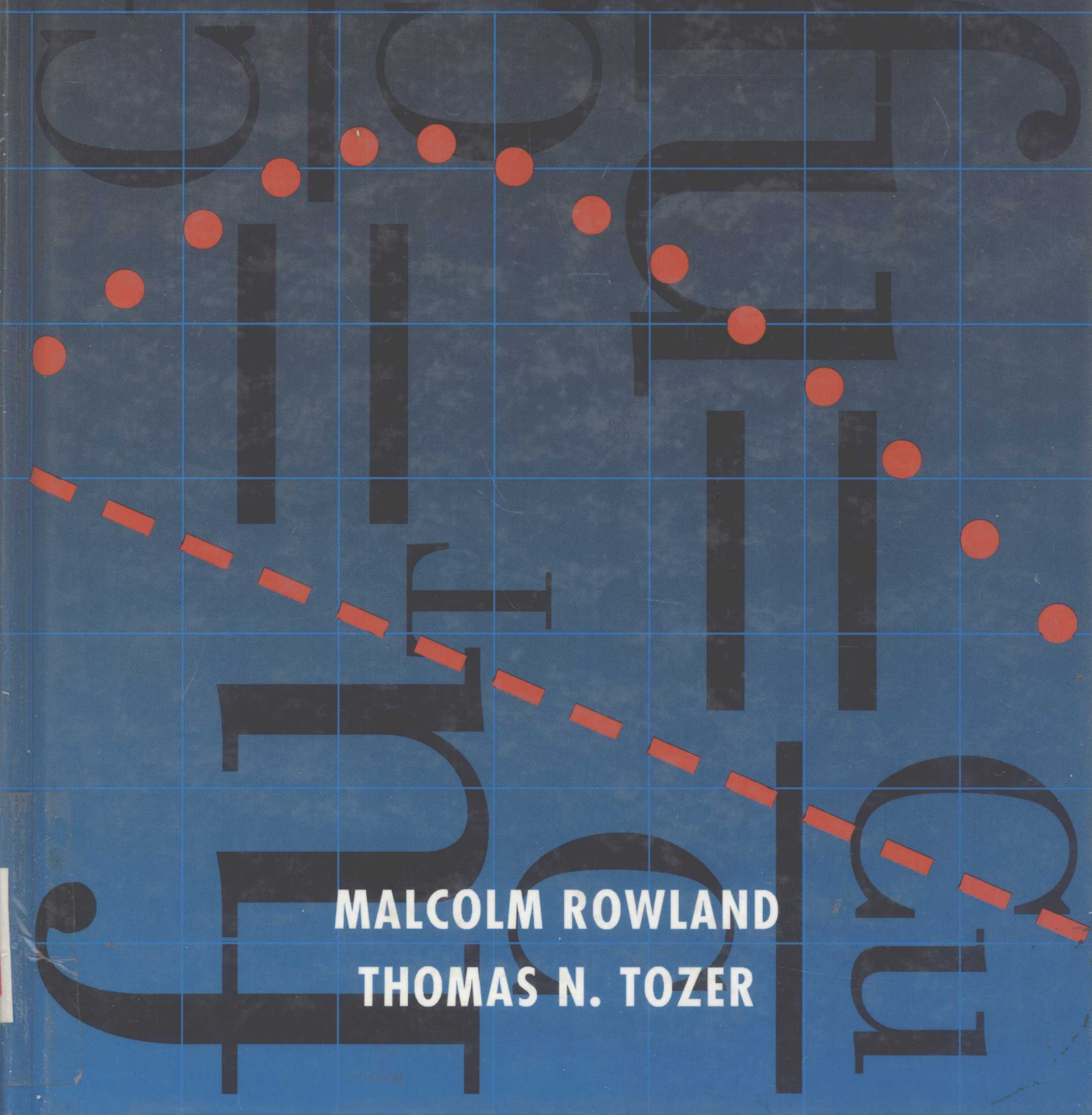
Clinical Pharmacokinetics

Concepts and Applications

third edition



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third edition

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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To Margaret and Dawn

PREFACE

PURPOSE OF TEXT

The third edition, in keeping with the first two editions, is a primer in pharmacokinetics with an emphasis on clinical applications. The book should be useful to any student, practitioner, or researcher who is interested or engaged in the development, evaluation, or use of medicines. Such persons include pharmacists, physicians, veterinarians, pharmaceutical scientists, toxicologists, analytical chemists, biochemists, and clinical chemists. It is an introductory text and therefore presumes that the reader has little or no experience or knowledge in the area. Previous exposure to certain aspects of physiology and pharmacology would be helpful, but it is not essential. Some knowledge of calculus is also desirable.

Our intent is to help the reader learn to apply pharmacokinetics in therapeutics. To this end, we emphasize concepts through problem solving with only the essence of required mathematics. In this respect, the book is a programmed learning text. At the beginning of each chapter, objectives are given to identify the salient points to be learned. To further aid in learning the material, examples are worked out in detail in the text. At the end of each chapter, except the first, there are problems that allow the reader to grasp the concepts of the chapter and to build on material given in previous chapters. The order of the problems in each chapter reflects consideration of both difficulty and how well the problems apply to chapter principles. The questions start with the less difficult ones and those that emphasize the principles.

ORGANIZATION AND CONTENT

As in the second edition, the book is divided into five sections: Absorption and Disposition Kinetics, Therapeutic Regimens, Physiologic Concepts and Kinetics, Individualization, and Selected Topics. Those wishing to gain a general overview of the subject need only study Sections One and Two, together with Chapter 13, Variability, and Chapter 18, Monitoring. Section Three deals with the physiologic concepts relevant to an understanding of the processes of absorption, distribution, and elimination. This section forms the basis for an appreciation of the material in Section Four, which is concerned with the identification, description, and accounting of variability in patients' responses to drugs. Covered here are general aspects of variability, followed by considerations of genetics, age and weight, disease, interacting drugs, and monitoring of drug concentrations.

Section Five contains selected topics. These are intended for those readers who wish to gain a more detailed insight into various aspects of clinical pharmacokinetics. The topics are distribution kinetics, pharmacologic response, metabolite kinetics, dose and time dependencies, turnover concepts, and dialysis. Each topic is generally self-contained; they have not been arranged in any particular sequence.

CHANGES IN THIRD EDITION

The 6-year gap between this third edition and the second, published in 1989, is shorter than the 9 years between the second and first editions. This shortening of the time span

between editions reflects the ever-gathering pace of progress and application of clinical pharmacokinetics. Despite this growth, which has required the inclusion of much new material, every effort has been made to contain the overall size of the book. This, in turn, has meant that some material has had to be condensed or deleted. It has also resulted in a much greater use of abbreviations, especially for units.

The number, topic, and sequence of chapters have been kept essentially the same as in the second edition. However, each chapter has been extensively revised and updated to ensure that the examples relate to currently prescribed drugs. A particular effort has been made to include stereochemistry, recognizing that isomers may have different kinetics and activity. There is also consideration of the increasing number of polypeptide and protein drugs emerging from advances in molecular biology and biotechnology. Although the kinetic concepts are the same, the physiologic handling of macromolecular compounds is quite distinct from that of typical small molecular weight drugs.

The presentation of the book has also been markedly improved through the use of color. The more important equations are now highlighted by means of color. Chapter number and section heading now appear at the top of each page layout to assist in cross-referencing. A table of frequently used symbols has been placed before Chapter 1 to facilitate redefining symbols, when necessary.

The range and number of problems at the end of each chapter and Appendix I (total of 87 new problems) have been substantially extended to assist in learning problem solving in pharmacokinetics. Most of the additional problems are taken from literature, rather than simulated, data.

The third edition contains 102 new figures and 20 new tables, reflecting, in large part, the advances made in recent years in our knowledge of the pharmacokinetics of drugs. The material on "Small Volume of Distribution" that comprised the last chapter of the second edition has been incorporated into Chapter 10, Distribution, and Appendix I–F.

We continue to adopt a uniform set of symbols and to use milligrams/liter (mg/L) as the standard measure of concentration. We do recognize, however, the increasing trend toward the adoption of molar units and have provided a factor for conversion between the two units of measurement in the pertinent figure captions. We shall only be convinced of the virtue of solely using the molar system of measurement when drugs are prescribed in such units.

ACKNOWLEDGMENTS

We wish to thank all the many students and readers who provided input that helped us shape this third edition. Their enthusiasm and encouragement have been a continual source of satisfaction. To the new reader, we hope that the book will succeed in helping you develop kinetic reasoning that will be of personal value in your professional practice.

We have been enormously gratified by the wide and diverse readership of the first two editions of the book. We would like to believe that the book has been instrumental in furthering rational management of drug therapy. We sincerely hope that the third edition will continue to do so.

Manchester, England
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DEFINITIONS OF SYMBOLS*

A	Amount of drug in body, mg or μmole.
Aa	Amount of drug at absorption site remaining to be absorbed, mg or μmole.
Ae	Cumulative amount of drug excreted unchanged in the urine, mg or μmole.
$Ael(m)$	Amount of metabolite eliminated, mg or μmole.
$Ae_{\tau,ss}$	Cumulative amount of drug excreted unchanged in the urine during a dosing interval at steady state, mg or μmole.
Ae_{∞}	Cumulative amount of drug excreted unchanged in the urine to time infinity after a single dose, mg or μmole.
$A(m)$	Amount of metabolite in body, mg or μmole.
A_{min}	The minimum amount of drug in body required to obtain a predetermined level of response, mg or μmole.
$A_{N,max}$; $A_{N,min}$	Maximum and minimum amounts of drug in body after the Nth dose of fixed size and given at a fixed dosing interval, mg or μmole.
$A_{N,t}$	Amount of drug in body at time t after the Nth dose, mg or μmole.
ARE	Amount of drug remaining to be excreted in urine after a single dose, mg or μmole.
A_{ss}	Amount of drug in body at steady state during constant-rate intravenous infusion, mg or μmole.
$A_{ss,av}$	Average amount of drug in body during a dosing interval at steady state, mg or μmole.
$A_{ss,max}$; $A_{ss,min}$	Maximum and minimum amounts of drug in body during a dosing interval at steady state on administering a fixed dose at a fixed dosing interval, mg or μmole.
$A_{ss,t}$	Amount of drug in body at time t within a dosing interval at steady state on administering a fixed dose at a fixed dosing interval, mg or μmole.
AUC	Area under the plasma drug concentration-time curve. Total area from time 0 to infinity is implied unless the local context indicates a specific time interval, e.g., dosing interval, mg-hr/L or μM-hr.
AUC_b	Total area under the blood drug concentration time curve, mg-hr/L or μM-hr.
$AUC(m)$	Area under the plasma metabolite concentration time curve, mg-hr/L or μM-hr.
AUC_{ss}	Area under the plasma drug concentration time curve within a dosing interval at steady state, mg-hr/L or μM-hr.
$AUMC$	Total area under the first moment-time curve, mg-hr^2/L or μM-hr^2.
C	Concentration of drug in plasma, mg/L or μM.

*Usual units are given.

$C(0)$ Initial plasma concentration, usually obtained by extrapolation to time zero, mg/L or μM.

C_1; C_2 Coefficients with units of concentration, mg/L or μM.

Ca Concentration of drug in fluids at the absorption site, mg/L or μM.

C_A Concentration of drug in arterial blood, mg/L or μM.

C_b Concentration of drug in blood, mg/L or μM.

Cbd Concentration of bound drug in plasma, mg/L or μM.

C_D Drug concentration in dialysate leaving dialyzer, mg/L or μM.

C_I Concentration of inhibitor of metabolism, mg/L or μM.

CL Total clearance of drug from plasma, L/hr.

CL_b Total clearance of drug from blood, L/hr.

CL_{bD} Dialysis clearance based on drug concentration in blood, L/hr.

$CL_{b,H}$ Hepatic clearance of drug from blood, L/hr.

CL_{cr} Renal clearance of creatinine, mL/min or L/hr.

CL_D Dialysis clearance based on drug concentration in plasma, L/hr.

CL_f Clearance associated with formation of a metabolite from a drug, L/hr.

CL_H Hepatic clearance of drug from plasma, L/hr.

CL_{int} Intrinsic clearance of drug in organ of elimination, L/hr.

$CL(m)$ Total clearance of a metabolite, L/hr.

CL_{PD} Peritoneal dialysis clearance based on drug concentration in plasma, L/hr.

CL_R Renal clearance of drug, L/hr.

CLu Clearance of unbound drug, L/hr.

$C(m)$ Concentration of metabolite in plasma, mg/L or μM.

C_{max} Highest drug concentration observed in plasma following administration of an extravascular dose, mg/L or μM.

$C(m)_{ss}$ Concentration of a metabolite at steady state during a constant-rate intravenous infusion of drug, mg/L or μM.

C_{min} Minimum concentration required to obtain a predetermined intensity of response, mg/L or μM.

$C_{N,max}$; $C_{N,min}$ Maximum and minimum concentrations of drug in plasma after the Nth dose on administering a fixed dose at equal dosing intervals, mg/L or μM.

C_{PC} Concentration of drug in peritoneal cavity, mg/L or μM.

C_{ss} Concentration of drug in plasma at steady state during a constant-rate intravenous infusion, mg/L or μM.

$C_{ss,av}$ Average drug concentration in plasma during a dosing interval at steady state on administering a fixed dose at equal dosing intervals, mg/L or μM.

$C_{ss,max}$; $C_{ss,min}$ Maximum and minimum concentrations of drug in plasma at steady state on administering a fixed dose at equal dosing intervals, mg/L or μM.

C_T Average concentration of drug in fluids outside plasma, mg/L or μM.

C_{TW} Drug concentration unbound in total body water, mg/L or μM.

C_{upper}; C_{lower} Maximum and minimum limits for plasma drug concentrations, mg/L or μM.

Cu Unbound drug concentration in plasma, mg/L or μM.

Cu_I Unbound plasma concentration of inhibitor, mg/L or μM.

C_V Concentration of drug in venous blood, mg/L or μM.

D_L Loading dose, mg or μmole.

D_M Maintenance dose of a fixed-dose regimen, mg or μmole.

$D_{M,max}$ Maximum maintenance dose to ensure that the plasma drug concentration remains within C_{upper} and C_{lower} limits during a dosing interval at steady state, mg or μmole.

E Extraction ratio, no units.

EC_{50} Concentration giving one-half the maximum effect, mg/L or μM.

E_H Hepatic extraction ratio, no units.

E_{max} Maximum effect, units of response measurement.

F Bioavailability of drug, no units.

f_{bd} Ratio of bound to total drug concentrations in plasma, no units.

f_D Dialysis clearance as a fraction of total clearance during a dialysis treatment, no units.

fe Fraction of drug systemically available that is excreted unchanged in urine, no units.

FEV_1 Forced expiratory volume in 1 second, L.

F_H Fraction of drug entering the liver that escapes elimination on single passage through that organ, no units.

fm Fraction of drug systemically available that is converted to a metabolite, no units.

Fm Fraction of administered dose of drug that enters the general circulation as a metabolite, no units.

F_R Fraction of filtered and secreted drug reabsorbed in the renal tubule, no units.

fu Ratio of unbound and total drug concentrations in plasma, no units.

fu' Ratio of unbound and total drug concentrations in plasma under conditions of altered binding, no units.

fu_b Ratio of unbound concentration in plasma and total drug concentration in blood, no units.

fu_P Ratio of unbound and total sites available for binding on a plasma protein, no units.

fu_R Ratio of unbound and average total drug concentrations in intracellular fluids, no units.

fu_T Ratio of unbound and total drug concentrations in tissues (outside plasma), no units.

γ Shape factor in concentration-response relationship, no units.

GFR Glomerular filtration rate, mL/min or L/hr.

k Elimination rate constant, hr^{-1}.

K_A Association constant for the binding of drug to protein, L/mole.

ka Absorption rate constant, hr^{-1}.

k_D Elimination rate constant while a patient is undergoing dialysis treatment, hr^{-1}.

ke Urinary excretion rate constant, hr^{-1}.

k_f Rate constant associated with the formation of a metabolite, hr^{-1}.

K_I Inhibition equilibrium constant, mg/L or μM.

$k(m)$ Rate constant for the elimination of a metabolite, hr^{-1}.

Km Michaelis-Menten constant, mg/L or μM.

Km' Michaelis-Menten constant, expressed in terms of total plasma concentration, mg/L or μM.

Kp Equilibrium distribution ratio of drug between tissue and blood or plasma, no units.

k_T Fractional rate at which drug leaves tissue, hr^{-1}.

k_t Fractional turnover rate, hr^{-1}.

λ_1; λ_2 Exponential coefficients, hr^{-1}.

m Slope of the center of the intensity of response versus log concentration curve, units of response.

MRT Mean time a molecule resides in body, hr.

n A unitless number.

N Number of doses, no units.

P Permeability coefficient, cm/min or cm/hr.

Q Blood flow, L/min or L/hr.

Q_D Dialysate flow in hemodialysis system, mL/min or L/hr.

Q_f Rate of filtrate flow from a hemofiltration system, mL/min or L/hr.

Q_H Hepatic blood flow (portal vein plus hepatic artery), L/min or L/hr.

ρ Ratio of concentration in blood cell to that unbound in plasma.

R_{ac} Accumulation ratio (index), no units.

Rd Ratio of unbound clearance of an individual patient to that of a typical patient, no units.

RF Renal function in an individual patient as a fraction of renal function in a typical patient, no units.

R_o Rate of constant intravenous infusion, mg/hr.

R_t Turnover rate, mg/hr.

S Salt form factor, no units.

SA Surface area, m^2.

τ Dosing interval, hr.

τ_{max} Maximum dosing interval to remain within C_{upper} and C_{lower} limits, hr.

t_{max} Time at which the highest drug concentration occurs following administration of an extravascular dose, min or hr.

t_d Duration of effect, hr.

t_{inf} Duration of a constant-rate infusion, hr.

Tm Maximum rate of drug transport (secretion) into renal tubule, mg/hr.

$t_{1/2}$ Half-life, hr.

t_t Turnover time, hr.

V Volume of distribution (apparent) based on drug concentration in plasma, L.

V_b Volume of distribution (apparent) based on drug concentration in blood, L.

V_B Blood volume, L.

V_D Volume of dialysate solution collected during a hemodialysis treatment, L.

V_1 Volume of initial dilution compartment, L.

Vm Maximum rate of metabolism by an enzymatically mediated reaction, mg/hr or μmole/hr.

$V(m)$ Volume of distribution (apparent) of a metabolite based on its plasma concentration, L.

V_P Plasma volume, L.

V_{PC} Volume of dialysate within the peritoneal cavity, L.

V_R Aqueous volume of intracellular fluids, L.

V_T Physiologic volume outside plasma into which drug distributes, L.

V_{ss} Volume of distribution (apparent) under steady-state conditions based on drug concentration in plasma, L.

V_{TW} Aqueous volume outside plasma into which drug distributes, L.

Vu Volume of distribution (apparent) based on unbound drug concentration in plasma, L.

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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 of a drug 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 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 magnitudes of the therapeutic and toxic responses are functions 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 a cost (in terms of side effects, toxicity, economics) is incurred with continuous 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 dose, interval between doses, and route of administration were selected, and the patient's progress followed. The desired effect and any signs of toxicity were carefully noted, and if necessary, the dosage regimen was adjusted empirically until an acceptable balance between the desired effect and 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 tetracycline have to be given every 6 to 8 hours to be effective, while digoxin can be given once 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 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 fluid 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 kidneys, that eliminate it from the body.

Figure 1–1 illustrates the events occurring after a dose of drug is administered orally. The rate at which drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and other tissues 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 both blood and 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*.

Table 1–1. Empirically Derived Usual Adult Dosage Regimens of Some Representative Drugs *Before* the Introduction of Clinical Pharmacokinetics[a]

DRUG	INDICATED USE	ROUTE	DOSAGE REGIMEN
Tetracycline	Treatment of Infections	Oral	250 mg every 6–8 hr
Digoxin	Amelioration of congestive cardiac failure	Oral	1.5–2 mg initially over 24 hr, thereafter 0.25–0.5 mg once a day
Oxytocin	Induction and maintenance of labor	Intravenous	0.2–4 milliunits/min by infusion
Morphine sulfate	Relief of severe pain	Intramuscular	10 mg when needed
		Oral	Not recommended because of reduced effectiveness

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

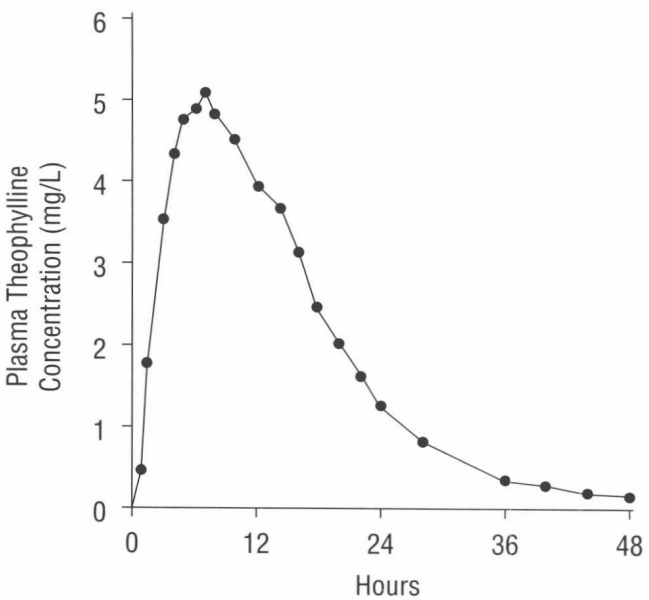

Fig. 1–1. Plasma concentration of theophylline in a subject following an oral dose of a 600-mg controlled-release formulation. Before the peak is reached, the rate of absorption exceeds that of elimination. At the peak, the two rates are equal; thereafter, the rate of elimination exceeds that of absorption. (Redrawn from Sauter, R., Steinijans, V.W., Diletti, E., Böhm, A., and Schulz, H.U.: Presentation of results in bioequivalence studies. Int. J. Clin. Pharmacol. Ther. Toxicol., *30*:S7–30, 1992.)

The events following drug administration can be divided into two phases, a *pharmacokinetic phase*, in which the adjustable elements of dose, dosage form, frequency, and route of administration are related to drug level–time relationships in the body, and a *pharmacodynamic phase*, in which the concentration of drug at the site(s) of action is related to the magnitude of the effect(s) produced (Fig. 1–2). Once both of these phases have been defined, a dosage regimen can be designed to achieve the therapeutic objective. Despite the greater amount of information required with this approach, it has several advantages over the empirical approach. First, and most obvious, distinction 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 aids the clinician in anticipating the optimal dosage regimen for an individual patient and in predicting what may happen when a dosage regimen is changed.

A basic tenet of clinical pharmacokinetics is that the magnitudes of both the desired response and toxicity are functions of the drug concentration at the site(s) of action. Accordingly, therapeutic failure results when either the concentration is too low, giving ineffective therapy, or is too high, producing unacceptable toxicity. Between these limits of concentration lies a region associated with therapeutic success; this region may be regarded as a "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 and more accessible site, *the plasma*.

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

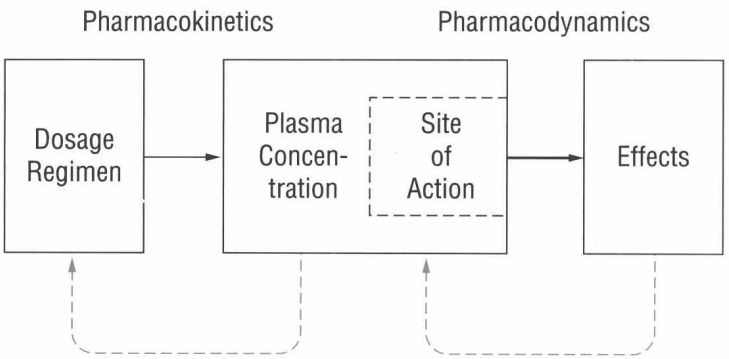

Fig. 1–2. An approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, either the plasma drug concentration-time data or the effects produced are used via pharmacokinetics as a feedback (dashed lines) to modify the dosage regimen to achieve optimal therapy.

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. Although a therapeutic response would have been achieved fairly promptly, toxicity would have ensued with continued administration when the concentration exceeded the upper limit of the therapeutic window.

The synthetic antimalarial agent, quinacrine, developed during World War II to substitute for the relatively scarce quinine, is an example. Quinacrine was either ineffective acutely against malaria or eventually produced unacceptable toxicity when a dosing rate sufficiently high to be effective acutely was maintained. Only after its pharmacokinetics had been defined was this drug used successfully. Quinacrine is eliminated slowly and accumulates extensively with repeated daily administration. The answer was to give large doses over the first few days to rapidly achieve therapeutic success, followed by small daily doses to maintain the plasma concentration within the therapeutic window.

The plateau situation in Fig. 1–3 shows that both the width of the therapeutic window and the speed of drug elimination govern the size of the maintenance dose and the frequency of administration. When the window is narrow and the drug is eliminated rapidly, small doses must be given often to achieve therapeutic success. Both cyclosporine and digoxin have a narrow therapeutic window, but because cyclosporine is eliminated much more rapidly than digoxin, it has to be given more frequently. Oxytocin is an extreme example; it also has a narrow therapeutic window but is eliminated within minutes. The only means of adequately ensuring a therapeutic concentration of oxytocin therefore is to infuse it at a precise and constant rate directly into the blood. This degree of control is not possible with other modes of administration. Besides, had oxytocin been given orally, this polypeptide hormone would have been destroyed by the proteolytic enzymes in the gastrointestinal fluids. Morphine, given orally, is also destroyed substantially before entering the general circulation, but for a reason different from that of oxytocin. Morphine is extensively metabolized on passage through the liver, an organ lying between the gastrointestinal tract and the general circulation.

Awareness of the benefits of understanding pharmacokinetics and concentration–response relationships has led in recent years to the extensive application of such information by the pharmaceutical industry to drug design, selection, and development. For example, a potent compound found to be poorly and unreliably absorbed and intended for oral administration may be shelved in favor of a somewhat less potent but more extensively and reliably absorbed compound. Also, many of the basic processes controlling both pharmacokinetics and response are similar across mammalian species such that data can be extrapolated from animals to predict quantitatively the likely behavior in humans. This quan-

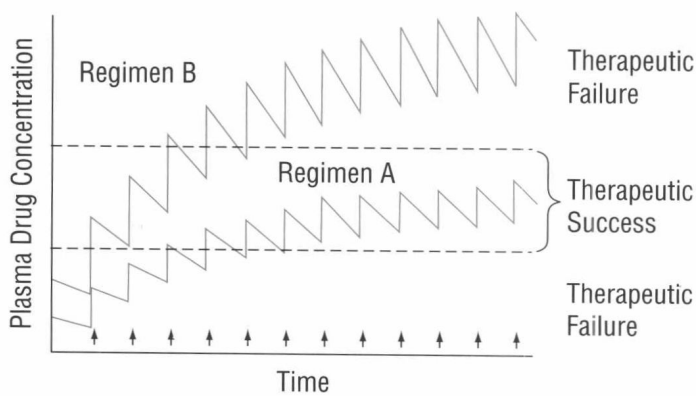

Fig. 1–3. When a drug is given in a fixed dose and at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is achieved more quickly, but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

titative framework improves the chances of selecting not only the most promising compounds but also the correct range of safe doses to first test in humans. Incorporation of a pharmacokinetic element with these early Phase I studies, usually in healthy subjects, together with assessment of any side effects produced, helps to define candidate dosage forms and regimens for evaluation in Phase II studies conducted in a small number of patients. These Phase II studies are aimed at defining the most likely safe and efficacious dosage regimens for use in the subsequent larger Phase III clinical trials, often involving many thousands of patients. Ultimately, some compounds prove to be of sufficient benefit and safety to be approved for a particular clinical indication by drug regulatory authorities. Even then the drug undergoes virtually continuous postmarketing surveillance to further refine its pharmacotherapeutic profile. This sequence of events in drug development and evaluation is depicted schematically in Fig. 1–4.

Figure 1–5 illustrates an important problem identified during drug development and therapy, variability. There is a wide range of daily dose requirements of the oral antico-

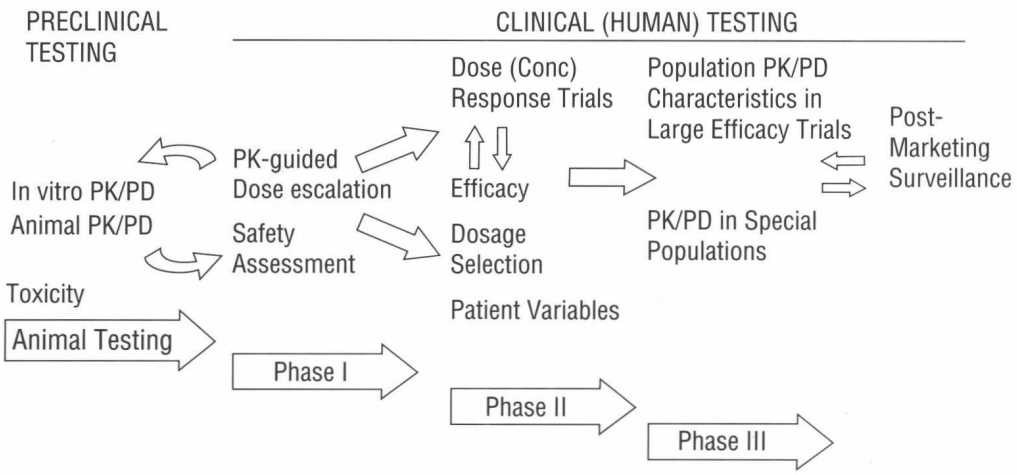

Fig. 1–4. The development and subsequent marketing of a drug. The prehuman data helps to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected patients, and the larger trials, respectively. Pharmacokinetic (PK) and pharmacodynamic (PD) data gathered during all phases of drug development help to efficiently define safe and effective dosage regimens for optimal individual use. Postmarketing surveillance helps to refine the PK/PD information.

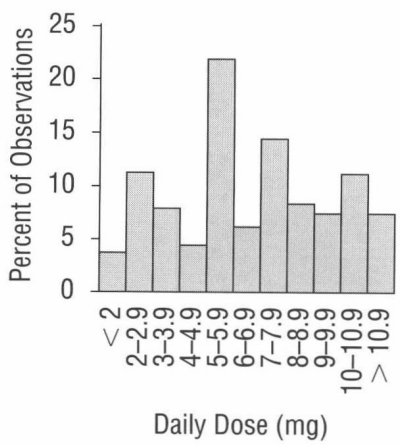

Fig. 1–5. The daily dose of warfarin required to produce similar prothrombin times in 200 adult patients varies widely. (1 mg/L = 3.3 μM). (Redrawn from Koch-Weser, J.: The serum level approach to individualization of drug dosage. Eur. J. Clin. Pharmacol. 9:1–8, 1975.)