An attempt has been made to establish uniformity for symbols and units throughout the book; definitions of symbols begin on p. 280. The liter is used as the standard measure of volume and hour as the standard unit of time. A special comment should be made on the choice of mg/liter for the

units of drug concentration. Although molarity has considerable utility and has been strongly advocated for common use, the dosage of drugs is most often expressed in milligrams. Until doses are given in molar units, we feel that mg/liter is the more convenient unit for concentration.

The book is divided into four sections: Concepts, Disposition and Absorption Kinetics, Therapeutic Regimens, and Individualization. Section I contains the fundamental concepts in drug absorption, distribution and elimination. Section II covers the kinetics of drug and metabolites following drug administration and integrates kinetics with the fundamental concepts. Section III deals with the basic elements of the design and evaluation of therapeutic regimens, while Section IV examines the causes of variability in human drug response, the adjustment of dosage based on age, weight, and renal function, explores the kinetic consequences of drug interactions, and presents principles for the monitoring of drug therapy using plasma concentrations. The sequence is intended to give the reader the basic underlying concepts, the quantitative tools, and the essence of the kinetic basis for variability in human drug response.

The content of the book, by design, has been limited. There are many important areas of pharmacokinetics either touched on only lightly or not covered at all. Most of these areas are more specialized, dealing with such topics as distribution dynamics, including multicompartment systems, dose and time dependencies, turnover concepts, dialysis, and kinetic considerations in the treatment of drug overdose. These and other specialized topics and a more detailed examination of the clinical pharmacokinetics of selected drugs, including digoxin, theophylline, and phenytoin, form the basis of a sequel to this book entitled Clinical Pharmacokinetics: Specialized Topics and Selected Drugs.

We wish to express our gratitude to Jere E. Goyan, Dean, and Sidney Riegelman, Associate Dean for Research Services, School of Pharmacy, University of California, for their encouragement. We also wish to acknowledge Paul Bailey of Manchester, England, for his preparation of the illustrations. We particularly wish to thank our past students whose comments have been so useful in formulating our ideas.

To the reader of the book we hope that we have succeeded in helping you develop kinetic reasoning that will be of personal value in your practice. In general perspective, we hope we have made some contribution to the development of a more rational management of drug therapy.

Manchester, England

San Francisco, California

MALCOLM ROWLAND

THOMAS N. TOZER

contents

1

why clinical pharmacokinetics?

THOSE patients who suffer from chronic ailments such as diabetes and epilepsy may have to take drugs every day for the rest of their lives. At the other extreme are those who take a single dose to relieve an occasional headache. The duration of drug therapy is usually between these extremes. The manner in which a drug is taken is called a *dosage regimen.* Both the duration of drug therapy and the dosage regimen depend on the therapeutic objectives, which may be either the cure, the mitigation, or the prevention of the disease. Because all drugs exhibit undesirable effects such as drowsiness, dryness of the mouth, gastrointestinal irritation, nausea, and hypotension, successful drug therapy is achieved by optimally balancing the desirable and the undesirable effects. To achieve optimal therapy, the appropriate "drug of choice" must be selected. This decision implies an accurate diagnosis of the disease, a knowledge of the clinical state of the patient, and a sound understanding of the pharmacotherapeutic management of the disease. Then the questions how much, how often, and how long, must be answered. The question "how much" recognizes that the magnitude of the response (therapeutic or toxic) is a function of the dose given. The question "how often" recognizes the importance of time, in that the magnitude of the effect eventually declines with time following a single dose of drug. The question "how long" recognizes that there is a cost (in terms of side effects, toxicity, economics) incurred with continued drug administration. In practice, these questions cannot be divorced from one another. For example, the convenience of giving a larger dose less frequently may be more than offset by an increased incidence of toxicity.

In the past, the answers to many important therapeutic questions were obtained by trial and error. The clinical investigator selected the dose, the interval between doses, and the route of administration and followed the patient's progress. The desired effect and any signs of toxicity were carefully noted, and if necessary the dosage regimen was adjusted empirically until a maximal desired effect with minimal toxicity was achieved. Eventually, after considerable experimentation on a large number of patients, reasonable dosage regimens were established (Table 1-1), but not without some regimens producing excessive toxicity or proving ineffective. Moreover, the above empirical approach left many questions unanswered. Why, for example, does theophylline have to be given every 6 to 8 hours to be effective, while digoxin can be given daily? Why must oxytocin be infused intravenously? Why is morphine more effective given intramuscularly than when given orally? Furthermore, this empirical approach contributes little, if anything, toward establishing a safe, effective

Table 1-1. Empirically Derived Usual Adult Dosage Regimens of Some Representative Drugs[a]

Drug	Indicated Use	Route	Dosage Regimen
Theophylline	Relief of asthma	Oral	160 mg every 6 hours
Digoxin	Amelioration of congestive heart failure	Oral	1.5–2 mg initially over 24 hours, thereafter 0.25–0.5 mg once a day
Oxytocin	Induction and maintenance of labor	Intravenous	0.2–4 milliunits/min infusion
Morphine sulfate	Relief of severe pain	Intramuscular	10 mg when needed
		Oral	Not used because of reduced effectiveness
Phenobarbital	Prevention of epileptic seizures	Oral	120–200 mg daily

[a]Taken from American Medical Association: Drug Evaluations. 2nd Edition. Publishers Science Group, Inc., Acton, Mass. 1973.

dosage regimen of another drug. That is, our basic understanding of drugs has not been increased.

To overcome some of the limitations of the empirical approach and to answer some of the questions raised, it is necessary to delve further into the events that follow drug administration. *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluids bathing the site(s) of action. From these observations the suggestion might be made that the therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration of therapy. However, rarely is a drug placed at its site of action. Indeed, most drugs are given orally, and yet they act in the brain, on the heart, at the neuromuscular junction, or elsewhere. A drug must therefore move from the site of administration to the site of action. Simultaneously, however, the drug distributes to all other tissues including those organs, notably the liver and the kidney, that eliminate it from the body. After a dose is administered, the rate at which a drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and in tissue rise, often sufficiently high to elicit the desired therapeutic effects and sometimes even to produce toxicity. Eventually, the rate of drug elimination exceeds the rate of its absorption, and thereafter, the concentration of drug in tissues declines and the effect(s) subsides. To administer drugs optimally, therefore, knowledge is needed not only of the mechanisms of drug absorption, distribution, and elimination but also of the kinetics of these processes, that is, *pharmacokinetics.* The application of pharmacokinetic principles to the therapeutic management of patients is *clinical pharmacokinetics.*

The problem of drug administration can now be divided into two phases, a *pharmacokinetic phase* that relates dose, frequency, and route of administration to drug level–time relationships in the body, and a *pharmacodynamic phase* that relates the concentration of drug at the site(s) of action to the magnitude of the effect(s) produced (Fig. 1-1). Once both of these phases have been defined, a dosage regimen can be de-

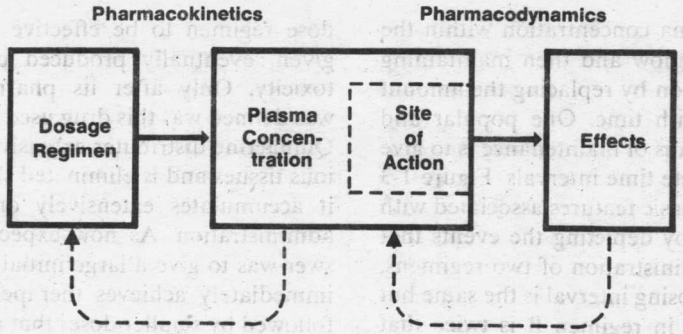

Figure 1-1. *An alternative approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then either the plasma drug concentration-time data or the effects produced, via pharmacokinetics, are used as a feedback to modify the dosage regimen to achieve optimal therapy.*

signed to achieve the therapeutic objective. Despite the greater amount of information required with this approach, it has several advantages. First, and most obvious, distinctions can be made between pharmacokinetic and pharmacodynamic causes of an unusual drug response. Second, the basic concepts of pharmacokinetics are common to all drugs; information gained about the pharmacokinetics of one drug can help in anticipating the pharmacokinetics of another. Third, understanding the pharmacokinetics of a drug often explains the manner of its use; occasionally such an understanding has saved a drug that otherwise may have been discarded or has suggested a more appropriate dosage regimen. Lastly, knowing the pharmacokinetics of a drug often aids in anticipating the outcome of a therapeutic maneuver.

Before examples are given of the application of clinical pharmacokinetics, the situation depicted in Figure 1-2 should be considered. Assuming the hypothesis that both the magnitude of the desired response and the degree of toxicity are a function of the drug concentration at the site(s) of action, two reasons for therapeutic failure are evident. Either therapy is ineffective because the concentration is too low or there is an unacceptable degree of toxicity because the concentration is too high. Between these limits of concentration lies a region associated with therapeutic success; this region may be regarded as the "therapeutic window." Rarely can the concentration of the drug at the site of action be measured directly; instead the concentration is measured at an alternative site, *the plasma*. Besides being a more convenient and accessible site of measurement, the concentration of a drug in plasma also probably reflects the drug concentration at the site of action.

Based on the foregoing considerations, an optimal dosage regimen might be defined as one that maintains the plasma concentration of a drug within its therapeutic window. For many drugs, this therapeutic objective is met by giving an initial dose to

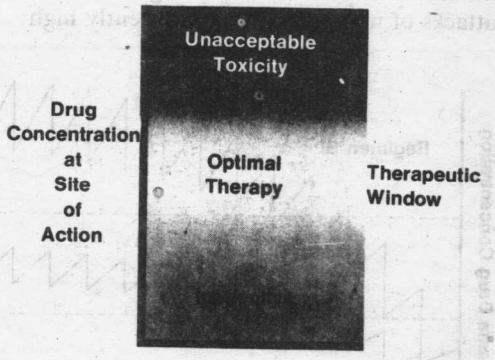

Figure 1-2. *Between certain limits of concentration lies a region associated with therapeutic success, the therapeutic window.*

achieve a plasma concentration within the therapeutic window and then maintaining this concentration by replacing the amount of drug lost with time. One popular and convenient means of maintenance is to give a dose at discrete time intervals. Figure 1-3 illustrates the basic features associated with this approach by depicting the events that follow the administration of two regimens, A and B; the dosing interval is the same but the dose given in regimen B is twice that given in regimen A. Because some drug always remains in the body from the preceding dose, accumulation occurs until, within a dosing interval, the amount lost equals the dose given; a characteristic saw-toothed plateau is then achieved. With regimen A, several doses had to be given before drug accumulation was sufficient to produce a therapeutic concentration. Had therapy been stopped before then, the drug might have been thought ineffective and perhaps abandoned prematurely. Alternatively, larger doses might have been tried, e.g., regimen B, in which case, although a therapeutic response would have been achieved fairly promptly, toxicity would have ensued on continued administration. Once again, the drug might have been abandoned. This almost happened with the synthetic antimalarial agent, quinacrine. Developed during World War II to substitute for the relatively scarce quinine, quinacrine was either ineffective against acute attacks of malaria, or, if a sufficiently high dose regimen to be effective acutely was given, eventually produced unacceptable toxicity. Only after its pharmacokinetics was defined was this drug used successfully. Quinacrine distributes extensively into various tissues and is eliminated slowly; hence it accumulates extensively on prolonged administration. As now expected, the answer was to give a large initial dose, which immediately achieves therapeutic success, followed by smaller doses that maintain the concentration within the therapeutic window.

An examination of the plateau situation in Figure 1-3 also shows that the size of the maintenance dose and the frequency of administration are governed by two factors: the width of the therapeutic window and the speed of drug elimination. When the window is narrow and the drug is eliminated rapidly, small doses must be given often to achieve therapeutic success. Both theophylline and digoxin have a narrow therapeutic window, but because it is eliminated much more rapidly than digoxin, theophylline has to be given the more frequently. Oxytocin is an extreme example; it also has a narrow therapeutic window, and it is eliminated within minutes. The only means of adequately ensuring a therapeutic concentration is therefore to infuse oxytocin at a precise and constant rate directly into the blood. Control is too erratic with any other mode of administration. Besides, had it been given orally, oxytocin would have

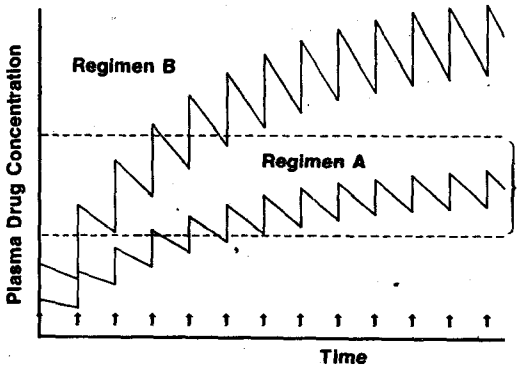

Figure 1-3. *When a drug is given at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is more quickly achieved but the plasma drug concentration is ultimately too high.*

been destroyed by the proteolytic enzymes in the gastrointestinal fluids. Morphine, given orally, is also substantially destroyed before entering the general circulation, but for a different reason than oxytocin. Morphine is rapidly metabolized in the liver, an organ lying between the gastrointestinal tract and the general circulation.

Figure 1-4 illustrates an important problem in drug therapy, variability. There is a wide range of daily dose requirements of the oral anticoagulant, warfarin, needed to produce a similar prothrombin time (an index of blood coagulability). Sources of variability in drug response include the patient's age, weight, degree of obesity, type and degree of severity of the disease, and the patient's genetic make-up, other drugs concurrently administered, and environmental factors. The result is that a standard dosage regimen of a drug may prove therapeutic in some patients, ineffective in others, and toxic in still others. The need to adjust the dosage regimen of a drug for an individual patient is evident; this need is clearly greatest for drugs that have a narrow therapeutic window, that exhibit a steep concentration-response curve, and that are critical to drug therapy. Examples are digoxin, used to treat congestive heart failure; phenytoin, used to prevent epileptic convulsions; theophylline, used to diminish chronic airway resistance in asthmatics; and lidocaine, used to suppress ventricular arrhythmias. With these drugs, and with many others, variability in pharmacokinetics is a major source of total variability in drug response. Accounting for the variability in pharmacokinetics more readily permits improved individual dosage adjustment.

Coadministration of several drugs to a patient, prevalent in clinical practice, is fraught with problems. Each agent may have been chosen rationally but when coadministered, the outcome can be unpredictable. Phenylbutazone, for example, devoid of anticoagulant activity, markedly potentiates the hypoprothrombinemic effect of the oral anticoagulant, warfarin. The possible causes of this change are many. Often, such drug interactions involve a change in the pharmacokinetics. Some drugs stimulate drug-metabolizing enzymes and hasten drug loss; others inhibit these enzymes and slow elimination. Many others displace a drug from plasma and tissue binding sites or interfere with its absorption. Such interactions are graded; the change in the pharmacokinetics of a drug varies continuously with the plasma concentration of the interacting drug and hence with time. Indeed, given in sufficiently high doses, any drug will probably interact with another drug. It is always a question of degree. Understanding the quantitative

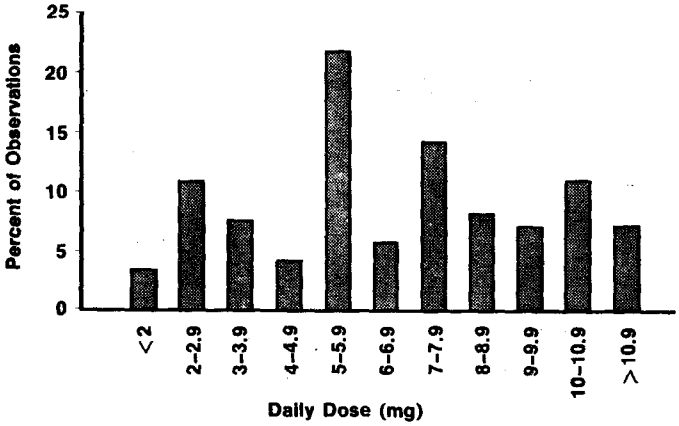

Figure 1-4. *The daily dose of warfarin, required to produce similar prothrombin times in 200 adult patients, varies widely. (Redrawn from Koch-Weser, J.: The serum level approach to individualization of drug dosage. Eur. J. Clin. Pharmacol., 9: 1–8, 1975.)*

elements of interactions ensures the more rational use of drugs that may have to be coadministered.

Figure 1-5 illustrates a situation in which monitoring of the drug concentration may be beneficial. Over the narrow range of the daily dose of the antiepileptic drug, phenytoin, the plateau plasma drug concentration varies markedly within the patient population. Yet the therapeutic window of phenytoin is very narrow, 7 to 20 mg/liter; beyond 20 mg/liter, the frequency and the degree of toxicity increase progressively with concentration. Here again, pharmacokinetics is the major source of variability. A pragmatic approach to this problem would be to adjust the dosage until the desired objective is achieved. Control on a dosage basis alone, however, has proved difficult. Control is achieved more readily and accurately given plasma drug concentration data and a knowledge of the pharmacokinetics of the drug.

Drug selection and therapy have traditionally been based solely upon observations of the effects produced. In this chapter, the application of pharmacokinetic principles to decision making in drug therapy has been illustrated. Both approaches are needed to achieve optimal drug therapy. This book emphasizes the pharmacokinetic approach. It begins with a consideration of the concepts basic to pharmacokinetics.

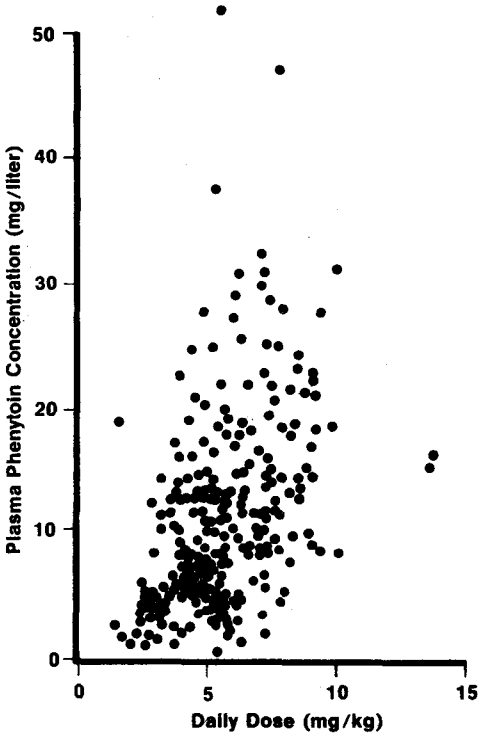

Figure 1-5. *Although on the average the plateau plasma drug concentration of phenytoin increases with the daily dose, there is considerable variation at any given daily dose. (Redrawn from Lund, L.: Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In Biological Effects of Drugs in Relation to Their Plasma Concentration. Edited by D.S. Davies, and B.N.C. Prichard. Macmillan, London and Basingstoke, 1973, pp. 227–238.)*

SECTION ONE

concepts

2

basic considerations

Objectives

The reader will be able to define the following terms:

1. **Pharmacokinetics**
2. **Intravascular and extravascular administration**
3. **Absorption**
4. **Disposition**
5. **Distribution**
6. **Metabolism**
7. **Excretion**
8. **First-pass effect**
9. **Enterohepatic cycling**

Useful clinical applications of pharmacokinetics can be made from basic principles and concepts. In this and subsequent chapters, these concepts are developed. It should be noted, however, that the concepts are only valid to the extent that they can then explain observations or that they can serve as a basis for making predictions.

Anatomic and Physiologic Considerations

Measurement of a drug in the body is limited usually to the blood, or plasma, and to the urine. Nonetheless, the limited information obtained has proved very useful. Such usefulness can be explained by anatomic and physiologic considerations of the events that occur to a drug following its administration.

Blood or plasma, in addition to being a practical and convenient site of measurement, is the most logical one for determining drug in the body. Blood both receives a drug from the site of administration following its absorption and carries the drug to all the tissues including the sites of action and the organs that eliminate it from the body.

The fate of a drug as it moves from the site of administration to the site(s) of elimination is depicted schematically in Figure 2-1. This scheme includes the processes of absorption and disposition. Disposition may be further subdivided into distribution, elimination, and enterohepatic cycling.

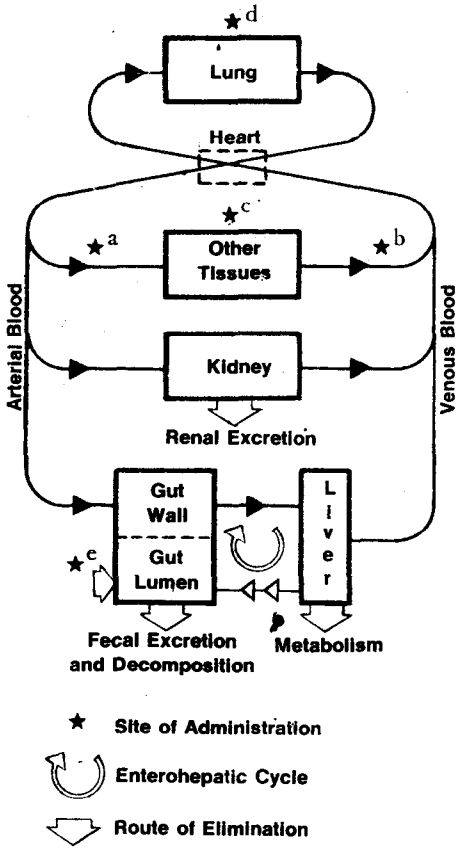

Figure 2-1. *Once absorbed from any of the many sites of administration, a drug is distributed by blood to all sites within the body including the eliminating organs. Sites of administration are:* a, *artery;* b, *peripheral vein;* c, *muscle and subcutaneous tissue;* d, *lung; and* e, *gastrointestinal tract. The* ⟶ *and the* ⟷ *lines with arrows refer to the mass movement of drug in blood and in bile, respectively. The absorption and disposition of virtually any drug can be followed from site of administration to site of elimination.*

Absorption

There are several sites at which drugs are commonly administered. These sites may be classified as either intravascular or extravascular. *Intravascular* administration refers to the placement of a drug directly into the blood, either intravenously or intra-arterially.

Extravascular modes of administration include the oral, sublingual, buccal, intramuscular, subcutaneous, pulmonary, and rectal routes. To enter the blood, drug administered extravascularly must be absorbed: No absorption step is required when a drug is administered intravascularly.

Distribution

Once absorbed, a drug is distributed to the various tissues of the body. The rate and the extent of distribution are determined by how well each tissue is perfused with blood, the binding of drug to plasma proteins and to tissue components, and the permeability of tissue membranes to the drug.

Elimination

The two principal organs of elimination, the liver and the kidney, are shown separately. The kidney is the primary site for excretion of the chemically unaltered, or unchanged, drug. The liver is the usual organ for drug metabolism; however, the kidney and other organs can also play an important metabolic role for certain drugs. The liver may also excrete unchanged drug into the bile. The lungs are, or may be, an important route for eliminating substances of high vapor pressure, for example the gaseous anesthetics. Another potential route of elimination is a mother's milk. Although not a significant route of elimination for the mother, the drug may be consumed in sufficient quantity to affect the suckling infant.

Enterohepatic Recycling

Once excreted into the bile, a drug may be reabsorbed from the gallbladder or from the intestinal tract. By doing so, the drug completes a cycle, the *enterohepatic cycle.* If all the drug is reabsorbed in this manner, biliary excretion is not a route of elimination; the cycling is then a component of distribution. The situation is analogous to