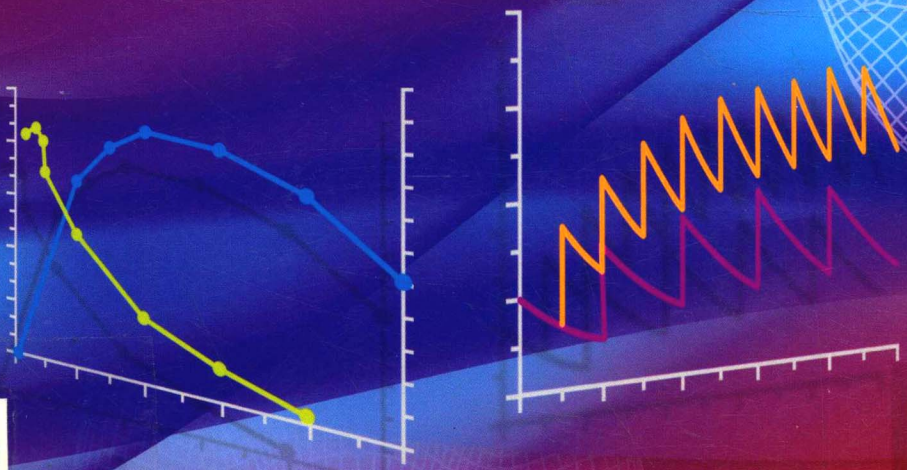
SECOND EDITION

ESSENTIALS OF Pharmacokinetics and Pharmacodynamics



Thomas N. Tozer
Malcolm Rowland

Wolters Kluwer

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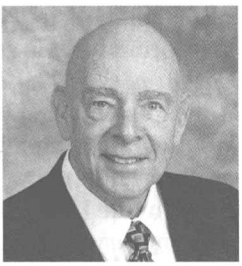
THOMAS N. TOZER

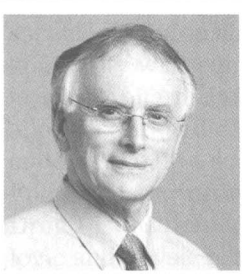


Dr. Tozer, Professor Emeritus of Biopharmaceutical Sciences and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California, received his BS, PharmD, and PhD degrees from the University of California, San Francisco. After a 2-year postdoctoral fellowship in the laboratory of Dr. B. B. Brodie, National Institutes of Health, Bethesda, Maryland, he joined the Faculty of the School of Pharmacy in San Francisco in 1965. Since obtaining emeritus status, he has taught courses and workshops in pharmacokinetics/pharmacodynamics and clinical pharmacokinetics at several institutions in the United States and Europe. For 10 years he was an Adjunct Professor of Pharmacology at the University of California, San Diego, where he taught biopharmaceutics and clinical pharmacokinetics at the Skaggs School of Pharmacy and Pharmaceutical Sciences.

Dr. Tozer, together with Dr. Malcolm Rowland, University of Manchester, authored the textbook, *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. He has published more than 155 scientific papers and book chapters on a variety of research topics with emphasis on the development and application of kinetic concepts in drug therapy. Dr. Tozer's research before retirement was focused in four areas: colon-specific drug delivery; toxicokinetics; kinetics of potential contrast agents for magnetic resonance imaging; and nonlinear pharmacokinetics. Other research included determination of drug disposition in disease states, particularly end-stage renal disease. Emphasis here was placed on evaluating and predicting when and how drug administration to renal disease patients should be altered.

Dr. Tozer was a corecipient of the 2000 Meritorious Manuscript Award, American Association of Pharmaceutical Scientists, and was a Visiting Professor (1996–1999) at the University of Manchester, Manchester, England. He is a Fellow of the American Association of Pharmaceutical Scientists and has served as a consultant to the Food and Drug Administration and to many pharmaceutical companies.

MALCOLM ROWLAND



Malcolm Rowland is Professor Emeritus and former Dean (1998–2001), Manchester School of Pharmacy, University of Manchester, and Adjunct Professor, Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California, San Francisco. He served as a Vice-President, International Pharmaceutical Federation (FIP, 2001–2009), the organization that represents and serves pharmacy and pharmaceutical sciences around the globe, and was President, European Federation of Pharmaceutical

Sciences (1996–2000). He received his Pharmacy degree and PhD from the University of London, and was on the faculty at the School of Pharmacy, University of California, San Francisco (1967–1975), before taking up a professorship at Manchester (1975–2004).

Dr. Rowland, together with Dr. Thomas Tozer, has authored the textbook *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. He has authored more than 300 scientific articles and chapters. His research interest is primarily in physiologically based pharmacokinetics and its application to drug development and clinical use. In particular, he has pioneered the concept and application of clearance, and developed approaches to the prediction of pharmacokinetics of drugs from a combination of physicochemical properties and in vitro information. He served as an editor of *Journal of Pharmacokinetics and Pharmacodynamics* (1973–2007), the premiere speciality journal dedicated to the subject, and has established workshops for teaching both basic and advanced level pharmacokinetics. He is an advisor to the pharmaceutical industry and sits on various scientific advisory boards.

Dr. Rowland has been awarded honorary doctorate degrees from the University of Poitiers (France), Uppsala (Sweden), and Athens (Greece), and Honorary Membership of the Royal College of Physicians (London). He received various awards including the 2012 Sheiner-Beal Award in Pharmacometrics, American Society of Clinical Pharmacology and Therapeutics; the 2011 Host Madsen Award, FIP; and the 2007 American College of Clinical Pharmacology (ACCP) Distinguished Investigator Award. He has been made a fellow of various professional organizations including the Academy of Medical Sciences, ACCP (Hon), the Royal Pharmaceutical Society of Great Britain, and the British Pharmacological Society.

PREFACE

This is the second edition of this textbook, which lays down the foundations of how exposure of drug within the body and response following drug administration are quantified and integrated, and how this vital information provides a rational approach to the establishment, optimization, and individualization of dosage regimens in patients. The title of the first edition began "*Introduction to...*," but so many readers of the first edition expressed the view that this textbook contained the very essence of the quantitative basis of drug therapy that we decided to change the title to *Essentials of Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy.* The book is intended for students and practitioners of pharmacy and medicine, as well as other health professionals, who need to understand the basic principles upon which quantitative decisions in drug therapy are based. It will also be a valuable resource and primer for those in the pharmaceutical and biotech industries involved in drug development, especially those from other backgrounds who have been given responsibility for the clinical development and evaluation of new drugs and those involved in the registration and regulation of drugs.

We are perhaps best known for our larger textbook *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*, now in its fourth edition. This widely read, more in-depth, textbook serves a more advanced readership. In a sense, this smaller *Essentials* textbook aims to meet the needs of another wide audience, those who apply the principles in clinical practice or who work on the clinical side of drug development, who are in need not only of a more simplified textbook but, in particular, one that links drug exposure within the body to drug response—that is, to the pharmacodynamics of drugs. It provides the key quantitative tools and principles of drug therapy without recourse to an extensive use of mathematics, although some use of mathematics is essential when dealing with the quantitative aspects of drug therapy. Furthermore, many examples of currently prescribed drugs are included in the book to emphasize its utility to contemporary practice.

The book begins with the basic principles underlying pharmacokinetics and pharmacodynamics, and finishes with the application of these principles to the establishment, maintenance, and optimization of dosage regimens for the individual patient. Relative to the first edition, the second has many more Study Problems, including many in the multiple choice format used in licensing examinations. There are also practice questions that allow the reader to calculate and appreciate the quantitative aspects of pharmacokinetics and pharmacodynamics. As some readers may have less familiarity with some of the medical terms needed to convey the therapeutic setting in which pharmacokinetic and pharmacodynamic data are acquired and applied, an appendix of medical terms and words used in the text has been included. Chapters 5 and 6 of the first edition have been expanded to four chapters on: Quantifying Events Following An Intravenous Bolus, Physiologic and Physicochemical Determinants of Drug Disposition, Quantifying Events Following An Extravascular Dose, and Physiologic and Physicochemical Determinants of Drug Absorption. The second edition also has a greater emphasis on protein drugs and has been reorganized and updated from

the first. With its emphasis on the integration of basic concepts, as well as concern for clarity of content in each chapter, great attention has been devoted to ensuring that the material content builds on knowledge from prior chapters as one progresses through the book.

Key elements in the organization of each chapter include Objectives at the beginning and a Summary and a Key Term Review toward the end. The Key Relationships of each chapter and Study Problems are provided at the end of each chapter. Detailed answers to the problems are provided in Appendix F. Definitions of Symbols and Medical Terms and Words used throughout the book are located in Appendices A and B. Appendices C, D, and E are intended as supplemental material for the interested reader. They also contain a few practice problems with answers to them in Appendix F. Further details on the organization of the book are given at the end of Chapter 1. Intentionally, coverage of the many concepts is not comprehensive; the book is meant to provide selected examples that illustrate the principles presented and to encourage the reader to give further thought to the concepts.

As an introductory text, this book should be particularly helpful to those teaching pharmacy and medical students within a separate course or within a pharmacology course or elective course in clinical pharmacology. In general, the textbook should be useful in all courses designed to train health professionals in the fundamental principles underlying the establishment of dosage regimens and individualization of drug administration to optimize drug therapy. We recognize that, in addition, some readers will treat this as a self-study textbook. Indeed, it has been written and organized to facilitate this mode of learning.

We wish to acknowledge all the students and colleagues, both in academia and the industry—too numerous to name individually—whose interactions over the years have provided the very "food for thought" for many parts of this book. Without their input, this book would not have been possible. Finally, and most importantly, our special thanks to our wives, Margaret and Dawn, for putting up with the many hours and temporary separations needed for us to work together to write this book.

THOMAS N. TOZER
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CONTENTS

CHAPTER 1

Opening Comments

THE CLINICAL SETTING

When asked, most patients can readily proffer the names of the drugs they are taking, or, if they do not know the names, they know the general reason they are taking them, such as for a heart problem, a backache, high blood pressure, or recurrent depression. They also know how often the medicine should be taken and whether it should be taken before, with, or after eating, although how well they adhere to the prescription label is another matter. However, when it comes to the question of dose, most patients are at best unsure or even have no idea of the strength of their medicine or the amount they are taking. This is because most patients, and many clinicians, think qualitatively rather than quantitatively, but dose is of paramount importance. To paraphrase Paracelsus, who lived some 500 years ago, "all drugs are poisons, it is just a matter of dose." A dose of 25 mg of aspirin does little to alleviate a headache; a dose closer to 300–600 mg is needed, with few ill effects. However, 10 g taken all at once can be fatal, especially in young children.

What determines the therapeutic dose of a drug and its manner and frequency of administration, as well as the events experienced over time by patients on taking the recommended dosage regimens, constitutes the body of this introductory book. It aims to demonstrate that there are principles common to all drugs, and that equipped with these principles, not only can many of the otherwise confusing events following drug administration be rationalized, but also the very basis of dosage regimens can be understood by addressing the key questions about a specific drug: How much? How often? For how long? That is, the principles form the quantitative basis of drug therapy. The intended result is the better and safer use of drugs for the treatment or amelioration of diseases or conditions suffered by patients. Keep in mind, for example, that still today some 7% of patients admitted into hospital are there because of adverse reactions, some life threatening, due to the inappropriate use of drugs, much of which is avoidable. Many additional patients receive suboptimal dosage or have adverse reactions, but not severe enough to require hospitalization.

It is possible, and it was common practice in the past, to establish the dosage regimen of a drug through trial and error by adjusting such factors as the dose and interval between doses and observing the effects produced, as depicted in Fig. 1-1 (next page). A reasonable regimen might eventually be established, but not without some patients experiencing excessive toxicity and others ineffective therapy. Certainly, this was

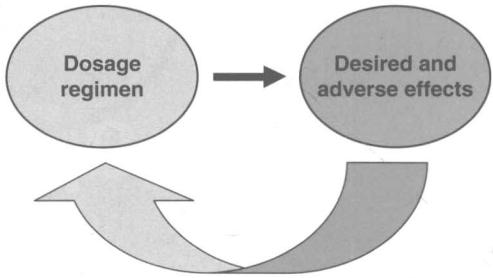

FIGURE 1-1 An empirical approach to the design of a dosage regimen. The effects, both desired and adverse, are monitored after the administration of a dosage regimen of a drug, and used to further refine and optimize the regimen through feedback (*curved arrow*).

the procedure to establish that digoxin needed to be given at doses between 0.1 and 0.25 mg only once a day for the treatment of congestive cardiac failure. On the other hand, morphine sulfate needed to be administered at doses between 10 and 50 mg up to six times a day to adequately relieve the chronic severe pain experienced by patients suffering from terminal cancer. However, this empirical approach not only fails to explain the reason for this difference in the regimens of digoxin and morphine, but also contributes little, if anything, toward establishing effective dosage regimens of other drugs. That is, our basic understanding as to how drugs behave and act within the body has not been increased.

Components of the Dose–Response Relationship

Progress in understanding the relationship between drug administration and response has only been forthcoming by realizing that concentrations at active sites—not doses—drive responses, and that to achieve and maintain a response, it is necessary to ensure the generation of the appropriate exposure profile of drug within the body. This in turn requires an understanding of the factors controlling this exposure profile. These ideas are summarized in Fig. 1-2, where now the relationship between drug administration and response produced, which we will refer to as "**dose–response,**" is divided into two components, **pharmacokinetics** and **pharmacodynamics** (with the root of both terms derived from the Greek *pharmacon*, meaning a drug, or, interestingly, also a poison). The pharmacokinetic component covers the relationship between the dosage regimen, which comprises such adjustable factors as dose, dosage form, frequency, and route of administration, and the concentration or exposure achieved in the body *with time*. The pharmacodynamic phase covers the relationship between drug exposure within the body and both the desired and adverse effects produced *with time*. In simple terms, pharmacokinetics

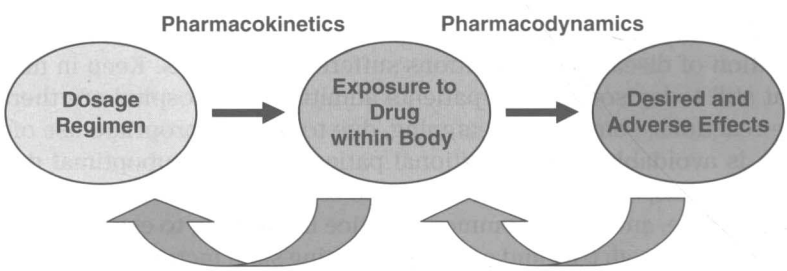

FIGURE 1-2 A rational approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, responses to the drug, together with pharmacokinetic information, are used as a feedback (*curved arrows*) to modify the dosage regimen to achieve optimal therapy.

may be viewed as the time-course of the body's handling of a drug, and pharmacodynamics as the body's response to drug exposure there.

Several other basic ideas have helped to place drug administration on a more rational footing. The first (partially alluded to above) is that the intensity or likelihood of an effect increases with increasing exposure to the drug, but only to some limiting, or maximum, value above which the response can go no higher. Second, drugs act on different components within the body, so that the maximum measured clinical effect produced by one drug may be very different from that of another. For example, both aspirin and morphine relieve pain. Whereas aspirin may relieve mild pain, it cannot relieve the severe pain experienced by patients with severe trauma or cancer even when given in massive doses. Here, morphine, or another opioid analgesic, is the drug of choice. The third (which follows in part from the second idea) is the realization that drugs produce a multiplicity of effects, some desired and some undesired, that when combined with the first idea, has the following implication. Too low an exposure within the body results in an inadequate desired response, whereas too high an exposure increases the likelihood and intensity of adverse effects. Expressed differently, there exists an optimal range of exposures between these extremes, the **therapeutic window,** shown schematically in Fig. 1-3. For some drugs, the therapeutic window is narrow, and therefore the margin of safety is small. For others, the window is relatively wide.

Armed with these simple ideas, one can now explain the reason for the differences in the dosing frequency among morphine, digoxin, and adalimumab. All three drugs have a relatively narrow therapeutic window. However, morphine is eliminated very rapidly from the body, and must be given frequently, up to 6 times a day, to maintain an adequate concentration to ensure relief of pain without excessive adverse effects, such as respiratory depression. Digoxin is more stable within the body, and so with

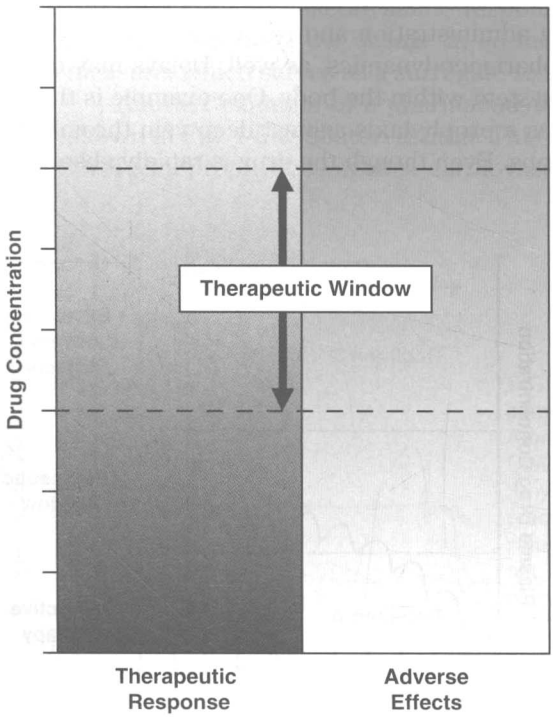

FIGURE 1-3 At higher concentrations or higher rates of administration on chronic dosing, the probability of achieving a therapeutic response increases (*shaded from black* [no response] *to white*), but so does the probability of adverse effects (*shaded from white* [no adverse effect] *to burnt orange* [severe adverse effects]). A window of opportunity, called the "therapeutic window," exists, however, in which the therapeutic response can be attained without an undue incidence of adverse effects.

little lost each day, a once-daily regimen suffices to treat atrial fibrillation and other heart diseases. For adalimumab, a subcutaneous dose given once every 2 weeks to treat rheumatoid arthritis patients is adequate because less than one-half of a dose is eliminated from the body within this time period. Unlike morphine and digoxin, adalimumab, a protein drug, is given subcutaneously because it is not absorbed when given orally.

These principles also helped to explain an enigma at the time concerning the pattern of effects seen with the synthetic antimalarial drug, quinacrine, developed during World War II. Given daily, 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 were these findings explained and the drug used successfully. Quinacrine is eliminated even more slowly than digoxin, with very little lost each day, such that it accumulates extensively with repeated daily administration of the same dose, as depicted schematically in Fig. 1-4. At low daily doses, the initial concentrations are too low to be effective, but eventually, the plasma concentration rises to within the therapeutic window. Increasing the daily dose shortens the time for the concentration to be within the therapeutic window, but, with the concentration still rising, eventually it becomes too high, and unacceptable toxicity ensues. Yet what was needed was rapid achievement, and subsequent maintenance, of adequate antimalarial concentrations without undue adverse effects. The answer developed was to give large doses over the first few days to rapidly achieve therapeutic concentrations, followed by smaller daily doses to maintain the concentration within the therapeutic window.

The lesson to be learned from the case of quinacrine, and indeed most drugs, is that only through an understanding of the temporal events that occur after the drug's administration can meaningful decisions be made regarding its optimal use.

Delays in drug response may also occur due to slow distribution to the target site, which is often in a cell within a tissue or organ, such as the brain. However, the issue of time delays between drug administration and response is not confined to pharmacokinetics, but extends to pharmacodynamics, as well. Delays may occur because of the nature of the affected system within the body. One example is that of the oral anticoagulant warfarin, used as a prophylaxis against deep vein thrombosis and other thromboembolic complications. Even though the drug is rapidly absorbed,

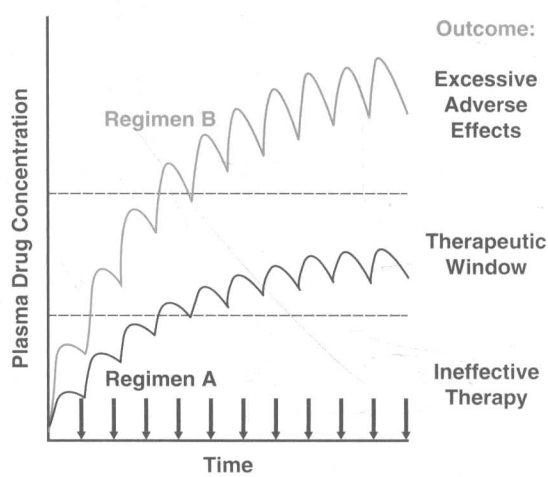

FIGURE 1-4 When a drug is given repetitively in a fixed dose and at a fixed time interval (*arrows*), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved, although not initially. With regimen B, the therapeutic objective is achieved more quickly, but the drug concentration is ultimately too high, resulting in excessive adverse effects.

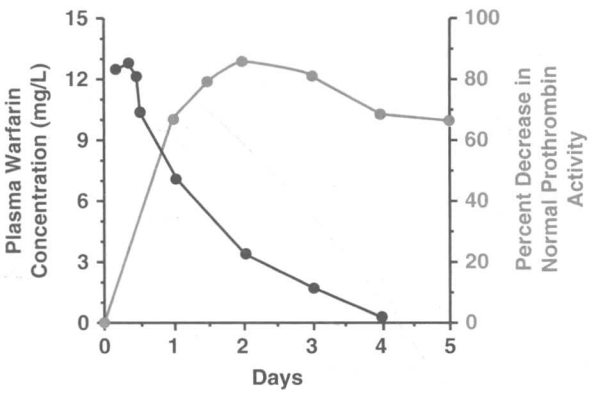

FIGURE 1-5 The sluggish response in the plasma prothrombin complex activity (*colored line*), which determines the degree of coagulability of blood, is clearly evident after administration of the oral anticoagulant, warfarin. Although the absorption of this drug into the body is rapid with a peak concentration seen within the first few hours, for the first 2 days after giving a single oral 1.5 mg/kg dose of sodium warfarin, response (defined as the percent decrease in the normal complex activity) steadily increases, reaching a peak after 2 days. Thereafter, the response declines slowly as absorbed drug is eliminated from the body. The data points are the averages of five male volunteers. (From Nagashima R, O'Reilly RA, Levy G. Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin. *Clin Pharmacol Ther* 1969;10:22–35.)

yielding high early concentrations throughout the body, as seen in Fig. 1-5, the peak effect, as manifested by prolongation of the clotting time, occurs approximately 2 days after a single dose of warfarin. Clearly, it is important to take this lag in response into account when deciding how much to adjust the dose to achieve and maintain a given therapeutic response. Failing to do so and attempting to adjust the dosage based on the response seen after 1 day, before the full effect develops, increases the danger of subsequently overdosing the patient. This can have serious consequences, such as internal hemorrhage, with this low margin-of-safety drug.

Another problem with drugs of a low margin of safety is that individualization of dosage is essential because of interindividual differences in both the pharmacokinetic behavior and pharmacodynamic response to the drug. For warfarin, this is accomplished by titrating the dosage in an individual to obtain a desired in vitro clotting measure, which serves as a surrogate to its clinical response.

Another example of a pharmacodynamic delay is seen with the statin drugs, as shown in Fig. 1-6 with atorvastatin. This class of drugs is used to lower blood cholesterol as a prophylaxis against cardiovascular complications such as atherosclerosis,

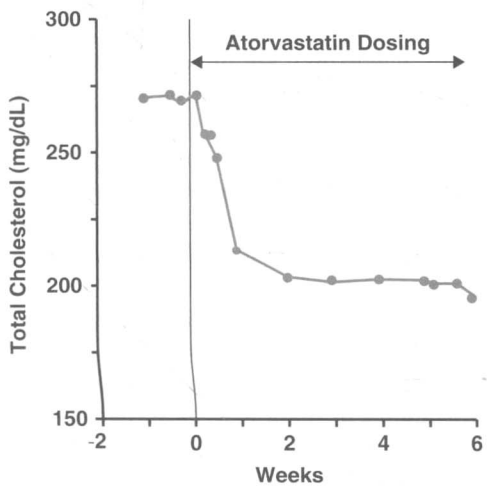

FIGURE 1-6 Plot of total cholesterol against time after oral administration of 5 mg atorvastatin once daily for 6 weeks. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Note that despite the relatively short half-life of atorvastatin (14 hours, not shown), it takes almost 2 weeks to see the full effect of inhibition of cholesterol synthesis. (Redrawn from Stern RH, Yang BB, Hounslow NJ, et al. Pharmacodynamics and pharmacokinetic-pharmacodynamic relationship of atorvastatin, an HMG-CoA reductase inhibitor. *J Clin Pharmacol* 2000;40:616–623.)

signaling the likely occurrence of myocardial infarction and stroke. Despite this statin being rapidly eliminated from the body, the full lowering of blood cholesterol takes from 2 to 3 weeks after chronic dosing. This slow response is associated with the slow turnover of the cholesterol pool within the body. Dose adjustment to ensure an adequate lowering of cholesterol in individual patients is common, and the findings shown in Fig. 1-6 imply that one needs to wait for at least 1 month before deciding whether any further dose adjustment is warranted.

As mentioned previously, an interesting feature of many drugs is that they exhibit different effects with concentration. An unusual but telling example is seen with clonidine. Originally developed as a nasal decongestant, when it was evaluated for this indication, some subjects became faint because of a then-unexpected hypotensive effect. Today, the therapeutic use of this drug is as an antihypertensive agent. However, further investigation showed that it was possible to produce not only a hypotensive effect but also hypertension, depending on the concentration. Clonidine acts on two classes of receptors, one causing a lowering of blood pressure and the other causing an elevation in blood pressure. At low concentrations within the body, and those achieved with therapeutic doses, the lowering effect on blood pressure predominates. However, at high concentrations, as might be achieved during an overdose, the hypertensive effect predominates, although this effect subsides and the hypotensive effect again predominates as the concentration within the body falls. For other drugs, such as warfarin, the mechanism of action is the same for producing desired and adverse effects. Warfarin's almost singular action is anticoagulation. Yet, this effect is defined as therapeutic when warfarin's concentration is such that it minimizes the risk of embolism and it is defined as adverse at higher concentrations, where the risk of internal hemorrhage is high, that is, where the anticoagulation effect becomes excessive. The lesson is clear. Understanding the specific concentration–response relationship of a drug helps in its management and optimal use.

Variability in Drug Response

If we were all alike, there would be only one dose strength and regimen of a drug needed for the entire patient population. But we are not alike; we often exhibit great interindividual variability in response to drugs. This is generally not so important for drugs with wide therapeutic windows, because patients can tolerate a wide range of exposures for similar degrees of benefit, particularly when the dose ensures that the beneficial effect is experienced by essentially all patients. In this case, a single dose of drug, the "one-dose-for-all" idea, suffices. Still, even then, some patients may not respond to therapy because they lack the receptor on which the drug acts or their receptor is different.

The problem of variability in both pharmacokinetics and pharmacodynamics becomes particularly acute for drugs with a medium-to-low therapeutic window, of which there are many. Examples include the immunosuppressive agent cyclosporine, used to prevent organ rejection after transplantation, and the antiepileptic drug phenytoin (Fig. 1-7), in addition to morphine, digoxin, and warfarin. For these drugs, the solution is the availability of an array of dose strengths, with titration of dosage to the patient's individual requirements.

The variability in the concentration of phenytoin is primarily pharmacokinetic in origin. Pharmacodynamics is also a cause of variability in response, as shown by the minimum alveolar concentration (deep in the lungs) of desflurane (Suprane), a general inhalation anesthetic, required to give the same depth of anesthesia in various age

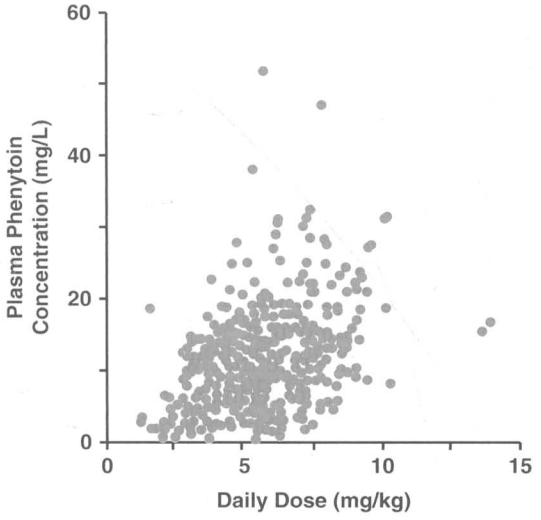

FIGURE 1-7 Although the average plasma concentration of phenytoin on chronic dosing tends to increase with the dosing rate, there is very large variation in the individual values for a given daily dose, even when normalized on a body weight basis. (Redrawn from Lund L. Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In: Davies DS, Prichard BNC, eds. *Biological Effects of Drugs in Relation to Their Plasma Concentration.* London and Basingstoke: Macmillan, 1973.)

groups (Fig. 1-8). The sensitivity to the drug is much greater in the elderly patient than in any other age group. The alveolar concentration has been used to measure systemic exposure to the drug in much the same way as a breath test has been used to assess blood levels of alcohol, another volatile substance.

The causes of variability in dose response are manifold. One important and pervasive cause is genetics. It has been known for many years that, when evaluated, identical twins exhibit only minute differences in the pharmacokinetics and response to drugs, even when they live apart and in different social environments, compared with the often experienced wide differences in response between nonidentical twins. The importance of genetics is also known from familial studies and studies in different ethnic groups. One example, again arising during World War II, which occurred when

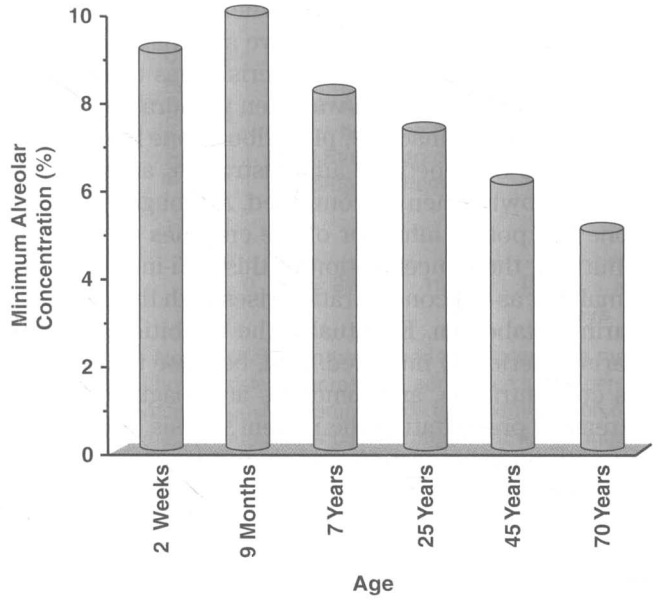

FIGURE 1-8 The minimum alveolar concentration (%, v/v) of desflurane required for general anesthesia varies with age. Elderly patients are clearly more sensitive to the anesthetic effect of the drug. (From table of data in *Physician's Desk Reference.* 60th Ed. Montvale, NJ: Medical Economics Co.; 2006:832.)

the fighting spread to tropical regions where malaria was rife, was the observation that approximately 10% of African American soldiers, but few Caucasians, developed acute hemolytic anemia, due to the abnormal and acute breakdown of red cells, when given a typical dose of the antimalarial drug primaquine. Subsequent investigations showed that this sensitivity to primaquine and some other chemically related antimalarial drugs was due to an inherited deficiency among many African Americans of an important enzyme, glucose 6-phosphate dehydrogenase (G6PD), which resides in red blood cells and is a component responsible for the integrity of the blood cells. On further checking, it was found that G6PD is located on the sex chromosome X and that more than 400 million people carry one of the many different variants of G6PD, which places them at risk for hemolysis when exposed to certain drugs.

Another example of the importance of genetics is the one that was experienced with the drug debrisoquine, a now defunct blood pressure lowering drug. In most patients, this proved to be an effective and benign drug, but in about 8% of Caucasians, even a modest dose caused a major hypotensive crisis. Because this adverse response was then unpredictable, in that there was no means of predicting who would manifest this severe adverse effect, the drug was withdrawn. With progress in deciphering the human genome or, more accurately, human genomes, we are beginning to understand the molecular basis of genetic differences. In the case of the debrisoquine-induced crisis, the cause was eventually traced to the presence within this minority Caucasian group of defective variants of a cytochrome-metabolizing enzyme located within the liver, which is almost exclusively responsible for metabolism of debrisoquine and many other drugs. Normally, debrisoquine is rapidly eliminated from the body, but an inability to readily remove this drug results in the usual doses of debrisoquine producing excessively high concentrations within the body and thus excessive effect. Today, increasingly, genomic information is helping to improve and individualize drug therapy.

In the 1970s, an elderly male patient suffered a bout of inflammatory pain, for which he was prescribed the effective anti-inflammatory drug phenylbutazone at the typical regimen of 100 mg three times daily. He was also susceptible to the development of deep vein thrombosis, for which he was prophylactically receiving warfarin. Everything was under satisfactory control until about a week later when a crisis occurred, caused by the sudden loss of control on warfarin with excessive anticoagulation and the danger of internal hemorrhage. Initially, the cause of this crisis was unclear, but eventually it was traced back to phenylbutazone, which was then withdrawn, and the crisis subsided, but slowly. Like digoxin and quinacrine, phenylbutazone is relatively stable within the body and accumulates on repetitive administration, as schematically depicted in Fig. 1-4, and declines slowly when discontinued. Although it was not known at the time, phenylbutazone is a potent inhibitor of the enzymes responsible for the metabolism of warfarin. Initially, the concentration of this anti-inflammatory drug is low, and inhibition is minimal, but as the concentration rises with time, so does the degree of inhibition of warfarin metabolism. Eventually, the inhibition is so severe that the elimination of warfarin is seriously impaired. And, because the regimen of warfarin was not changed, its concentration, and hence its anticoagulant effect, progressively and insidiously increased, precipitating the patient's crisis. The failure to initially associate the problem with phenylbutazone was due to the considerable time delay between the initiation of this drug and the crisis, but the reason, as just explained, is really all too plain to see. The issue of time is all-pervasive, and one ignores this component at one's peril.