Drug Therapy in Dental Practice: General Principles

Part 1—Pharmacokinetic Considerations

Daniel E. Becker, DDS

Professor of Allied Health Sciences, Sinclair Community College, and Associate Director of Education, General Dental Practice Residency, Miami Valley Hospital, Dayton, Ohio

The fundamental principles that govern drug therapy are often overlooked by the busy clinician. This disregard frequently results in the use of particular drugs and regimens that may be less than ideal for the clinical situation being managed. By convention, these principles are categorized as pharmacokinetic and pharmacodynamic. Pharmacokinetic processes include drug absorption, distribution, biotransformation (metabolism), and elimination, essentially reflecting the influence of the body on the drug administered. Pharmacodynamics deals with the actual mechanisms of action and the effects a drug produces on the patient. This latter topic will be addressed in a future continuing education article.

Key Words: Drug therapy; Pharmacokinetics; Dental pharmacology.

Pharmacokinetic processes are major determinants of the intensity and duration of a drug's effect. The clinician's primary consideration when administering a drug is bioavailability. This refers to the fraction of an administered dose that reaches the systemic circulation or targeted tissue in active form. A drug administered topically on a mucosal lesion or one injected intravenously (IV) will be 100% bioavailable, but a number of variables may reduce the bioavailability of a drug administered by other routes.

ABSORPTION

The process by which a drug enters the circulation is called absorption and in most cases is a simple matter of diffusion; the drug moves from high to low concentration. Concentration of the drug is high at the site of administration and it will diffuse into nearby capillaries, provided that the drug is able to penetrate local tissues presenting as barriers. For example, a drug administered topically on skin must penetrate the epidermis (stratified squamous epithelium) whereas one administered orally (PO) must penetrate the gastric or intestinal mucosa (simple columnar epithelium) to reach the capillaries. In both cases, a drug requires some degree of lipid solubility to facilitate diffusion through these cell membranes. Polar or ionized (charged) molecules are water soluble and therefore are absorbed poorly when administered topically or PO. Water solubility does not hinder absorption as much following intramuscular or subcutaneous injection, because drug molecules are deposited near capillaries and can diffuse between loosely-joined endothelial cells. Obviously, IV administration obviates any requirement for drug absorption. (See Figure 1.)

Systemic serum concentrations, which reflect bioavailability, will vary according to the route by which a drug is administered. Those administered intravenously will produce concentrations that are almost instantaneous and much higher than those following intramuscular injection, which in turn are more rapid and higher than those following PO administration. It's all about perfusion (blood flow) and barriers at the site of administration. If effective serum concentrations are to be achieved, the dose of a drug administered PO is gen-

Received August 28, 2006; accepted for publication September 1, 2006.

Address correspondence to Dr Daniel Becker, Miami Valley Hospital, Dayton, OH 45409; dan.becker@sinclair.edu.

Anesth Prog 53:140–146 2006
© 2006 by the American Dental Society of Anesthesiology
ISSN 0003-3006/06
SSDI 0003-3006(06)

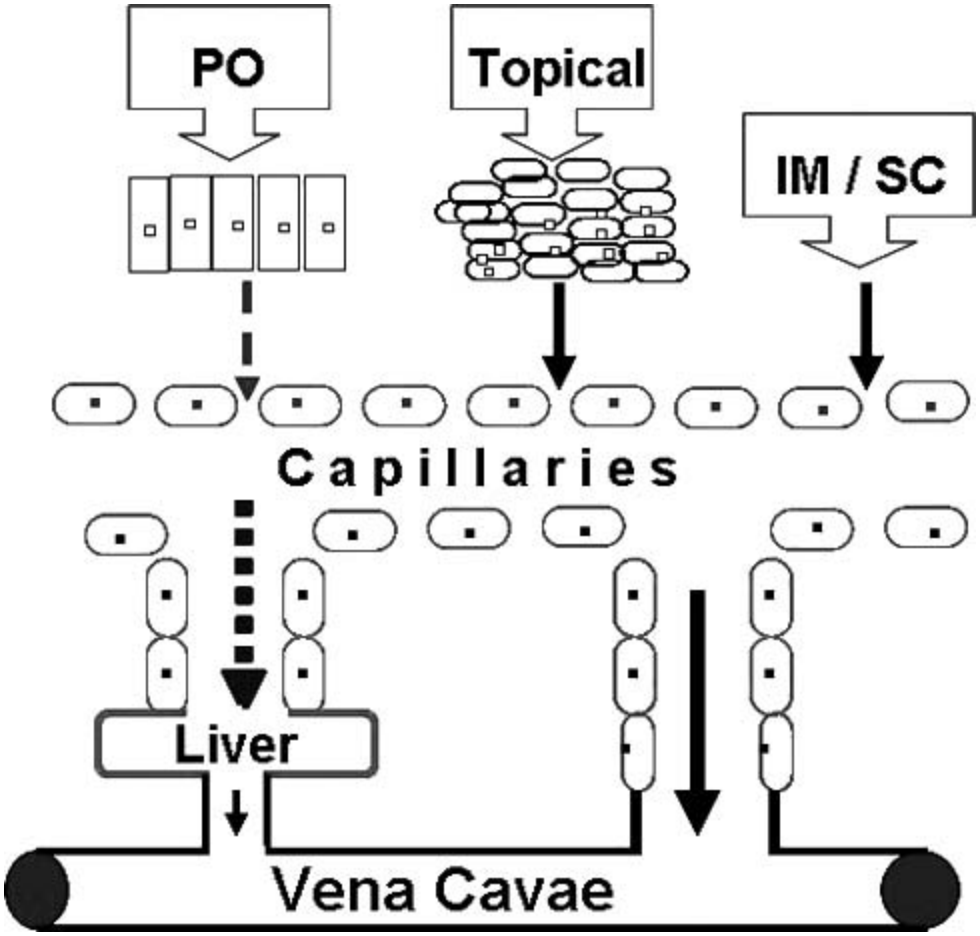

Figure 1. Drug absorption. Following oral (PO) or topical administration, a drug requires lipid solubility in order to diffuse through the epithelium to reach the capillaries. When administered by intramuscular (IM) or subcutaneous (SC) injection, lipid solubility is not required to reach the capillaries. Once absorbed following PO administration, a drug must travel through the portal system to liver before reaching systemic circulation (venae cavae). See text for further explanation.

erally greater than that selected for parenteral routes. Following absorption through gastric or intestinal mucosa into capillaries, a drug is still not bioavailable, because these capillaries lead to the portal system, and the drug must pass through the liver before it gains access to the systemic circulation. This subjects the drug to first-pass metabolism, which reduces its bioavailability if the parent drug is converted to inactive metabolites. Additional reasons for oral-parenteral differences in dose include slow dissolution, poor lipid solubility, binding to foods, and degradation (chemical change) in gastric juices. Drugs absorbed through, or injected into, oral mucous membranes bypass the portal circulation and thereby avoid first-pass metabolism. This is the rationale for administering nitroglycerin tablets under the tongue. When swallowed, nitroglycerin undergoes >90% first-pass metabolism to inactive metabolites. However, topical sublingual administration cannot assure 100% bioavailability, because one cannot ascertain the portion of the drug that is swallowed and subjected to the same processes as those following PO administration. For example, a sublingual dose of triazolam 0.25 mg will exhibit greater bioavailability than when the drug is administered PO, but the precise fraction is conjecture. The issue becomes even more clouded following repeated doses.

DISTRIBUTION

The dispersion of a drug from the bloodstream into body tissues is called distribution. As a drug is absorbed, its concentration in blood, or more precisely in serum, rises, and it will diffuse out of capillaries into tissues. The rate and extent at which a drug is distributed is determined by the degree of a particular tissue's perfusion (blood supply) and the drug's solubility or affinity for the tissue. For example, diazepam and tetracycline undergo

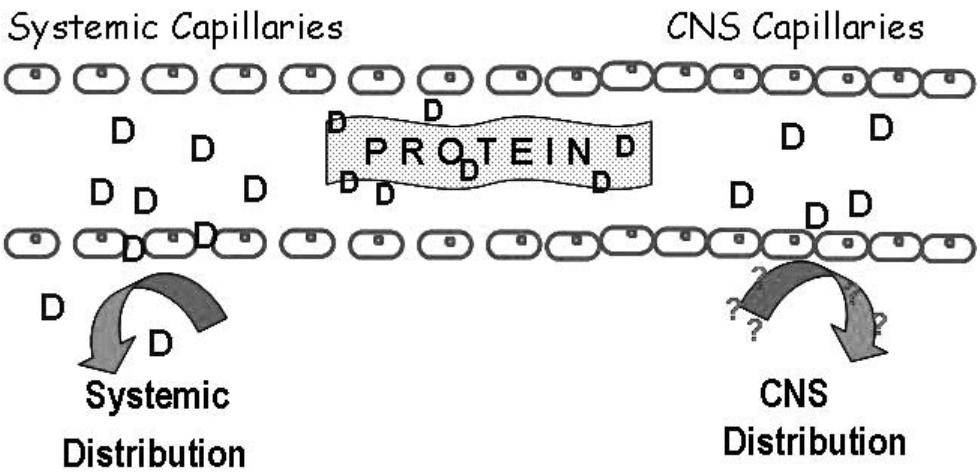

Figure 2. Drug distribution. Drug molecules (D) circulate in blood stream unbound and bound to plasma proteins. Only unbound drug is free to distribute into tissues. Systemically, distribution is a simple matter of diffusion through the loosely-joined endothelium of the capillaries. Distribution to the brain requires lipid solubility because the capillary endothelium is tightly bound and wrapped with astrocytes.

comparable distribution to skeletal muscle, because skeletal muscle is highly perfused. However, diazepam is more soluble in lipid and is distributed better to fatty tissues despite their limited blood supply. Drugs having reasonable lipid solubility, such as sedatives, are distributed in direct relation to perfusion: first to brain, kidney, and liver, followed by muscle and remaining viscera, and finally to adipose tissue and bone.

It is essential to appreciate that a drug concentrated in serum favors diffusion or distribution from capillaries into most tissues, not merely those targeted for the drug effect. However, the nature of a given capillary network may limit this tendency. Capillaries within the central nervous system have tight endothelial junctions and are wrapped by astrocytes.[1] This unique structure is termed the blood-brain barrier, and drugs must have some degree of lipid solubility if they are to distribute into the brain. A similar arrangement of capillary junctions is found in the placenta and limits distribution of water-soluble drugs from the maternal to the fetal tissues. Still, one must assume that fetal tissue is potentially exposed to any medication, regardless of its solubility. For this reason, any drug must be used cautiously during pregnancy. (See Figure 2.)

While in the bloodstream, drugs bind weakly to plasma proteins; they bind and unbind readily as their concentration in serum changes. (See Figure 2.) For example, consider a drug that exhibits 70% protein binding. This means that at any given instant, 70% of all drug molecules circulating in the bloodstream are bound to plasma proteins. At this instant, the fraction of the drug bound to these proteins is trapped or stored within the plasma, and cannot undergo distribution or elimination.[1,2] Only the 30% that is unbound in serum is free to distribute. But as some of the drug molecules leave the bloodstream because of distribution or elimination, 70% of those remaining will be protein-bound. During the research and development of a drug, scientists calculate the percentage of protein binding in order to establish dosage recommendations based on the availability of the unbound drug. However, undesirable interactions can occur if drugs compete with one another for protein binding sites, altering the fraction of the drug that is free to distribute. For example, furosemide (Lasix) can displace warfarin (Coumadin) from plasma protein.[3] This interaction increases the level of free warfarin and may result in serious episodes of hemorrhage.

Diminished amounts of plasma protein available for drug binding may increase the intensity of a drug's effect because more will be available for distribution to the target site. This consideration is generally overstated, especially for geriatric patients, who are frequently more sensitive to drugs than younger patients. Formerly, this was attributed to diminished plasma protein concentration, allowing a greater unbound portion of an administered dose. However, this is relatively insignificant in the otherwise healthy geriatric population.[4] Reasons more plausible for increased sensitivity and residual drug effects in geriatric patients include an age-related reduction in renal and hepatic function, which reduces clearance, and a high proportion of body fat, which tends to retain lipid-soluble drugs.[5]

BIOTRANSFORMATION (METABOLISM)

The term *parent drug* denotes the molecular structure of a drug at the time it is administered. Once absorbed,

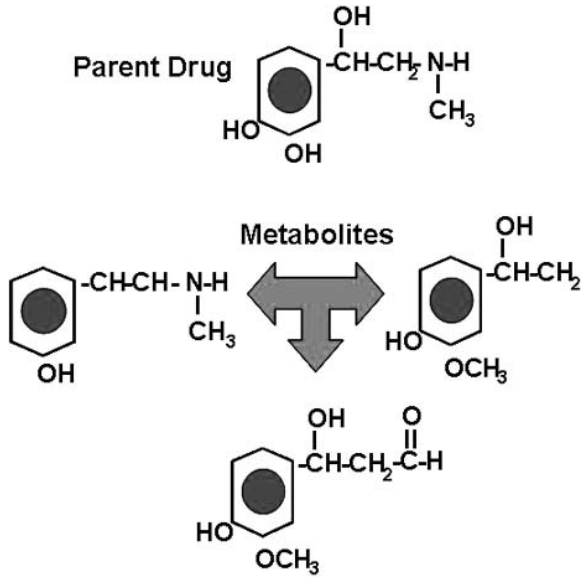

Figure 3. Parent drug and metabolites. Following administration, a parent drug may be converted to any number of metabolites. In this example, the parent drug is converted to 3 separate metabolites. Parent drugs and their metabolites can be active, inactive, toxic, or nontoxic. Furthermore, each has a separate pattern of elimination.

parent drugs may be subjected to chemical change called biotransformation (metabolism), which results in altered molecules called metabolites. (See Figure 3.) The gut wall and liver harbor the greatest concentration of metabolizing enzymes, which are often described as microsomal enzymes because they are concentrated in vesicles within the endoplasmic reticulum of cells. It should be mentioned, however, that enzymes are ubiquitous and catalyze biotransformation at countless additional sites. For example, succinylcholine and articaine are hydrolyzed within the bloodstream by plasma cholinesterases.

Both parent drugs and their metabolites can have varied degrees of pharmacological activity, designated active or inactive, and can also vary in their potential for toxicity. For example, a sedative that is active as a parent drug might be converted to 3 inactive metabolites but also to one that is active and sedative, but another that is active and cardiotoxic. Furthermore, each of these molecular forms can exhibit varied patterns of distribution and elimination. When prescribing or administering a drug, the clinician should be familiar with its particular metabolic profile. Meperidine offers an excellent example. The parent drug is active as an analgesic and has an elimination half-life ($T_{1/2\beta}$) of 2–3 hours, but one of its metabolites, normeperidine, is active as a central nervous system stimulant and has a $T_{1/2\beta}$ of 15–20 hours. Chronic use of this drug (>2 days) will allow accumulation of the toxic metabolite.

Drugs absorbed following PO administration may be subjected to hepatic metabolism before entering the systemic circulation. First-pass metabolism contributes to poor bioavailability when active parent drug is converted to inactive metabolites before it reaches systemic circulation. However, first-pass metabolism is not always a disadvantage. Some parent drugs are inactive and are designated as *prodrugs*. Prodrugs, such as codeine, are generally administered PO so that they are subjected to first-pass conversion to an active metabolite that is therapeutic, eg, codeine is converted to morphine.

Microsomal enzymes responsible for biotransformation of most drugs belong to a large superfamily designated as cytochrome P-450 (CYP). The most important families of CYPs are CYP3A4 and CYP2D6, based on the number of drugs they metabolize respectively.[1,6] (Note on nomenclature: The term cytochrome is derived from the color of liver cells, dark red, attributed to the iron content of the enzymes, and P450 refers to the UV light wavelength absorbed by the enzymes. The numbers and letters following CYP refer to the families and specific genes responsible for synthesis of the particular enzymes.)

Consequences may follow inhibition or induction of CYP activity. Any decrease in microsomal activity, such as that associated with aging or liver disease, warrants a reduction in dosage for most medications. Also, it is not uncommon for patients to receive several medications, often prescribed by different practitioners. This may require that one consult reference texts regarding each drug's influence on microsomal enzyme activity. For example, phenobarbital induces CYP3A4 enzymes to such an extent that the intensity and duration of action for concurrent medications may be significantly reduced. Examples of drug interactions that may impact dental practice are summarized in the Table.

DRUG ELIMINATION

Elimination refers to the removal of the active drug from the bloodstream, and is accomplished by either excretion or metabolism. Active drugs that are water soluble are generally excreted in urine; this is described as renal clearance. Drugs that are lipid soluble are generally biotransformed to water-soluble metabolites, which can then be excreted in urine. However, the liver is credited with the drug's elimination because it removed the active drug by converting it to inactive metabolites. This is described as hepatic clearance. Although inactive metabolites may remain in serum and have not been eliminated per se, the active drug has nevertheless been removed. The term elimination refers to removing active molecules from the bloodstream, not from the body.

Exemplary Drug Interactions Involving Cytochrome P450 Enzymes (CYP)[6,7]

CYP	*Normal Substrates: May Compete With One Another When Taken Concurrently*	*Drugs That May Inhibit the Action of the Designated Enzyme Family*	*Drugs That May Induce the Action of the Designated Enzyme Family*
2D6	To be effective, codeine, hydrocodone, and oxycodone are converted to their principal active metabolites by these enzymes	Cimetidine (Tagamet), fluoxetine (Prozac), paroxetine (Paxil), other SSRIs	Rifampin
3A4	Clarithromycin (Biaxin), erythromycin, alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), alfentanil (Alfenta) and fentanyl are inactivated by these enzymes	Clarithromycin (Biaxin), erythromycin, amiodarone (Cordarone), most protease inhibitors, grapefruit juice	Barbituates, carbamazepine (Tegretol), phenytoin (Dilantin), St. John's wort

Although renal and hepatic patterns of clearance are the primary manners in which active drugs are eliminated, additional mechanisms are also possible. For example, active drugs that remain lipid soluble may be excreted in bile and eliminated fecally, or scant portions of a drug may be excreted in breast milk and should be considered when prescribing for any patient who is nursing an infant.[1] However, these patterns are generally insignificant quantitatively.

The $T_{1/2\beta}$ of a drug is the time required for elimination processes to reduce the concentration in blood by 50%. It should not be confused as representing the time in which half the drug is eliminated. Following 1 half-life, the concentration is reduced to 50%; following a second half-life, it is reduced to 25%; and so on. By convention, the drug is considered as completely eliminated following 4 half-lives.

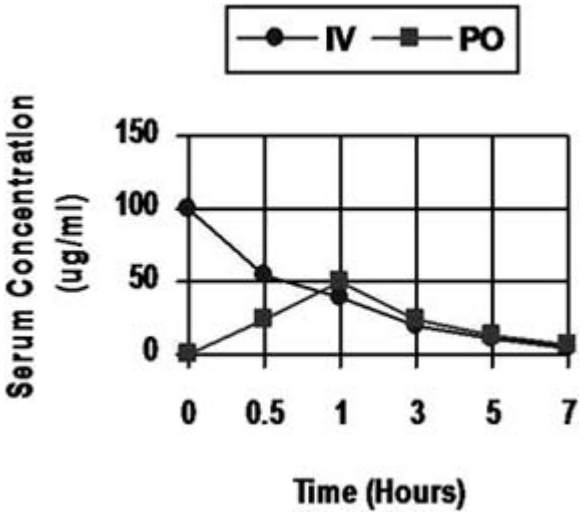

Figure 4. Drug half-life. This graph illustrates the changes in serum concentration of a drug following intravenous (IV) and oral (PO) administration. Following IV administration, the concentration is high within seconds and declines rapidly during the first 30 minutes. This decline is attributed primarily to distribution. Once this process is completed, serum concentration drops more gradually, reflecting elimination. Following PO administration, serum concentration increases as the drug is absorbed, until it peaks in 1 hour. This peak is never as high as that following IV administration because as the drug is absorbed, it is distributed and perhaps eliminated, while the remaining drug is continuing to be absorbed. Starting at 1 hour, however, concentration drops at the same rate regardless of the route by which it was administered. In each case the elimination half-life ($T_{1/2\beta}$) is 2 hours. Following absorption and distribution of drugs, the process of elimination is identical, regardless of how a drug is administered.

Drug half-life is illustrated by using a time-concentration curve (Figure 4). Following an intravenous injection, serum concentration drops rapidly because of distribution before processes of elimination (clearance) commence. (The time for distribution to reduce blood concentration is designated as distribution half-life or $T_{1/2\alpha}$.) A drug administered PO is absorbed slowly from the GI tract and never achieves serum concentrations comparable to those for intravenous administration. Fractions of drug absorbed initially are distributed, and perhaps eliminated, while the remainder is being absorbed. For this reason, serum concentrations never reach those observed following intravenous administration. However, once the processes of absorption and distribution are completed, the pattern of elimination ($T_{1/2\beta}$) is identical, regardless of the route of administration. For the time-concentration curve illustrated in Figure 4, the $T_{1/2\beta}$ is approximately 2 hours. Following a single dose, 4 half-lives must pass before the drug is eliminated entirely. Conversely, steady-state serum concentrations can be achieved following 4 doses, provided that each is administered after 1 half-life.[1] At steady state, the amount of drug administered is identical to the amount of drug eliminated during the defined interval of time. Therefore, information regarding drug half-life is used not only to predict the time required to completely eliminate a drug, but also to guide dosage strategy to sustain steady-state serum concentrations. This latter consideration is not so relevant in dentistry, but can be paramount when managing chronic medical conditions such as osteoarthritis or psychiatric disorders.

A common misconception is that drug half-life can be used to predict duration of drug effect, such as analgesia or sedation. Although the drug continues to be present

in the blood for several half-lives, this does not identify the point at which the concentration falls below that required to sustain an effect. Consider the benzodiazepine sedatives as an example. The half-life for the active parent drug, diazepam (Valium), and its active metabolites ranges from 20 to 80 hours. However, the actual sedative effect following a single dose of diazepam is shorter than that following an equipotent dose of lorazepam (Ativan), whose half-life ranges only from 10 to 20 hours.[8] Diazepam may persist in the body for a longer period, but it doesn't appear to influence the targeted tissue (brain) for this duration, at least not enough for procedural sedation. During intravenous sedation and anesthesia, the distribution half-life of a drug is used to more accurately predict duration of sedation. This, along with other processes, determines a concept referred to as context-sensitive half-time and will be a topic of a future continuing education article in this journal.

Reference texts list drug half-lives in ranges, eg, 2–7 hours, because renal and liver function can vary considerably. Any compromise in renal or liver function will delay clearance and increase the $T_{1/2\beta}$ of a drug. For example, both renal and hepatic clearance is reduced by 50% by age 65.[4,5] Always anticipate longer half-lives for elderly patients and consider that even residual amounts of drug remaining in the system may have some influence on the more fragile members of this population.

REFERENCES

1. Buxton ILO. Pharmacokinetics and pharmacodynamics. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 11th edition. New York, NY: McGraw-Hill; 2006.

2. Wood M. Plasma binding and limitation of drug access to site of action. *Anesthesiology.* 1991;75:721–723.

3. Olin BR, Hebel SK, Dombek CE, eds. *Drug Facts and Comparisons.* 2006 ed. St Louis, MO: Facts and Comparisons, Inc; 2006.

4. Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the elderly. *N Engl J Med.* 1989;321:303–309.

5. Rousseau P. Pharmacologic alterations in the elderly: special considerations. *Hosp Formulary* 1987;22:543–545.

6. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med.* 2005;352:2211–2221.

7. Abramowicz M, ed. Drug Interactions. *Med Lett Drugs Ther.* 2003;45:46–48.

8. Greenblatt DJ. Elimination half–life of drugs: value and limitations. *Annu Rev Med.* 1985;36:421–427.

CONTINUING EDUCATION QUESTIONS

1. A drug injected sublingually will be subjected to all of the following pharmacokinetic processes EXCEPT:
   A. Absorption.
   B. First-pass metabolism.
   C. Distribution.
   D. Elimination.

2. All of the following would be correct regarding a highly lipid-soluble drug compared to one that is water soluble EXCEPT:
   A. It is more likely to undergo renal clearance.
   B. It distributes more easily to the brain.
   C. It is absorbed more efficiently following PO administration.
   D. It distributes more readily to fetal tissues.

3. Danophyline is a prodrug. Ninety-five percent of an administered dose is recovered as the active metabolite in urine, with a $T_{1/2\beta}$ of 5.5 hours. All of the following are correct regarding this drug EXCEPT:
   A. It undergoes renal clearance.
   B. It requires a day for elimination to be completed.
   C. It is likely to be more effective if administered topically sublingually than PO.
   D. It may be less effective for a patient with significant liver disease.

4. All of the following are accurate statements regarding a drug's $T_{1/2\beta}$ EXCEPT:
   A. It can be used to calculate the time until the drug is totally cleared.
   B. It reflects the time for metabolism or excretion to reduce serum concentration by 50%.
   C. It can be used to calculate a dosage schedule to achieve steady-state serum concentrations.
   D. Its principal use is to predict the duration of clinical effect.