# Clinical Pharmacokinetics
## Concepts and Applications

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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# 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*                                            Malcolm Rowland
*San Francisco, California*                                      Thomas N. Tozer

# CONTENTS

# VARIABILITY

**OBJECTIVES**

The reader will be able to:

1. List six major sources of variability in drug response.
2. Evaluate whether variability in drug response is caused by a variability in pharmacokinetics, pharmacodynamics, or both, given response and pharmacokinetic data.
3. State why variability around the mean and shape of the frequency distribution histogram of a parameter are as important as the mean itself.
4. Explain how variability in hepatic enzyme activity manifests itself in variability in both pharmacokinetic parameters and plateau plasma drug concentrations for drugs of high and low hepatic extraction ratios.
5. Suggest an approach for initiating a dosage regimen for an individual patient, given patient population pharmacokinetic data and the individual's measurable characteristics.

Thus far, the assumption has been made that all people are alike. True, as a species, humans are reasonably homogeneous, but differences among people do exist including their responsiveness to drugs. Accordingly, there is a frequent need to tailor drug administration to the individual patient. A failure to do so can lead to ineffective therapy in some patients and toxicity in others.

This section of the book is devoted to individual drug therapy. A broad overview of the subject is presented in this chapter. Evidence for and causes of variation in drug response, and approaches toward individualizing drug therapy are examined. Subsequent chapters deal in much greater detail with genetics (Chap. 14), age and weight (Chap. 15), disease (Chap. 16), interactions between drugs within the body (Chap. 17), and monitoring of plasma concentration of a drug as a guide to individualizing drug therapy (Chap. 18).

Before proceeding, a distinction must be made between an individual and the population. Consider, e.g., the results of a study designed to examine the contribution of an acute disease to variability in drug response. Suppose, of 30 patients studied during and after recovery, only 2 showed a substantial difference in response; in the remainder the difference was insignificant. Viewed as a whole, the disease would not be considered as a significant source of variability, but to the two affected patients it would. Moreover, to avoid toxicity, the dosage regimen of the drug may need to be reduced in these two patients during the disease. The lesson is clear: Average data are useful as a guide; but ultimately, information pertaining to the individual patient is all-important.

On a similar but broader point, substantial differences in response to most drugs exist among patients. Such *inter*individual variability is often reflected by a variety of marketed dose strengths of a drug. Because variability in response within a subject (*intra*individual) is generally much smaller than *inter*individual variability, once well-established, there is

usually little need to subsequently adjust an individual's dosage regimen. Clearly, if *intra*individual variability were large and unpredictable, trying to titrate dosage for an individual would be an extremely difficult task, particularly for drugs with narrow therapeutic windows. Stated differently, a drug that exhibits a high *intra*individual variability in pharmacokinetics can be prescribed only if it has a wide therapeutic window.

## EXPRESSIONS OF INDIVIDUAL DIFFERENCES

Evidence for interindividual differences in drug response comes from several sources. Variability in the dosage required to produce a given response is illustrated in Figure 1–5 (Chap. 1), which shows the wide range in the daily dose of warfarin needed to produce a similar degree of anticoagulant control. Variability in the intensity of response with time to a set dose is seen with the neuromuscular agent doxacurium (Fig. 13–1). As illustrated in Figs. 13–2, and 13–3, which show frequency distribution histograms of the plateau plasma concentration of the antidepressant drug nortriptyline, to a defined daily dose of the drug and the plateau unbound plasma concentration of warfarin required to produce a similar degree of anticoagulant control, variability exists in both pharmacokinetics and pharmacodynamics. Variability in pharmacokinetics was also illustrated by the wide scatter in the plateau plasma concentration of phenytoin seen following various daily doses of this drug (see Fig. 1–6, Chap. 1).

## The Need for Models

The magnitude and relative contribution of pharmacokinetics and pharmacodynamics to variability in response to a given dosage within a patient population vary with the drug and, to some extent, the condition being treated. For example, with a nonsteroidal anti-inflammatory drug, the relative contribution of pharmacodynamic variability may be different when the endpoint is the relief of a headache than when it is the relief from chronic aches and pains associated with inflamed joints. In clinical practice, attempts to assign the relative contribution to pharmacokinetics and pharmacodynamics may be made based on direct observations of plasma concentration and response. The assignment could be strongly influenced, however, by the timing of the observations and the magnitude of the response,
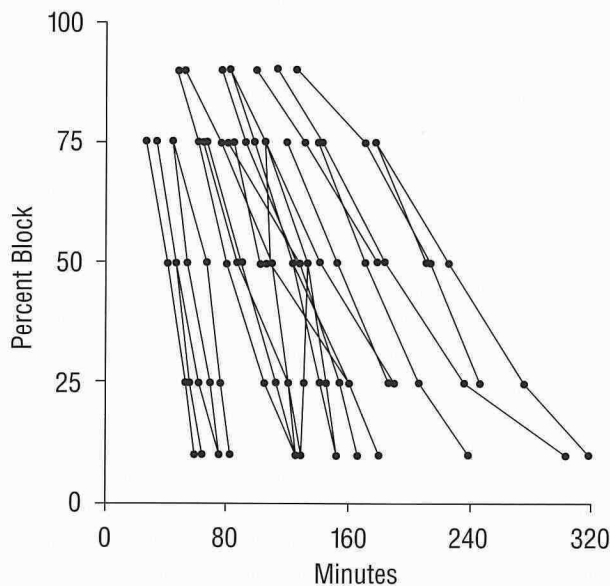


**Fig. 13–1.** The degree of neuromuscular blockage with time after an i.v. bolus dose of 0.04 mg/kg doxacurium to patients varies widely. (1 mg/L = 0.97 μM) (Modified from Schmith, V.D., Fiedler-Kelly, J., Abou-Donia, M., Huffman, C.S., and Grasela, T.H.: Population pharmacodynamics of doxacurin. Clin. Pharmacol. Ther., 52:528–536, 1992.)

as illustrated in Fig. 13–4. Here, a drug that displays little interpatient variability in $C_{max}$, $t_{max}$ and in maximum effect, but large variability in half-life and concentration needed to produce 50% maximum response, is given orally at two doses, one that achieves close to maximal response in all patients and one that does not. At the higher dose, observations made at $C_{max}$ would suggest little variability in either concentration or pharmacodynamics, with perhaps a greater assignment of variability to the former, as variation in plasma concentration produces relatively little change in response. At later times after this higher dose, substantial variability is observed in both concentration and response. In contrast, for
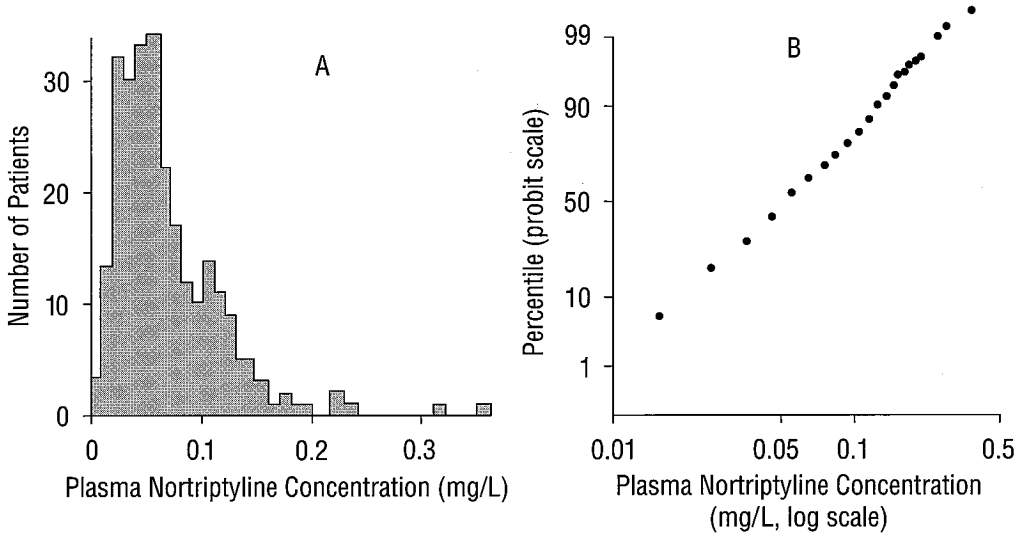
**Fig. 13–2.** *A,* The plateau plasma concentration of nortriptyline varies widely in 263 patients receiving a regimen of 25 mg nortriptyline orally three times daily. *B,* The concentrations are log-normally distributed, as seen from the straight line, when the percentiles of the cumulative number of patients are plotted on probit scale against the logarithm of the concentration. (1 mg/L = 3.8 μM) (Redrawn and calculated from Sjoqvist, F., Borga, O., and Orme, M.L.E.: Fundamentals of clinical pharmacology. *In* Drug Treatment. Edited by G.S. Avery. Edinburgh, Churchill Livingstone, 1976, pp. 1–42.)
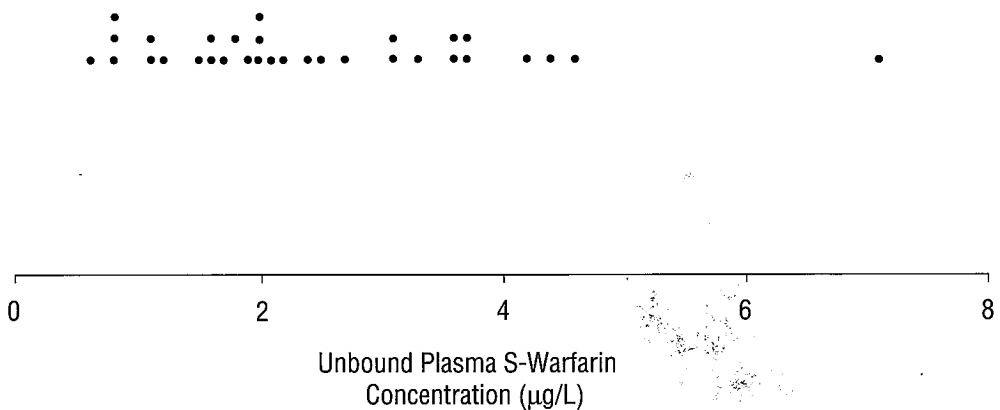
**Fig. 13–3.** The unbound plateau concentration of the predominately active S-warfarin associated with a similar degree of anticoagulation, varies widely among a group of 38 patients receiving racemic warfarin. (1 mg/L = 3.3 μM) (Adapted from Chan, E., McLachlan, A.J., Pegg, M., Mackay, A.D., Cole, R. B., and Rowland, M.: Disposition of warfarin enantiomers and metabolites in patients during multiple dosing. Br. J. Clin. Pharmacol., 37:563–569, 1994.

**Fig. 13–4.** The interindividual variability in concentration and response varies with dose and time of observation. Shown are plasma concentrations (left) and responses (right) following large and small doses of a drug that displays little interpatient variability in $C_{max}$, $t_{max}$ and maximum response, but large interpatient variability in half-life and concentration needed to produce 50% maximum response. High dose (top): at $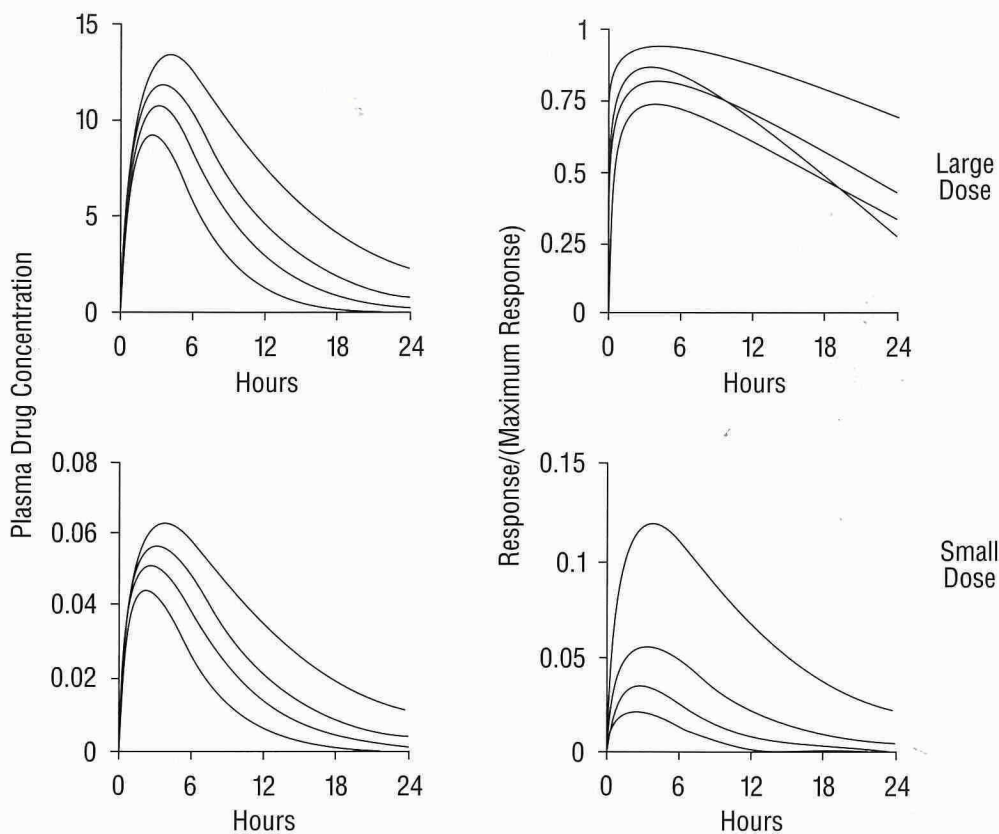t_{max}$, the maximum response in all patients is produced with little variability in either $C_{max}$ or response. Greater variability in concentration and response is seen at later times. Low dose (bottom): at $t_{max}$, variability in $C_{max}$ is still low, but that in response is now considerable.

the lower dose, at $t_{max}$ there is still little interpatient variability in $C_{max}$, but now there is considerable variability in response. This dependence on dose and time in the assignment of variability is minimized by expressing variability not in terms of observations but rather in terms of the parameter values defining pharmacokinetics and pharmacodynamics, that is, in $F$, $ka$, $CL$, and $V$ for pharmacokinetics, and in maximal response, concentration to achieve 50% of the maximum response, and the factor defining the steepness of the concentration–response relationship for pharmacodynamics (Chap. 20, Pharmacologic Response). Once variability in these parameters is defined, the expected variability in concentration and response within the patient population associated with given dosage regimens can be estimated. The accuracy of the models defining pharmacokinetics and pharmacodynamics is obviously critical to an understanding of variability in patient response. Where appropriate, these models should incorporate such factors as protein binding, active metabolites, and tolerance.

## DESCRIBING VARIABILITY

Knowing how a particular parameter varies within the patient population is important in therapy. To illustrate this statement consider the frequency distributions in clearance of

the three hypothetical drugs shown in Fig. 13–5. The mean, or central tendency, for all three drugs is the same, but the variability about the mean is very different. For Drugs A and B, the distribution is unimodal and normal; here the mean represents the typical value of clearance expected in the population. As variability about the mean is much greater for Drug B than for Drug A, one has much less confidence that the mean of Drug B applies to an individual patient. For Drug C, distribution in clearance is bimodal, signifying that there are two major groups within the population: those with high and low clearances. Obviously, in this case, the mean is one of the most unlikely values to be found in this population.

Generally, distributions of pharmacokinetic parameters or observations are unimodal rather than polymodal, and they are often skewed rather than normal, as seen, e.g., in the frequency distribution of plateau plasma concentrations of nortriptyline (Fig. 13–2A). A more symmetrical distribution is often obtained with a logarithmic transformation of the parameter; such distributions are said to be log-normal. A common method of examining for log-normal distribution is to plot the cumulative frequency, or percentile, on a probit scale against the logarithm of the variable. The distribution is taken to be log-normal if the points lie on a straight line. As can be seen in Fig. 13–2B, this is the case for the plateau plasma concentration of nortriptyline. In such cases the median, or value above and below which there are equal numbers, differs from the mean. For nortriptyline, examination of Fig. 13–2B indicates that the median concentration is 0.05 mg/L, which is less than the average value of 0.069 mg/L.

A comment on the quantitation of variability is needed here. Variance is a measure of the deviations of the observations about the mean; it is defined as the sum of the squares of these deviations. While useful to convey variability within a particular set of observations, variance does not allow ready comparison of variability across sets of observations of different magnitude. Suppose, e.g., clearance in an individual is 50 mL/min and the mean is 100 mL/min; the squared deviation is 2500 $(mL/min)^2$. If instead clearance had been quoted in L/min, the squared deviation would be $(0.05 - 0.1)^2$, or 0.0025 $(L/min)^2$. Coefficient of variation, which expresses variability with respect to the mean value, overcomes this problem. Specifically, it is the square root of variance (the standard deviation) normalized to the mean. In the example above, the deviation normalized to the mean is 0.5 and is independent of the units of clearance. Furthermore, a large coefficient of variation now always signifies a high degree of variability. Subsequently, in the book, *high* and *low variability* refer to distributions that have high and low coefficients of variation, respectively.
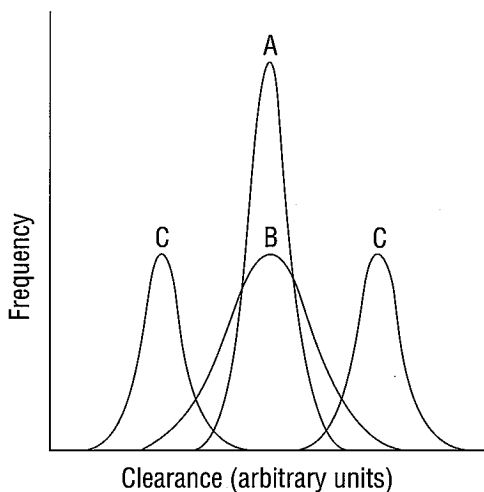


**Fig. 13–5.** As the frequency distributions for the clearance of three hypothetical drugs (A, B, C) show, it is as important to define variability around the mean and the shape of the frequency distribution curve as it is to define the mean itself.

## WHY PEOPLE DIFFER

The reasons why people differ in their responsiveness to drugs in medicinal products are manifold and include, in general order of importance, genetics, disease, age, drugs given concomitantly, and a variety of environmental factors. Although inheritance accounts for a substantial part of the differences in response among individuals, much of this variability is largely unpredictable. Increasingly, however, this source of variability, particularly that related to drug metabolism, is being understood and made more predictable using the tools of molecular biology (Chap. 14, Genetics).

Disease can be an added source of variation in drug response. Usual dosage regimens may need to be modified substantially in patients with renal function impairment, hepatic disorders, congestive cardiac failure, thyroid disorders, gastrointestinal disorders, and other diseases. The modification may apply to the drug being used to treat the specific disease but may apply equally well to other drugs the patient is receiving. For example, to prevent excessive accumulation and so reduce the risk of toxicity, the dosage of the antibiotic gentamicin used to treat a pleural infection of a patient must be reduced if the patient also has compromised renal function. Similarly, hyperthyroidic patients require higher than usual doses of digoxin, a drug used to improve cardiac efficiency. Moreover, a modification in dosage may arise not only from the direct impairment of a diseased organ but also from secondary events that accompany the disease. Drug metabolism, e.g., may be modified in patients with renal disease; plasma and tissue binding of drugs may be altered in patients with uremia and hepatic disorders.

Age, weight, and concomitantly administered drugs are important because they are sources of variability that can be taken into account. Gender-linked differences in hormonal balance, body composition, and activity of certain enzymes manifest themselves in differences in both pharmacokinetics and responsiveness, but overall, the effect of gender is small.

Table 13–1 lists examples of additional factors known to contribute to variability in drug response. Perhaps the most important factor is noncompliance. Noncompliance includes the taking of drug at the wrong time, the omission or supplementation of prescribed dose, and the stopping of therapy, either because the patient begins to feel better or because of development of side-effects that the patient considers unacceptable. Whatever the reason, these problems lie in the area of patient counselling and education. Occasionally, plasma concentration data are used as an objective measure of noncompliance.

Pharmaceutical formulation and the process used to manufacture a product can be important as both can affect the rate of release, and hence entry, into the body (Chap. 9).

**Table 13–1. Additional Factors Known to Contribute to Variability in Drug Response**

| FACTORS | OBSERVATIONS AND REMARKS |
| --- | --- |
| Noncompliance | A major problem in clinical practice; solution lies in patient education. |
| Route of administration | Patient response can vary on changing the route of administration. Not only pharmacokinetics of drug but also metabolite concentrations can change. |
| Food | Rate and occasionally extent of absorption are affected by eating. Effects depend on composition of food. Severe protein restriction may reduce the rate of drug metabolism. |
| Pollutants | Drug effects are often less in smokers and workers occupationally exposed to pesticides; a result of enhanced drug metabolism. |
| Time of day and season | Diurnal variations are seen in pharmacokinetics and in drug response. These effects have been sufficiently important to lead to the development of a new subject, chronopharmacology. |
| Location | Dose requirements of some drugs differ between patients living in town and in the country. |

A well-designed formulation diminishes the degree of variability in the release character-istics of a drug *in vivo*. Good manufacturing practice, with careful control of the process variables, ensures the manufacture of a reliable product. Drugs are given enterally, topi-cally, parenterally, and by inhalation. Route of administration not only can affect the con-centration locally and systemically but also can alter the systemic concentration of metab-olite compared with that of drug (Chap. 21). All these factors can profoundly affect the response to a given dose or regimen.

Food, particularly fat, slows gastric emptying and so decreases the rate of drug absorp-tion. Oral bioavailability is not usually affected by food, but there are many exceptions to this statement. Food is a complex mixture of chemicals, each potentially capable of inter-acting with drugs. Recall from Chap. 9, e.g., that the oral bioavailability of tetracycline is reduced when taken with milk, partly because of the formation of an insoluble complex with calcium. Recall also that a slowing of gastric emptying may increase the oral bioavail-ability of a sparingly soluble drug, such as griseofulvin. Diet may also affect drug metab-olism. Enzyme synthesis is ultimately dependent on protein intake. When protein intake is severely reduced for prolonged periods, particularly because of an imbalanced diet, drug metabolism may be impaired. Conversely, a high protein intake may cause enzyme induc-tion.

Chronopharmacology is the study of the influence of time on drug response. Many endogenous substances, e.g., hormones, are known to undergo cyclic changes in concen-tration in plasma and tissue with time. The amplitude of the change in concentration varies among substances. The period of the cycle is often diurnal, approximately 24 hr, although there may be both shorter and longer cycles upon which the daily one is superimposed. The menstrual cycle and seasonal variations in the concentrations of some endogenous substances are examples of cycles with a long period. Drug responses may therefore change with time of day, day of the month, or season of the year. Particular note of this phenom-enon is taken in cancer chemotherapy. Many chemotherapeutic agents have very narrow margins of safety and are given in combination. Appropriate phasing in the timing of ad-ministration of each drug during the day can improve the margin of safety.

Cigarette smoking tends to reduce clinical and toxic effects of some drugs, including chlordiazepoxide, diazepam, and theophylline. The drugs affected are extensively metab-olized by hepatic oxidation; induction of the drug-metabolizing enzymes is the likely cause. Many environmental pollutants exist in higher concentrations in the city than in the country; they can also stimulate synthesis of hepatic metabolic enzymes.

## Identifying the Sources of Variability

In practice, all the above-mentioned factors can contribute to observed variability in re-sponse, and care must be taken to ensure an appropriate conclusion is reached when trying to assign causes of variability. Consider, e.g., the data displayed in Fig. 13–6 which show the half-lives of phenylbutazone, a once widely used drug, in healthy subjects and in patients with hepatic disease (primarily cirrhosis). Initially, no difference was revealed between the two groups, except for a greater variability in the half-life among the patients with hepatic disease (Fig. 13–6A). When, however, both groups were further subdivided on the basis of whether they received other drugs, a clearer picture emerged (Fig. 13–6B). Of those receiving no other drugs, patients with hepatic disease handled phenylbutazone more slowly than did healthy subjects. Evidently, some of the other drugs received hasten phen-ylbutazone elimination.

Various strategies can be employed to identify sources of variability in response. The classic design is one in which as many of the variables as possible are fixed, apart from the one of interest. For example, to test if renal disease affects the pharmacokinetics of a drug,
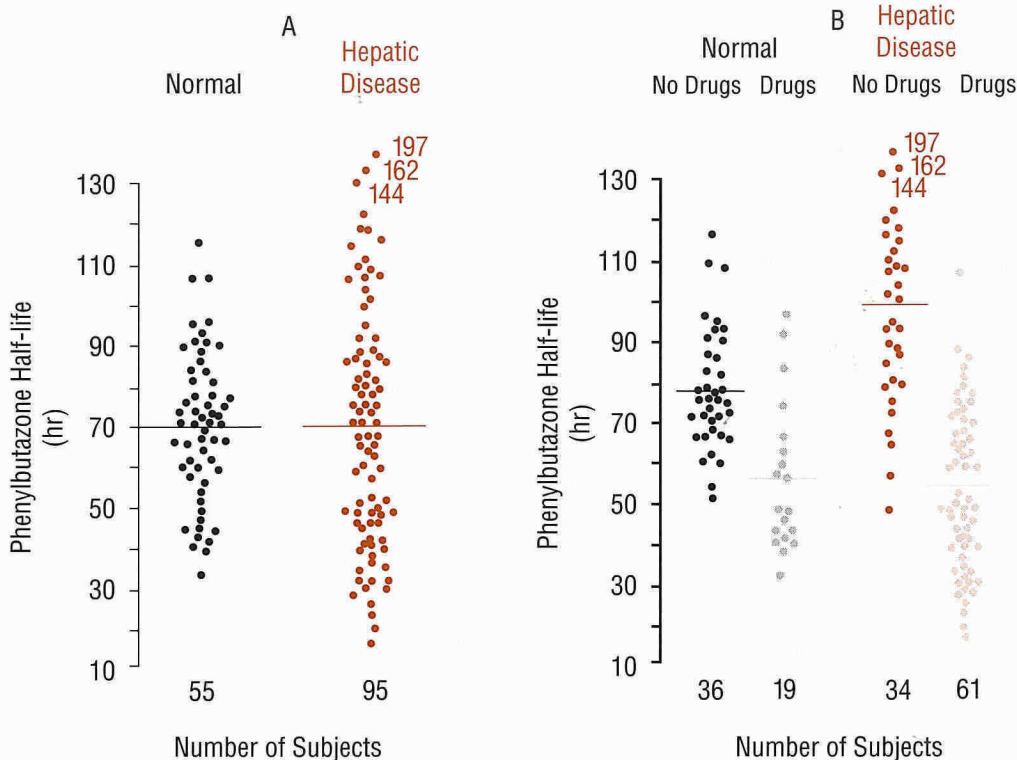
**Fig. 13–6** *A*, No difference is seen between the average half-life of phenylbutazone (horizontal line) in normal subjects (black points) and that in patients with hepatic disease (colored points). *B*, After separating those who take other drugs (light points) from those who do not (dark points), the prolonged elimination of phenylbutazone in patients with hepatic disease becomes evident. In both groups the half-life tends to be shorter when other drugs are taken concurrently. (Redrawn from Levi, A.J., Sherlock, S., and Walker, D.: Phenylbutazone and iso-niazid metabolism in patients with liver disease in relation to previous drug therapy. Lancet, *1*:1275–1279, 1968.)

all other factors such as age, gender, other drugs, and diet should be held constant. The ideal would be a longitudinal cross-over design in which each patient acts as his or her own control. This design is often not possible, however. The patient with renal disease is generally not available for study prior to the disease, and renal disease is generally irreversible. The penalty for deviating from such a design is greater variability with loss of efficiency, such that many more patients are needed to allow a firm conclusion to be made about the contribution of a factor to variability. The benefit of loosening the design, however, is that many patients who might otherwise be excluded can be a part of the study. In this category, e.g., are elderly patients suffering from several diseases and requiring many drugs, including the one of interest. Care must still be taken, however, to ensure that a sufficient number of patients are included with each of the attributes or conditions of interest.

## DEFINING THE DOSE–RESPONSE RELATIONSHIP

Variability has an important bearing on the *estimation* of dose–response relationships in clinical trials. A common procedure is to divide patients into several groups, each group receiving a different dose of drug such as 5, 10, or 20 mg. An attempt to establish a dose–response relationship is then made on the mean data for each group, using variability within groups to test for levels of statistical significance. A problem arises when much of the variability between dose and response resides in pharmacokinetics such that there is considerable overlap in the plasma concentrations among the groups. Thus, individuals from

the high- and low-dose groups can have the same plasma concentration (and response), namely, those in the low-dose group with a low clearance and those in the high-dose group with a high clearance of the drug. The overall effect, by increasing variability within each group, is to weaken the ability to detect a dose–response relationship.

One solution is to increase the number of subjects in each group to reduce the uncertainty of estimating the mean response at each dose level. Here, the problem is often one of not knowing in advance how many subjects would be needed in the trial, as well as the added expense of an increased number of subjects. Another solution is to expose each patient to several dose levels of the drug. This last solution has the distinct advantage of not only increasing the chances of establishing a dose–response relationship, but also of providing an estimate of interpatient variability in the relationship. Unfortunately, in practice, this design is not always possible, especially for drugs for which the full effect only occurs after several months or longer into drug administration. A third solution is the concentration-controlled clinical trial. In this approach, the pharmacokinetics of the drug is first evaluated in the patient cohort and then, based on this information, doses are adjusted so that the plasma concentration in each patient lies in one of several tightly defined bands. This more elaborate, and sometimes more expensive, design enables much clearer statements to be made about the concentration–response relationship and about interpatient variability in pharmacokinetics. However, it may have limited utility for dose recommendations, if a poor correlation is found between plasma drug concentration and response. Many other designs, varying in complexity, each with advantages and disadvantages, can be envisaged. In all cases, variability is a central issue.

## KINETIC MANIFESTATIONS

Considerable variability in enzymatic activity and, to a lesser extent, in plasma and tissue binding exists even among healthy individuals. How such variability manifests itself, in pharmacokinetic parameters and in such measurements as plateau plasma concentration, depends on the hepatic extraction ratio and route of administration of the drug. For example, the large interindividual variability in half-life of theophylline (Fig. 13–7) can be explained primarily by variations in hepatic enzyme activity, probably associated with variations in the amounts of the enzymes responsible for metabolism of this compound. This conclusion is based on theophylline being predominantly metabolized in the liver, having a low extraction ratio, and being only moderately bound to plasma and tissue components. In contrast, such a high degree of variability in enzymatic activity is expected to be masked in the clearance of a drug having a high hepatic extraction ratio, because clearance tends to be perfusion rate-limited and hepatic blood flow is relatively constant among healthy individuals. Moreover, unless plasma and tissue binding are highly variable, volume of distribution, and hence disposition kinetics, of such a drug are much the same for all healthy individuals. This is so for propranolol (Fig. 13–8) a drug of high hepatic clearance.

As described in Chap. 11, when considering induction and inhibition, changes in hepatic enzyme activity result in variations in oral bioavailability for a drug with a high hepatic extraction ratio. Accordingly, with subsequent disposition being controlled by hepatic perfusion, a series of similarly shaped plasma drug concentration-time profiles, but reaching different peak concentrations, should be seen among individuals with varying enzyme activity receiving the same oral dose of drug. This is indeed seen with propranolol (Fig. 13–8). In contrast, for a drug with a low hepatic extraction ratio, such as theophylline, variation in enzymatic activity is reflected by variation in clearance (and half-life) rather than in oral bioavailability (and maximum plasma concentration), which is always high (Fig. 13–7).

The impact of variability in oral bioavailability, because of a high first-pass effect, depends on the intended use of a drug. It may result in patients' needing different single oral

**Fig. 13–7.** Five healthy subjects each received 350 mg theophylline orally, in solution as an elixir. Large differences in *AUC* are seen, but in contrast to propranolol (Fig. 13–8), the peak concentrations are almost identical. These observations are as expected for theophylline, a drug of low hepatic extraction that is extensively metabolized in the liver. Variability in hepatic enzyme activity is manifested primarily in variability in clearance, and hence half-life; the weight-corrected volume of distribution of theophylline is relatively constant. Oral bioavailability is close to 100% in all subjects, and because absorption occurred much faster than elimination, peak concentrations are similar. Each symbol refers to a different subject. (Data provided by S. Toon, personal observations.)
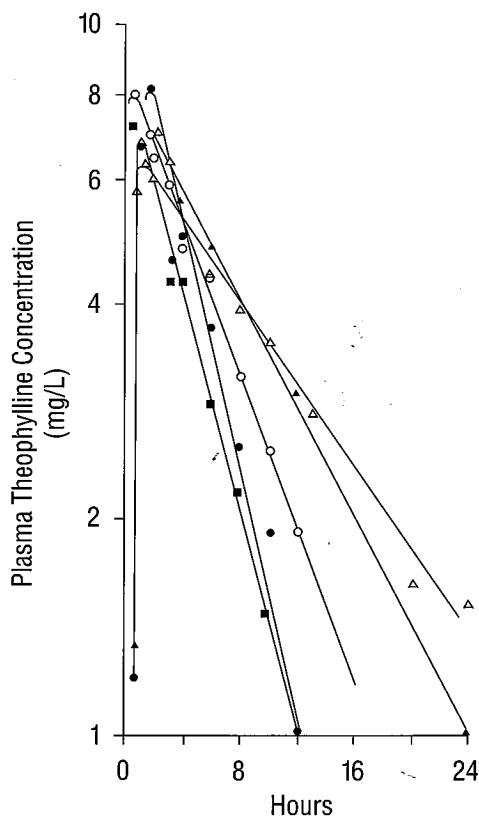


doses to produce the same effect, as might be the case if the drug is to be used as a sedative hypnotic or to relieve a headache. However, if the drug is intended for chronic use, the degree of variability in average plateau concentration should not be inherently different from that which exists for a drug of low hepatic clearance and having the same degree of variability in enzymatic activity. (Fig. 13–9). This statement is based on the following reasoning. At plateau, the average concentration ($C_{ss,av}$) is given by

$$C_{ss,av} = \frac{F \cdot \text{Dose}}{CL \cdot \tau} \qquad 1$$

where $\tau$ is the dosing interval. For a drug of high hepatic clearance, variability in $C_{ss,av}$ reflects variability in enzyme activity through $F$; whereas, for a drug of low hepatic clearance, variability in $C_{ss,av}$ reflects variability in enzyme activity through $CL$ (with $F \simeq 1$). In both cases the oral dosing rate (Dose/$\tau$) would need to be adjusted by the same degree to maintain a common $C_{ss,av}$ within subjects. This is achieved by adjusting the dose for the high-clearance drug (as half-life is relatively constant) and perhaps by a mixture of adjusting dose and dosing interval (given that half-life varies) for the low-clearance drug. Of major importance is the underlying variation in enzyme activity, which differs from one enzyme system to another. Obviously, to minimize variation in pharmacokinetics, molecules would need to be selected which, if metabolized, are substrates of enzyme systems that show the least variability among subjects. Unfortunately, current information is insufficient to make this selection.
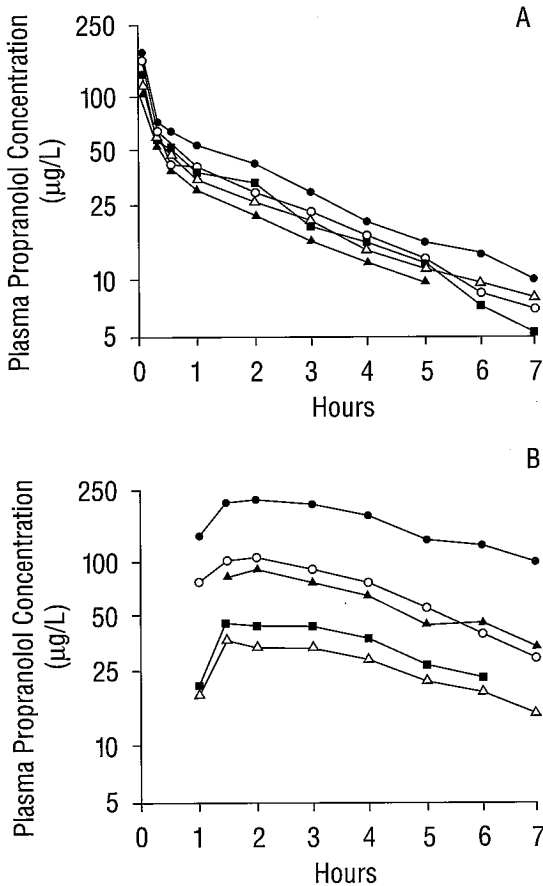
**Fig. 13–8.** Five healthy subjects each received propranolol i.v. (10 mg over 10 min) and orally (80 mg) on separate occasions. The plasma concentration-time profiles were very similar following i.v. administration (A), but showed large differences, particularly in peak concentration and AUC, following oral administration (B). Such differences in variability with the two routes of administration are expected for propranolol, a drug of high hepatic extraction. Variability in hepatic enzyme activity among the group is manifested primarily in variability in oral bioavailability (16–60%), rather than in differences in clearance (1 L/min) which is perfusion rate-limited, or hence in half-life (1 mg/L = 3.9 μM). (Redrawn from Shand, D.G., Nuckolls, E.M., and Oates, J.A.: Plasma propranolol levels in adults, with observations in four children. Clin. Pharmacol. Ther., 11:112–120, 1970. Reproduced with permission of C.V. Mosby.)
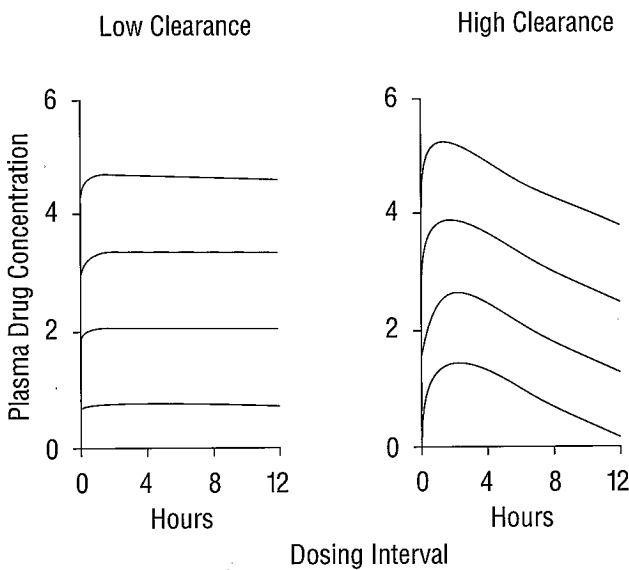


**Fig. 13–9.** Expected plasma drug concentration-time profiles during a dosing interval at steady state following chronic oral administration of a drug; changes in hepatic enzyme activity for a drug of low extraction ratio (left) and high extraction ratio (right). In this simulation both drugs are substrates for the same enzyme, the concentration (and intrinsic clearance) of which varies ninefold. The result is a corresponding ninefold variation in the average concentration. Prediction is based on the well-stirred model of hepatic elimination.

It follows from the foregoing that there is no inherent reason to believe that a set variation in enzyme activity (caused by a variation in concentration of enzymes, inhibitors, or inducers) should cause a greater *intra*individual variation in pharmacokinetic parameters, or in $C_{ss,av}$, for a drug of high hepatic extraction than for one of low hepatic extraction.

## DOSE STRENGTHS

Products are frequently marketed as unit doses of defined strength, such as 50 or 100 mg. Obviously, if the therapeutic index is sufficiently wide, all patients can receive the same dose strength almost irrespective of any differences in pharmacokinetics among the patient population. A narrow therapeutic index necessitates the manufacture of several dose strengths, however. Although the final number of strengths chosen depends on many practical issues, a rough estimate of the number can be calculated in the following manner for drugs intended for chronic maintenance therapy.

Suppose that the maximum and minimum clearance values that encompass 95% of the patient population, designated $CL_{max}$ and $CL_{min}$, respectively, differ by a factor of six. That is, $CL_{max} = 6 \cdot CL_{min}$. It would then follow from the familiar relationship

$$\frac{F \cdot \text{Dose}}{\tau} = CL \cdot C_{ss,av} \qquad\qquad 2$$

that the range of dosing rates needed would be sixfold if the object was to obtain the same $C_{ss,av}$ in all patients. In practice, the therapeutic index is sufficiently wide to allow some tolerance. Let average plateau concentrations within 20% of the optimal value be acceptable. Accordingly, the highest dosing rate that could be given to a patient with a clearance value of $CL_{min}$ is one that produces a $C_{ss,av}$ that is 1.2 times the optimal value; the lowest dosing rate that could be given to a patient with a clearance of $CL_{max}$ is one that produces a $C_{ss,av}$ that is 0.8 times the optimal value. The range of associated dosing rates (and hence amounts, if the dosing interval is kept constant) is fourfold. Now, usually, adjacent dose strengths differ by a factor of 2. Therefore, in the current example, if the smallest dose strength is 50 mg, it would be reasonable to market three dose strengths, 50-mg, 100-mg, and 200-mg products, which would suffice for 95% of the population. Of the outstanding 5%, those with a particularly high clearance may be accommodated with a larger-than-usual maintenance dose, comprising a combination of the marketed unit dose strengths, or they may receive a marketed dose strength more frequently. Those with a particularly low clearance value may be accommodated by taking the lowest available dose strength less frequently than usual, because the half-life in this group is likely to be the longest in the population.

## ACCOUNTING FOR VARIABILITY

It remains to be seen how information on variability can be used to devise an optimal dosage regimen of a drug for treatment of a disease in an individual patient. Obviously, the desired objective would be most efficiently achieved if the individual's dosage requirements could be calculated *before administering the drug*. While this ideal cannot be totally met in practice, some success may be achieved by adopting the following type of approach, which applies when all patients require the same (unbound) plasma concentration range. The approach is to move from the population pharmacokinetic parameter estimates to the individual patient's values.

The first step is to identify the most variable parameter within the patient population. Variability in the various pharmacokinetic parameters within the patient population differs widely among drugs, as shown in Table 13–2 for a number of representative drugs. For some drugs, such as digoxin and propranolol, there is substantial variability in absorption, but for different reasons. With digoxin the variability is caused primarily by differences in pharmaceutical formulation, but with propranolol it is caused by differences in the extent of first-pass loss, as mentioned previously (Fig. 13–8). For other drugs, such as theophylline, the only substantial variability is in clearance. With others, amiodarone and phenytoin included, significant variability exists in all parameters. Finally, for some, considerable variability exists in plasma protein binding.

The next step is to try to accommodate as much of the variability as possible with measurable characteristics. If the characteristic is discrete and independent, this can be achieved by partitioning the population into subpopulations. For example, as illustrated for clearance in Fig. 13–10, if the discrete characteristics are hepatic disease and smoking, then the population would be divided into four categories: those who smoke and have no hepatic disease; those who smoke and have hepatic disease; those who have hepatic disease

**Table 13–2.   Degree of Variability in the Oral Absorption, Disposition, and Specific Distribution of Representative Drugs Within the Patient Population**[a]

| DRUG | F | V | Cl | fu |
|------|---|---|-----|-----|
| Amiodarone | + | + + | + | + + |
| Cyclosporine | + | − | + | + |
| Digoxin | + | + | + + | − |
| Ibuprofen | − | − | + | + |
| Interferon Alfa | N/A | + | + | ? |
| Lithium | − | − | + | − |
| Phenobarbital | − | − | + | − |
| Phenytoin | + | + | + + | + + |
| Propranolol | + + | + + | + | + + |
| Quinidine | + | + + | + | + |
| Salicylic acid | − | + | + + | + + |
| Theophylline | − | − | + + | − |

[a]Symbols: − = little variability; + = moderate variability; + + = substantial variability; NA = not applicable.
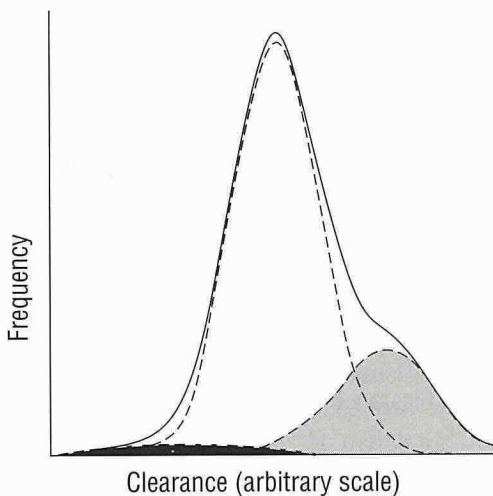


**Fig. 13–10.**  The frequency distribution of clearance within the total patient population (——) is a function of the shape of the frequency distribution within the various subpopulations that comprise the total patient population and the relative sizes of each of these subpopulations. In this simulation the variables are smoking and hepatic disease, and the subpopulations are: (---)—those who neither have hepatic disease nor smoke (78.4%), the majority; (shaded gray)—those who smoke but have no hepatic disease (19.6%); (shaded black)—those who have hepatic disease but do not smoke (1.6%); and those who both smoke and have hepatic disease. The size of the last subpopulation is too small (0.4%) to be seen in this figure. The average values for clearance in the four subpopulations were set at 1, 1.5, 0.5, and 0.75 units, respectively, assuming that smoking increases clearance by induction and that clearance is reduced in hepatic disease.

Frequency

Clearance (arbitrary scale)

but do not smoke; and those who neither have hepatic disease nor smoke. The relative size and shape of the distribution curve of each subpopulation determine the frequency distribution for the entire population. If, on the other hand, the measurable characteristic is continuous, such as age, weight, or degree of renal function, it may be possible to find a functional relationship with one or more pharmacokinetic parameters, as seen, e.g., between the renal clearance of the cephalosporin, ceftazidime (and many other drugs), and creatinine clearance, a graded measure of renal function (Fig. 13–11).

To envisage how the entire strategy would work, consider the data in Fig. 13–12 for a drug, partly metabolized in the liver and partly excreted unchanged, for which population pharmacokinetics are: oral bioavailability, 0.82; volume of distribution, 10.3 L; renal clearance, 6.7 L/hr; and metabolic clearance, 16.2 L/hr. Depicted are four tablets, representing



**Fig. 13–11.** The renal clearance of the cephalosporin, ceftazidime, varies in direct proportion to creatinine clearance in a group of 19 patients with varying degrees of renal function. (Drawn from the data of van Dalen, R., Vree, T.B., Baars, A.M., and Termond, E.: Dosage adjustment for ceftazidime in patients with impaired renal function. Euro. J. Clin. Pharmacol., *30*:597–605, 1986.)
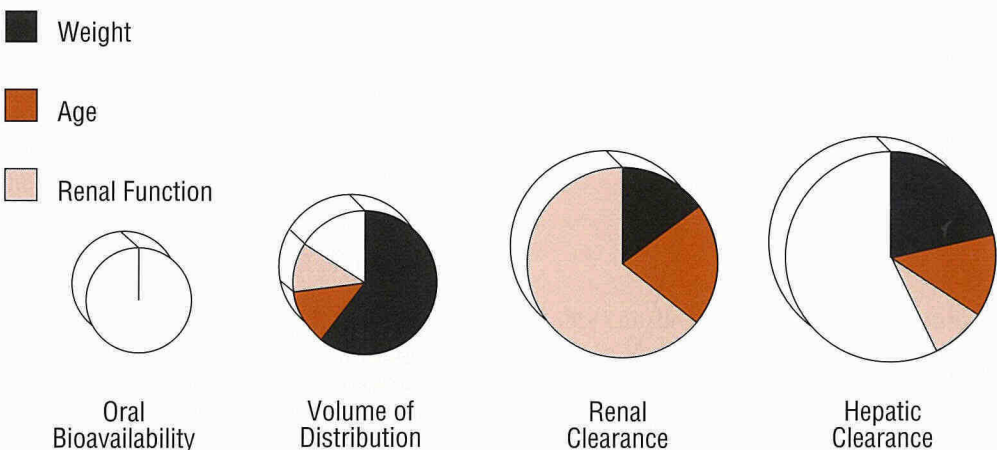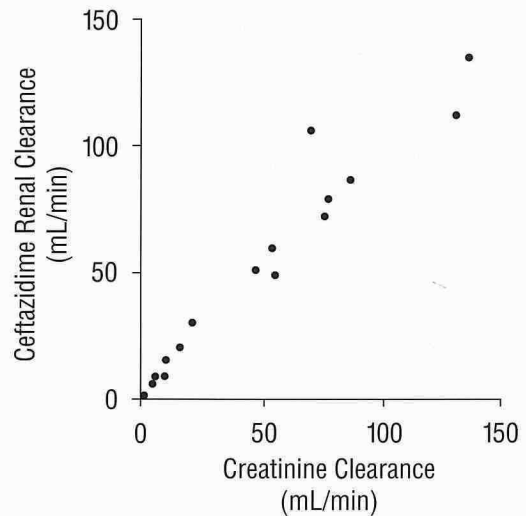


**Fig. 13–12.** Schematic representation of variability in various pharmacokinetic parameters within a population. The size of each tablet is related to the degree of variability in the parameter. The portion of the tablet labeled weight, age, or renal function reflect the fractions of the total variability accounted for by each of these factors.

oral bioavailability, volume of distribution, renal clearance, and metabolic clearance. The size of each tablet is a measure of variability of that parameter within the patient population. For this drug, oral bioavailability is the least and hepatic clearance is the most variable. Stated differently, greatest confidence exists in assigning the population value of oral bioavailability to the patient; least confidence exists in assigning the population value of hepatic clearance to the patient. Moreover, as the population value for hepatic clearance is much greater than that for renal clearance, variability in total clearance within the population is also high.

Not unexpectedly, weight accounts for most of the variability in volume of distribution and for some of the variability in hepatic clearance. Age, separated from its influence on body weight, accounts for some of the variability in hepatic clearance and, to a lesser extent, in volume of distribution. Renal function also accounts for almost all the variability in renal clearance. Surprisingly perhaps, renal function helps to explain some of the variability in metabolic clearance and volume of distribution, but drug distribution and metabolism can be altered in patients with renal function impairment (see Chap. 16). None of the variability in oral bioavailability is accounted for but, as mentioned, it is small and acceptable.

Finally, the inability to account for most of the variability in metabolic clearance should be noted. None of the characteristics included could adequately account for the influence of genetics, disease, and other drugs on this parameter. Markers of genetic control of drug metabolism have been developed that help to explain much of the inherited interindividual differences in metabolic clearance of certain drugs (Chap. 14). Few, however, are employed clinically.

Returning to the individual patient, correcting the population pharmacokinetics for the patient's weight, age, and renal function should give reasonable individual estimates of $F$, $V$, and $CL_R$ but little confidence in the estimate of $CL_H$ and hence total clearance. As the ratio $F/V$ strongly influences the peak plasma concentration after a single dose, reasonable confidence can be expected in estimating the patient's loading dose, if required. However, since the ratio $F/CL$ controls the average plateau concentration, less confidence can be expected in estimating the patient's maintenance dose requirements. If the therapeutic index of the drug is sufficiently narrow, there may be a case for monitoring the plasma concentration to aid in adjusting the maintenance dosing rate through feedback as described in Chap. 18 (Concentration Monitoring). Nonetheless, the estimate of maintenance dose based on the information provided in Fig. 13–12 should be better than using the mean parameter values for the whole population. Clearly, if the drug had just been excreted unchanged, the probability of being able to estimate the correct dosage regimen for the patient would have been much higher.

The approach presented above for predicting an individual's dosage regimen before administering the drug is based on the assumption that little interindividual variability in pharmacodynamics exists. This is not always so. Sometimes, most of the variability in response is due to differences in pharmacodynamics. Although knowing the mean pharmacokinetic parameters of the drug may help to explain the time course in response, quantifying pharmacokinetic variability adds little to the ability to predict individual dosage. Nonetheless, the basic strategy still holds: to determine the relative contribution of measurable characteristics, such as age and weight, to response within the patient population, and then use the individual's characteristics to predict his or her initial dosage regimen. Frequently, however, age, weight, and other measurable characteristics fail to account for much of the variability in pharmacodynamics. Then, there is little choice but to start the individual patient on the typical dosage regimen, which may be far from the individual's requirement. Subsequent adjustment in the regimen is made based on response produced. Here, as with feedback based on plasma concentration, the use of a model helps in dose adjustment (Chap. 18, Concentration Monitoring).

## STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. a. List three major sources of variability in response to drugs.
   b. What pharmacokinetic parameters vary the most in the patient population for digoxin, phenytoin, theophylline, and ibuprofen?
2. Discuss briefly why mean pharmacokinetic parameters alone are not sufficient to characterize how a drug is handled in the patient population.
3. Suggest which pharmacokinetic parameter is most likely to explain the variation in the plateau concentration of nortriptyline shown in Fig. 13–2. The drug is lipophilic, stable in the gastrointestinal tract, and little is excreted unchanged.
4. By coincidence, the weight, age, and renal function of the patient, discussed under the section "Accounting for Variability" corresponded to the patient population values. Yet, when the pharmacokinetics of the drug was studied in the patient, the values of $F$, 0.42, and $V$, 22 L, were considerably different (outside the 99% confidence intervals) from the population values of $F$, 0.82, and $V$, 10.3 L. Briefly discuss how this could arise.
5. Lithium, used in the treatment of patients with manic depression, is administered chronically. The therapeutic window of this drug is narrow (0.4 to 1.4 milliequivalents/L), its $fe$ is 1, its and dosage requirements vary widely among patients.
   a. What is a major cause of this variability in dosage?
   b. What characteristic of a patient should help to tailor his or her dosage requirement?
6. In a group of healthy subjects, the average pharmacokinetic parameters of the β-adrenergic blocking agent alprenolol, which is eliminated almost exclusively by hepatic metabolism, were found to be volume of distribution, 230 L; clearance, 1.06 L/min; and half-life, 2.5 hr. After i.v. administration, values of these parameters differed little within this group; yet, when the drug was ingested orally, both peak plasma concentration and $AUC$ varied over a fivefold range. Suggest why variability in the observed plasma concentration-time curve is much greater after oral than after i.v. administration.
7. The following data (Table 13–3) were obtained in a study of the pharmacokinetic variability of a drug that is predominantly excreted unchanged, $fe = 0.98$. The drug was infused intravenously in five subjects at a constant rate of 20 mg/hr for 48 hr. The fraction unbound was found to be independent of drug concentration but did vary among the subjects.

**Table 13–3.**

| Subject | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Steady-state plasma concentration (mg/L) | 2.5 | 1.6 | 3.0 | 1.5 | 2.3 |
| Postinfusion Half-life (hr) | 14.4 | 5.9 | 4.7 | 9.9 | 8.2 |
| Fraction unbound | 0.1 | 0.15 | 0.09 | 0.16 | 0.01 |

a. Analyze the data to identify the most and the least variable (use the *range/mean* as your index of variability) of the following parameters: Clearance based on unbound drug ($CLu$), fraction unbound in plasma ($fu$), and fraction unbound in tissue ($fu_T$). Use a $V_{TW}$ of 39 L.
b. Discuss briefly the therapeutic implications of these data with regard to the rate of attainment and maintenance of a "therapeutic" concentration in the various subjects.

8. The 95% confidence interval of clearance of a drug within a patient population is 1.5 to 7.5 L/hr, a difference of fivefold. Other pharmacokinetic parameters, $F$ and $V$, vary much less. Therapeutic activity resides exclusively with the drug, and not the metabolites. Discuss the potential impact of this variability in clearance on the attempt to define a dose–response relationship within a patient population, using a design in which patients are randomly assigned to one of three groups receiving a multiple-dose regimen of either 50, 100, or 200 mg daily of the drug.