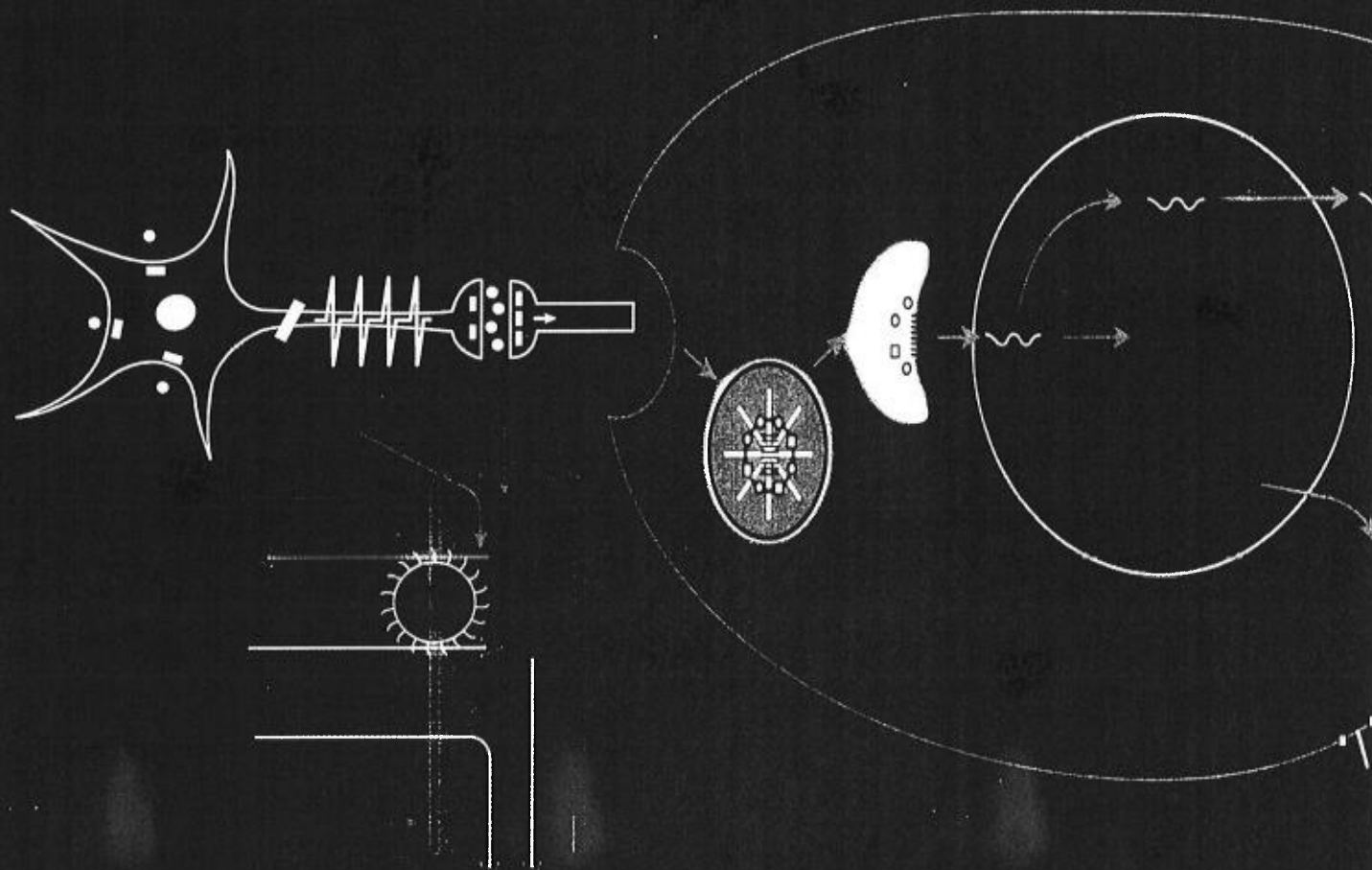


SIXTH EDITION

MODERN PHARMACOLOGY

with Clinical Applications

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Charles R. Craig • Robert E. Stitzel



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EDITION

MODERN PHARMACOLOGY with Clinical Applications

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MODERN PHARMACOLOGY with Clinical Applications

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PREFACE

The sixth edition of *Modern Pharmacology With Clinical Applications* continues our commitment to enlisting experts in pharmacology to provide a textbook that is up-to-date and comprehensive. Designed to be used during a single semester, the book focuses on the clinical application of drugs within a context of the major principles of pharmacology. It is meant to serve students in medicine, osteopathy, dentistry, pharmacy, and advanced nursing, as well as undergraduate students.

SUMMARY OF FEATURES

This edition includes a number of new or updated features that further enhance the appeal of the text.

Study Questions: Each chapter includes five to seven examination questions (following the United States Medical Licensing Examination guidelines) with detailed answers to help students test their knowledge of the covered material.

Case Studies: Appearing at the end of each chapter, case studies present students with real-life examples of

clinical scenarios and require them to apply their knowledge to solve the problem.

Refined Focus: In this edition, we chose to focus more on drug classes rather than on individual drugs, eliminate unnecessary detail such as chemical structures, and maintain emphasis on structure–activity relationships in drug action and development.

Updated Information: This edition also includes new information from the clinic and the laboratory. Emerging information has been added within chapters and when appropriate (as in the case of herbal drugs and erectile dysfunction), through the addition of new chapters.

With these revisions, we hope we have provided a book that is readable, up-to-date, comprehensive but not exhaustive, and accurate—a text that supplies both students and faculty with a clear introduction to modern pharmacotherapeutics.

Charles R. Craig
Robert E. Stitzel

ACKNOWLEDGMENT

The editors began working together on *Modern Pharmacology* almost 25 years ago. We are grateful to be working together still as colleagues and friends and

are very pleased to dedicate this sixth edition to a new generation of students, and to our grandchildren, Kaya Seneca Stitzhal and Andrew, Megan, and Taylor Craig.

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5

Pharmacokinetics

Timothy S. Tracy

Pharmacokinetics is the description of the time course of a drug in the body, encompassing absorption, distribution, metabolism, and excretion. In simplest terms, it can be described as what the body does to the drug. Pharmacokinetic concepts are used during drug development to determine the optimal formulation of a drug, dose (along with effect data), and dosing frequency. For drugs with a wide therapeutic index (difference between the minimum effective dose and the minimum toxic dose), knowledge of the drug's pharmacokinetic properties in that individual patient may not be particularly important. For example, nonsteroidal antiinflammatory drugs, such as ibuprofen, have a wide therapeutic index, and thus knowledge of the pharmacokinetic parameters in a given individual is relatively unimportant, since normal doses can vary from 400 to 3200 mg per day with no substantial difference in acute toxicity or effect. However, for drugs with a narrow therapeutic index, knowledge of that drug's pharmacokinetic profile in an individual patient has paramount importance.

If there is little difference between the minimum effective dose and the toxic dose, slight changes in a drug's pharmacokinetic profile, or even simply interindividual differences, may require dosage adjustments to minimize toxicity or maximize efficacy. For example, the blood concentrations of the antiasthmatic drug theophylline must usually be maintained within the range of 10–20 $\mu\text{g/mL}$. At concentrations below this, patients may not obtain relief of symptoms, while concentrations above 20 $\mu\text{g/mL}$ can result in serious toxicities, such as seizures, arrhythmias, and even death. Thus, a drug's pharmacokinetic profile may have important clinical significance beyond its use in drug development.

DRUG CONCENTRATION–TIME PROFILES AND BASIC PHARMACOKINETIC PARAMETERS

The time course of a drug in the body is frequently represented as a concentration–time profile in which the concentrations of a drug in the body are measured analytically and the results plotted in semilogarithmic form against time. A representative profile of a drug given intravenously is presented in Figure 5.1. Drug concentrations are measured in samples typically taken from the brachial vein, since this vein is readily accessible, since sampling results in minimal patient discomfort and since obtained values reflect the concentrations of drug in the bloodstream. Concentrations in the blood may not be identical to concentrations at the site of action, such as a receptor, but one hopes they serve as a surrogate that correlates in a proportional manner.

Figure 5.1 shows that for a drug given intravenously, maximum concentrations are achieved almost instantaneously, since absorption across membranes is not required, though distributive processes may also occur (not depicted for the sake of simplicity). The concentrations of drug in the blood decline over time according to the elimination rate of that particular drug. More commonly, drug is given via extravascular routes (e.g., orally), so absorption and distribution must occur, and therefore it will take some time before maximum concentrations are achieved.

The blood concentration–time profile for a theoretical drug given extravascularly (e.g., orally) is shown in Figure 5.2. Some pharmacokinetic parameters, such as C_{max} , T_{max} , *area under the curve*, and *half-life*, can be estimated by visual inspection or computation from a con-

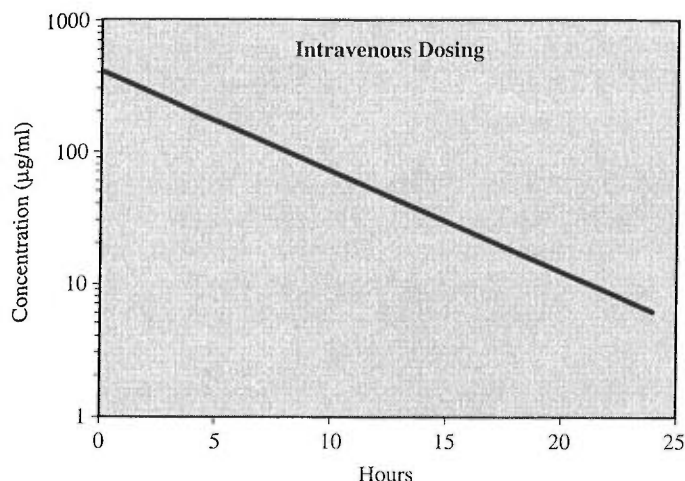


FIGURE 5.1

Concentration–time profile for a hypothetical drug administered intravenously. Following intravenous dosing of a drug, blood concentrations of the drug reach a maximum almost immediately. Y-axis is logarithmic scale.

centration–time profile. $C_{\max}$ is defined as the maximum concentration achieved in the blood. In Figure 5.2, $C_{\max}$ can be estimated to be approximately 225 µg/mL. The other pharmacokinetic parameter that can be easily estimated from a concentration–time profile is $T_{\max}$, or the time needed to reach maximum concentration. In Figure 5.2, the $T_{\max}$ is estimated by visual inspection to be approximately 2 hours. The same drug in a formulation that permits a faster rate of absorption would have a shorter $T_{\max}$ and generally a higher $C_{\max}$ than the formulation with slower absorptive properties. Likewise, all other things being equal, a drug with a slower elimi-

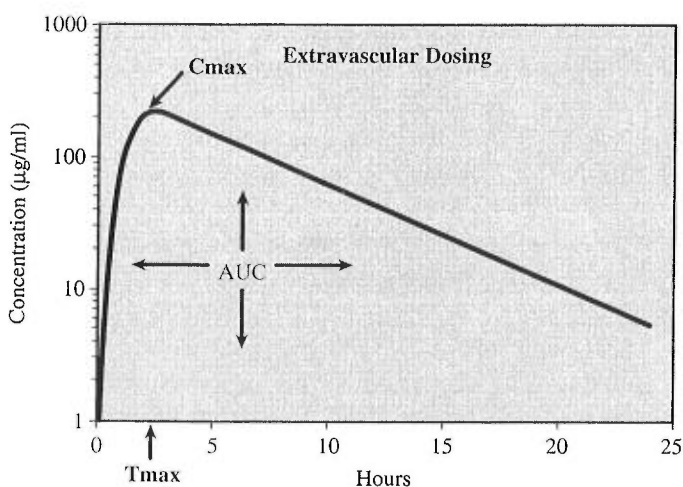


FIGURE 5.2

Concentration–time profile for a hypothetical drug administered extravascularly. $C_{\max}$, maximum concentration achieved. $T_{\max}$, time required to achieve maximum concentration. AUC = Area under the curve. Y-axis is on logarithmic scale.

nation rate will generally exhibit a longer $T_{\max}$ and higher $C_{\max}$. Once administered, a drug begins undergoing absorption, distribution, metabolism, and excretion all at once, not in a sequential fashion, such that all of these processes are involved in determining the shape of a concentration–time profile.

One indicator of the overall exposure of a person to a drug is through the calculation of the *area under the curve* (AUC). As the name implies, AUC is the mathematically integrated area under the concentration–time curve and is most commonly calculated using the trapezoidal rule of mathematics. In Figure 5.2, the AUC is represented by the shaded area. Though the shape of the concentration–time profile may affect the AUC for a drug, two drugs with entirely different concentration–time profile shapes may have the same AUC. It is, in fact, this property that makes calculating the AUC useful, because it can be used to assess the person's overall exposure to a drug, even though the individual may have reached different $T_{\max}$ and $C_{\max}$ values from those of other individuals. Furthermore, as will be discussed shortly, AUC is also useful for calculating another pharmacokinetic parameter, clearance.

An additional parameter that can be determined from a concentration–time profile is the half-life of the drug, that is, the time it takes for half of the drug to be eliminated from the body. Half-life determination is very useful, since it can readily be used to evaluate how long a drug is expected to remain in the body after termination of dosing, the time required for a drug to reach steady state (when the rate of drug entering the body is equal to the rate of drug leaving the body), and often the frequency of dosing. The following equation is used to calculate the half-life of a drug:

$$t_{1/2} = \frac{0.693}{k_e}$$

where $t_{1/2}$ is the half-life and k_e is the elimination rate constant calculated from the slope of the declining portion of the concentration–time profile (Fig. 5.3). By definition, half-life denotes that 50% of the drug in the body at a given time will be eliminated over the calculated period. However, this does not mean that the same *amount* of drug is eliminated each half-life. For example, Figure 5.3 shows that during the first half-life period (0–5 hours) the drug concentration is reduced from 100 µg/mL to 50 µg/mL. However, during the second half-life period (5–10 hours), even though the amount in the body is reduced by 50%, the concentration falls only from 50 µg/mL to 25 µg/mL (a reduction in concentration of 25 µg/mL). This concept is also illustrated in Table 5.1. It takes approximately five half-lives for 97% of the drug to be eliminated from the body (regardless of the duration of the half-life). Thus, if one wished to switch a patient from one drug to another but not have both drugs present in substantial quantities,

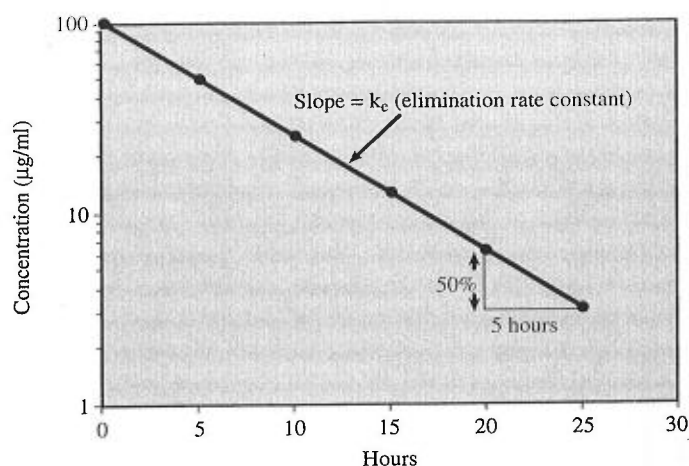


FIGURE 5.3

Elimination of a hypothetical drug with a half-life of 5 hours. The drug concentration decreases by 50% every 5 hours (i.e., $t_{1/2} = 5$ hours). The slope of the line is the elimination rate (k_e).

the clinician must wait five half-lives (in this case, 25 hours) before administering the second drug. It will also require five half-lives for a drug to reach steady state (see Pharmacokinetics of Single Versus Multiple Dosing, later in the chapter), again, independent of the duration of the half-life. Steady state is when the amount of drug entering the body is equal to the amount of drug being eliminated in a given period. Finally, it is a rule of thumb (though certainly not absolute) that drugs are generally dosed every half-life (with allowance for rounding to convenient intervals). Thus, the concept of half-life has considerable importance for determining dosing frequency or adjusting doses in a patient.

ADDITIONAL PHARMACOKINETIC PARAMETERS

Bioavailability

Bioavailability (designated as F) is defined as the fraction of the administered drug reaching the systemic circulation as intact drug. Bioavailability is highly dependent on both the route of administration and the drug formulation. For example, drugs that are given intravenously exhibit a bioavailability of 1, since the entire dose reaches the systemic circulation as intact drug. However, for other routes of administration, this is not necessarily the case.

Subcutaneous, intramuscular, oral, rectal, and other extravascular routes of administration require that the drug be absorbed first, which can reduce bioavailability. The drug also may be subject to metabolism prior to reaching the systemic circulation, again potentially reducing bioavailability. For example, when the β -blocking agent propranolol is given intravenously, $F = 1$, but when it is given orally, $F = \sim 0.2$, suggesting that only approximately 20% of the administered dose reaches the systemic circulation as intact drug.

With respect to the effect of drug formulation on bioavailability, the drug digoxin provides a good example. Given orally as a solution, the bioavailability of digoxin approaches $F = 1$, suggesting essentially complete bioavailability and one that approaches that of the intravenous formulation. Digoxin liquid capsules also exhibit $F = \sim 1$ when given orally and thus are also completely available. However, for digoxin tablets, $F = \sim 0.7$, suggesting incomplete bioavailability, probably because of lack of absorption.

Two types of bioavailability can be calculated, depending on the formulations available and the information required. The gold standard is a calculation of the *absolute* bioavailability of a given product compared to

TABLE 5.1 Elimination Characteristics of a Drug with a 5-Hour Half-life

Concentration at Beginning of Period ^a	Concentration at End of Period ^a	Period (hours)	Percent of Original Concentration
100.00	50.000	0–5	50.000
50.00	25.000	5–10	25.000
25.00	12.500	10–15	12.500
12.50	6.250	15–20	6.250
6.25	3.125	20–25	3.125

Half of the concentration at the beginning of any period is eliminated during the period. Thus, each successive half-life removes less drug, but the concentration at the beginning of the period is reduced by 50% during the period.

^aMicrograms per milliliter.

the intravenous formulation ($F = 1$). The absolute bioavailability of a drug can be calculated as:

$$F = \frac{Dose_{iv} \cdot (AUC_{0-\infty})_{other}}{Dose_{other} \cdot (AUC_{0-\infty})_{iv}}$$

where the route of administration is other than intravenous (e.g., oral, rectal). For calculation of absolute bioavailability, complete concentration-time profiles are needed for both the intravenous and other routes of administration.

The other computation is that of *relative* bioavailability. This calculation is determined when two products are compared to each other, not to an intravenous standard. This is commonly calculated in the generic drug industry to determine that the generic formulation (e.g., a tablet) is bioequivalent to the original formulation (e.g., another tablet). Thus, bioavailability is not routinely calculated in an individual patient but reserved for product development by a drug manufacturer. However, it is important to have an idea of how formulations or routes of administration differ with respect to bioavailability so as to allow proper dosage adjustment when changing formulations or routes of administration.

Clearance

Clearance is a pharmacokinetic parameter used to describe the efficiency of irreversible elimination of drug from the body. More specifically, clearance is defined as the volume of blood from which drug can be completely removed per unit of time (e.g., 100 mL/minute). Clearance can involve both metabolism of drug to a metabolite and excretion of drug from the body. For example, a molecule that has undergone glucuronidation is described as having been cleared, even though the molecule itself may not have left the body. Clearance of drug can be accomplished by excretion of drug into the urine, gut contents, expired air, sweat, and saliva as well as metabolic conversion to another form. However, uptake of drug into tissues does not constitute clearance.

In the broadest sense, total (systemic) clearance is the clearance of drug by all routes. Total (systemic) clearance (Cl) can be calculated by either of the equations given below:

$$Cl = Vd \cdot k_e$$

or

$$Cl = \frac{Dose}{AUC}$$

where Vd is the volume of distribution (see below) and the remainder of the parameters are as defined previously. One must give the drug intravenously to assure 100% bioavailability, because lack of 100% bioavail-

ability can change the dose numerator, which is required to calculate total clearance. Frequently, however, one wishes to calculate drug clearance but intravenous administration is not feasible. In this situation, the apparent clearance (also called oral clearance) can be estimated by the following equation:

$$Cl_{app} = \frac{Dose \cdot F}{AUC}$$

and can be rearranged to give

$$\frac{Cl_{app}}{F} = \frac{Dose}{AUC}$$

The term *apparent clearance* is used because the bioavailability of the compound is unknown. Thus, estimations of apparent clearance will always be higher than the true systemic clearance because of this unknown bioavailability.

The final clearance value that is frequently calculated is that of renal clearance, or that portion of clearance that is due to renal elimination. Renal clearance is calculated as:

$$Cl_r = \frac{Ae}{AUC}$$

where Ae is the total amount of drug excreted unchanged into the urine. Calculation of renal clearance is especially useful for drugs that are eliminated primarily by the kidney.

Because clearance estimates the efficiency of the body in eliminating drug, the calculation of clearance can be especially useful in optimizing dosing of patients. Since this parameter includes both the volume of distribution and the elimination rate, it adjusts for differences in distribution characteristics and elimination rates among people, thus permitting more accurate comparisons among individuals. However, as stated earlier, by far the easiest clearance parameter to estimate is that of apparent (oral) clearance, since it does not require intravenous administration, yet this parameter can be profoundly affected by bioavailability of the drug.

Volume of Distribution

Vd relates a concentration of drug measured in the blood to the total amount of drug in the body. This mathematically determined value gives a rough indication of the overall distribution of a drug in the body. For example, a drug with a Vd of approximately 12 L (i.e., interstitial fluid plus plasma water) is probably distributed throughout extracellular fluid but is unable to penetrate cells. In general, the greater the Vd, the greater the diffusibility of the drug.

The volume of distribution is not an actual volume, since its estimation may result in a volume greater than the volume available in the body (~40 L in a 70-kg

adult). Such a value will result if the compound is bound or sequestered at some *extravascular* site. For example, a highly lipid-soluble drug, such as thiopental, that can be extensively stored in fat depots may have a V_d considerably in excess of the entire fluid volume of the body. Thus, because of their physicochemical characteristics, different drugs can have quite different volumes of distribution in the same person.

The antiinflammatory drug ibuprofen, for example, typically exhibits a volume of distribution of 0.14 L/kg such that for a 70-kg person, the V_d would be 10.8 L. This volume (10.8 L) is approximately equal to the plasma volume of a person that size, suggesting that this drug does not distribute widely into tissues (though it does reach tissues to some degree to exert its action). In contrast, the antiarrhythmic amiodarone has a V_d of 60 L/kg, giving a total V_d of 4200 L for this same 70-kg person. This large V_d suggests that amiodarone distributes widely throughout the body; in fact, it does distribute to various tissues, such as the liver, lungs, eyes, and adipose tissue. Since the total volume of the body does not equal 4200 L, it can clearly be seen that this is not a "real" volume but one that relates the blood concentration to the amount of drug in the body.

Protein Binding

Most drugs bind to plasma proteins such as albumin and α_1 -acid glycoprotein (AGP) to some degree. This becomes clinically important as it is assumed that only unbound (free) drug is available for binding to receptors, being metabolized by enzymes, and eliminated from the body. Thus, the free fraction of drug is important. For example, phenytoin is approximately 90% bound to plasma proteins, leaving 10% of the concentration in the blood as free drug and available for pharmacological action and metabolism. If the presence of renal disease or a drug interaction were to alter the degree of protein binding to only 80%, this change could have substantial clinical consequences. Even though the total percent bound changes relatively little, the net result is to double the amount of free drug. In fact, for phenytoin, this can have clinical consequences. However, for most drugs, displacement from protein binding sites results in only a transient increase in free drug concentration, since the drug is rapidly redistributed into other body water compartments. Thus, interactions or changes in protein binding in most cases have little clinical effect despite these theoretical considerations.

PHARMACOKINETICS OF SINGLE VERSUS MULTIPLE DOSING

Administration of single doses of a drug are occasionally encountered in clinical practice, but it is more common to use single doses to determine the pharmacoki-

netic profile of a drug. Figures 5.1 and 5.2 illustrate such a use of single doses. Following a single dose, concentrations can be monitored until no longer analytically detectable and a complete pharmacokinetic profile is described.

In clinical practice, drugs are more commonly administered in multiple doses, with the second dose usually given before the first dose is completely eliminated. Figure 5.4 shows a representative time-concentration profile for multiple dosing of a drug with a $t_{1/2}$ of 8 hours. With each successive dose up to approximately five doses, the concentration of drug keeps increasing, a phenomenon known as accumulation. The final concentrations of drug reached depend on the elimination rate of the drug, the dosing frequency, and the actual dose. Thus, for a given drug, *concentrations* will reach higher steady-state values if the drug is given more frequently or in greater doses. In contrast, the *time* to reach steady state is affected by neither the dose amount nor dosing frequency. The time to reach steady state is solely affected by the elimination rate (which is reflected in the $t_{1/2}$). Giving a larger dose or giving the dose more often will not change the time needed to reach steady state (except in the case of a bolus dose, as discussed later).

Just as it takes approximately five half-lives for a drug to be essentially (97%) eliminated, it also requires five half-lives for a drug to reach steady state. This is exemplified in the concentration-time profiles of Figure 5.4. The hypothetical drug in this example has a half-life of 8 hours and is dosed every 8 hours. The graph shows that at about 40 hours (five half-lives), the maximum and minimum concentrations become consistent, indi-

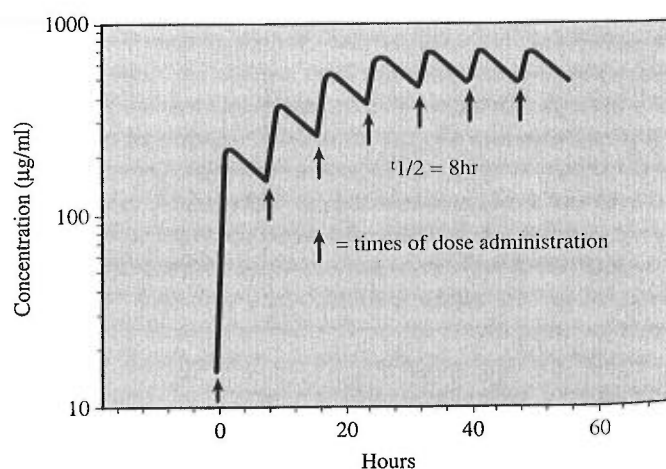


FIGURE 5.4

Concentration-time profile for a hypothetical drug administered orally in multiple doses. The drug is administered once every half-life (i.e., every 8 hours). Drug continues to accumulate (i.e., concentrations rise) until steady state (rate in = rate out) is reached at approximately 5 half-lives (about 40 hours).

cating achievement of a steady state of concentration (drug input = drug elimination).

The only practical method for achieving steady-state concentrations prior to five half-lives is to administer a bolus dose of drug (a dose much higher than normal and designed to bring concentrations up to steady state immediately) followed by standard dosing (Figure 5.5). In this way, the "accumulation" of drug occurs rapidly because of the large amount of drug given initially. However, bolus doses must be calculated in accordance with both the drug's pharmacokinetic parameters and the physiological characteristics of the individual to avoid potential toxicities.

NONLINEAR PHARMACOKINETICS

The underlying assumption in the discussion of these concepts is that the drug of interest follows linear pharmacokinetic principles; that is, the concentrations achieved are proportional to the dose given. For example, a doubling of the dose will produce a doubling of the blood concentration. For some drugs, however, this is not the case: an increase in dose may produce a concentration much greater than expected. For example, increases in dosage of the antiepileptic agent phenytoin above approximately 300 mg daily usually produce a

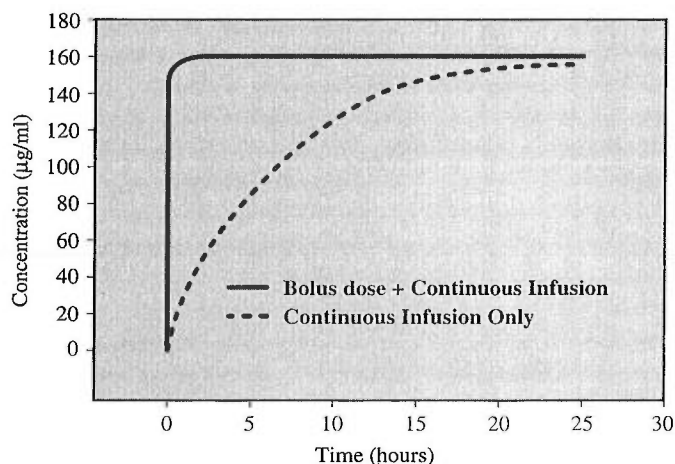


FIGURE 5.5

Theoretical depiction of plasma concentrations following either an intravenous bolus dose immediately followed by initiation of a continuous intravenous infusion or initiation of a continuous intravenous infusion only.

greater than expected increase in blood concentrations. This is illustrated in the graph of Figure 5.6, which shows that for a hypothetical patient, phenytoin blood concentrations are plotted against dose of phenytoin. The graph demonstrates that as one approaches doses that result in therapeutic concentrations of phenytoin, the rise in concentrations becomes nonlinear such that an increase in dose from 300 to 400 mg (33% increase) produces a 300% increase in phenytoin concentration. Thus, it is easy to see how toxicity may arise quickly following what was seemingly a small increase in dose; under linear circumstances such a small increase in dose would have resulted in concentrations still within the therapeutic range. This nonlinearity often occurs because the drug-metabolizing enzymes for the drug become saturated at typical blood concentrations, such that despite increases in dose, drug is still metabolized at the same rate and blood concentrations go up unexpectedly. In this case, following Michaelis-Menten enzyme kinetics, the maximum velocity (V_{max}) has been reached and the rate of drug metabolism remains constant.

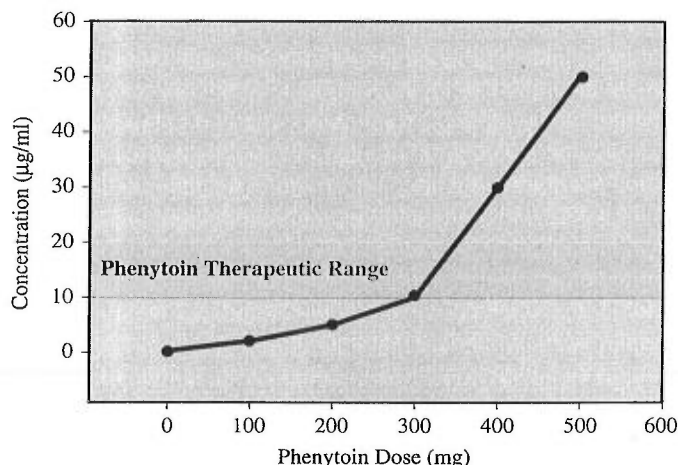


FIGURE 5.6

Theoretical depiction of phenytoin concentrations achieved following various doses of the antiepileptic phenytoin. Shaded area indicates the therapeutic range of phenytoin concentrations: below 10 µg/mL, results in subtherapeutic effect; above 20 µg/mL, results in toxicity. Within the therapeutic range, a relatively small increase in dose results in a greater than proportional increase in concentration, suggesting nonlinear pharmacokinetics.

Study QUESTIONS

- Frequently it is useful to consider the overall exposure of a person to a drug during the dosing interval. Which of the following pharmacokinetic parameters defines the exposure of a person to a drug?
 - $C_{\max}$
 - $T_{\max}$
 - AUC (area under the curve)
 - Half-life
 - Clearance
- Organs such as the liver remove exogenous chemicals, such as drugs, from the body. For drugs such as phenytoin, for which the difference between the minimum effective concentration and the minimum toxic concentration is small, clinicians must calculate the rate at which a given individual removes drug from the body. The volume of fluid from which drug can be completely removed per unit of time (rate of drug removal) is termed:
 - Distribution
 - Clearance
 - Metabolism
 - Excretion
- For a drug such as piroxicam with a 40-hour half-life and being dosed once daily (i.e., every 24 hours), steady state will be reached *shortly following* which DOSE (not which half-life)?
 - 1st dose
 - 3rd dose
 - 5th dose
 - 8th dose
 - 12th dose
- Volume of distribution (V_d), though not a physiological volume, helps a clinician to estimate drug distribution in the body. Drugs distribute throughout the body to differing degrees depending on a number of factors. Which of the following factors is TRUE concerning drug distribution?
 - In general, a drug with a higher degree of plasma protein binding will have a lower volume of distribution.
 - All drugs distribute to the same degree in all tissues.
 - The binding of drugs to tissues has no relationship to the distribution of drug in the body.
 - In general, lipophilic drugs distribute to a lesser extent than hydrophilic drugs.
- A clinician must be concerned with the amount of a drug dose that reaches the systemic circulation, since this will affect the plasma concentration and therapeutic effects observed. The fraction of a dose reaching the systemic circulation as unchanged drug (i.e., intact) is defined as:

- Theoretical dose
- $C_{\max}$
- Bioavailability
- Ideal dose

ANSWERS

- C.** The AUC (area under the curve) best describes the overall exposure of a person to a given drug over the course of the dosing interval. It describes the concentration of drug integrated over the period assessed, usually the dosing interval. A ($C_{\max}$) is not correct, as $C_{\max}$ gives the maximum concentration achieved but does not reveal how long measurable concentrations of the drug were present or how long until this concentration was achieved. B ($T_{\max}$) only refers to the time until the maximum concentration is achieved, again not giving a reference to overall exposure over time. D (half-life) simply describes how much time is required for the concentration to decrease by one-half. Finally, clearance (E) is the volume of fluid (usually plasma) from which drug can be removed per unit of time and as such does not define exposure.
- B.** Clearance is defined as the volume of fluid from which drug is completely removed per unit of time and as such is a measure of the body's ability to remove drug by whatever manner (e.g., elimination, metabolism, excretion). Distribution is the theoretical volume to which the drug distributes and metabolism and excretion are simply methods of clearing drug.
- D.** Approximately five half-lives are required for a drug to reach steady-state concentrations. Since piroxicam has a half-life of 40 hours, it will require approximately 200 hours before steady state is reached. If given every 24 hours, shortly after the 8th dose (192 hours at exactly the 8th dose) steady state will be reached.
- A.** Drugs with a higher degree of plasma protein binding in general have a lower volume of distribution, since the plasma proteins (and thus the drug bound to the plasma protein) tend to stay in the plasma and not distribute to the extravascular tissues. Different drugs can have widely disparate volumes of distribution, so B is incorrect. Tissue binding of drugs is extremely important to drug distribution and can override plasma protein binding, so C is incorrect. Finally, D is incorrect, since in general the more lipophilic a drug is, the greater volume of distribution it has.
- C.** Bioavailability describes the portion of the drug that reaches the systemic circulation without being

metabolized or eliminated. Bioavailability is highly dependent on the drug and the route of administration. $C_{\max}$ (B) is incorrect, since this is only the maximum concentration reached following a dose and gives no measure of the amount reaching the circulation. The other terms (ideal dose and theoretical dose) are fabricated.

SUPPLEMENTAL READING

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Rowland M and Tozer TN. Clinical Pharmacokinetics (3rd ed.). Baltimore: Williams & Wilkins, 1995.

Schumacher GE. Therapeutic Drug Monitoring. Norwalk, CT: Appleton & Lange, 1995.

CASE Study How Long Until My Warfarin Dose Stabilizes?

A 67-year-old woman with atrial arrhythmia has been treated for 3 years with the antiarrhythmic amiodarone 200 mg and the anticoagulant warfarin 10 mg, both daily. The patient began having liver and ocular toxicity due to amiodarone. The physician decided to discontinue amiodarone therapy because of these adverse effects. Upon checkup, a month after discontinuation of amiodarone, the patient's international normalized ratio (INR), a measure of blood clotting, was greatly elevated, placing the patient at risk for bleeding. The physician reduced the dose of warfarin to 7.5 mg daily. The half-life of amiodarone is approximately 35 days. For how long should the physician continue to monitor the INR?

ANSWER: The half-life of amiodarone is 35 days. Approximately five half-lives are required for functionally complete drug elimination. Thus, it will take approximately 6 months (5 half-lives) before the amiodarone is eliminated from the body. Since amiodarone strongly inhibits metabolism of S-warfarin (active enantiomer), it will continue to affect warfarin metabolism for 6 months following discontinuation of amiodarone. Thus, the dose of warfarin will have to be monitored approximately every month and adjusted if necessary. This monthly monitoring should be continued for at least 6 months, until the metabolism of warfarin stabilizes and a constant dose of warfarin can again be maintained.

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