

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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WHY CLINICAL PHARMACOKINETICS?

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

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

To overcome some of the limitations of the empirical approach and to answer some of the questions raised, it is necessary to delve further into the events that follow drug administration. *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluid bathing the site(s) of action. From these observations the suggestion might be made that the therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration

of therapy. However, rarely is a drug placed at its site of action. Indeed, most drugs are given orally, and yet they act in the brain, on the heart, at the neuromuscular junction, or elsewhere. A drug must therefore move from the site of administration to the site of action. Simultaneously, however, the drug distributes to all other tissues including those organs, notably the liver and the kidneys, that eliminate it from the body.

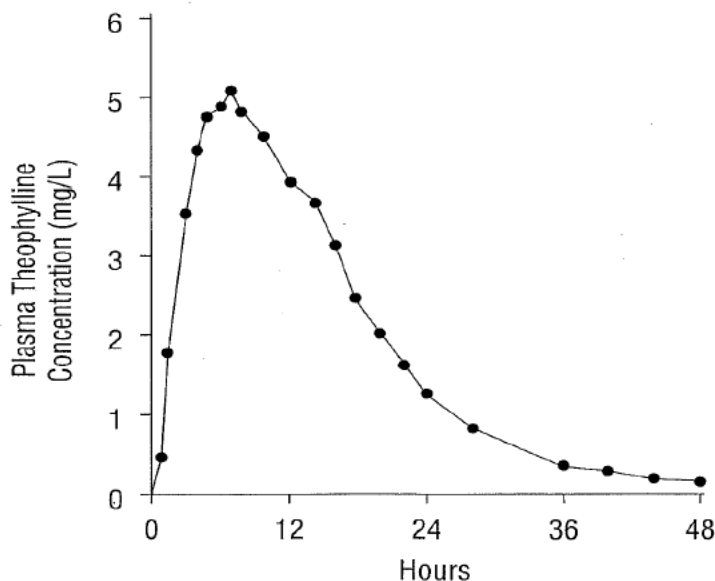
Figure 1-1 illustrates the events occurring after a dose of drug is administered orally. The rate at which drug initially enters the body exceeds its rate of elimination; the concentrations of drug in blood and other tissues rise, often sufficiently high to elicit the desired therapeutic effects and sometimes even to produce toxicity. Eventually, the rate of drug elimination exceeds the rate of its absorption, and thereafter, the concentration of drug in both blood and tissues declines and the effect(s) subsides. To administer drugs optimally, therefore, knowledge is needed not only of the mechanisms of drug absorption, distribution, and elimination but also of the kinetics of these processes, that is, *pharmacokinetics*. The application of pharmacokinetic principles to the therapeutic management of patients is *clinical pharmacokinetics*.

Table 1-1. Empirically Derived Usual Adult Dosage Regimens of Some Representative Drugs Before the Introduction of Clinical Pharmacokinetics*

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

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

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



The events following drug administration can be divided into two phases, a *pharmacokinetic phase*, in which the adjustable elements of dose, dosage form, frequency, and route of administration are related to drug level–time relationships in the body, and a *pharmacodynamic phase*, in which the concentration of drug at the site(s) of action is related to the magnitude of the effect(s) produced (Fig. 1–2). Once both of these phases have been defined, a dosage regimen can be designed to achieve the therapeutic objective. Despite the greater amount of information required with this approach, it has several advantages over the empirical approach. First, and most obvious, distinction can be made between pharmacokinetic and pharmacodynamic causes of an unusual drug response. Second, the basic concepts of pharmacokinetics are common to all drugs; information gained about the pharmacokinetics of one drug can help in anticipating the pharmacokinetics of another. Third, understanding the pharmacokinetics of a drug often explains the manner of its use; occasionally such an understanding has saved a drug that otherwise may have been discarded or has suggested a more appropriate dosage regimen. Lastly, knowing the pharmacokinetics of a drug aids the clinician in anticipating the optimal dosage regimen for an individual patient and in predicting what may happen when a dosage regimen is changed.

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

Based on the foregoing considerations, an optimal dosage regimen might be defined as one that maintains the plasma concentration of a drug within the therapeutic window. For many drugs, this therapeutic objective is met by giving an initial dose to achieve a plasma concentration within the therapeutic window and then maintaining this concentration by replacing the amount of drug lost with time. One popular and convenient means of maintenance is to give a dose at discrete time intervals. Figure 1–3 illustrates the basic features associated with this approach by depicting the concentrations that follow the administration of two regimens, A and B. The dosing interval is the same but the dose given in regimen B is twice that given in regimen A. Because some drug always remains in the body from preceding doses, accumulation occurs until, within a dosing interval, the amount lost equals the dose given; a characteristic saw-toothed plateau is then achieved. With regimen A,

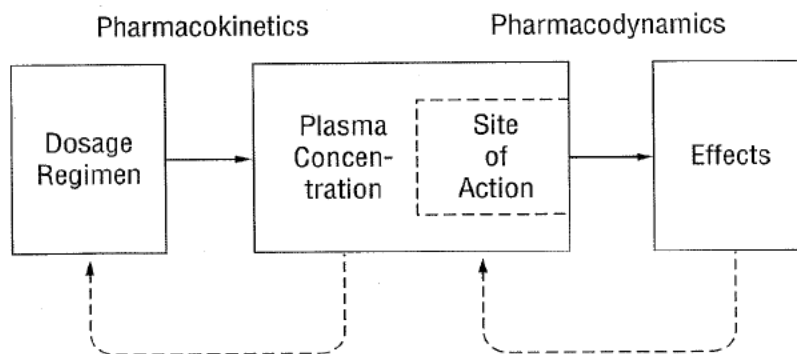


Fig. 1–2. An approach to the design of a dosage regimen. The pharmacokinetics and the pharmacodynamics of the drug are first defined. Then, either the plasma drug concentration–time data or the effects produced are used via pharmacokinetics as a feedback (dashed lines) to modify the dosage regimen to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

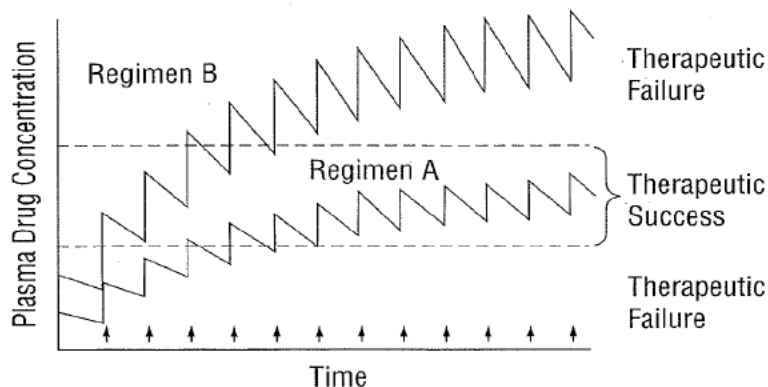
several doses had to be given before drug accumulation was sufficient to produce a therapeutic concentration. Had therapy been stopped before then, the drug might have been thought ineffective and perhaps abandoned prematurely. Alternatively, larger doses might have been tried, e.g., regimen B. Although a therapeutic response would have been achieved fairly promptly, toxicity would have ensued with continued administration when the concentration exceeded the upper limit of the therapeutic window.

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

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

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

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



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

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

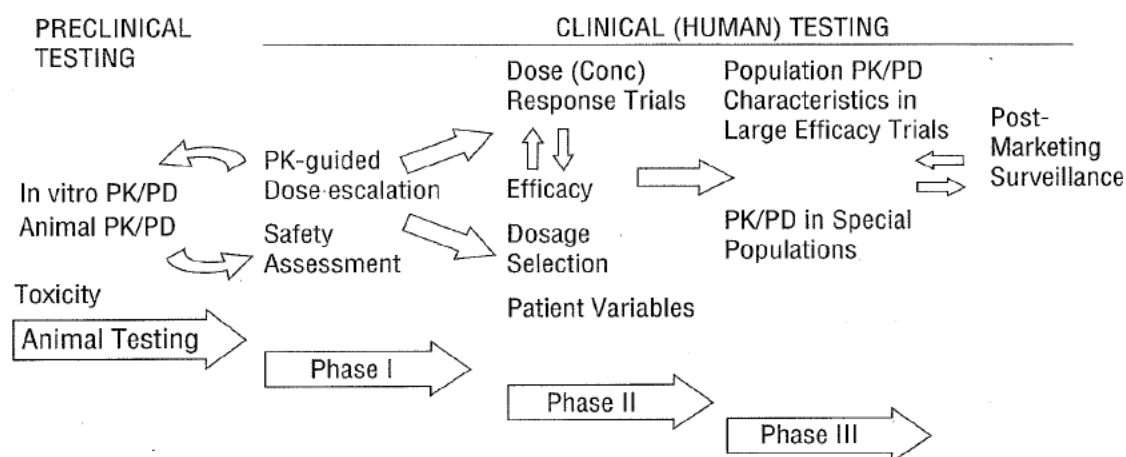


Fig. 1-4. The development and subsequent marketing of a drug. The prehuman data helps to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected patients,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

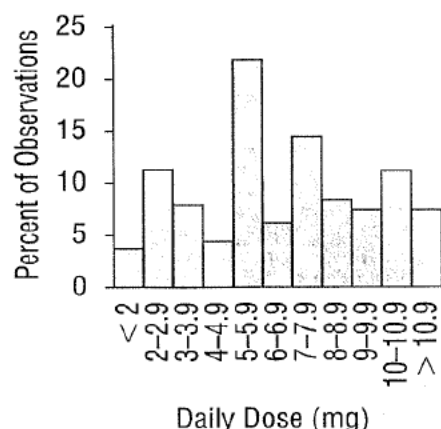


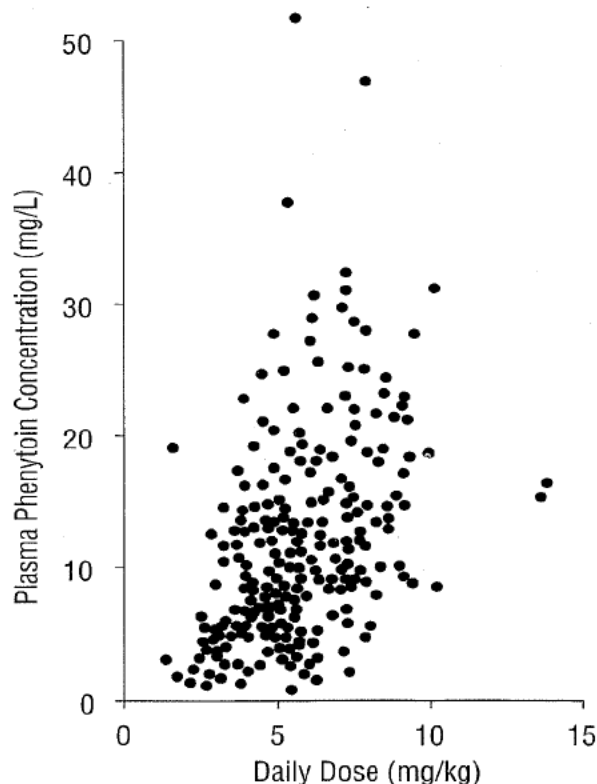
Fig. 1-5. The daily dose of warfarin required to produce similar prothrombin times in 200 adult patients varies widely. (1 mg/L = 3.3 μ M). (Redrawn from Koch-Weser, J.: The serum level approach to individualization of drug dosage. *Eur. J. Clin. Pharmacol.* 9:1-8, 1975.)

agulant warfarin needed to produce a similar prothrombin time (an index of blood coagulability). Sources of variability in drug response include the patient's age, weight, degree of obesity, type and degree of severity of the disease, the patient's genetic makeup, other drugs concurrently administered, and environmental factors. The result is that a standard dosage regimen of a drug may prove therapeutic in some patients, ineffective in others, and toxic in still others. The need to adjust the dosage regimen of a drug for an individual patient is evident; this need is clearly greatest for drugs that have a narrow therapeutic window, that exhibit a steep concentration–response curve, and that are critical to drug therapy. Examples are digoxin, used to treat some cardiac disorders; phenytoin, used to prevent epileptic convulsions; theophylline, used to diminish chronic airway resistance in asthmatics; and cyclosporine, an immunosuppressant used in organ transplantation. With these drugs, and with many others, variability in pharmacokinetics is a major source of total variability in drug response.

It is becoming increasingly common to gain as much information on variability as possible during drug development by gathering, albeit limited, individual plasma concentration and response data in a large population of patients during Phase III clinical trials. Attempts are then made to account for this variability in terms of such patient characteristics as age and weight. These *population* pharmacokinetic/pharmacodynamic studies form a basis for dosage regimen recommendations in clinical practice.

Coadministration of several drugs to a patient, prevalent in clinical practice, can pose problems. Although the response produced by each drug alone may be predictable, that produced by the combination may be less certain and occasionally unpredictable. Ketoconazole, for example, devoid of immunosuppressant activity, potentiates the effect of cyclosporine. Possible causes of this kind of effect are many. In this instance, as in many others, the interaction involves a change in pharmacokinetics. Some drugs stimulate drug-

Fig. 1-6. Although the average plateau plasma concentration of phenytoin tends to increase with the dosing rate, there is considerable variation in the individual values. (One mg/L = 3.97 μ M.) (Redrawn from Lund, L.: Effects of phenytoin in patients with epilepsy in relation to its concentration in plasma. In *Biological Effects of Drugs in Relation to Their Plasma Concentration*. Edited by D.S. Davies and B.N.C. Prichard, Macmillan, London and Basingstoke, 1973, pp. 227–238.)



metabolizing enzymes and hasten drug loss; others inhibit these enzymes and slow elimination. Still others interfere with drug absorption. Such interactions are graded; the change in the pharmacokinetics of a drug varies continuously with the plasma concentration of the interacting drug and hence with time. Indeed, given in sufficiently high doses, almost any drug can interact with another. It is always a question of degree. Understanding the quantitative elements of interactions ensures the more rational use of drugs that may need to be coadministered.

Figure 1-6 illustrates a situation in which monitoring of the drug concentration may be beneficial. Over the narrow range of the daily dose of the antiepileptic drug phenytoin, the plateau plasma drug concentration varies markedly within the patient population. Yet the therapeutic window of phenytoin is narrow, 7 to 20 mg/L; beyond 20 mg/L, the frequency and the degree of toxicity increase progressively with concentration. Here again, pharmacokinetics is the major source of variability. A pragmatic approach to this problem would be to adjust the dosage until the desired objective is achieved. Control on a dosage basis alone, however, has proved difficult. Control is achieved more readily and accurately when plasma drug concentration data and the pharmacokinetics of the drug are known.

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

DOSE AND TIME DEPENDENCIES

OBJECTIVES

The reader will be able to:

1. List at least 10 sources of dose (or time) dependence in drug absorption, distribution, and elimination.
2. Recognize dose- (or time-) dependent kinetics from either plasma or urine data showing such behavior.
3. Graphically depict the kinetic behavior of a drug when the situation and the cause of a dose (or time) dependence are given.
4. On analyzing data in which a dose (or time) dependence occurs, identify which pharmacokinetic parameters are affected, and assign probable causes to the observation.
5. Demonstrate the kinetic consequences at steady state of a change in the rate of input, V_m or K_m , of a drug showing saturable Michaelis-Menten metabolism.
6. Define saturable first-pass metabolism, describe how it can occur, and discuss its kinetic consequences.

An epileptic patient who has not responded to phenytoin after 2 weeks on 300 mg/day is observed to have a plasma concentration of 4 mg/L. Twenty days after the daily dose has been increased to 500 mg, the patient develops signs of toxicity, nystagmus, and ataxia; the plasma concentration of phenytoin is now 36 mg/L. Why should only a 67% increase in daily dose give rise to a ninefold increase in plasma concentration? The answer lies in the dose-dependent kinetic behavior of this drug.

Normally, plasma (or blood) concentration, unbound concentration, and amount of drug and its metabolites excreted in urine at any given time all increase in direct proportion to dose, when drug is administered in either a single dose or in multiple doses. Therefore, on correcting such observations for the dose administered, the values should superimpose at all times. This is referred to as the *principle of superposition*. When superposition occurs, the pharmacokinetics of a drug is said to be *dose-independent*, or *linear*.

There are many reasons why the principle of superposition may not hold. Among them are the administration of a drug by different routes, in different dosage forms, or by different methods (bolus or infusion). These are examples of dependencies on dosage form and route of administration. They are not the subject of this chapter. Other reasons for lack of superposition include changes in pharmacokinetic parameters themselves with size of dose administered or dosing rate, when all other factors are held constant. The pharmacokinetics of such drugs are said to be *dose-dependent*. When there is a lack of superposition on administering a drug on separate occasions or a lack of predictability following repeated or continuous dosing, based on single-dose data, the drug is said to show *time-dependent kinetics*. Such behaviors are sources of variability in drug response. Although

relatively uncommon, they occur frequently enough in drug therapy to warrant special consideration. In drug overdose, they are more the rule than the exception.

This chapter deals with identification and consequences of dose-dependent and time-dependent kinetics. The major intent is to establish a general awareness of this topic.

EVIDENCE

Five pharmacokinetic parameters (F , k_a , V , CL_R , and CL_H) basically define and summarize the time-course of a drug in the body. Usually, none of these parameters systematically changes with dose in the same individual. But in *dose-dependent kinetics*, any one or a combination of these parameters appears to change with administration of different doses. The parameters change during continuous or repeated administration when kinetics show *time dependence*.

Both dose-dependent and time-dependent kinetic behaviors defy easy quantitative description and prediction. The first step in evaluating this behavior is to identify its occurrence. Subsequent steps involve determining the parameters affected and the likely mechanism(s) of the nonlinearity. There are many potential causes of dose and time dependencies. Table 22-1 lists examples of representative causes together with the pharmacokinetic parameters affected. Let us now consider examples of drugs for which there is evidence of nonlinear behavior in absorption or disposition. For many of these examples, therapeutic implications and means of accommodating or circumventing the problems are given.

ABSORPTION

Dose or time dependencies in drug absorption may be reflected by a change in either bioavailability or rate-time profile of absorption. These dependencies most often arise from three sources following oral administration. First are solubility and dissolution limitations in the release of drug from a dosage form in the gastrointestinal tract. Second is saturability

Table 22-1. Representative Causes of Dose- (or Time-) Dependent Kinetics and Selected Drug Examples

	EXAMPLE	PARAMETER AFFECTED ^a	
I. <i>Gastrointestinal Absorption</i>			
A. Saturable transport in gut wall	Amoxycillin	F	↓
B. Drug comparatively insoluble	Griseofulvin	F	↓
C. Saturable gut wall or hepatic metabolism on first pass	Nicardipine	F	↑
II. <i>Distribution</i>			
A. Saturable plasma protein binding	Naproxen	V , f_u	↑
B. Saturable tissue binding		V , f_{uT}	↓; ↑
III. <i>Renal Excretion</i>			
A. Active secretion (saturable)	Penicillin G	CL_R	↓
B. Active reabsorption (saturable)	Ascorbic acid	CL_R	↑
C. Decrease in urine pH	Salicylic acid	CL_R	↓
D. Saturable plasma protein binding	Disopyramide	CL_R	↑
E. Nephrotoxicity ^b	Aminoglycosides	CL_R	↓
F. Increase in urine flow ^b	Theophylline	CL_R	↑
IV. <i>Hepatic Metabolism</i>			
A. Capacity-limited kinetics, cofactor limitation, etc.	Phenytoin	CL_H	↓
B. Enzyme induction ^b	Carbamazepine	CL_H	↑
C. Hepatotoxicity ^b	Acetaminophen	CL_H	↓
D. Saturable plasma protein binding	Prednisolone	CL_H	↑
E. Decreased hepatic blood flow	Propranolol	CL_H	↓
F. Inhibition by metabolite ^b	Lidocaine	CL_H	↓

^aDirection of change: ↑ increase, ↓ decrease on increasing dose.

^bTime-dependent as well as dose-dependent.

in a transport mechanism for passage across the gastrointestinal membranes. Last is saturability in metabolism during a drug's first pass through the gut wall and the liver.

Solubility

Dissolution can be the cause of dose dependency in bioavailability for drugs with low aqueous solubility, when given orally in relatively large doses. With a fixed transit time through the gastrointestinal tract, the amount of drug absorbed is unlikely to increase in proportion to the dose administered. An example is griseofulvin (Fig. 22-1). For this sparingly soluble drug (solubility is 10 mg/L), bioavailability decreases as the dose is increased from 250 to 500 mg.

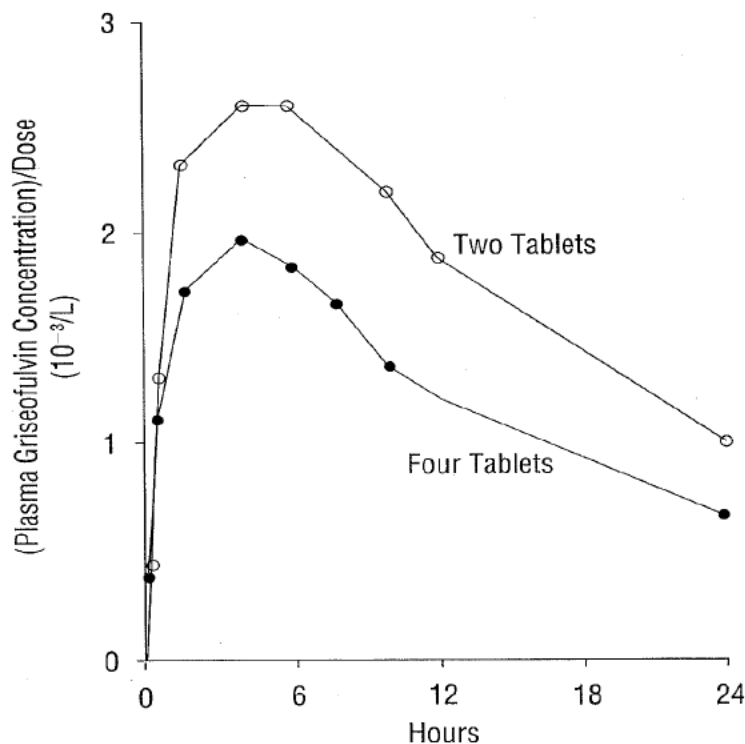
Saturable Active Transport

For a few drugs, absorption from the gastrointestinal tract occurs by a capacity-limited transport mechanism. An example is that of amoxycillin, a polar β -lactam antibiotic. This drug is absorbed by a peptide transport mechanism in the small intestine. This conclusion is supported by the observation that bioavailability decreases with increased dose, but the peak time changes little (Fig. 22-2). The decrease in bioavailability is explained by the capacity-limited nature of the transport process. The lack of a major change in the peak time is a consequence of the limited region in the small intestine from which absorption can occur. The dose size does not influence the time between ingestion and movement past the site of transport.

Saturable First-Pass Metabolism

Nicardipine, a dihydropyridine calcium-channel blocker, exhibits dose dependence in its oral bioavailability (Table 22-2) because of saturability in its metabolism on first pass

Fig. 22-1. Plasma concentration, normalized to dose, as a function of time following the oral administration of two tablets (upper curve ○) and four tablets (lower colored curve, ●) of ultramicrozized griseofulvin (125 mg/tablet) (1 mg/L = 2.8 μ M). (Adapted from data in Barrett, W.E., and Bianchine, J.R.: The bioavailability of ultramicrozized griseofulvin (GRIS-PEC®) tablets in man. *Curr. Ther. Res.*, 18:501-509, 1975.)



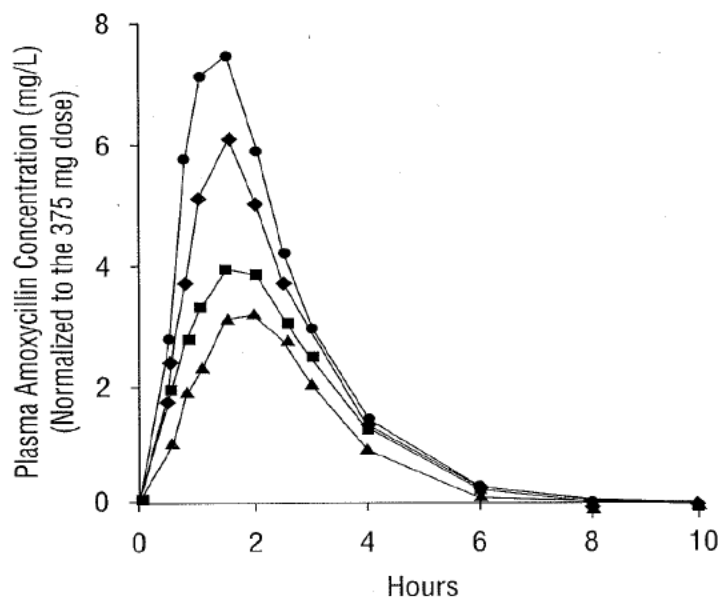


Fig. 22-2. Mean amoxicillin plasma concentrations after single oral doses of 375 (●), 750 (◆), 1500 (■), and 3000 (▲) mg. The concentrations are normalized to those expected for a 375-mg dose ($C = C(\text{observed}) \times 375/\text{Dose}(\text{mg})$). Note the decrease in the C_{max} and AUC values, and the similarity in t_{max} on increasing the dose. The observations are explained by oral bioavailability decreasing with dose with little or no change in peak time. (1 mg/L = 2.7 μM). (Data from Sjøvall, J., Gunnar, A., and Westerlund, D.: Dose-dependent absorption of amoxicillin and bacampicillin. *Clin. Pharmacol. Ther.*, 38:241–250, 1985. Interpretation from Reigner, B.G., Couet, W.R., Guedes, J.-P., Fourtillan, J.-B., and Tozer, T.N.: Saturable rate of cefatrizine absorption after oral administration to humans. *J. Pharmacokinetic. Biopharm.*, 18:17–34, 1990.)

Table 22-2. Saturable First-Pass Metabolism of Nifedipine Observed at Steady State Following Oral Doses of 10 to 40 mg Every 8 hr^a

DOSE (mg)	BIOAVAILABILITY (%)
10	19(4) ^b
20	22(5)
30	28(5)
40	38(6)

^aData from Wagner, J.G., Ling, T.L., Mroczek, E.J., Freedman D., Wu, A., Huang, B., Massey, I.J., and Roe, R.R.: Single intravenous dose and steady-state oral dose pharmacokinetics of nifedipine in healthy subjects. *Biopharm. Drug. Dispos.*, 8:133–148, 1987.

^bMean and SE of data from 6 subjects.

through the liver. The data in the table were acquired during an 8-hr dosing interval at steady state (3 days into regimen). An i.v. radiolabeled tracer dose (0.885 mg) was given concurrently with the 30-mg dose to determine oral bioavailability.

Saturable first-pass metabolism occurs for a number of orally administered drugs that are highly extracted by the liver or intestinal tissues. Additional examples are listed in Table 22-3. For several of these drugs, dose dependence in oral bioavailability is observed without an apparent change in elimination half-life. This behavior can be understood by realizing that the concentration of drug reaching the liver during absorption can be much higher than that after absorption is over. Consider, for example, the following conditions: Distribution is instantaneous; all drug reaches the liver intact; input of drug from the gastrointestinal tract is first-order with a k_a of 0.05 min⁻¹ (14-min half-life); oral bioavailability at low doses is 0.1; volume of distribution is 250 L; total hepatic blood flow, Q_H , is 1.35 mL/min; and absorption is faster than elimination.

Table 22-3. Examples of Drugs Showing Saturable First-Pass Metabolism in the Liver or Gut Wall After Oral Administration of Therapeutic Doses

Alprenolol	Methoxysalen	Propranolol
5-Fluorouracil	Nifedipine	Salicylamide
Hydralazine	Propoxyphene	Verapamil

The initial rate of input into the portal vein, $ka \cdot \text{Dose}$, is also the initial rate of entry of drug into the liver, $Q_H \cdot C_{\text{initial}}$. Consequently, after a 100-mg dose,

$$C_{\text{initial}} = \frac{ka \cdot \text{Dose}}{Q_H} = 3.7 \text{ mg/L} \quad 1$$

The concentration in the blood entering the liver after absorption is finished would have a maximum value of

$$C_{\text{max}} = \frac{F \cdot \text{Dose}}{V} = 0.04 \text{ mg/L} \quad 2$$

The actual value of C_{max} should be less because some drug is eliminated during the absorption phase. As can be seen, the contribution of absorbed drug to the concentration entering the liver during first pass is much greater than that recycled from the rest of the body. Indeed, the ratio of C_{initial} to C_{max} is

$$\frac{C_{\text{initial}}}{C_{\text{max}}} = \frac{ka \cdot V}{F \cdot Q_H} = 92 \quad 3$$

Thus, the larger the value of ka or V or the smaller the value of F at low (nonsaturating) doses, the greater is the ratio $C_{\text{initial}}/C_{\text{max}}$ and the more likely there is to be a separation in the degree of saturation of metabolism during absorption and elimination phases. All the drugs listed in Table 22-3 show saturable first-pass metabolism and have pharmacokinetic parameters that favor a high value of $C_{\text{initial}}/C_{\text{max}}$.

SATURABILITY OF PLASMA PROTEIN AND TISSUE BINDING

A limited number of binding sites exist on plasma proteins. Recall from Table 10-4 that the plasma concentration of albumin is usually 43 g/L or 600 μM (molecular weight = 67,000 g/mole). At one binding site per albumin molecule, there is then a limiting concentration of 600 μM for the bound drug. For α_1 -acid glycoprotein, the limitation occurs at about 15 μM , a much lower concentration. The sites to which drugs bind in the tissues may be similarly limited. Consequently, the volume of distribution depends on drug concentration, a *concentration-dependent* behavior. Changes in binding tend to become appreciable when more than 20% of the available sites are occupied. This number, corresponding to 120 μM for one binding site on albumin, is arbitrary but useful for predicting the likelihood of concentration-dependent binding. For a drug with a molecular weight of 250, 120 μM corresponds to a concentration of 30 mg/L.

For drugs that show saturable binding to plasma proteins, the volume of distribution is expected to increase with plasma concentration, except when the volume of distribution is small (less than 0.2 L/kg, see Chap. 10, Distribution). Conversely, for drugs that show saturability in binding to tissues, the volume of distribution decreases as plasma concentration is increased. Because of the potential dependence on the fraction unbound in plasma and the dependence of half-life on both clearance and volume of distribution, dose dependence in distribution may be difficult to identify and quantify, unless plasma protein binding is measured. Consider the example of naproxen.

The AUC of naproxen following single doses fails to increase linearly with dose when doses above those maximally recommended (500 mg) are given (Fig. 22-3). Without any other information, this nonlinear observation might be explained by either a decrease in bioavailability or an increase in clearance, in that

$$AUC = \frac{F}{CL} \cdot \text{Dose}$$

4

The increase in clearance may be due to induction of metabolism or saturable binding to plasma proteins. As naproxen is a drug of low clearance (Dose/AUC calculated from data in Fig. 22-3A varies from 0.3 to 1.3 L/hr), the peak concentrations observed at doses of 1 to 4 g (Fig. 22-3B) provide information to distinguish between these possibilities. If one approximates a concentration of 110 mg/L when most of a 1000-mg dose is in the body, a value of V/F of approximately 9 L can be estimated. This small volume suggests strong binding to plasma proteins. The maximum concentrations obtained are in the region where nonlinear binding is expected for naproxen, a weak acid that binds to albumin. With a molecular weight of 230 g/mole, 100 and 200 mg/L correspond to concentrations of 430 and 870 μM , values approximating that (600 μM) of serum albumin. This is the condition in which f_u is expected to increase with higher doses. Thus, with minimal information, a probable source of nonlinearity, saturable binding to plasma albumin, can be deduced.

The therapeutic consequence of decreased binding to plasma proteins at higher daily doses of a drug of low extraction ratio differs dramatically from that of drug-induced increased enzyme activity (autoinduction). When binding decreases (f_u increases), the steady-state total plasma concentration is not increased much on doubling the rate of administration. The steady-state unbound concentration, however, doubles as a consequence of no change in unbound clearance. The intensities of toxic and therapeutic responses are expected to increase accordingly. In contrast, an increase in enzyme activity would affect both unbound and total concentrations proportionally. Thus, if autoinduction occurs, only a minor increase in response would be expected at higher rates of administration.

The expected change in the time-course of a drug in plasma when plasma protein binding exhibits nonlinear behavior is complex. Changes occur in both volume of distribution (Chap. 10) and clearance (Chap. 11). The magnitude of the changes depends on both the volume of distribution and the extraction ratio of the drug. Furthermore, because volume

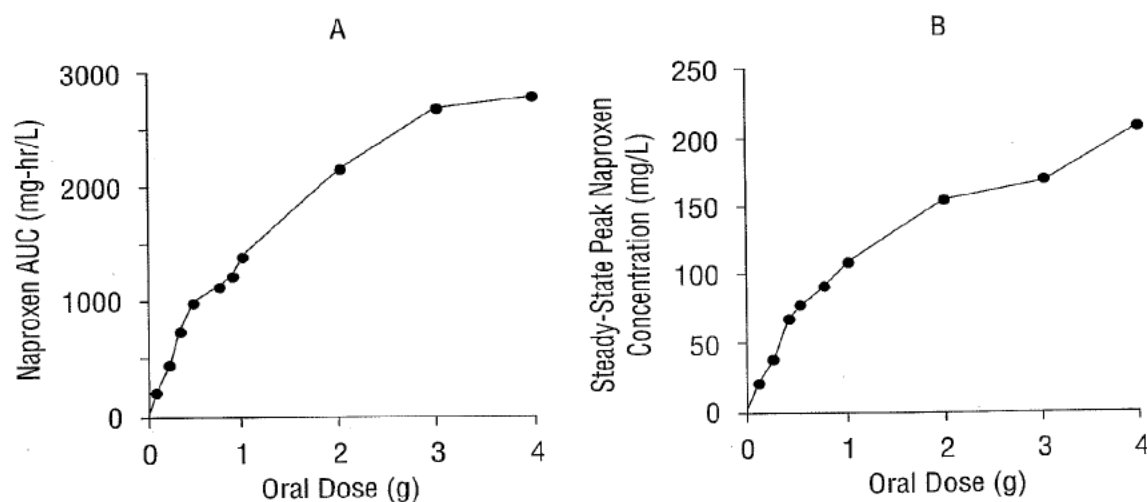


Fig. 22-3. The AUC of naproxen increases with the size of a single oral dose but not in direct proportion; the AUC appears to approach a limiting value (A). Nonlinearity is also observed in the peak concentration (B). These observations are consistent with either a decrease in F or an increase in CL with decreasing dose. As explained in the text, saturable binding to plasma albumin is most probably responsible (1 mg/L = 4.3 μM). (Modified from Runkel, R., Chaplin, M.D., Sevelius, H., Ortega, E., and Segre, E.: Pharmacokinetics of naproxen overdoses. Clin. Pharmacol. Ther., 20:269-277, 1976).

of distribution changes with amount in body, the decline of the plasma concentration does not reflect, in direct proportion, the disappearance of drug from the body. The slope of the semilogarithmic decline in the concentration-time curve is then not a good measure of the fractional rate of elimination. The qualitative effect of saturable binding to plasma proteins for a drug with a small volume of distribution is demonstrated by the decreasing slope of the unbound cefonicid concentration with time on a semilogarithmic plot (Fig. 22-4) after a single 30-mg/kg i.v. dose. The difference between the decline of the total and unbound concentrations (Fig. 22-4A) is explained by the decrease in the fraction unbound with time (Fig. 22-4B). The apparent one-compartmental nature of the total concentration decline is explained by virtually all drug in the body being bound to albumin.

The ACE inhibitor trandolaprilat, formed following oral administration of trandolapril, shows nonlinear plasma and tissue protein binding, as do other agents in this pharmacologic class. Evidence of nonlinearity in trandolaprilat kinetics is provided in Fig. 22-5. Both AUC (Fig. 22-5A) and plasma concentration (Fig. 22-5B), particularly during the terminal phase, fail to increase in direct proportion to the oral dose of trandolapril, over the eightfold range (0.5 to 4.0 mg) studied. Also, contrary to the expectation of linear kinetics, dosing daily, which is relatively frequent compared to the long terminal half-life, does not lead to extensive accumulation (Fig. 22-5C). Thus, when a 2-mg dose of trandolapril is administered orally for 10 days, the accumulation ratio of trandolaprilat ($AUC_{ss}/AUC_{(t,1)}$, Eq. 25, Chap. 7) is only 1.49. Direct evidence of concentration-dependent plasma protein binding of trandolaprilat is shown in Fig. 22-5D and Table 10-4. It should be noted that the range of concentrations, 0.5 to 5 $\mu\text{g/L}$, over which the fraction unbound changes threefold, covers most of the plasma trandiloprilat concentrations obtained following the oral doses of trandolapril (Fig. 22-5B, C).

The observations above can be rationalized as follows. The extremely low plasma concentration at which saturable binding occurs suggests a binding protein of much lower concentration than albumin or α_1 -acid glycoprotein (see Table 10-4). The body of evidence

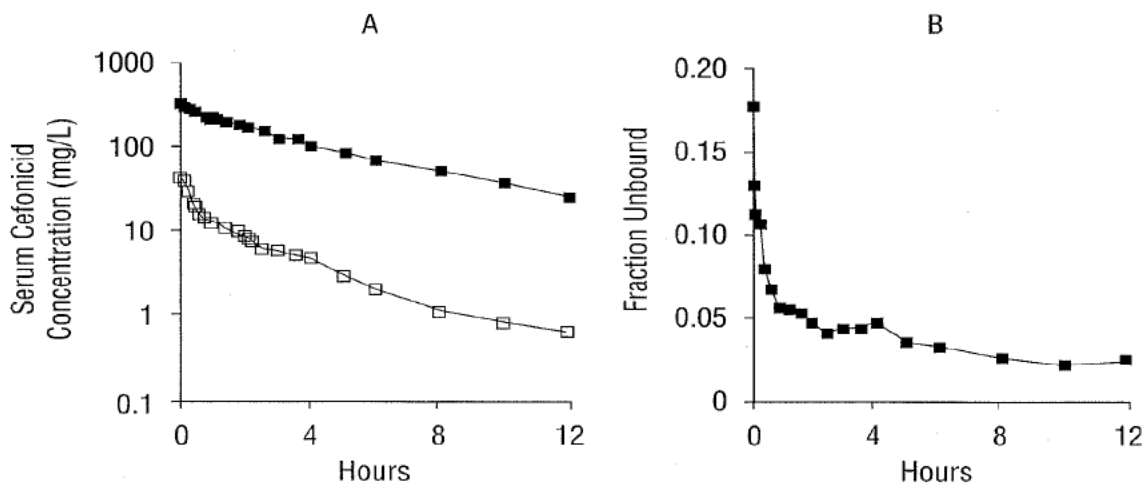


Fig. 22-4. A, Mean total (■) and unbound (□) plasma cefonicid concentrations with time in six volunteers after a single i.v. dose of 30 mg/kg given over 5 min. Note the much more rapid decline of the unbound concentration during the first 2 hr. B, The difference between the declines of the two curves in A is explained by a rapid decrease in the fraction unbound with time. As a consequence of the limited capacity of serum albumin to bind cefonicid, the high total concentrations at early times tend to approach the capacity for binding (1 mg/L = 1.84 μM). (Redrawn from Dudley, M.N., Shyu, W.-C., Nightingale, C.H., and Quintiliani, R.: Effect of saturable serum protein binding on the pharmacokinetics of unbound cefonicid in humans. *Antimicrob. Agents Chemother.*,

points to *ACE* itself being responsible. This high-affinity, low-capacity enzyme resides in both plasma and the endothelial linings of the vasculature, the latter site being interpreted as tissue binding when viewed from plasma data. Trandolaprilat, a relatively polar molecule, is restricted in its distribution mainly to extracellular spaces and is cleared systemically, mostly by renal excretion. Renal excretion is primarily via glomerular filtration, so that renal clearance shows concentration dependence associated with saturable protein binding. At high concentrations of trandolaprilat, which saturate *ACE*, renal clearance is high and elimination rapid. As the plasma concentration falls, the fraction bound to plasma and tissue *ACE* increases, thereby diminishing the unbound pool and lowering renal clearance. The net effect is a much slower elimination of material from the body. Thus, the biphasic decline of plasma trandolaprilat, seen in the semilogarithmic plots (Fig. 22-5B) is due to concentration-dependent protein binding and not distribution kinetics. Notice, that had only one dose of drug been administered, one could not have readily distinguished between concentration-dependent binding and distribution kinetics as the cause of the apparent biexponential decline of the plasma data. Finally, the lack of appreciable accumulation on multiple dosing arises because after each dose, most of the systematically available trandolaprilat is eliminated before reaching the terminal phase. Thus, nonlinear binding to the active site, *ACE*, appears to explain virtually all of trandolaprilat's odd kinetic behavior.

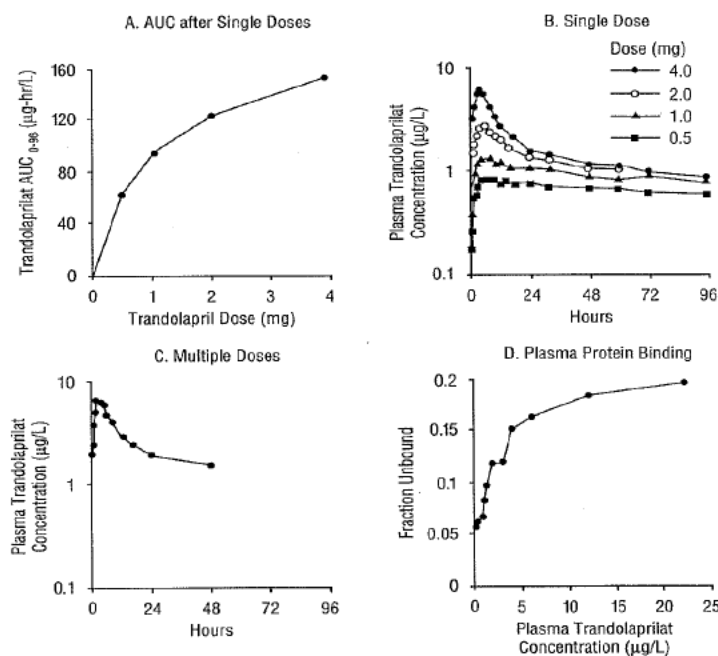


Fig. 22-5. Trandolaprilat, the active metabolite of trandolapril, exhibits nonlinear kinetic behavior. A, The AUC (0 to 96 hr) of the metabolite does not increase in direct proportion to the dose of trandolapril over the dose range of 0.5 to 4 mg. B, A semilogarithmic plot of mean plasma trandolaprilat concentrations after oral doses of 0.5, 1.0, 2.0, and 4.0 mg shows nonlinearity in that the curves are not equally spaced by a factor of 2 in the vertical direction for each of the successive doses. The lack of proportionality with dose is particularly evident at later times. C, Administration of 2.0 mg of trandolapril daily for 10 days fails to produce the degree of accumulation of trandolaprilat, as viewed from the concentration-time profile within a dosing interval at steady state (24 hr) that is predicted based on the long terminal decline in plasma concentration observed following a single 2.0-mg dose (see B). D, Binding of trandolaprilat to plasma proteins shows nonlinearity in that the fraction unbound increased with increasing concentration. (1 mg/L = 2.4 μM). (Data in A and B from Lenfant, B., Mouren, M., Bryce, T., De Lauture, D., and Strauch, G.: Trandolapril: Pharmacokinetics of single oral doses in male healthy volunteers, *J. Cardiovasc. Pharmacol.*, in press, 1994; Data in C from Arnor, P., Wade, A., Engfelt, P., Mouren M., Stepniwski, J.P., Sultan, E., Bryce, T., and Lenfant, B: Pharmacokinetics and pharmacodynamics of trandolapril after repeated administration. *J. Cardiovasc. Pharmacol.*, in press, 1994; Data in D from B. Lenfant, personal communication.)

CONCENTRATION-DEPENDENT RENAL EXCRETION

Renal clearance can vary with plasma concentration. Both filtration and reabsorption are usually passive processes, the rates of which are directly related to plasma concentration. In contrast, active secretion and active reabsorption are saturable processes with maximum capacities. This is shown in Fig. 22-6, for active secretion. The rate of tubular secretion increases in direct proportion to the plasma concentration until the transport approaches an upper limit often called the T_M value. Consequently, clearance by secretion decreases as plasma concentration increases. This is observed for the antimicrobial agent dicloxacillin (Fig. 22-7). On increasing the dose from 1 to 2 g, the renal clearance, assessed by Ae_{∞}/AUC , is reduced. Extrarenal clearance is unaffected. With an f_u of 0.04, the unbound renal clearance is about 2600 mL/min following the 1-g dose. This value greatly exceeds the usual glomerular filtration rate of 120 mL/min, indicating that this drug is extensively secreted into the tubular lumen (see Chap. 11, Elimination). At these doses, secretion shows concentration dependence and, as a consequence, the AUC increases disproportionately with dose. The body exposure to the drug and the half-life are disproportionately increased, considerations for the therapeutic use of large doses.

Secretion never occurs alone; filtration is always a component, and passive reabsorption may or may not be. Figure 22-6 also demonstrates how the rate of excretion of a drug that undergoes filtration and secretion, such as penicillin, always increases with plasma concentration. Even though the rate of secretion approaches an upper limit the rate of filtration continues to increase directly with unbound plasma concentration.

Fig. 22-6. The rate of renal secretion has a limiting value, the maximum transport rate (T_M), whereas the rate of filtration increases in direct proportion to the plasma concentration of a drug. Consequently, the rate of excretion of a drug that is both filtered and secreted, but not reabsorbed, increases with its plasma concentration. The increase, however, is not in direct proportion. Drug is either not bound in plasma or f_u remains constant throughout the range of plasma concentrations.

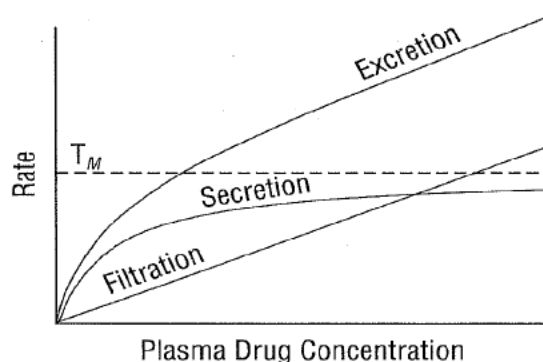
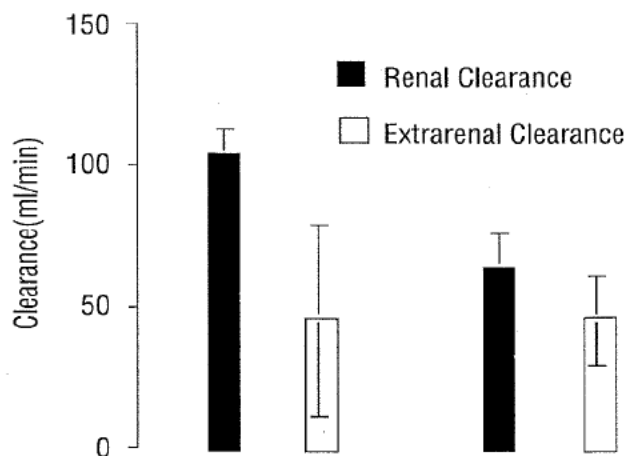


Fig. 22-7. Renal clearance of dicloxacillin, as measured by Ae_{∞}/AUC , is decreased following a 2-g i.v. dose relative to that observed after a 1-g i.v. dose. The extrarenal clearance is not affected by dose. Saturable secretion of drug into the renal tubule explains the decrease in renal clearance. Mean $\pm$ SD (bars) (1 mg/L = 2.1 μ M). (Data from Naufa, E.H., and Mattie, H.: Dicloxacillin and cloxacillin: Pharmacokinetics in healthy and hemodialysis subjects. Clin. Pharmacol. Ther., 20:98-108, 1976.)



Renal clearance is the rate of drug excretion divided by its plasma concentration. A drug that is only filtered, and is not bound in plasma, has the same renal clearance at all concentrations, as shown schematically in curve A of Fig. 22-8. Curve B depicts the events that occur for a drug that is actively secreted. In the region of plasma concentrations well below those required to approach saturation, renal clearance is highest and is relatively insensitive to changes in drug concentration. The therapeutic concentrations of most actively secreted drugs lie within this region. At higher plasma concentrations, renal clearance decreases; the lower limiting value is that contributed by both filtration and passive reabsorption.

The renal clearances of ascorbic acid, disopyramide, and the protein superoxide dismutase all increase with increasing concentrations, but for different reasons. Ascorbic acid (vitamin C) is normally conserved in the body by active reabsorption from the renal tubule. When the plasma concentration is excessive, the capacity of the reabsorption mechanism is exceeded, and the vitamin appears in large amounts in the urine (Fig. 22-9). The consequence of nonlinear excretion following oral administration of vitamin C is illustrated by the data in Table 22-4. Although statistically significant, note that the plasma concentration does not increase much even when megadoses are given. Another nonlinear mechanism also contributes to this observation. The bioavailability of the vitamin decreases with increasing dose (not shown) because it is absorbed in the intestine by a saturable process. The combined effect of saturable gastrointestinal absorption and renal tubular reabsorption is that only a relatively small change in the steady-state plasma concentration occurs, even when the daily oral dose is increased greatly.

Rather than saturable reabsorption, nonlinear binding to α_1 -acid glycoprotein causes renal clearance (based on total concentration) of disopyramide to be greater at earlier times after a 1.5-mg/kg i.v. dose (Fig. 22-10A). Unbound renal clearance, on the other hand, shows no evidence of nonlinearity (Fig. 22-10B). The greater total clearance coincides with a higher total concentration and a lower binding ($f_u \uparrow$) at earlier times.

The nonlinearity in renal clearance of the experimental protein drug superoxide dismutase is related to renal metabolism (Fig. 22-11). This protein, protective against cell injury that is due to oxygen-derived free radicals or superoxides, is filtered and then partially

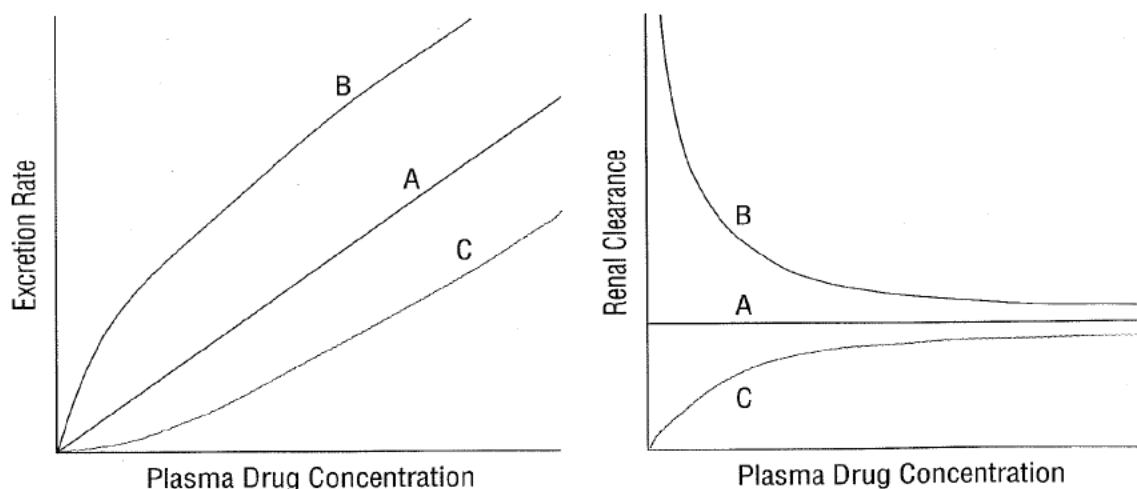


Fig. 22-8. Relationships between either rate of excretion (on left) or renal clearance (on right) and plasma concentration depend on whether the drug undergoes filtration only (curve A), filtration and secretion (curve B), or filtration and active reabsorption (curve C). The drug is either not bound to plasma proteins, or f_u does not change in the concentration range shown.

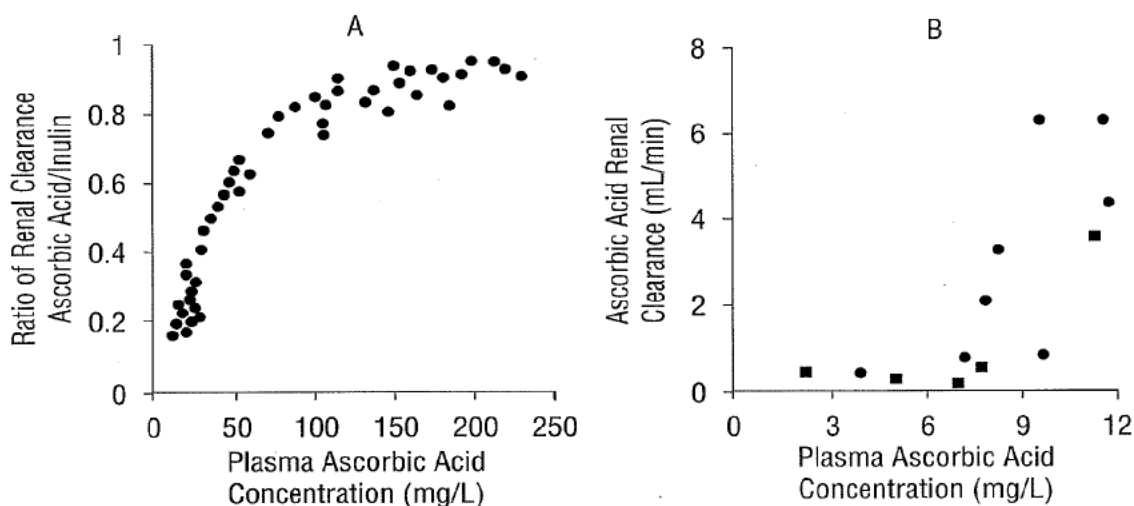


Fig. 22-9. A, The renal clearance of ascorbic acid relative to that of inulin increases dramatically at plasma concentrations well above the values of 4 to 15 mg/L typical for normal dietary conditions. The increase occurs at higher ascorbic acid plasma concentrations because the rate of filtration exceeds the capacity of the facilitated transport mechanism to reabsorb the vitamin from the tubular lumen. At high concentrations, the renal clearance of ascorbic acid approaches that of inulin, a compound that is only filtered. The high concentrations were produced following i.v. injections of 1500 to 6000 mg of ascorbic acid (1 mg/L = 5.7 μ M). (Adapted from Ralli, E.P., Friedman, G.J., and Rubin, S.H.: The mechanism of the excretion of vitamin C by the human kidney. *J. Clin. Invest.*, 17:765-770, 1940.) B, In the plasma concentration range resulting from daily oral doses of 30 to 180 mg, renal clearance of ascorbic acid ranges from negligible to 4 to 8 mL/min (3 to 6% of the expected inulin clearance) in 22- to 45-year-old male subjects while on diets essentially free of vitamin C. Each symbol (●, ■) represents a group of subjects studied in one experiment with different intakes of ascorbic acid per day. (Adapted from Kallner, A., Hartmann, D., and Hornig, D.: Steady-state turnover and body pool of ascorbic acid in man. *Am. J. Clin. Nutr.*, 32:530-539, 1979.)

Table 22-4. Steady-State Trough Plasma Ascorbic Acid Concentrations in Healthy Adults Taking Various Doses of the Vitamin Twice Daily for 3 to 4 Weeks^a

GROUP	PLASMA ASCORBIC ACID CONCENTRATION ^b (mg/L)
1. No supplementary dose, 6 subjects. Daily dietary intake of 50-75 mg expected.	9 $\pm$ 0.6 ^c
2. 1 to 3 g/day, 11 subjects.	15.4 $\pm$ 1.6 ^d
3. 8 to 12 g/day, 6 subjects.	19.5 $\pm$ 2.0 ^d

^aAdapted from Yew, M.-L.S.: Megadose vitamin C supplementation and ascorbic acid and dehydroascorbic acid levels in plasma and lymphocytes. *Nutr. Rep. Intern.*, 30:597-601, 1984.

^bBlood sampled in the morning before the next dose.

^cMean $\pm$ standard error of the mean.

^dSignificantly different from group 1.

metabolized in the renal tubular cells. At higher plasma concentrations, metabolism of the filtered drug becomes saturable with a resultant increase in renal clearance, an observation commonly reported for other proteins of comparable size. Note that the apparent upper limit of renal clearance (40 mL/min/70 kg) is less than the glomerular filtration rate, a probable consequence of filtration of this protein being incomplete because of its large molecular size (M.W. = 32,000 g/mole). Although no specific cut-off in molecular weight can be given, filtration of proteins above 30,000 g/mole falls off rapidly with increasing molecular size. Above 70,000 g/mole, only a small fraction is filtered except in glomerular disease (See Chap. 11, Elimination, p. 178).

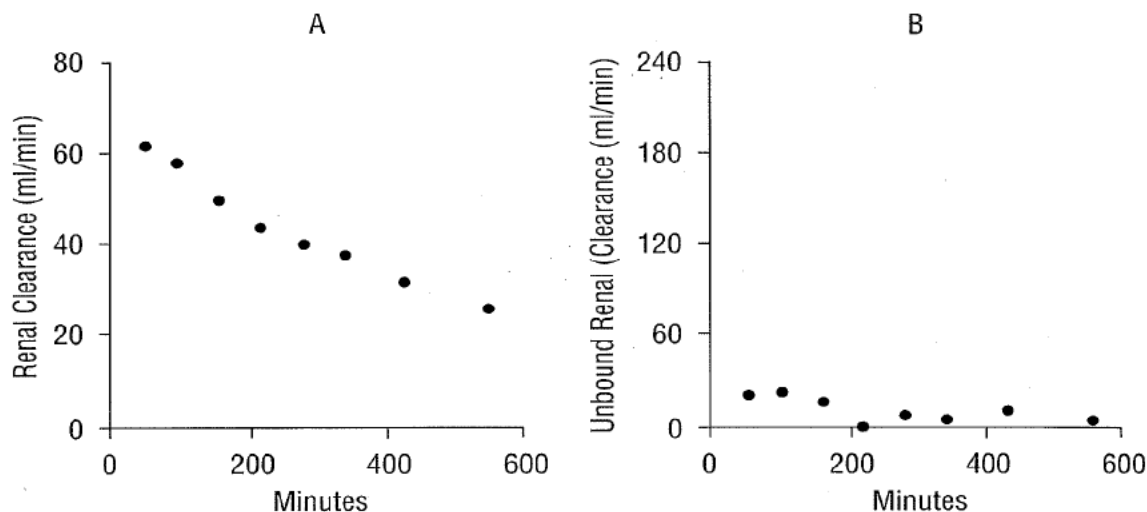


Fig. 22-10. A, The renal clearance of disopyramide in an individual subject shows changes with time after a single 1.5-mg/kg i.v. dose. B, Unbound renal clearance, on the other hand, does not appear to change over the corresponding time period. The initial plasma concentrations were in the range of 2 to 4 mg/L. These total concentrations are expected to produce nonlinear binding to α_1 -acid glycoprotein, the protein to which this drug primarily binds in plasma (see Chap. 10, Distribution) (1 mg/L = 2.9 μ M). (Modified from Giacomini, K.M., Swezey, S.E., Turner-Tamiyasu, K., and Blaschke, T.F.: The effect of saturable binding to plasma proteins on the pharmacokinetic properties of disopyramide. *J. Pharmacokinet. Biopharm.*, 10:1-14, 1982.)

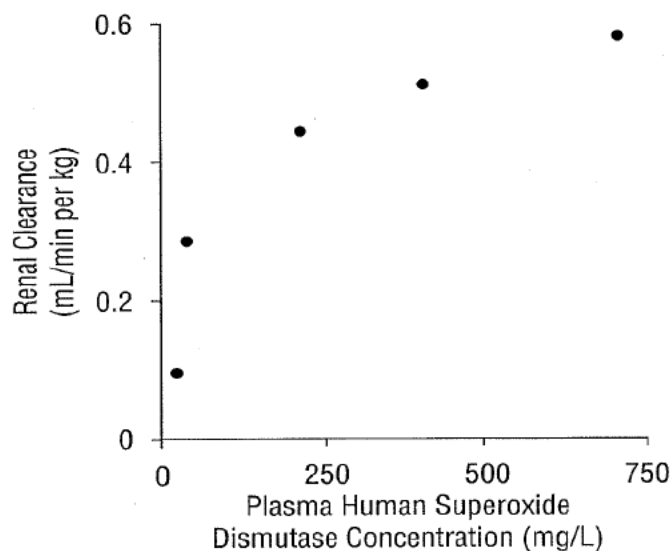


Fig. 22-11. Mean renal clearance of recombinant human superoxide dismutase increases at higher plasma concentrations after an i.v. dose of 45 mg/kg in eight subjects. The experimental drug is filtered in the glomerulus and partially metabolized by tubular cells. At higher plasma concentrations, the rate of filtration exceeds the ability of the tubular cells to absorb and metabolize the drug (1 mg/L = 0.031 μ M). (Modified from Tsao, C., Greene, P., Odland, B., and Brater, D.C.: Pharmacokinetics of recombinant human superoxide dismutase in healthy volunteers. *Clin. Pharmacol. Ther.*, 50:713-720, 1991.)

Renal clearance may also show concentration dependence when the drug (1) produces changes in pH and its tubular reabsorption is pH-dependent, e.g., salicylate; (2) is a diuretic and renal passive clearance is flow-dependent, e.g., theophylline; or (3) causes nephrotoxicity, e.g., an aminoglycoside. The mechanisms of the last two drugs are also time-dependent. Theophylline produces diuresis soon after its administration, but this effect, and consequently its renal clearance, decrease with time. The nephrotoxic effect of

aminoglycosides, on the other hand, develops with dose and duration of exposure to the drug.

CAPACITY-LIMITED METABOLISM

Perhaps the most dramatic dose-dependent kinetic mechanism is that of *capacity-limited metabolism*, a characteristic typical of enzymatic reactions. Recall from Chap. 11 (Eq. 11) that

$$\text{Rate of metabolism} = \frac{V_m \cdot C_u}{K_m + C_u} \quad 5$$

for a drug showing saturable Michaelis-Menten kinetics. Also, recall that in this case

$$\text{Unbound metabolic clearance} = \frac{V_m}{K_m + C_u} \quad 6$$

The social and therapeutic consequences of Michaelis-Menten kinetics are now explored with two examples, alcohol and phenytoin.

Alcohol

At doses usually consumed, the metabolism of alcohol is capacity-limited. Although metabolized by both alcohol dehydrogenase and cytochrome P450-2E1, the elimination kinetics of alcohol has been approximated by a Michaelis-Menten model of a single enzyme. This simplified kinetic model is subsequently presented.

The maximum rate of metabolism, V_m , and the Michaelis constant, K_m , are approximately 10 g/hr and 100 mg/L, respectively. The pharmacologic effects of alcohol, which does not bind to plasma proteins, become apparent when the plasma concentration is about 200 mg/L, concentrations above 5000 mg/L are potentially lethal. Thus, the concentration range in which alcohol exerts its pharmacologic effects is well above its K_m .

Table 22-5 shows the calculated rate of metabolism and clearance of alcohol as a function of the concentration at the metabolic site. Note that rate of metabolism of alcohol is essentially constant, zero-order, and close to V_m throughout the range of concentrations associated with activity. Accordingly, clearance decreases at high concentrations. At low concentrations, the intrinsic clearance (V_m/K_m) approaches 100 L/hr or 1.6 L/min, a value

Table 22-5. Calculated Rate of Metabolism and Clearance of Alcohol as a Function of the Concentration at the Metabolic Site

CONCENTRATION AT SITE (mg/L)	RATE OF METABOLISM ^a (g/hr)	CLEARANCE ^b (L/hr)
7000	9.9	1.4
5000	9.8	2.0
3000	9.7	3.2
1000	9.1	9.1
500	8.3	17
200	6.7	33
100	5.0	50
50	3.3	67
10	0.91	91

^aRate of metabolism = $V_m \cdot C_u / (K_m + C_u)$; $V_m = 10$ g/hr, $K_m = 100$ mg/L.

^bClearance = $V_m / (K_m + C_u)$.

in excess of hepatic blood flow. Thus, at very low concentrations, the extraction ratio is sufficiently high so that the rate of metabolism is partially limited by hepatic perfusion. Under these conditions oral bioavailability is expected to be reduced.

The consequences of zero-order elimination can be dramatic. The usual-size drink, 45 mL, of 40% v/v whiskey contains about 18 mL, or 14 g, of alcohol. Drinking this quantity of alcohol each hour exceeds the eliminating capacity of the body. Consequently, alcohol accumulates until ultimately either coma or death intervenes.

Alcohol distributes evenly throughout total body water; its volume of distribution is therefore 42 L. Accordingly, approximately 200 g of alcohol are needed in the body to achieve a concentration, about 5000 mg/L, that can produce coma or, occasionally, death. But, since the rate of ingestion, 14 g/hr, exceeds the rate of metabolism, 10 g/hr, by only 4 g/hr, this rate of drinking must be maintained for at least 2 days (a total of 48 drinks) to accumulate 200 g of alcohol. This degree of accrual can occur within 5 hr (20 drinks) when four drinks are consumed every hour, because this rate of ingestion, 56 g/hr, exceeds the maximum metabolic capacity by 46 g/hr.

If the rate of ingestion is reduced to one-half drink (or 7 g/hr), then, with respect to the effect of alcohol, one can drink with virtual impunity as now shown. By definition, of steady state, rate of elimination matches rate of administration (or input), R_o .

$$R_o = \frac{V_m \cdot C_{u_{ss}}}{K_m + C_{u_{ss}}} \quad 7$$

or on rearrangement

$$C_{u_{ss}} = \frac{K_m \cdot R_o}{V_m - R_o} \quad 8$$

Using the previously given values for K_m and V_m and an R_o value of 7 g/hr, the plateau concentration of alcohol is 230 mg/L, which produced only a marginal effect.

Reflect on the calculations above. Chronically imbibing one-half a drink of whiskey per hour produces little or no effect, but taking one drink per hour becomes lethal. There can be no standard dosage regimen to maintain the effects of alcohol. Maintenance of effect requires titration of dosage to the effect itself.

The consequence of capacity-limited metabolism on the time-course of a drug in the body when input rate is changed is also demonstrated with alcohol. When alcohol is administered 10 min after ingesting water, light cream, or a glucose solution (80 g/240 mL), the plasma concentration-time profiles differ profoundly (Fig. 22-12). Compared to water, administration of light cream and 33% glucose, foods that delay gastric emptying, lower both *AUC* and peak concentration and increase time to reach the peak. These observations can be explained by the nearly zero-order metabolism of alcohol. To emphasize the point, assume that both elimination and input are strictly zero-order, as shown in Fig. 22-13. Decreasing the input rate, for a given total dose administered, lowers *AUC* and peak concentration as well as increases the peak time. Clearly, oral bioavailability in the presence of zero-order elimination and variable input rates cannot be assessed by conventional area ratio methods.

Phenytoin

Therapeutic problems encountered with capacity-limited metabolism are classically exemplified by phenytoin. Typical V_m and K_m values of this drug are 500 mg/day and 0.4 mg/L, although the values vary widely. The value of K_m is usually expressed in terms of

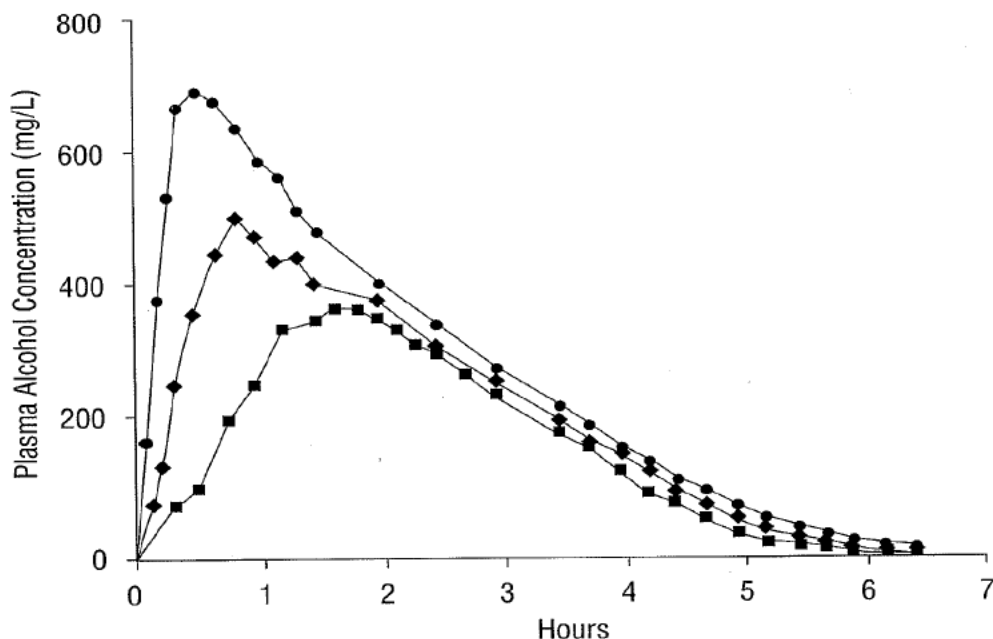
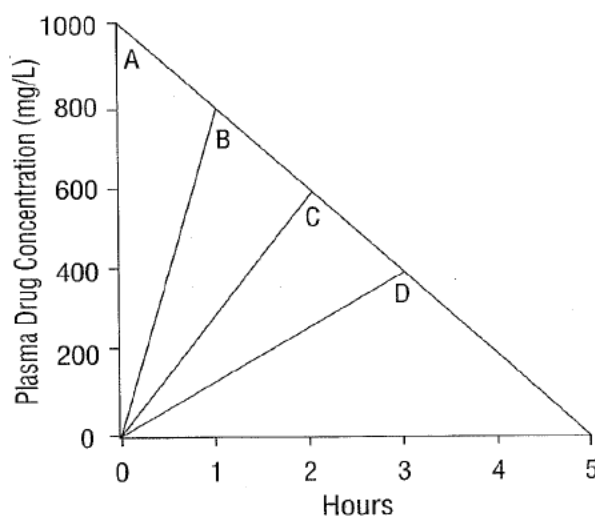


Fig. 22-12. A decrease in the absorption rate of alcohol, produced by slowing gastric emptying, causes peak concentrations and *AUC* to decrease and time to reach the peak to increase. The effect differs from that expected of first-order kinetics by the observed decrease in *AUC*. This observation is explained by a constant rate of elimination at almost all concentrations, as illustrated schematically in Fig. 22-13. Alcohol, 45 mL of 95% ethanol in 105 mL of orange juice, was administered 10 min after 240 mL of tap water (●); 240 mL of light cream (◆); or 240 mL of a 33% glucose solution (■) (1 mg/L = 22.0 μ M). (Redrawn from data of Sedman, A.J., Wilkinson, P.K., Sakmar, E., Weidler, D.J., and Wagner, J.G.: Food effects on absorption and metabolism of alcohol. Reprinted by permission, from *Journal of Studies on Alcohol*, Vol. 37, pp. 1197-1214, 1976. Copyright by Journal of Studies on Alcohol, Inc., Rutgers Center of Alcohol Studies, New Brunswick, NJ 08903.)

Fig. 22-13. As a consequence of zero-order elimination, the plasma concentrations at the end of a 50-g dose of a drug by bolus injection (A) and constant-rate infusions of 1- (B), 2- (C), and 3- (D) hr durations are quite different from those expected with first-order kinetics. The amount in the body at the end of each infusion is the difference between dose and amount lost during the infusion period. Consequently, the concentration at the end of each of the infusions is the same as that expected at that time following the i.v. bolus dose. Note that the slower the input rate, the smaller is *AUC* and the lower is peak concentration. The time to peak is, of course, increased. Furthermore, if the dose had been infused over a 5-hr period, i.e., at 10 g/hr, output would have matched input and there would have been no *AUC* in this hypothetical example.



total, rather than unbound, concentration. Since f_u is typically 0.1, the apparent K_m for total concentration, K_m' , is equal to 4 mg/L.

Plateau. Perhaps the most striking consequence of the kinetics of this drug is the relationship observed between steady-state plasma concentration and rate of administration, as shown in Fig. 22-14. A greatly disproportionate increase in concentration is observed in, and above, the therapeutic concentration range, 10 to 20 mg/L. As a result, the difference between the daily dose giving ineffective therapeutic concentrations, less than 10 mg/L, and that producing potentially toxic concentrations, above 20 mg/L, is narrow.

The observed increase in concentration can be explained by rearrangement of Eq. 8.

$$\frac{C_{u_{ss}}}{K_m} = \frac{C_{ss}}{K_m'} = \frac{R_o}{V_m - R_o} \quad 9$$

The consequences of Michaelis-Menten metabolism result when either the desired steady-state unbound concentration is above K_m (K_m' for total concentration) or the rate of administration required to achieve these concentrations approaches V_m .

Because of its kinetics, only small changes in phenytoin input caused, for example, by a change in salt form (acid and sodium salt are used) or in bioavailability can produce relatively large changes in the steady-state concentration. To illustrate this point, consider a male patient with K_m' and V_m values of 3 mg/L and 425 mg/day, respectively, and who has an average steady-state concentration of 12 mg/L when taking 200 mg orally every 12 hr. On switching from his current dosage form (bioavailability = 0.85) to one with a bioavailability of 0.95, it is seen, by setting $R_o = F \cdot D/\tau$ in Eq. 9, that the average steady-state concentration is expected to increase to 25 mg/L. Thus, a minor change in bioavailability (0.85 to 0.95) causes a major change (12 to 25) in the steady-state concentration when the dosing rate approaches the V_m value.

Time to Plateau. Because of capacity-limited metabolism, the time to reach steady state varies with the rate of administration. Figure 22-15 shows the approach to plateau during each of four dosing rates, which increase by small increments from 300 to 425 mg/day, in a patient with typical V_m and K_m' values. Note that the time to reach 90% of plateau increases progressively with the rate of administration. These disproportionate changes in the steady-state concentration and the time required to reach them are major problems in optimally dosing phenytoin and interpreting its concentrations. Even though

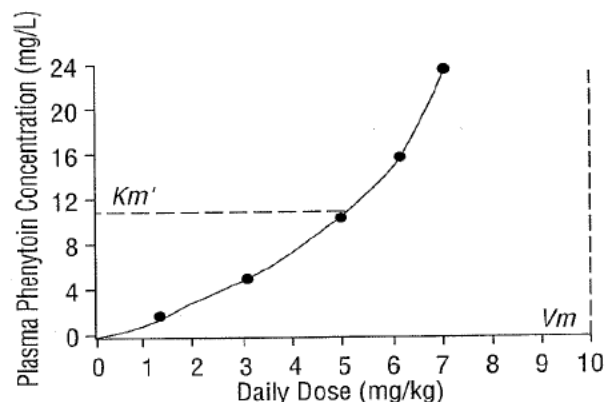


Fig. 22-14. The steady-state plasma phenytoin concentration increases disproportionately with rate of administration (given twice daily) of phenytoin, a drug that is virtually eliminated by a single metabolic pathway, that exhibits typical Michaelis-Menten enzyme kinetics. The estimated V_m , the maximum rate of metabolism, and K_m' , the total plasma concentration at which the rate is half of the maximum (colored line), are shown. All the data were obtained in the same individual whose K_m' and V_m values are considerably higher than the typical ones of 4 mg/L and 7 mg/kg/day. (1 mg/L = 4.0 μ M.) (Adapted from Martin, E., Tozer, T.N., Sheiner, L.B., and Riegelman, S.: The clinical pharmacokinetics of phenytoin. J. Pharmacokinetic. Biopharm., 5:579-596, 1977. Reproduced with permission of Plenum Publishing Corp.)

Fig. 22-15. Following administration (i.v. infusion is simulated) of phenytoin at constant rates of 300, 350, 400, and 425 mg/day, the plasma concentration approaches steady-state values of 6, 9.3, 16, and 22.7 mg/L, respectively (colored lines). Not only are the steady-state concentrations disproportionately increased, but so is the time required to approach the plateau. The arrows indicate the time required to reach 90% of the plateau value. The following parameter values were used: K_m' , 4 mg/L; V_m , 500 mg/day; V , 50 L (1 mg/L = 4.0 μ M). (Reproduced by permission of publisher. Redrawn from Winter, M.E., and Tozer, T.N., Phenytoin, Chap. 25, in *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*, 3rd edition, edited by W.E. Evans, J.J. Schentag, and W.J. Jusko, published by Applied Therapeutics, Inc., Spokane, Washington, 1992.)

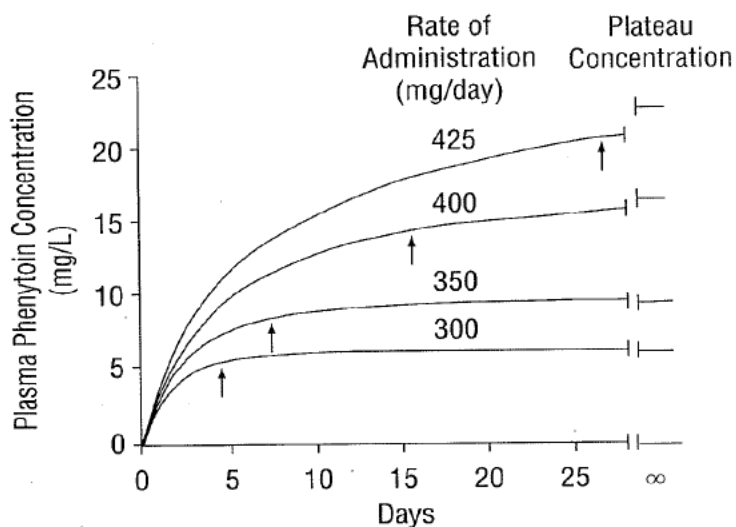
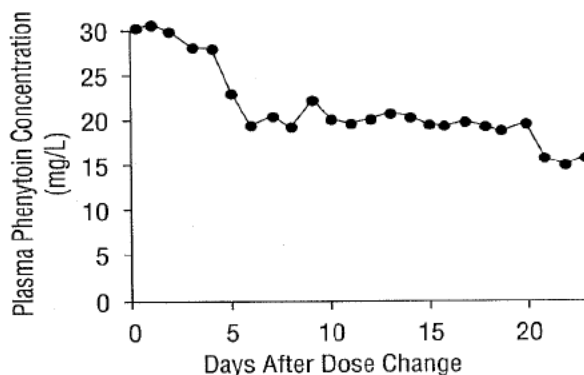


Fig. 22-16. On decreasing the daily dose from 250 to 200 mg/day, the plasma phenytoin concentration (obtained daily just before the morning dose) declines slowly toward a new steady state. Note that a 20% reduction in the daily dose leads to a 50% decrease in the concentration at steady state (the concentration stabilized after Day 23) (1 mg/L = 4.0 μ M). (Redrawn from Theodore, W.H., Qu, Z.-P., Tsay, J.-Y., Pitlick, W., and Porter, R.J.: Phenytoin: The pseudosteady-state phenomenon. *Clin. Pharmacol. Ther.*, 35:822-825, 1984. Reproduced with permission of C.V. Mosby.)



the approach to plateau is usually somewhat quicker on reducing doses than on increasing them, it can still take a long time, as shown in Fig. 22-16.

Because clearance, and hence half-life, are functions of the plasma concentration, the meanings of these parameters are lost when capacity-limited metabolism occurs. For this reason, these parameters should not be used for predicting or summarizing the kinetics of drugs showing this kind of behavior. The parameters of choice are those of the appropriate nonlinear model (K_m and V_m for Michaelis-Menten kinetics and V).

Alterations in Metabolism. Another therapeutically important facet of the kinetics of phenytoin is altered metabolism brought about by other drugs and disease states. Either K_m' or V_m can be altered, but the effect on plasma concentration is different. From Eq. 9 it can be seen that the phenytoin concentration at steady state is directly proportional to K_m' . Thus, a condition such as competitive inhibition of metabolism, which affects the K_m' value, produces corresponding changes in the steady-state phenytoin concentration.

For example, when cimetidine inhibits phenytoin metabolism, thereby increasing Km' from 4 to 6 mg/L, the steady-state unbound and total phenytoin concentrations are expected to increase by 50% as well.

In contrast, either an increase in Vm , brought about by enzyme induction, or a decrease in Vm , caused by the presence of hepatic cirrhosis, is expected to produce disproportionate change in the steady-state phenytoin concentration. This is seen by taking the ratio of the two different concentrations, $Cu_{ss,1}$ and $Cu_{ss,2}$ (Eq. 9), that result from the unaltered, Vm_1 , and altered, Vm_2 , values, respectively.

$$\frac{Cu_{ss,2}}{Cu_{ss,1}} = \frac{Vm_1 - R_o}{Vm_2 - R_o} \quad 10$$

For example, when $R_o = 300$ mg/day, $Vm_1 = 500$ mg/day, and $Vm_2 = 400$ mg/day, the unbound concentration at steady state is doubled, $Cu_{ss,2}/Cu_{ss,1} = 2$. If Vm_2 is 600 mg/day, the ratio is 0.67. Thus, a 20% decrease in Vm doubles the steady-state concentration; whereas a 20% increase in Vm reduces the steady-state concentration by 33%. Note that a Vm of 300 mg/day results in a concentration approaching infinity, and that with a Vm below 300 mg/day, steady state can never be achieved. The input rate would then always exceed Vm , and Eqs. 5 to 10 would not be applicable.

Alcohol and phenytoin represent extreme cases in that almost all the elimination of each drug occurs by a single saturable pathway. More commonly, a drug is metabolized by several pathways, and only one or two of them approaches saturation. Then, saturation has less effect on total clearance. The extent of the effect depends on fm , the fraction of drug eliminated by the saturable pathway at low drug concentrations. Only if fm is 0.5, or greater, under nonsaturating conditions is total clearance materially affected by saturation of the pathway. Examples of drugs in this category include propranolol, theophylline, and salicylic acid.

TIME-DEPENDENT DISPOSITION

The study of changes in response to drug administration or kinetics with time of day, month, or year is an area called *chronopharmacology*. The pharmacokinetic component is *time-dependent kinetics* or *chronopharmacokinetics*. Carbamazepine shows time dependence in its disposition (Chap. 23, p. 430). The decrease in its peak concentration on repetitive oral administration indicates that either oral bioavailability decreases or clearance increases with time. The latter has been shown to explain the observation caused by carbamazepine inducing its own metabolism. This *autoinduction* is also dose- and concentration-dependent, a property common to many time-dependent processes.

Autoinduction has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated doses or continuous administration. Furthermore, it may be associated with the induction of metabolism (same enzymatic pathway) of coadministered drugs, producing a drug interaction.

Although enzyme induction is perhaps the most common cause of time-dependent kinetics, there are many other reasons for this behavior. For example, diurnal variations in renal function, urine pH, α_1 -acid glycoprotein concentration, gastrointestinal physiology (food and drink), and cardiac output all occur. Chronic effects of a drug on its own renal and hepatic elimination have also been seen, as previously mentioned.

Aminoglycosides can produce renal toxicity with chronic administration. Because these antibiotics are primarily eliminated by renal excretion, a diminishing renal function with time may cause greater drug accumulation and therefore more toxicity. There is clearly a

need to monitor therapy and to limit the duration of therapy, especially in patients who already have compromised renal function.

An example of diurnal changes in drug absorption and disposition is shown in Fig. 22-17. Median data are shown (because of skewed distribution of values) for eight subjects who received an oral 80-mg dose of verapamil at various times during the day. Note that administration in the evening produces a lower peak drug concentration and, as such, may produce less effect than does administration in the morning.

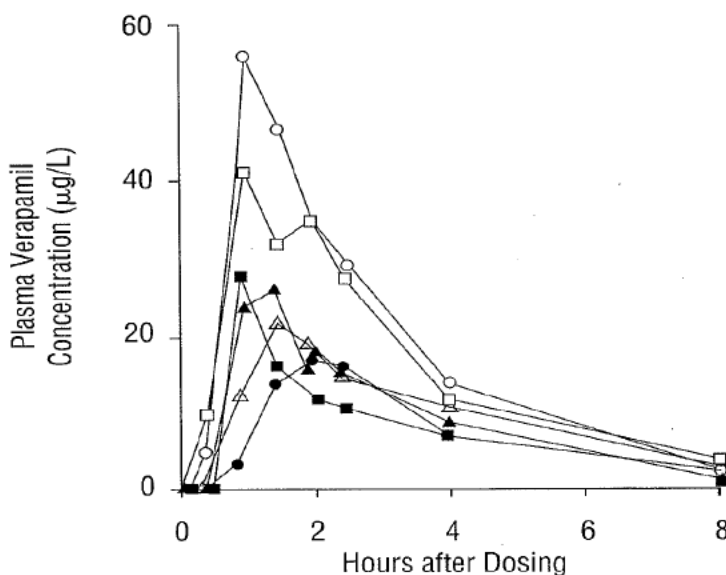
Food is a major cause of diurnal variations. Gastric emptying is slowed or delayed by food (see Fig. 9-7), often resulting in a decrease in the peak concentration and an increase in the time of its occurrence following a single dose.

NONLINEAR METABOLITE FORMATION OR ELIMINATION

Nonlinear formation or elimination of a metabolite is of therapeutic interest when it accounts for some or all of either the therapeutic response, or toxicity, or both. The consequences of such nonlinearities depend on the cause and the site of occurrence. At the end of Chap. 21, the ratio of *AUC* values for metabolite and drug was explored as a means of evaluating changes in drug metabolism from one occasion to another. The ratios can also be used to assess sources of dose dependence.

Table 22-6 lists kinetic changes expected for a drug that forms two sequential metabolites following a single i.v. dose. Using the principles given in Chap. 21, the consequences of capacity-limited metabolism at each of the sites in the metabolic scheme can be assessed. For a compound with nonlinear metabolism, *AUC* increases with respect to the dose administered; the *AUC* of the product of the nonlinear pathway decreases with respect to the *AUC* of its precursor. If the site of nonlinearity involves the first of three consecutive steps, the ratio of areas of the last two products remains constant, though both areas may be decreased with respect to the dose given.

Fig. 22-17. Median plasma verapamil concentration-time profiles for eight subjects, each given a single 80-mg tablet of drug at the following times: 4:00 A.M. ($\blacktriangle$); 8:00 A.M. ($\circ$); noon ($\square$); 4:00 P.M. ($\triangle$); 8:00 P.M. ($\bullet$), and midnight ($\blacksquare$). Food was withheld 2 hr before to 2 hr after drug administration, as food is known to affect verapamil absorption. To minimize a delay in esophageal transit, subjects took the tablets while standing and remained so for 15 min. The kinetics of the drug appears to change with the time of administration during the day. Factors other than food and posture may be responsible, e.g., changes in hepatic blood flow (verapamil has a high hepatic extraction ratio), enzyme activity, or protein binding (1 mg/L = 2.2 μ M). (From Hla, K.K., Latham, A.N., and Henry, J.A.: Influence of time of administration on verapamil pharmacokinetics. *Clin. Pharmacol. Ther.*, 51:366-370, 1992.)



The general tendencies for changes in steady-state concentrations following chronic dosing are the same as those for AUC after a single dose. Here, however, the compound (drug or metabolite) with capacity-limited metabolism may not reach steady state if it is formed at a rate that exceeds its V_m .

Dose-dependence is expected in the degree of autoinduction for drugs that undergo this behavior. Such is observed with carbamazepine. As shown in Fig. 22-18A, the steady-state concentration of carbamazepine fails to increase in direct proportion to daily dose ($C_{ss,av}/(D/\tau)$ decreases). Furthermore, the ratio of the steady-state concentrations of the metabolite carbamazepine-10,11-epoxide and carbamazepine increase with dose (Fig. 22-18B). These results demonstrate nonlinearity in the formation of the metabolite. The directions of the changes suggest that formation clearance of the epoxide is increased.

RECOGNITION OF NONLINEARITIES

Nonlinearities are often apparent in graphic and tabular presentations of data. The interpretation of such kinetic behavior often requires a methodical analysis of the information. This analysis may be accomplished using the following steps:

1. Compare the observation to that expected for linear kinetics.
2. Identify the kinetic parameter(s) that appear(s) to be altered and the direction of the change.
3. Determine the primary pharmacokinetic parameter(s) CL_H , CL_R , V , ka , and F that appear to be affected. Also evaluate if f_u is altered.
4. Consider the mechanism(s) consistent with the changes observed.

Urinary Recovery

Nonlinearities are often first identified from recovery of drug and metabolites in urine. This is the case for salicylic acid, as shown in Table 22-7.

Analysis

Step 1. Dose dependence in salicylic acid is apparent from changes in the fraction of a single oral dose recovered as unchanged drug and as the metabolites, salicyluric acid and glucuronide conjugates. With linear kinetics, the fraction of each compound recovered remains the same regardless of dose.

Table 22-6. Consequences of Capacity-Limited Processes in the Sequential Metabolism of a Drug Given in a Single Dose

MODEL	$\frac{AUC}{DOSE}$	$\frac{AUC(m_1)}{AUC}$	$\frac{AUC(m_2)}{AUC(m_1)}$
1. $D \rightarrow M_1 \rightarrow M_2 \rightarrow$	$\leftrightarrow^a$	$\leftrightarrow$	$\leftrightarrow$
2. $D \Rightarrow^b M_1 \rightarrow M_2 \rightarrow$	$\uparrow^c$	$\downarrow$	$\leftrightarrow$
3. $D \rightarrow M_1 \Rightarrow M_2 \rightarrow$	$\leftrightarrow$	$\uparrow$	$\downarrow$
4. $D \rightarrow M_1 \rightarrow M_2 \Rightarrow$	$\leftrightarrow$	$\leftrightarrow$	$\uparrow$
5. $D \rightarrow M_1 \rightarrow M_2 \rightarrow$	$\uparrow^c$	$\leftrightarrow$	$\rightarrow$

^a $\leftrightarrow$, little or no change; $\uparrow$, increase; $\downarrow$, decrease on increasing the dose.

^b $\Rightarrow$, capacity-limited metabolism of Michaelis-Menten type.

^cThe affected pathway is the major route of elimination at nonsaturating doses. Otherwise, little change is expected.

Fig. 22-18. A, The steady-state concentration of carbamazepine fails to increase in direct proportion to the daily dose, evidence of nonlinear kinetics. B, The ratio of the concentrations of the metabolite, carbamazepine-10,11-epoxide, and carbamazepine increase with dosing rate. These observations indicate that either the clearance of formation increases or the clearance of elimination of the epoxide decreases at higher dosing rates. The former, a consequence of dose-dependent autoinduction of metabolite formation, is the explanation. Each point in both graphs is the mean of data from 77 patients. (Carbamazepine: 1 mg/L = 4.2 μ M; carbamazepine 10,11-epoxide: 1 mg/L = 4.0 μ M.) (Adapted from Kudriakova, T.B., Sirotsa L.A., Rozova, G.I., and Gorkov, V.A.: Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites. *Br. J. Clin. Pharmacol.*, 33:611-615, 1992.)

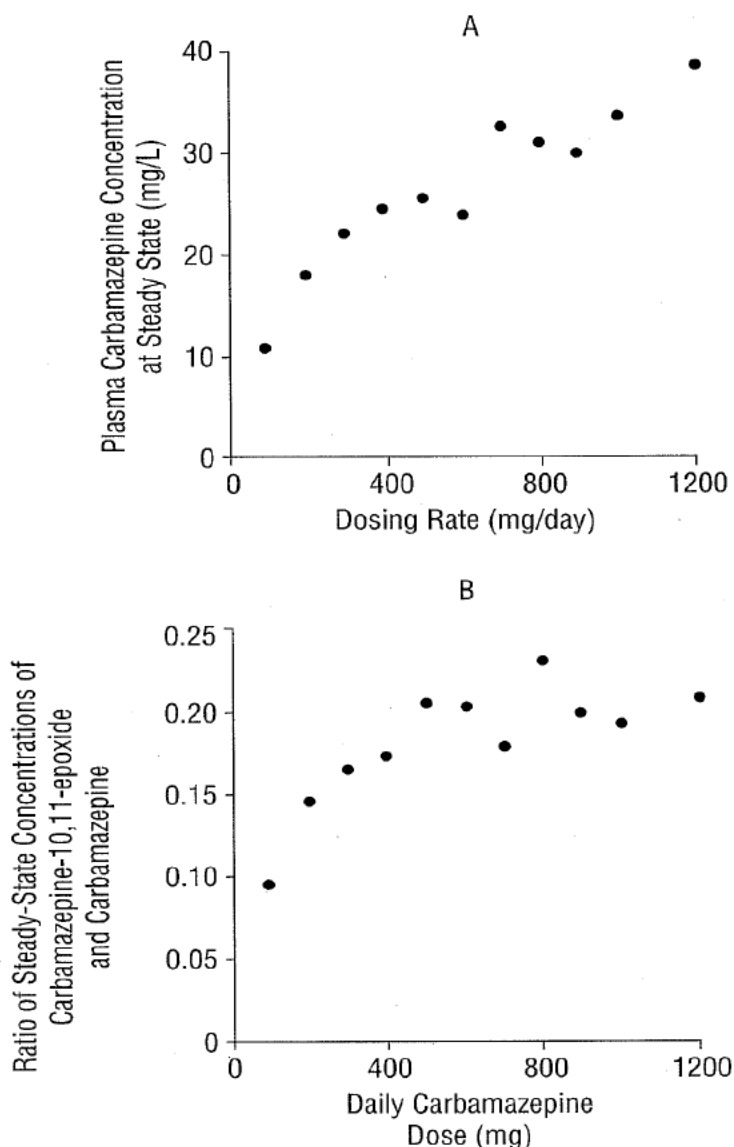


Table 22-7. Urinary Recovery of Salicylic Acid and its Metabolites as a Percent of a Single Oral Dose^a

DOSE (mg)	SALICYLIC ACID	SALICYLURIC ACID	SALICYL PHENOLIC AND ACYL GLUCURONIDES
192	3	83	17
767	5	70	24
1533	17	59	24
3000	14	50	30

^aDose and recovery expressed in equivalents of salicylic acid. (Adapted from Levy, G.: Pharmacokinetics of salicylate elimination in man. *J. Pharm. Sci.*, 54:959-967, 1965.)

Steps 2 to 4. The increased percent recovered as unchanged drug on increasing dose could be explained by an increased bioavailability, an increased renal clearance, or a capacity limitation in its metabolism. This is seen from the relationships $Ae_{\infty}/\text{Dose} = fe \cdot F$ and $fe = CL_R/(CL_R + CL_{NR})$. Without further information, these possibilities cannot be distinguished. The decreased recovery of the major metabolite, salicyluric acid, and the nearly complete total recovery (as drug and metabolites) at all of the doses suggest that increased bioavailability may not be the explanation (see Chap. 21). Increased bioavailability would increase metabolite recovery as well, which was not the case.

Concentration-Time Profile

Figure 22-19 is a semilogarithmic plot of plasma salicylic acid concentration with time after a single 3-g oral dose.

Analysis

Step 1. The slope of the decline is greater at low than at high concentrations. When linear kinetics operates, there is either no change in slope or a greater slope at early times while distribution is occurring (Chap. 19, Distribution Kinetics).

Step 2. The half-life shortens as time passes or as concentration declines.

Step 3. It appears that either CL increases or V decreases with time or with falling concentration.

Step 4. From the dose and maximum concentration (around 200 mg/L) and the conclusion based on urinary data (and independent i.v. data) that salicylic acid is totally absorbed after oral administration, the volume of distribution is estimated to be about 15 L. Being so small, V is unlikely to decrease much with either time or decreasing concentration. An increase in CL with time or at lower concentrations would occur if elimination of salicylic acid is capacity-limited. The data in Table 22-7 indicate that salicylic acid is extensively

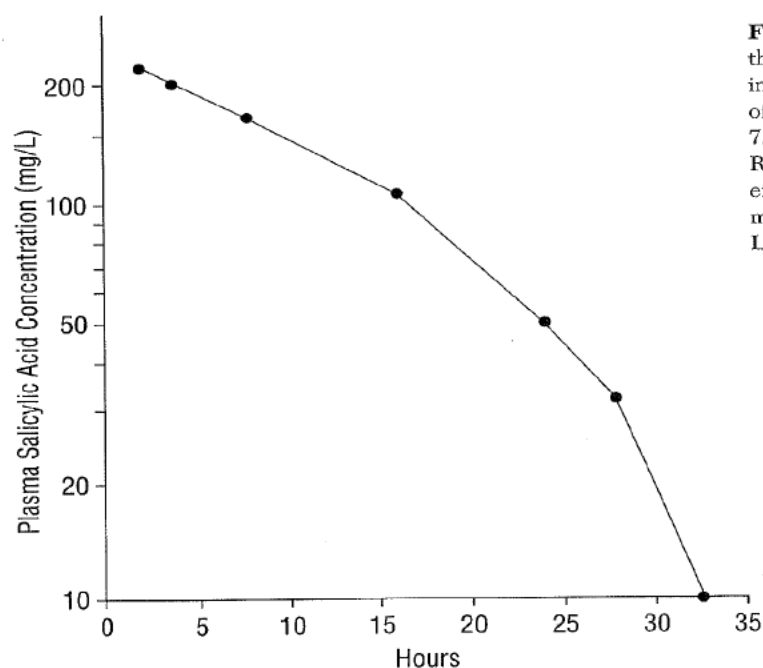


Fig. 22-19. Semilogarithmic plot of the plasma concentration of salicylic acid in a subject following a single oral dose of 3 g of sodium salicylate (1 mg/L = 7.2 μ M). (Adapted from data in Salassa, R.M., Bollman, J.L., and Dry, T.J.: The effect of para-aminobenzoic acid on the metabolism and excretion of salicylate. *J. Lab. Clin. Med.*, 33:1393-1401, 1948.)

converted to several metabolites. However, the pronounced increase in fraction excreted as unchanged salicylic acid with increasing dose (Table 22-7) implies that saturability of a major metabolic pathway is likely at the 3-g dose level.

Protein Binding Data

The incorporation of binding data further clarifies the nature of nonlinearities present, as shown in Fig. 22-20.

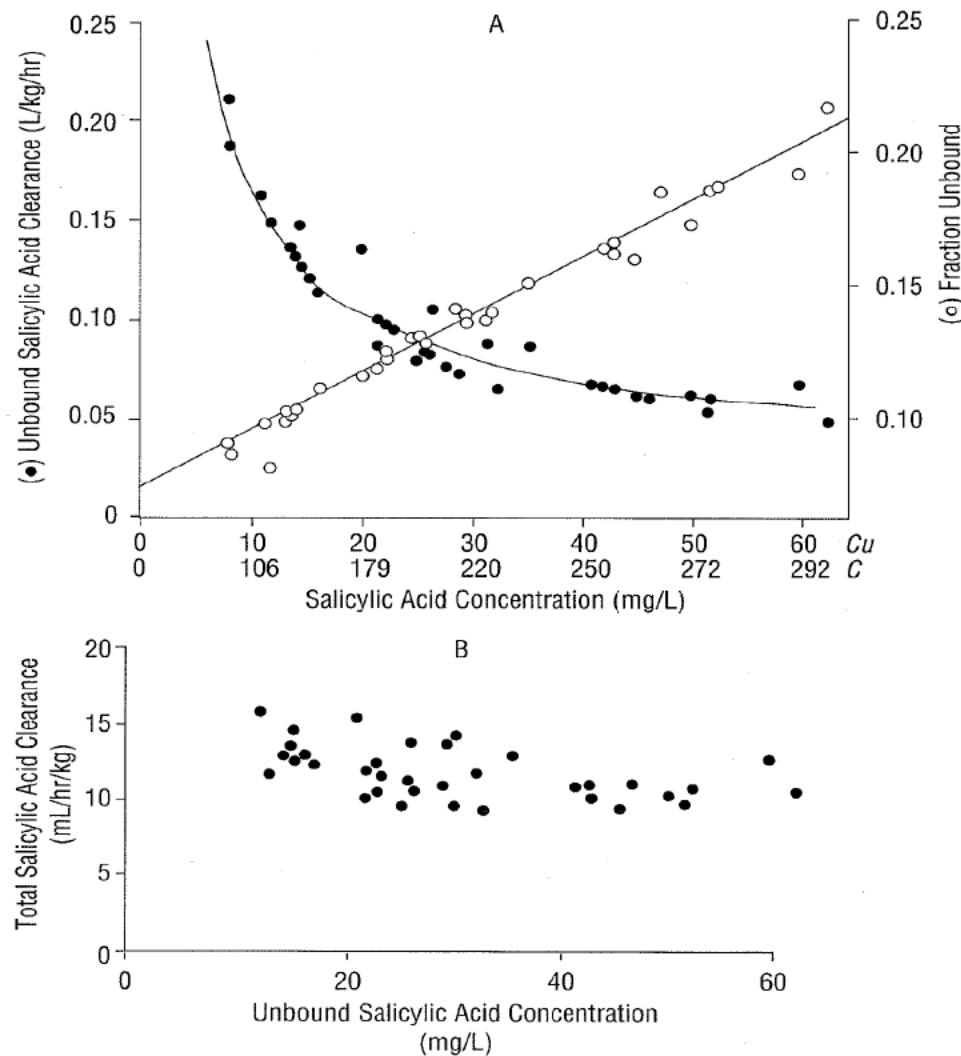


Fig. 22-20. A, The clearance of unbound drug (●, colored line), determined under steady-state conditions, and the fraction unbound in plasma (○) vary inversely with each other as the salicylic acid concentration is increased. The corresponding total plasma concentrations are superimposed on the linear scale of the unbound drug concentration (1 mg/L = 7.2 μ M). (Redrawn from Furst, D.E., Tozer, T.N., and Melmon, K.L.: Salicylate clearance: The result of protein binding and metabolism. Clin. Pharmacol. Ther., 26:380-389, 1979. Reproduced with permission of C.V. Mosby.) B, The total clearance of salicylic acid, determined under steady-state conditions, remains essentially constant within the range of therapeutic concentrations; a fortuitous consequence of the essentially equivalent and opposing effects of saturable plasma protein binding and saturable metabolism (1 mg/L = 7.2 μ M).

Analysis

Step 1. As observed in Fig. 22-20A, f_u increases with increasing concentration in the antirheumatic therapeutic range, 100 to 300 mg/L, indicating nonlinearity of salicylic acid binding to plasma proteins. Nonlinearity in CL_u is also uncovered. As shown in Fig. 22-20B, salicylic acid has a low clearance even at low concentrations. As such, CL_u should remain constant if elimination processes are unaffected by the concentration (dose) of salicylic acid.

Steps 2-3. The parameters affected are identified in this case, f_u and CL_u .

Step 4. The mechanisms involved appear to be saturable binding to plasma proteins and some form of capacity-limited elimination. From the additional information in Table 22-7 and Fig. 22-19, the capacity limitation must lie with metabolism.

Interestingly, total clearance is relatively constant throughout the therapeutic range of salicylic acid (C_u between 10 and 60 mg/L). This is a consequence of the opposing tendencies of the two forms of nonlinearity. Clearance decreases with concentration because of capacity-limited metabolism. Saturable binding, on the other hand, tends to increase clearance at higher concentrations, $CL = f_u \cdot CL_u$. The decrease in unbound clearance, the consequence of saturability in two major metabolic pathways of salicylic acid (formation of salicyluric acid and salicyl phenolic glucuronide) leads to a disproportionate increase in unbound concentration with increasing dosing rate (Fig. 22-21). Further information on the specific nonlinear metabolic pathways requires isolating the metabolic pathways. This has been accomplished by comparing the rates of urinary excretion of each metabolite to the amount of salicylic acid in the body, a procedure analogous to the determination of renal clearance. The method is applicable if the rate of excretion of metabolite equals its rate of formation, as is the case for salicylic acid after a single dose and for all drugs under steady-state conditions.

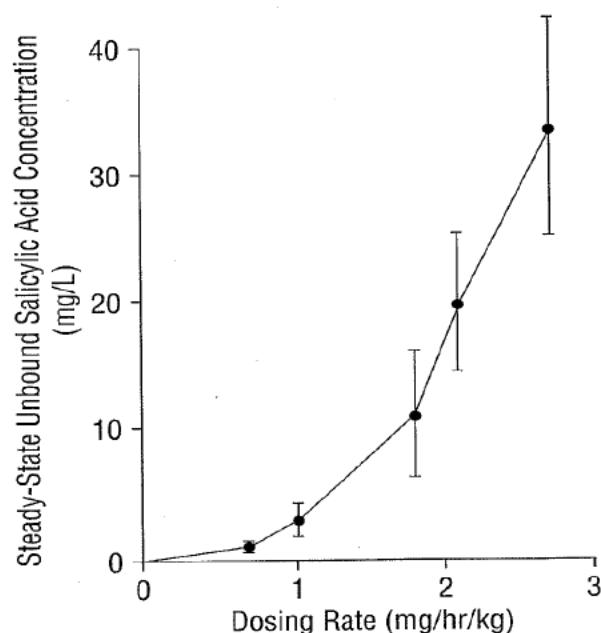


Fig. 22-21. The steady-state unbound concentration of salicylic acid in plasma (mean $\pm$ SD) increases disproportionately with the dosing rate of aspirin. Aspirin is completely converted to the measured metabolite, salicylic acid. The disproportionate increase reflects the saturability of two of salicylic acid's major pathways of elimination, formation of salicyl phenolic glucuronide and salicyluric acid (1 mg/L = 7.2 μ M). (Redrawn from Tozer, T.N., Tang-Liu, D.D.-S., and Riegelman, S.: Linear vs. nonlinear kinetics. In Topics in Pharmaceutical Sciences. Edited by D. Breimer and P. Speiser. New York, Elsevier, 1981, pp. 3-17.)

THERAPEUTIC CONSEQUENCES

The therapeutic consequences of dose-dependent kinetics are perhaps best considered under steady-state conditions. Here, dose dependence in rate-time profile of absorption is of little or no consequence unless bioavailability (extent) is also altered. Alterations in bioavailability are important in that unbound concentration and amount in the body at steady state may change disproportionately on changing dose. Conditions that cause dose dependence in bioavailability may also produce increased variability in this parameter at the same dose. For example, consider two drugs, a dissolution rate-limited one, such as griseofulvin, and one that is highly extracted on passing across the gastrointestinal membranes or through the liver, such as alprenolol. Changes in gastric emptying and in other physiologic factors can produce large variations in the bioavailability of these drugs. The effect of rapid gastric emptying may be a decrease in bioavailability of griseofulvin because of less time for mixing and dissolution but an increase in bioavailability of alprenolol because of saturability in intestinal and hepatic metabolism.

Clinically, the most dramatic source of dose dependence is capacity-limited metabolism. Only small changes in bioavailability may produce large changes in the steady-state concentration. Under these conditions, careful titration of an individual patient's dosage requirement is needed, especially if the drug has a narrow therapeutic index. Moreover, this source of dose-dependence also produces large interpatient variability in steady-state concentration, as observed for phenytoin in Fig. 1-5.

Time-dependent kinetics is perhaps best typified by autoinduction. Another cause is decreased renal function on continued administration of a nephrotoxic drug. If the drug is primarily renally eliminated, the therapeutic consequence of the latter cause is clear and opposite to that of autoinduction.

In general, if two drugs are equivalent in all respects except for one showing either a dose- or time-dependent kinetic behavior, then the one showing linear kinetics is the drug of choice.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Circle the number(s) of the one or more *correct* answers to each of the following multiple-choice questions. Briefly discuss those answers that may be ambiguous (situations in which the statement may be true or false).
 - a. Capacity-limited metabolism of a drug is associated with:
 1. A less than proportional increase in the steady-state plasma concentration on increasing the total daily dose.
 2. An apparent half-life that is longer at low than at high concentrations.
 3. A decrease in the rate of metabolism as the amount of drug in the body is increased.
 4. All of the above.
 5. None of the above.
 - b. A mean steady-state plasma concentration obtained after 30 doses that is much higher than that predicted from the value of clearance obtained after a single dose suggests that:
 1. Induction has occurred.
 2. The volume of distribution has decreased.
 3. A metabolite may be acting as an inhibitor of drug elimination.
 4. None of the above.

- c. The following steady-state plasma drug concentrations have been observed in a subject following various constant daily oral dosages:

DOSING RATE (mg/day)	STEADY-STATE PLASMA CONCENTRATION (mg/l)
500	45
1000	56
1500	62

These data are consistent with and may be explained by:

1. Decreased bioavailability
 2. Increased clearance
 3. Decreased plasma protein binding
 4. Increased volume of distribution on increasing the dosing rate.
- d. The total cumulative amounts of drug collected in the urine within 48 hours (essentially Ae_{∞}) following various single oral doses of a drug, administered on separate occasions, are shown below.

DOSE (mg)	AMOUNT EXCRETED UNCHANGED IN 48 HR (mg)
50	1.1
100	2.8
200	9.0

These data are consistent with and may be explained by:

1. Saturable active transport in the wall of the gastrointestinal tract
 2. Saturable first-pass metabolism
 3. Saturable active renal tubular secretion
 4. Saturable active renal tubular reabsorption
2. Define *saturable first-pass hepatic metabolism*, and describe how this dose-dependent kinetic behavior can be seen after oral administration without observing it after an equivalent i.v. bolus dose.
3. The steady-state plasma concentration of phenylbutazone relative to the dose administered decreased when given orally at anti-inflammatory doses of 200 to 400 mg/day (Fig. 22-22). The drug is primarily bound to albumin.
- a. Draw a line on both graphs of Fig. 22-22 (bottom of p. 420) showing the relationships expected when kinetics are linear.
 - b. Suggest an explanation for the observations, given the additional information that only negligible amounts of phenylbutazone appear in urine and feces at all doses examined.
4. For *each* of the tables on the top of p. 420, indicate *all* of the possibilities in the following list that might explain the dose-dependent kinetics observed for each drug.

List of Explanations

- I. Saturable hepatic metabolism
- II. Saturable renal tubular reabsorption
- III. Saturable renal active secretion
- IV. Saturable plasma protein binding with extraction ratio approaching one in organs of elimination
- V. Saturable plasma protein binding with extraction ratio approaching zero in organs of elimination
- VI. Saturable metabolism during first pass of drug through the intestines or the liver
- VII. Saturable gastrointestinal transport

a.

Table 22-8.

Single oral dose (mg)	300	600	900
Area under blood concentration-time curve (mg·hr/L)	3	10	19

b.

Table 22-9.

Rate of i.v. infusion (mg/hr)	5	10	15
Steady-state plasma concentration (mg/L)	2	6.5	14

c.

Table 22-10. One-Compartment Drug

Single i.v. dose (mg)	50	100	200	400
Initial blood concentration (mg/L)	1.1	2.0	4.3	8.7
Area under blood concentration-time curve (mg·hr/L)	20	55	160	410

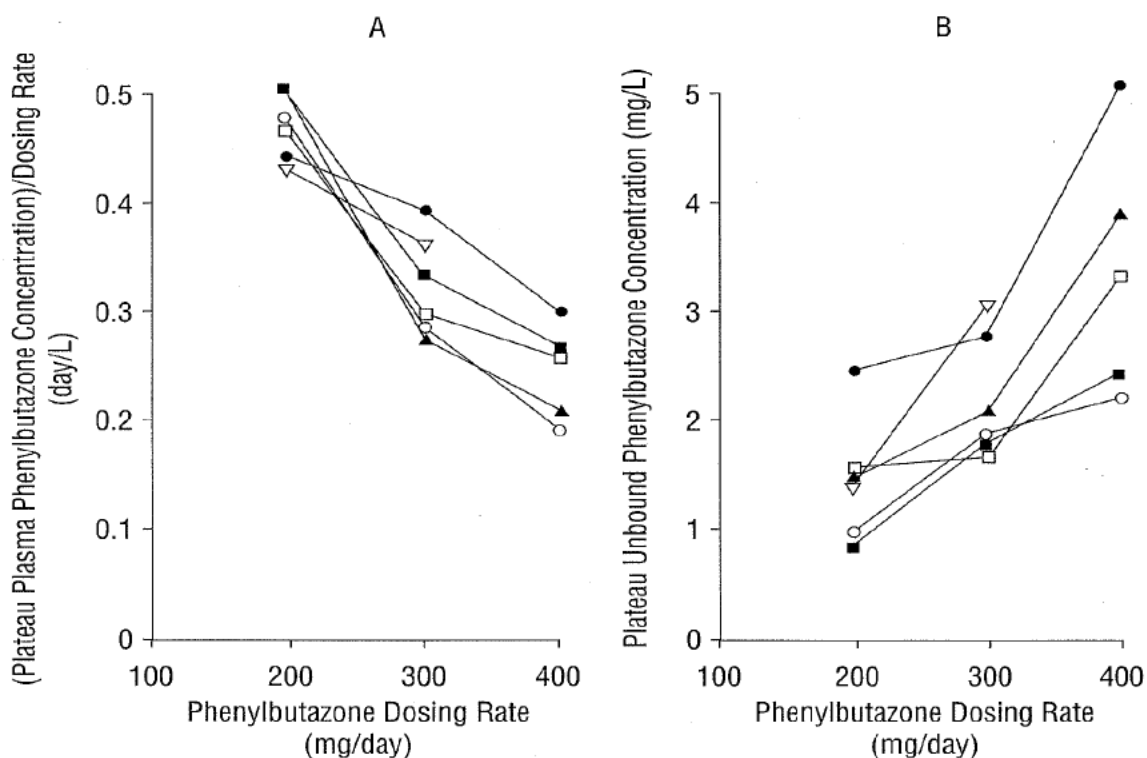


Fig. 22-22. Conditions at plateau for phenylbutazone. Events were monitored in patients receiving increasing daily doses (200 to 400 mg); each dose was maintained for a minimum of 3 weeks. Displayed are the total plasma concentration, normalized to the daily dose administered (A), and the unbound concentration (B) at plateau. Each symbol corresponds to data from one patient (1 mg/L = 3.2 μ M). (Redrawn from Higham, C., Aarons, L.J., Holt, P.J.L., Lynch, M., and Rowland, M.: A chronic dose-ranging study of the pharmacokinetics of phenylbutazone in rheumatoid arthritic patients. *Br. J. Clin. Pharmacol.*, 12:123-129, 1981. Reproduced with permission of Blackwell Scientific Publications.)

5. The relationship between glucose urinary excretion rate and its plasma concentration in a healthy individual is displayed in Table 22–11. Prepare a graph of glucose renal clearance in milliliters per minute as a function of its plasma concentration, and briefly explain the observation.

Table 22–11. Glucose Excretion Rate at Various Plasma Glucose Concentrations

Excretion rate (mg/min)	5	66	151	256	400	520	631
Plasma glucose concentration (g/L)	2.00	3.01	3.98	5.03	6.05	7.08	7.99

6. The data in Table 22–12 were observed for disopyramide (M.W. = 339.5 g/mole) in two different subjects, each receiving various rates of i.v. infusion. Approximately 55% of disopyramide, a basic drug that binds to α_1 -acid glycoprotein, is normally excreted unchanged in urine. The remainder is metabolized.

Based on the information above, give two possible explanations for the dose-dependence of disopyramide clearance.

Table 22–12.

SUBJECT	INFUSION RATE (mg/min)	STEADY-STATE CONCENTRATION (mg/L)
J.J.	0.039	0.70
	0.077	1.15
	0.154	2.01
	0.309	2.48
B.H.	0.08	0.82
	0.16	1.30
	0.32	2.30
	0.64	2.90
	1.05	4.09
	1.94	5.56

7. Table 22–13 is intended to summarize the direction of change expected in the disposition parameters and in total and unbound steady-state blood concentrations of a drug, relative to the rate of i.v. administration, when there is a dose dependency in absorption, distribution, or elimination. Complete the table by indicating $\uparrow$ for increase, $\downarrow$ for decrease, or $\leftrightarrow$ for little or no change.

Table 22–13. Disposition Kinetics and Total and Unbound Steady-State Blood Drug Concentrations as a Function of Dose-Dependency in Each of Several Sources Following Oral and i.v. Administrations

SOURCE OF DOSE DEPENDENCY	DIRECTION OF CHANGE ^a WITH INCREASED TOTAL DAILY DOSE	VOLUME OF ^b DISTRIBUTION	CLEARANCE	HALF-LIFE	[CONCENTRATION RATE OF ADMINISTRATION] ^c	
					TOTAL	UNBOUND
Oral Administration						
Bioavailability	↓	↔				
Absorption rate constant	↓	↔				
Intravenous Administration						
Fraction unbound in blood						
Low extraction ratio drug	↑	↑				
High extraction ratio drug	↑					
Fraction unbound in tissue	↑			↔		
Metabolic clearance	↑			↑		
Renal clearance	↓			↓		

^aOnly one example of each direction of change is shown.

^bThe volume of distribution is at least ten times the blood volume.

^cThe average steady-state total and unbound blood drug concentrations relative to the rate of administration.

8. Four mechanisms that produce dose-dependent kinetics together with supplemental information obtained under linear conditions, are listed below. Graphically show, on the plots requested, the kinetic consequences of each of these mechanisms. Draw a *solid line* for the observation expected when the kinetics are linear and a *dashed line* for the situation in which dose-dependent behavior occurs. General tendencies, rather than specific functionalities, are sought.
- | | Plot Requested |
|---|--|
| a. Saturable first-pass metabolism (oral administration of a single dose) | $\frac{\text{Dose}}{\text{AUC}}$ vs. Dose |
| b. Saturable reabsorption in the renal tubule ($F = 0.9$; $f_e = 0.5$; drug given as single oral dose) | $\frac{\text{Ae}_\infty}{\text{AUC}}$ vs. Dose |
| c. Capacity-limited metabolism ($f_e = 0.01$, drug infused intravenously at a constant rate) | C_{ss} vs. Infusion rate |
| d. Saturable binding to plasma proteins (single oral dose) | C_u vs. C |
9. The data in Fig. 22-7 for dicloxacillin were presented without associated plasma protein binding information (not provided in the article). The renal clearance of the drug, as assessed from $\text{Ae}_\infty/\text{AUC}$, decreased on increasing the dose from 1 to 2 g. Dicloxacillin, a weak acid with a molecular weight of 470 g/mole, is extensively bound to albumin ($f_u = 0.04$ at 10 mg/L) and produces a peak concentration of about 60 mg/L after oral administration of 2 g. Could saturable binding to a plasma protein explain the decrease in $\text{Ae}_\infty/\text{AUC}$ with the larger dose?
10. Table 22-14 lists plasma heparin activity determined by the amount of hexadimethrine bromide required to neutralize heparin activity using thrombin-induced coagulation as an endpoint.

Table 22-14. Heparin Activity in Plasma After Single i.v. Injections of 25 and 75 Units/kg of Heparin on Separate Occasions in a Healthy Subject^a

TIME (min)	DOSE (Units/kg)	HEPARIN ACTIVITY	
		25	75
10		0.313 ^b	—
15		—	0.872
20		0.238	—
30		0.175	—
40		0.106	—
45		—	0.592
60		0.06 ^c	0.420
90		—	0.249
120		—	0.228
150		—	0.161
180		—	0.083

^aModified from Bjornsson, T.D., Wolfram, K.M., and Kitchell, B.B.: Heparin kinetics determined by three assay methods. Clin. Pharmacol. Ther., 31:104-113, 1982.

^bActivity in units/mL.

^cPoint added for didactic purposes.

- Plot both sets of activity-time data on the same semilogarithmic graph.
- Do the data suggest dose-dependent kinetic behavior? If so, which pharmacokinetic parameters appear to be affected?
- Could the kinetic behavior be explained by capacity-limited elimination of the Michaelis-Menten type? Briefly discuss.
- Heparin is a natural heterogeneous mucopolysaccharide consisting of polymeric units of different chain length and chemical composition with molecular weights

ranging from 3,000 to 40,000 g/mole. Could the nonlinear kinetic behavior be explained by the simultaneous assay of multiple components? Briefly discuss.

11. Using the data in Table 12-8 (problem 5 of Chap. 12 Study Problems) together with information in Fig. 22-23, answer the following questions.
 - a. Briefly explain why the apparent *AUC* of (+)-methylphenidate is about 10 to 20 times higher than that for the (–)-isomer (Fig. 22-23A) following a 30-mg oral dose of racemate. Is your explanation consistent with the similar half-lives of the two isomers?
 - b. Is your explanation in “a” consistent with the observed lack of a difference in the *AUC* values of the ritalinic acid metabolites of the respective isomers?
 - c. The ritalinic acid metabolites appear to decline with the same half-life as the (+) and (–) isomers of methylphenidate after the 30-mg dose. How would you account for this observation?
 - d. Explain why the plasma concentration of (–)-ritalinic acid appears to be about 20% higher in the first 2 hr than (+)-ritalinic acid.
 - e. In Fig. 22-23B, the *AUC* of (+)-methylphenidate increases disproportionately with dose of racemate over the range 10 to 40 mg. How do you explain this apparent nonlinearity?

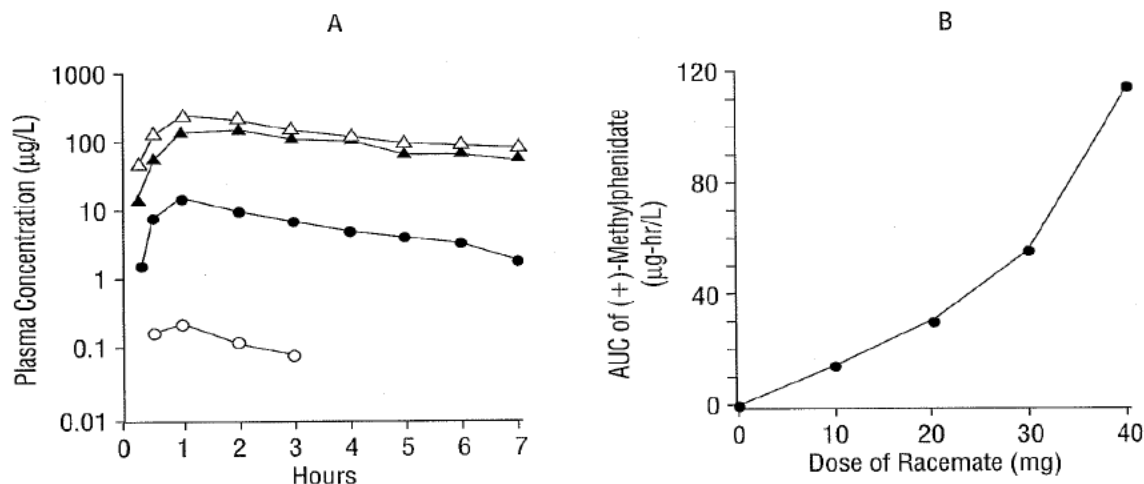


Fig. 22-23. A, The plasma concentrations of (+)-methylphenidate (●), (–)-methylphenidate (○) and their respective metabolites (in color), (+)-ritalinic acid (▲), and (–)-ritalinic acid (△) after the oral administration of 30 mg of racemic methylphenidate hydrochloride to a volunteer. B, The relationship between the *AUC* of (+)-methylphenidate and dose following oral administration of 10, 20, 30, and 40 mg of the racemate to the same volunteer. (Methylphenidate: 1 mg/L = 4.3 μM; ritalinic acid: 1 mg/L = 4.1 μM.) (Adapted from Aoyama, T., Kotaki, H., Sasaki, T., Sawada, Y., Honda, Y., and Iga, T.: Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur. J. Clin. Pharmacol.*, 44:79–84, 1993.)