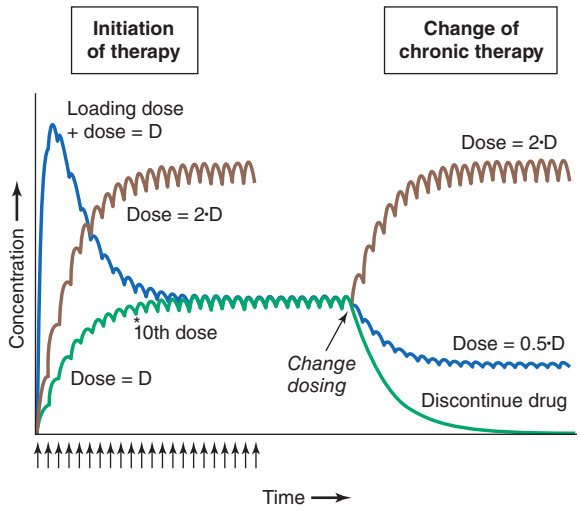

FIGURE 5-4 Drug accumulation to steady state. In this simulation, drug was administered (arrows) at intervals = 50% of the elimination half-life. Steady state is achieved during initiation of therapy after ~5 elimination half-lives, or 10 doses. A loading dose did not alter the eventual steady state achieved. A doubling of the dose resulted in a doubling of the steady state but the same time course of accumulation. Once steady state is achieved, a change in dose (increase, decrease, or drug discontinuation) results in a new steady state in ~5 elimination half-lives. *(Adapted by permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003. Copyright 2003 with permission from Elsevier.)*

Clinical Implications of Drug Distribution In some cases, pharmacologic effects require drug distribution to peripheral sites. In this instance, the time course of drug delivery to and removal from these sites determines the time course of drug effects; anesthetic uptake into the central nervous system (CNS) is an example.

LOADING DOSES For some drugs, the indication may be so urgent that administration of "loading" dosages is required to achieve rapid elevations of drug concentration and therapeutic effects earlier than with chronic maintenance therapy (Fig. 5-4). Nevertheless, the time required for true steady state to be achieved is still determined only by the elimination half-life.

RATE OF INTRAVENOUS ADMINISTRATION Although the simulations in Fig. 5-2 use a single intravenous bolus, this is usually inappropriate in practice because side effects related to transiently very high concentrations can result. Rather, drugs are more usually administered orally or as a slower intravenous infusion. Some drugs are so predictably lethal when infused too rapidly that special precautions should be taken to prevent accidental boluses. For example, solutions of potassium for intravenous administration >20 mEq/L should be avoided in all but the most exceptional and carefully monitored circumstances. This minimizes the possibility of cardiac arrest due to accidental increases in infusion rates of more concentrated solutions.

Transiently high drug concentrations after rapid intravenous administration can occasionally be used to advantage. The use of midazolam for intravenous sedation, for example, depends upon its rapid uptake by the brain during the distribution phase to produce sedation quickly, with subsequent egress from the brain during the redistribution of the drug as equilibrium is achieved.

Similarly, adenosine must be administered as a rapid bolus in the treatment of reentrant supraventricular tachycardias (Chap. 276) to prevent elimination by very rapid ($t_{1/2}$ of seconds) uptake into erythrocytes and endothelial cells before the drug can reach its clinical site of action, the atrioventricular node.

Clinical Implications of Altered Protein Binding Many drugs circulate in the plasma partly bound to plasma proteins. Since only unbound (free) drug can distribute to sites of pharmacologic action, drug response is related to the free rather than the total circulating plasma drug concentration. In chronic kidney or liver disease, protein binding may be decreased and thus drug actions increased. In some situations (myocardial infarction, infection, surgery), acute phase reactants transiently increase drug binding and thus decrease efficacy. These changes assume the greatest clinical importance for drugs that are highly protein-bound since even a small change in protein binding can result in large changes in free drug; for example, a decrease in binding from 99% to 98% doubles the free drug concentration from 1% to 2%. For some drugs (e.g., phenytoin), monitoring free rather than total drug concentrations can be useful.

ELIMINATION

Drug elimination reduces the amount of drug in the body over time. An important approach to quantifying this reduction is to consider that drug concentrations at the beginning and end of a time period are unchanged and that a specific volume of the body has been "cleared" of the drug during that time period. This defines clearance as volume/time. Clearance includes both drug metabolism and excretion.

Clinical Implications of Altered Clearance While elimination half-life determines the time required to achieve steady-state plasma concentration (C_{ss}), the *magnitude* of that steady state is determined by clearance (Cl) and dose alone. For a drug administered as an intravenous infusion, this relationship is:

$$C_{ss} = \text{dosing rate}/Cl \qquad \text{or} \qquad \text{dosing rate} = Cl \cdot C_{ss}$$

When drug is administered orally, the average plasma concentration within a dosing interval ($C_{avg,ss}$) replaces C_{ss}, and the dosage (dose per unit time) must be increased if bioavailability (F) is less than 1:

$$\text{Dose/time} = Cl \cdot C_{avg,ss}/F$$

Genetic variants, drug interactions, or diseases that reduce the activity of drug-metabolizing enzymes or excretory mechanisms lead to decreased clearance and, hence, a requirement for downward dose adjustment to avoid toxicity. Conversely, some drug interactions and genetic variants increase the function of drug elimination pathways, and hence, increased drug dosage is necessary to maintain a therapeutic effect.

ACTIVE DRUG METABOLITES

Metabolites may produce effects similar to, overlapping with, or distinct from those of the parent drug. Accumulation of the major metabolite of procainamide, *N*-acetylprocainamide (NAPA), likely accounts for marked QT prolongation and torsades des pointes ventricular tachycardia (Chap. 276) during therapy with procainamide. Neurotoxicity during therapy with the opioid analgesic meperidine is likely due to accumulation of normeperidine, especially in renal disease.

Prodrugs are inactive compounds that require metabolism to generate active metabolites that mediate the drug effects. Examples include many angiotensin-converting enzyme (ACE) inhibitors, the angiotensin receptor blocker losartan, the antineoplastic irinotecan, the antiestrogen tamoxifen, the analgesic codeine (whose active metabolite morphine probably underlies the opioid effect during codeine administration), and the antiplatelet drug clopidogrel. Drug metabolism has also been implicated in bioactivation of procarcinogens and in generation of reactive metabolites that mediate certain adverse drug effects (e.g., acetaminophen hepatotoxicity, discussed below).

THE CONCEPT OF HIGH-RISK PHARMACOKINETICS

When plasma concentrations of active drug depend exclusively on a single metabolic pathway, any condition that inhibits that pathway (be it disease-related, genetic, or due to a drug interaction) can lead to dramatic changes in drug concentrations and marked variability in drug action. This problem of high-risk pharmacokinetics is especially pronounced in two settings. *First*, variability in bioactivation of a prodrug can lead to striking variability in drug action; examples include decreased CYP2D6 activity, which prevents analgesia by codeine, and decreased CYP2C19 activity, which reduces the antiplatelet effects of clopidogrel. The *second* setting is drug elimination that relies on