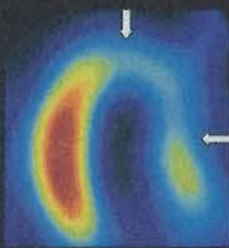


16th Edition



PRINCIPLES OF
**Internal
Medicine**



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Harrison's
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cine is practiced. One of the repeated admonitions of EBM pioneers has been to replace reliance on the local "gray-haired expert" (who may be often wrong but rarely in doubt) with a systematic search for and evaluation of the evidence. But EBM has not eliminated the need for subjective judgments; each systematic review presents the interpretation of an "expert," whose biases remain largely invisible to the consumer of the review. In addition, meta-analyses cannot generate evidence where there are no adequate randomized trials, and most of what clinicians face will never be thoroughly tested in a randomized trial. For the foreseeable future, excellent clinical reasoning skills and experience supplemented by well-designed quantitative tools and a keen appreciation for individual patient preferences will continue to be of paramount importance in the professional life of medical practitioners.

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3 PRINCIPLES OF CLINICAL PHARMACOLOGY

Dan M. Roden

Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among physicians and among the lay community that the outcome of drug therapy varies widely among individuals. While this variability has been perceived as an unpredictable, and therefore inevitable, accompaniment of drug therapy, this is not the case. The goal of this chapter is to describe the principles of clinical pharmacology that can be used for the safe and optimal use of available and new drugs.

Drugs interact with specific target molecules to produce their beneficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two important components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resultant description of the relationship between drug concentration and time is termed *pharmacokinetics*. The second component of variability in drug action comprises the processes that determine variability in drug actions despite equivalent drug delivery to effector drug sites. This description of the relationship between drug concentration and effect is termed *pharmacodynamics*. As discussed further below, pharmacodynamic variability can arise as a result of variability in function of the target molecule itself or of variability in the broad biologic context in which the drug-target interaction occurs to achieve drug effects.

Two important goals of the discipline of clinical pharmacology are (1) to provide a description of conditions under which drug actions vary among human subjects; and (2) to determine mechanisms underlying this variability, with the goal of improving therapy with available drugs as well as pointing to new drug mechanisms that may be effective in the treatment of human disease. The first steps in the discipline were empirical descriptions of the influence of disease X on drug action Y or of individuals or families with unusual sensitivities to adverse drug effects. These important descriptive findings are now being replaced by an understanding of the molecular mechanisms underlying variability in drug actions. Thus, the effects of disease, drug coadministration, or familial factors in modulating drug action can now be reinterpreted as variability in expression or function of specific genes whose products determine pharmacokinetics and pharmacodynamics. Nevertheless, it is the personal interaction of the patient with the physician or other health care provider that first identifies unusual variability in drug actions; maintained alertness to unusual drug responses continues to be a key component of improving drug safety.

Unusual drug responses, segregating in families, have been recognized for decades and initially defined the field of *pharmacogenetics*. Now, with an increasing appreciation of common polymorphisms across the human genome, comes the opportunity to reinterpret de-

scriptive mechanisms of variability in drug action as a consequence of specific DNA polymorphisms, or sets of DNA polymorphisms, among individuals. This approach defines the nascent field of *pharmacogenomics*, which may hold the opportunity of allowing practitioners to integrate a molecular understanding of the basis of disease with an individual's genomic makeup to prescribe personalized, highly effective, and safe therapies.

INDICATIONS FOR DRUG THERAPY It is self-evident that the benefits of drug therapy should outweigh the risks. Benefits fall into two broad categories: those designed to alleviate a symptom, and those designed to prolong useful life. An increasing emphasis on the principles of evidence-based medicine and techniques such as large clinical trials and meta-analyses have defined benefits of drug therapy in specific patient subgroups. Establishing the balance between risk and benefit is not always simple: for example, therapies that provide symptomatic benefits but shorten life may be entertained in patients with serious and highly symptomatic diseases such as heart failure or cancer. These decisions illustrate the continuing highly personal nature of the relationship between the prescriber and the patient.

Some adverse effects are so common, and so readily associated with drug therapy, that they are identified very early during clinical use of a drug. On the other hand, serious adverse effects may be sufficiently uncommon that they escape detection for many years after a drug begins to be widely used. The issue of how to identify rare but serious adverse effects (that can profoundly affect the benefit-risk perception in an individual patient) has not been satisfactorily resolved. Potential approaches range from an increased understanding of the molecular and genetic basis of variability in drug actions to expanded postmarketing surveillance mechanisms. None of these have been completely effective, so practitioners must be continuously vigilant to the possibility that unusual symptoms may be related to specific drugs, or combinations of drugs, that their patients receive.

Beneficial and adverse reactions to drug therapy can be described by a series of dose-response relations (Fig. 3-1). Well-tolerated drugs demonstrate a wide margin, termed the *therapeutic ratio*, *therapeutic index*, or *therapeutic window*, between the doses required to produce a therapeutic effect and those producing toxicity. In cases where there is a similar relationship between plasma drug concentration and effects, monitoring plasma concentrations can be a highly effective aid in managing drug therapy, by enabling concentrations to be maintained above the minimum required to produce an effect and below the concentration range likely to produce toxicity. Such monitoring has been most widely used to guide therapy with specific agents, such as certain antiarrhythmics, anticonvulsants, and antibiotics. Many of the principles in clinical pharmacology and examples outlined below—that can

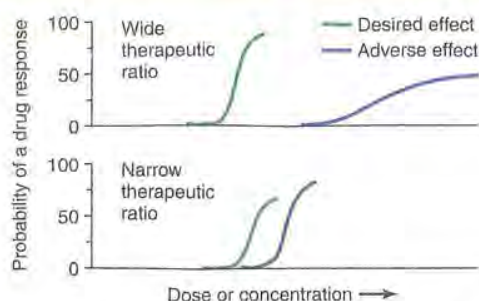


FIGURE 3-1 The concept of a therapeutic ratio. Each panel illustrates the relationship between increasing dose and cumulative probability of a desired or adverse drug effect. *Top.* A drug with a wide therapeutic ratio, i.e., a wide separation of the two curves. *Bottom.* A drug with a narrow therapeutic ratio; here, the likelihood of adverse effects at therapeutic doses is increased because the curves are not well separated. Further, a steep dose-response curve for adverse effects is especially undesirable, as it implies that even small dosage increments may sharply increase the likelihood of toxicity. When there is a definable relationship between drug concentration (usually measured in plasma) and desirable and adverse effect curves, concentration may be substituted on the abscissa. Note that not all patients necessarily demonstrate a therapeutic response (or adverse effect) at any dose, and that some effects (notably some adverse effects) may occur in a dose-independent fashion.

be applied broadly to therapeutics—have been developed in these arenas.

PRINCIPLES OF PHARMACOKINETICS

The processes of absorption, distribution, metabolism, and elimination—collectively termed *drug disposition*—determine the concentration of drug delivered to target effector molecules. Mathematical analysis of these processes can define specific, and clinically useful, parameters that describe drug disposition. This approach allows prediction of how factors such as disease, concomitant drug therapy, or genetic variants affect these parameters, and how dosages therefore should be adjusted. In this way, the chances of undertreatment due to low drug concentrations or adverse effects due to high drug concentrations can be minimized.

BIOAVAILABILITY When a drug is administered intravenously, each drug molecule is by definition available to the systemic circulation. However, drugs are often administered by other routes, such as orally, subcutaneously, intramuscularly, rectally, sublingually, or directly into desired sites of action. With these other routes, the amount of drug actually entering the systemic circulation may be less than with the intravenous route. The fraction of drug available to the systemic circulation by other routes is termed *bioavailability*. Bioavailability may be <100% for two reasons: (1) absorption is reduced, or (2) the drug undergoes metabolism or elimination prior to entering the systemic circulation. Bioavailability (F) is defined as the area under the time-concentration curve (AUC) after a drug dose, divided by AUC after the same dose intravenously (Fig. 3-2A).

Absorption Drug administration by nonintravenous routes often involves an absorption process characterized by the plasma level increasing to a maximum value at some time after administration and then declining as the rate of drug elimination exceeds the rate of absorption (Fig. 3-2A). Thus, the peak concentration is lower and occurs later than after the same dose given by rapid intravenous injection. The extent of absorption may be reduced because a drug is incompletely released from its dosage form, undergoes destruction at its site of administration, or has physicochemical properties such as insolubility that prevent complete absorption from its site of administration.

The rate of absorption can be an important consideration for determining a dosage regimen, especially for drugs with a narrow therapeutic ratio. If absorption is too rapid, then the resulting high concentration may cause adverse effects not observed with a more slowly absorbed formulation. At the other extreme, slow absorption is

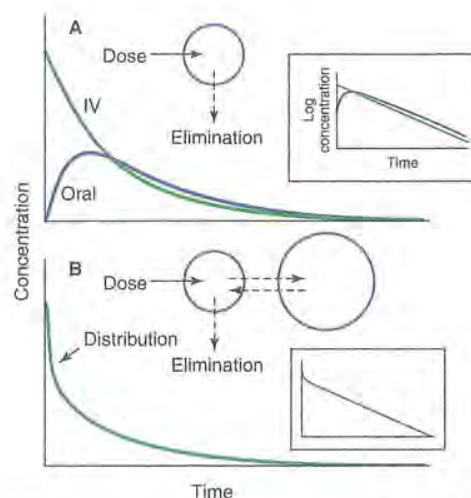


FIGURE 3-2 Idealized time-plasma concentration curves after a single dose of drug. *A.* The time course of drug concentration after an instantaneous intravenous (IV) bolus or an oral dose in the one-compartment model shown. The area under the time-concentration curve is clearly less with the oral drug than the IV, indicating incomplete bioavailability. Note that despite this incomplete bioavailability, concentration after the oral dose can be higher than after the IV dose at some time points. The inset shows that the decline of concentrations over time is linear on a log-linear plot, characteristic of first-order elimination, and that oral and IV drug have the same elimination (parallel) time course. *B.* Note that despite this incomplete bioavailability, concentration when drug is both distributed to and from a peripheral compartment and eliminated from the central compartment. The rapid initial decline of concentration reflects not drug elimination but distribution.

deliberately designed into “slow-release” or “sustained-release” drug formulations in order to minimize variation in plasma concentrations during the interval between doses, because the drug’s rate of elimination is offset by an equivalent rate of absorption controlled by formulation factors (Fig. 3-3).

Presystemic Metabolism or Elimination When a drug is administered orally, it must transverse the intestinal epithelium, the portal venous system, and the liver prior to entering the systemic circulation (Fig. 3-4). At each of these sites, drug availability may be reduced; this mechanism of reduction of systemic availability is termed *presystemic elimination*, or *first-pass elimination*, and its efficiency assessed as extraction ratio. Uptake into the enterocyte is a combination of passive and active processes, the latter mediated by specific drug uptake transport molecules. Once a drug enters the enterocyte, it may undergo metabolism, be transported into the portal vein, or undergo excretion back into the intestinal lumen. Both excretion into the intestinal lumen and metabolism decrease systemic bioavailability. Once a drug passes this enterocyte barrier, it may also undergo uptake (again often by specific uptake transporters such as the organic cation transporter or organic anion transporter) into the hepatocyte, where bioavailability can be further limited by metabolism or excretion into the bile.

The drug transport molecule that has been most widely studied is

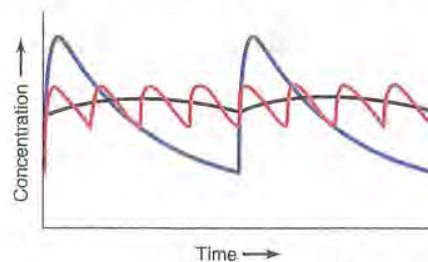


FIGURE 3-3 Concentration excursions between doses at steady state as a function of dosing frequency. With less frequent dosing (blue), excursions are larger; this is acceptable for a wide therapeutic ratio drug (Fig. 3-1). For narrower therapeutic ratio drugs, more frequent dosing (red) may be necessary to avoid toxicity and maintain efficacy. Another approach is use of a sustained-release formulation (black) that in theory results in very small excursions even with infrequent dosing.

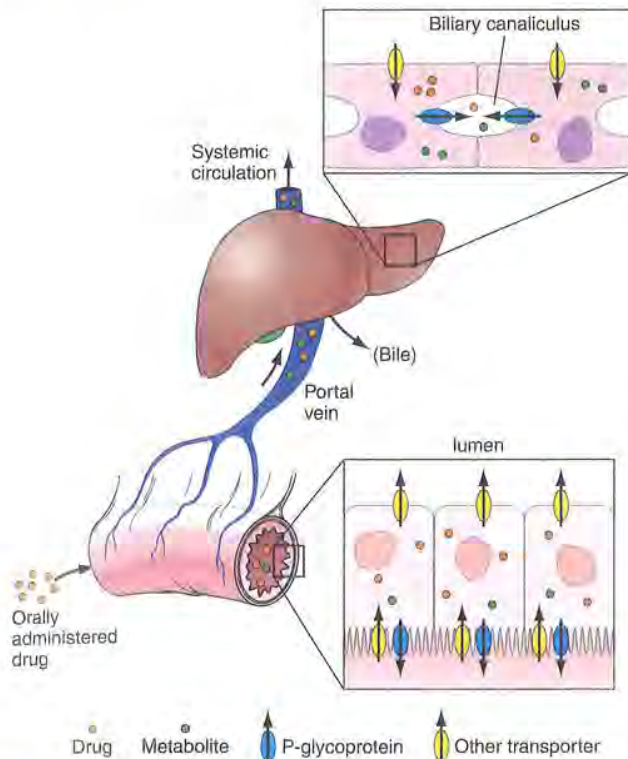


FIGURE 3-4 Mechanism of presystemic clearance. After drug enters the enterocyte, it can undergo metabolism, excretion into the intestinal lumen, or transport into the portal vein. Similarly, the hepatocyte may accomplish metabolism and biliary excretion prior to the entry of drug and metabolites to the systemic circulation. [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.]

P-glycoprotein, the product of the normal expression of the *MDR1* gene. P-glycoprotein is expressed on the apical aspect of the enterocyte and on the canalicular aspect of the hepatocyte (Fig. 3-4); in both locations, it serves as an efflux pump, thus limiting availability of drug to the systemic circulation.

Most drug metabolism takes place in the liver, although the enzymes accomplishing drug metabolism may be expressed, and hence drug metabolism may take place, in multiple other sites, including kidney, intestinal epithelium, lung, and plasma. Drug metabolism is generally conceptualized as "phase I," which generally results in more polar metabolites that are more readily excreted, and "phase II," during which specific endogenous compounds are conjugated to the drugs or their metabolites, again to enhance polarity and thus excretion. The major process during phase I is drug oxidation, generally accomplished by members of the cytochrome P450 (CYP) monooxygenase superfamily. CYPs that are especially important for drug metabolism (Table 3-1) include CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19, CYP1A2, and CYP2E1, and each drug may be a substrate for one or more of these enzymes. The enzymes that accomplish phase II reactions include glucuronyl-, acetyl-, sulfo- and methyltransferases. Drug metabolites may exert important pharmacologic activity, as discussed further below.

Clinical Implications of Altered Bioavailability Some drugs undergo near-complete presystemic metabolism and thus cannot be administered orally. Lidocaine is an example; the drug is well absorbed but undergoes near-complete extraction in the liver, so only lidocaine metabolites (which may be toxic) appear in the systemic circulation following administration of the parent drug. Similarly, nitroglycerin cannot be used orally because it is completely extracted prior to reaching the systemic circulation. The drug is therefore used by the sublingual or transdermal routes, which bypass presystemic metabolism.

Other drugs undergo very extensive presystemic metabolism but can still be administered by the oral route, using much higher doses

than those required intravenously. Thus, a typical intravenous dose of verapamil would be 1 to 5 mg, compared to the usual single oral dose of 40 to 120 mg. Even small variations in the presystemic elimination of very highly extracted drugs such as propranolol or verapamil can cause large interindividual variations in systemic availability and effect. Oral amiodarone is 35 to 50% bioavailable because of poor solubility. Therefore, prolonged administration of usual oral doses by the intravenous route would be inappropriate. Administration of low-dose aspirin can result in exposure of cyclooxygenase in platelets in the portal vein to the drug, but systemic sparing because of first-pass decacylation in the liver. This is an example of presystemic metabolism being exploited to therapeutic advantage.

FIRST-ORDER DISTRIBUTION AND ELIMINATION Most pharmacokinetic processes are first order; i.e., the rate of the process depends on the amount of drug present. In the simplest pharmacokinetic model (Fig. 3-2A), a drug bolus is administered instantaneously to a central compartment, from which drug elimination occurs as a first-order process. The first-order (concentration-dependent) nature of drug elimination leads directly to the relationship describing drug concentration (C) at any time (t) following the bolus:

$$C = (\text{dose}/V_c) \cdot e^{-(0.69/t_{1/2})}$$

where V_c is the volume of the compartment into which drug is delivered and $t_{1/2}$ is elimination half-life. As a consequence of this relationship, a plot of the logarithm of concentration vs time is a straight line (Fig. 3-2A, inset). *Half-life* is the time required for 50% of a first-order process to be complete. Thus, 50% of drug elimination is accomplished after one drug elimination half-life; 75% after two; 87.5% after three, etc. In practice, first-order processes such as elimination are near-complete after four to five half-lives.

In some cases, drug is removed from the central compartment not only by elimination but also by distribution into peripheral compartments. In this case, the plot of plasma concentration vs time after a bolus demonstrates two (or more) exponential components (Fig. 3-2B). In general, the initial rapid drop in drug concentration represents not elimination but drug distribution into and out of peripheral tissues (also first-order processes), while the slower component represents drug elimination; the initial precipitous decline is usually evident with administration by intravenous but not other routes. Drug concentrations at peripheral sites are determined by a balance between drug distribution to and redistribution from peripheral sites, as well as by elimination. Once the distribution process is near-complete (four to five distribution half-lives), plasma and tissue concentrations decline in parallel.

Clinical Implications of Half-Life Measurements The elimination half-life not only determines the time required for drug concentrations to fall to near-immeasurable levels after a single bolus, but it is the key determinant of the time required for steady-state plasma concentrations to be achieved after any change in drug dosing (Fig. 3-5). This applies to the initiation of chronic drug therapy (whether by multiple oral doses or by continuous intravenous infusion), a change in chronic drug dose or dosing interval, or discontinuation of drug. When drug effect parallels drug concentrations, the time required for a change in drug dosing to achieve a new level of effect is therefore determined by the elimination half-life.

During chronic drug administration, a point is reached at which the amount of drug administered per unit time equals drug eliminated per unit time, defining the *steady state*. With a continuous intravenous infusion, plasma concentrations at steady state are stable, while with chronic oral drug administration, plasma concentrations vary during the dosing interval but the time-concentration profile between dosing intervals is stable (Fig. 3-5).

DRUG DISTRIBUTION Distribution from central to peripheral sites, or from extracellular to intracellular sites, can be accomplished by passive mechanisms such as diffusion or by specific drug transport mech-

TABLE 3-1 Molecular Pathways Mediating Drug Disposition^a

Molecule	Substrates ^c	Inhibitors ^c
CYP3A	Calcium channel blockers; antiarrhythmics (lidocaine, quinidine, mexiletine); HMG-CoA reductase inhibitors ("statins"; see text); cyclosporine, tacrolimus; indinavir, saquinavir, ritonavir	Amiodarone; ketoconazole; itraconazole; erythromycin; clarithromycin; ritonavir
CYP2D6 ^b	Timolol, metoprolol, carvedilol; phenformin; codeine; propafenone; flecainide; tricyclic antidepressants; fluoxetine, paroxetine	Quinidine (even at ultralow doses); tricyclic antidepressants; fluoxetine, paroxetine
CYP2C9 ^b	Warfarin; phenytoin; glipizide; losartan	Amiodarone; fluconazole; phenytoin
CYP2C19 ^b	Omeprazole; mephenytoin	
Thiopurine S-methyltransferase ^b	6-Mercaptopurine, azathioprine	
N-acetyl transferase ^b	Isoniazid; procainamide; hydralazine; some sulfonamides	
UGT1A1 ^b	Irinotecan	
Pseudocholinesterase ^b	Succinylcholine	
P-glycoprotein	Digoxin; HIV protease inhibitors; many CYP3A substrates	Quinidine; amiodarone; verapamil; cyclosporine; itraconazole; erythromycin

^a A listing of CYP substrates, inhibitors, and inducers is maintained at <http://medicine.iupui.edu/flockhart/clinlist.html>.

^b Clinically important genetics variants described.

^c Inhibitors affect the molecular pathway and thus may affect substrate.

anisms that are only now being defined at the molecular level. Models such as those shown in Fig. 3-2 allow derivation of a volume term for each compartment. These volumes rarely have any correspondence to actual physiologic volumes, such as plasma volume or total-body water volume. For many drugs the central volume may be viewed conveniently as a site in rapid equilibrium with plasma. Central volumes and volume of distribution at steady state can be used to estimate tissue drug uptake and, in some cases, to adjust drug dosage in disease. In a typical 70-kg human, plasma volume is ~3 L, blood volume is ~5.5 L, and extracellular water outside the vasculature is ~42 L. The volume of distribution of drugs extensively bound to plasma proteins but not to tissue components approaches plasma volume; warfarin is an example. However, for most drugs, the volume of distribution is far greater than any physiologic space. For example, the volume of distribution of digoxin and tricyclic antidepressants is hundreds of liters, obviously exceeding total-body volume. This indicates that these drugs are largely distributed outside the vascular system, and the proportion of the drug present in the plasma compartment is low. As a consequence, such drugs are not readily removed by dialysis, an important consideration in overdose.

Clinical Implications of Drug Distribution Digoxin accesses its cardiac site of action slowly, over a distribution phase of several hours. Thus after an intravenous dose, plasma levels fall but those at the site of action increase over hours. Only when distribution is near-complete does the concentration of digoxin in plasma reflect pharmacologic effect. For this reason, there should be a 6- to 8-h wait after administration before plasma levels of digoxin are measured as a guide to therapy.

Animal models have suggested, and clinical studies are confirming, that limited drug penetration into the brain, the "blood-brain barrier," often represents a robust P-glycoprotein-mediated efflux process from capillary endothelial cells in the cerebral circulation. Thus drug distribution into the brain may be modulated by changes in P-glycoprotein function.

LOADING DOSES For some drugs, the indication may be so urgent that the time required to achieve steady-state concentrations may be too long. Under these conditions, administration of "loading" dosages may result in more rapid elevations of drug concentration to achieve therapeutic effects earlier than with chronic maintenance therapy (Fig. 3-5). Nevertheless, the time required for true steady state to be achieved is still determined only by elimination half-life. This strategy is only appropriate for drugs exhibiting a defined relationship between drug

dose and effect. A loading dose can be estimated from the desired plasma level (C) and the apparent volume of distribution (V):

$$\text{Loading dose} = C \times V$$

Alternatively, the loading amount required to achieve steady-state plasma levels can also be determined if the fraction of drug eliminated during the dosing interval and the maintenance dose are known. For example, if the fraction of digoxin eliminated daily is 35% and the planned maintenance dose is 0.25 mg daily, then the loading dose required to achieve steady-state levels would be $(0.25/0.35) \approx 0.75$ mg.

In congestive heart failure, the central volume of distribution of lidocaine is reduced. Therefore, lower-than-normal loading regimens are required to achieve equivalent plasma drug concentrations and to avoid toxicity.

RATE OF INTRAVENOUS ADMINISTRATION Although the simulations in Fig. 3-2 use a single intravenous bolus, this is very rarely appropriate 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. Thus, administration of a full loading dose of lidocaine (3 to 4 mg/kg) as a single bolus often results transiently in very high concentrations, with a risk of adverse effects such as seizures. Since the distribution half-life of the drug is 8 min, a more appropriate loading regimen is the same dose, administered as two to four divided boluses every 8 min, or a rapid infusion (e.g., 10 mg/min for 20 min).

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

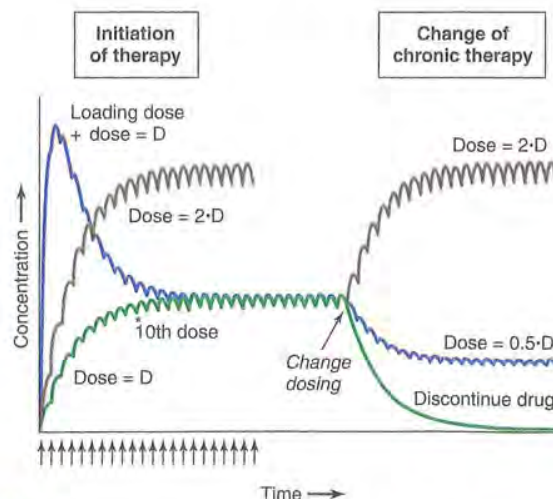


FIGURE 3-5 Drug accumulation to steady state. In this simulation, drug was administered (arrows) at intervals = 50% of the elimination half-life. Steady state is achieved during initiation of therapy after ~5 elimination half-lives, or 10 doses. A loading dose did not alter the eventual steady state 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.]

meq/L should be avoided in all but the most exceptional and carefully monitored circumstances. This minimizes the possibility of cardiac arrest, which can occur as a result of accidental increases in infusion rates of more concentrated solutions.

Procainamide, which is almost totally absorbed after oral administration, can be given orally as a single 1000-mg loading dose with little risk of hypotension. However, administration by the intravenous route is more safely accomplished by giving the dose in fractions of about 100 mg at 5-min intervals or, more conveniently, as a 20-mg/min infusion over 50 min to avoid hypotension during the distribution phase.

As these examples illustrate, excessively rapid administration of many drugs can lead to catastrophic consequences that result from high concentrations in the blood during the distribution phase. In contrast, for some centrally active drugs, the higher concentration of drug during the distribution phase after intravenous administration is 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. 214), 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.

PLASMA 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 most cases, the degree of binding is fairly constant across the therapeutic concentration range; in this case, when plasma drug concentration is used to adjust doses, total levels in plasma can be used without resulting in significant error.

Clinical Implications of Altered Protein Binding For drugs that are normally highly bound to plasma proteins (>90%), small changes in the extent of binding (e.g., due to disease) produce a large change in the amount of unbound drug, and hence drug effect. The acute-phase reactant α_1 -acid glycoprotein binds to basic drugs, such as lidocaine or quinidine, and is increased in a range of common conditions, including myocardial infarction, surgery, neoplastic disease, rheumatoid arthritis, and burns. This increased binding can lead to reduced pharmacologic effects at therapeutic concentrations of total drug. Conversely, conditions such as hypoalbuminemia, liver disease, and renal disease can decrease the extent of drug binding, particularly of acidic and neutral drugs, such as phenytoin. Here, plasma concentration of free drug is increased, so drug efficacy and toxicity are enhanced if total (free + bound) drug is used to monitor therapy.

CLEARANCE When drug is eliminated from the body, the amount of drug in the body declines over time. An important concept in quantifying this reduction is to consider that drug concentration 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 is a measure of the efficiency of drug removal that encompasses both drug metabolism as well as drug excretion.

Clinical Implications of Altered Clearance ■ **ADJUSTING DRUG DOSAGES** While elimination half-life determines the time required to achieve steady-state plasma concentrations (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

$$C_{ss} = \text{dosing rate}/Cl \quad \text{or} \quad \text{dosing rate} = Cl \times C_{ss}$$

When drug is administered orally, the average plasma concentration within a dosing interval ($C_{avg,ss}$) replaces C_{ss} , and bioavailability (F) must be included:

$$F \times \text{dosing rate} = Cl \times C_{avg,ss}$$

Genetic variants, drug interactions, or diseases that reduce the activity of drug-metabolizing enzymes or excretory mechanisms may lead to decreased clearance and hence a requirement for downward dose adjustment to avoid toxicity. Genetic variants may reduce expression of CYPs (or other drug-metabolizing enzymes) or may result in normal expression of enzymes that have reduced function; in either case, dose requirements may need to be reduced. Conversely, some drug interactions and genetic variants increase CYP expression, and hence increased drug dosage may be necessary to maintain a therapeutic effect.

Clearance varies among drugs but is constant for most drugs over the therapeutic range of concentrations. In some cases, elimination becomes saturated at high doses, and the process then occurs at a fixed amount per unit time (zero order). With such nonlinear elimination kinetics, an increase in drug dosage is followed by a disproportionate rise in drug concentration, which can carry a risk of toxicity. Drugs that undergo zero-order elimination at therapeutic dosages include phenytoin, theophylline, and ethanol. Monitoring plasma concentrations of these agents is an indispensable guide to adjusting dose.

THE CONCEPT OF HIGH-RISK PHARMACOKINETICS Many drugs undergo elimination by multiple drug-metabolizing or excretory pathways. In this case, absence of one pathway (due to a genetic variant or drug interaction) may not have a large impact on drug concentrations or drug actions. However, other drugs utilize a single pathway exclusively for drug elimination. Under this scenario, 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 hence effect. Examples of this phenomenon are discussed further below and include digoxin toxicity when P-glycoprotein, the major route of digoxin elimination, is inhibited and potentially fatal bone marrow aplasia due to azathioprine or 6-mercaptopurine in patients with genetically determined absence of function of thiopurine S-methyltransferase (TPMT). A dual-pathway example is the antiarrhythmic flecainide, which is eliminated by both renal excretion and CYP2D6-mediated metabolism. Rare patients with both renal dysfunction and absent CYP2D6 activity (on a genetic basis or because of drug interactions) may develop severe adverse reactions related to high plasma concentrations.

ACTIVE DRUG METABOLITES A major role of drug metabolism is generation of more polar compounds that then readily undergo renal or biliary excretion. From an evolutionary point of view, drug metabolism probably developed as a defense against noxious xenobiotics (foreign substances, e.g., from plants) to which our ancestors inadvertently exposed themselves. The organization of the drug uptake and efflux pumps, and the location of drug metabolism in the intestine and liver prior to drug entry to the systemic circulation (Fig. 3-4), support this idea of a primitive protective function.

However, drug metabolites are not necessarily pharmacologically inactive. Metabolites may produce effects similar to, overlapping with, or distinct from those of the parent drug. For example, *N*-acetylprocainamide (NAPA) is a major metabolite of the antiarrhythmic procainamide. While it exerts antiarrhythmic effects, its electrophysiologic properties differ from those of the parent drug. Indeed, NAPA accumulation is the usual explanation for marked QT prolongation and torsades de pointes ventricular tachycardia (Chap. 214) during therapy with procainamide. Thus, the common laboratory practice of adding procainamide to NAPA concentrations to estimate a total therapeutic effect is inappropriate.

Some drugs are administered in an inactive form and require metabolism to generate active metabolites that mediate the drug effects. Examples include many angiotensin-converting enzyme (ACE) inhibitors and the analgesic codeine (whose active metabolite morphine probably underlies the opioid effect during codeine administration). Codeine and procainamide metabolism are also variable on a genetic basis, further contributing to variability in drug effects. Drug metab-

olism 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).

PRINCIPLES OF PHARMACODYNAMICS

Once a drug accesses a molecular site of action, it alters the function of that molecular target, with the ultimate result of a drug effect that the patient or physician can perceive. For drugs used in the urgent treatment of acute symptoms, little or no delay is anticipated (or desired) between the drug-target interaction and the development of a clinical effect. Examples include vascular thrombosis, shock, malignant hypertension, status epilepticus, or arrhythmias. For many conditions, however, the indication for therapy is less urgent, and in fact a delay between the interaction of a drug with its pharmacologic target(s) and a clinical effect is common. Pharmacokinetic mechanisms that can contribute to such a delay include uptake into peripheral compartments or generation and accumulation of active metabolites. A common pharmacodynamic mechanism is that the clinical effect develops as a downstream consequence of the initial molecular effect the drug produces. Thus, administration of a proton-pump inhibitor or an H_2 -receptor blocker produces an immediate increase in gastric pH but ulcer healing that is delayed. Cancer chemotherapy inevitably produces delayed therapeutic effects, often long after drug is undetectable in plasma and tissue. Translation of a molecular drug action to a clinical effect can thus be highly complex and dependent on the details of the pathologic state being treated. These complexities have made pharmacodynamics and its variability less amenable than pharmacokinetics to rigorous mathematical analysis. Nevertheless, some clinically important principles can be elucidated.

A therapeutic drug effect assumes the presence of underlying pathophysiology. Thus, a drug may produce no action, or a different spectrum of actions, in unaffected individuals compared to patients. Further, concomitant disease can complicate interpretation of response to drug therapy, especially adverse effects. For example, increasing dyspnea in a patient with chronic lung disease receiving amiodarone therapy could be due to drug, underlying disease, or an intercurrent cardiopulmonary problem. Thus the presence of chronic lung disease, and interpretation of the symptom of increasing dyspnea, is one factor that should be considered in selection of antiarrhythmic therapies. Similarly, high doses of anticonvulsants such as phenytoin may cause neurologic symptoms, which may be confused with the underlying neurologic disease.

The concept that a drug interacts with a specific molecular receptor does not imply that the drug effect will be constant over time, even if stable drug and metabolite concentrations are maintained. The drug-receptor interaction occurs in a complex biologic milieu that itself can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and antiarrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or ischemia. Thus, the effects of these drugs may vary depending on the external milieu. Receptors may be up- or downregulated by disease or by the drug itself. For example, β -adrenergic blockers upregulate β -receptor density during chronic therapy. While this effect does not usually result in resistance to the therapeutic effect of the drugs, it may produce severe β agonist-mediated effects (such as hypertension or tachycardia) if the blocking drug is abruptly withdrawn.

PRINCIPLES OF DOSE SELECTION

The desired goal of therapy with any drug is to maximize the likelihood of a beneficial effect while minimizing the risk of adverse effects. Previous experience with the drug, in controlled clinical trials or in postmarketing use, defines the relationships between dose (or plasma concentration) and these dual effects and provides a starting point for initiation of drug therapy.

Figure 3-1 illustrates the relationships among dose, plasma con-

centrations, efficacy, and adverse effects and carries with it several important implications:

1. *The target drug effect should be defined when drug treatment is started.* With some drugs, the desired effect may be difficult to measure objectively, and the onset of efficacy can be delayed for weeks or months; drugs used in the treatment of cancer and psychiatric disease are examples. Sometimes, a drug is used to treat a symptom, such as pain or palpitations, and here it is the patient who will report whether the selected dose is effective. In yet other settings, such as anticoagulation or hypertension, the desired response is readily measurable.

2. *The nature of anticipated toxicity often dictates the starting dose.* If side effects are minor, it may be acceptable to start at a dose highly likely to achieve efficacy and downtitrate if side effects occur. However, this approach is rarely if ever justified if the anticipated toxicity is serious or life-threatening; in this circumstance, it is more appropriate to initiate therapy with the lowest dose that may produce a desired effect.

3. *The above considerations do not apply if these relationships between dose and effects cannot be defined.* This is especially relevant to some adverse drug effects (discussed in further detail below) whose development is not readily related to drug dose.

4. *If a drug dose does not achieve its desired effect, a dosage increase is justified only if toxicity is absent and the likelihood of serious toxicity is small.* For example, a small percentage of patients with strong seizure foci require plasma levels of phenytoin $>20 \mu\text{g/mL}$ to control seizures. Dosages to achieve this effect may be appropriate, if tolerated. Conversely, clinical experience with flecainide suggests that levels $>1000 \text{ ng/mL}$, or dosages $>400 \text{ mg/d}$, may be associated with an increased risk of sudden death; thus dosage increases beyond these limits are ordinarily not appropriate, even if the higher dosage appears tolerated.

Other mechanisms that can lead to failure of drug effect should also be considered; drug interactions and noncompliance are common examples. This is one situation in which measurement of plasma drug concentrations, if available, can be especially useful. Noncompliance is an especially frequent problem in the long-term treatment of diseases such as hypertension and epilepsy, occurring in $\geq 25\%$ of patients in therapeutic environments in which no special effort is made to involve patients in the responsibility for their own health. Multidrug regimens with multiple doses per day are especially prone to noncompliance.

Monitoring response to therapy, by physiologic measures or by plasma concentration measurements, requires an understanding of the relationships between plasma concentration and anticipated effects. For example, measurement of QT interval is used during treatment with sotalol or dofetilide to avoid marked QT prolongation that can herald serious arrhythmias. In this setting, evaluating the electrocardiogram at the time of anticipated peak plasma concentration and effect (e.g., 1 to 2 h postdose at steady state) is most appropriate. Maintained high aminoglycoside levels carry a risk of nephrotoxicity, so dosages should be adjusted on the basis of plasma concentrations measured at trough (predose). On the other hand, ensuring aminoglycoside efficacy is accomplished by adjusting dosage so that peak drug concentrations are above a minimal antibacterial concentration. For dose adjustment of other drugs (e.g., anticonvulsants, antiarrhythmics), concentration should be measured at its lowest during the dosing interval, just prior to a dose at steady state (Fig. 3-5), to ensure a maintained therapeutic effect.

CONCENTRATION OF DRUGS IN PLASMA AS A GUIDE TO THERAPY Factors such as interactions with other drugs, disease-induced alterations in elimination and distribution, and genetic variation in drug disposition combine to yield a wide range of plasma levels in patients given the same dose. Hence, if a predictable relationship can be established between plasma drug concentration and beneficial or adverse drug effect, measurement of plasma levels can provide a valuable tool to guide selection of an optimal dose. This is particularly true when there is a narrow range between the plasma levels yielding therapeutic and adverse ef-

fects, as with digoxin, theophylline, some antiarrhythmics, aminoglycosides, cyclosporine, and anticonvulsants. The common situation of first-order elimination implies that average, maximum, and minimum steady-state concentrations are related linearly to the dosing rate. Accordingly, the maintenance dose may be adjusted on the basis of the ratio between the desired and measured concentrations *at steady state*; for example if a doubling of the steady-state plasma concentration is desired, the dose should be doubled.

For drugs that have zero-order kinetics (e.g., phenytoin and theophylline), plasma concentrations change disproportionately more than the alteration in the dosing rate. In this situation, changes in dose should be small to minimize the degree of unpredictability, and plasma concentration monitoring should be used to ensure that dose modification achieves the desired level.

DETERMINATION OF MAINTENANCE DOSE An increase in dosage is usually best achieved by changing the drug dose but not the dosing interval, e.g., by giving 200 mg every 8 h instead of 100 mg every 8 h. However, this approach is acceptable only if the resulting maximum concentration is not toxic and the trough value does not fall below the minimum effective concentration for an undesirable period of time. Alternatively, the steady state may be changed by altering the frequency of intermittent dosing but not the size of each dose. In this case, the magnitude of the fluctuations around the average steady-state level will change—the shorter the dosing interval, the smaller the difference between peak and trough levels (Fig. 3-3).

Fluctuation within a dosing interval is determined by the relationship between the dosing interval and the drug's half-life. If the dosing interval is equal to the drug's half-life, fluctuation is about twofold, which is usually acceptable. With drugs that have a low therapeutic ratio, dosage changes should be conservative (<50% dose change) and not more frequent than every three to four half-lives. Other drugs, such as many antihypertensives, have little dose-related toxicity so the therapeutic ratio is large. Even if drug is eliminated rapidly, it can be given infrequently. Thus, 75 mg of captopril will result in reduced blood pressure for up to 12 h, even though captopril elimination half-life is about 2 h; this is because the dose raises the concentration of drug in plasma many times higher than the threshold for its pharmacologic effect.

EFFECTS OF DISEASE ON DRUG CONCENTRATION AND RESPONSE

RENAL DISEASE Renal excretion of parent drug and metabolites is generally accomplished by glomerular filtration and by specific drug transporters, only now being identified. If a drug or its metabolites are primarily excreted through the kidneys and increased drug levels are associated with adverse effects, drug dosages must be reduced in patients with renal dysfunction to avoid toxicity. The antiarrhythmics dofetilide and sotalol undergo predominant renal excretion and carry a risk of QT prolongation and arrhythmias if doses are not reduced in renal disease. Thus, in end-stage renal disease, sotalol can be given as 40 mg after dialysis (every second day), compared to the usual daily dose, 80 to 120 mg every 12 h. The narcotic analgesic meperidine undergoes extensive hepatic metabolism, so that renal failure has little effect on its plasma concentration. However, its metabolite, normeperidine, does undergo renal excretion, accumulates in renal failure, and probably accounts for the signs of central nervous system excitation, such as irritability, twitching, and seizures, that appear when multiple doses of meperidine are administered to patients with renal disease. Protein binding of some drugs (e.g., phenytoin) may be altered in uremia, so measuring free drug concentration may be desirable.

In non-end-stage renal disease, changes in renal drug clearance are generally proportional to those in creatinine clearance, which may be measured directly or estimated from the serum creatinine (Chap. 259). This estimate, coupled with the knowledge of how much drug is normally excreted renally vs nonrenally, allows an estimate of the dose adjustment required. In practice, most decisions involving dosing adjustment in patients with renal failure use published recommended adjustments in dosage or dosing interval based on the severity of renal

dysfunction indicated by creatinine clearance. Any such modification of dose is a first approximation and should be followed by plasma concentration data (if available) and clinical observation to further optimize therapy for the individual patient.

LIVER DISEASE In contrast to the predictable decline in renal clearance of drugs in renal insufficiency, the effects of hepatitis or cirrhosis on drug disposition range from impaired to increased drug clearance, in an unpredictable fashion. Standard tests of liver function are not useful in adjusting doses. First-pass metabolism may decrease, and thus oral bioavailability increase, as a consequence of disrupted hepatocyte function, altered liver architecture, and portacaval shunts. The oral availability for high-first-pass drugs such as morphine, meperidine, midazolam, and nifedipine is almost doubled in patients with cirrhosis, compared to those with normal liver function. Therefore, the size of the oral dose of such drugs should be reduced in this setting.

HEART FAILURE AND SHOCK Under conditions of decreased tissue perfusion, the cardiac output is redistributed to preserve blood flow to the heart and brain at the expense of other tissues (Chap. 216). As a result, drugs may be distributed into a smaller volume of distribution, higher drug concentrations will be present in the plasma, and the tissues that are best perfused (the brain and heart) will be exposed to these higher concentrations. If either the brain or heart is sensitive to the drug, an alteration in response will occur. As well, decreased perfusion of the kidney and liver may impair drug clearance. Thus, in severe congestive heart failure, in hemorrhagic shock, and in cardiogenic shock, response to usual drug doses may be excessive, and dosage reduction may be necessary. For example, the clearance of lidocaine is reduced by about 50% in heart failure, and therapeutic plasma levels are achieved at infusion rates only about half those usually required. The volume of distribution of lidocaine is also reduced, so loading regimens should be reduced.

DRUG USE IN THE ELDERLY Aging results in changes in organ function, especially of the organs involved in drug disposition. Therefore, pharmacokinetics are often different in elderly individuals than in younger adults. In the elderly, multiple pathologies and medications used to treat them result in more drug interactions and adverse effects.

Even in the absence of kidney disease, renal clearance may be reduced by 35 to 50% in elderly patients. Dosage adjustments are therefore necessary for drugs that are eliminated mainly by the kidneys. Because muscle mass and therefore creatinine production are reduced in older individuals, a normal serum creatinine concentration can be present even though creatinine clearance is impaired; dosages should be adjusted on the basis of creatinine clearance, as discussed above. Aging also results in a decrease in the size of and blood flow to the liver and possibly in the activity of hepatic drug-metabolizing enzymes; accordingly, the hepatic clearance of some drugs is impaired in the elderly. As with liver disease, these changes are not readily predicted.

Elderly patients may display altered drug sensitivity. Examples include increased analgesic effects of opioids, increased sedation from benzodiazepines and other CNS depressants, and increased risk of bleeding while receiving anticoagulant therapy, even when clotting parameters are well controlled. Exaggerated responses to cardiovascular drugs are also common because of the impaired responsiveness of normal homeostatic mechanisms. Conversely, the elderly display decreased sensitivity to β -adrenergic receptor blockers.

Adverse drug reactions are especially common in the elderly, because of altered pharmacokinetics and pharmacodynamics, the frequent use of multidrug regimens, and concomitant disease. For example, use of long half-life benzodiazepines is linked to the occurrence of hip fractures in elderly patients, perhaps reflecting both a risk of falls from these drugs (due to increased sedation) and the increased incidence of osteoporosis in elderly patients. In population surveys of the noninstitutionalized elderly, as many as 10% had at least one adverse drug reaction in the previous year.

Accordingly, optimization of drug therapy in the elderly, particularly in frail patients, is often difficult, as these multiple factors accentuate interindividual variability in drug response. Initial doses should be less than the usual adult dosage and should be increased slowly. The number of medications, and doses per day, should be kept as low as possible.

GENETIC DETERMINANTS OF THE RESPONSE TO DRUGS

PRINCIPLES OF GENETIC VARIATION AND HUMAN TRAITS (See also Chap. 58)

Variants in the human genome resulting in variation in level of expression or function of molecules important for pharmacokinetics and pharmacodynamics are increasingly recognized. These may be mutations (very rare variants, often associated with disease) or polymorphisms, variants that are much more common in a population. Variants may occur at a single nucleotide or involve insertion or deletion of one or more nucleotides. They may be in the exons (coding regions) or introns. Exonic polymorphisms may or may not alter the encoded protein, and variant proteins may or may not display altered function. Similarly, polymorphisms in intronic regions (including those that regulate gene expression) may or may not alter protein level.

As variation in the human genome is increasingly well documented, associations are being described between polymorphisms and various traits (including response to drug therapy). Some of these rely on well-developed chains of evidence, including in vitro studies demonstrating variant protein function, familial aggregation of variant allele with the trait, and association studies in large populations. In other cases, the associations are less compelling. Identifying "real" associations is one challenge that must be overcome before genomics, and in particular the concept of genotyping to identify optimal drugs (or dosages) in individual patients prior to prescribing, can be considered for widespread clinical practice. Nevertheless, the appeal of this approach is considerable.

Rates of drug efficacy and adverse effects often vary among ethnic groups. Many explanations for such differences are plausible; genomic approaches have now established that functionally important variants determining differences in drug response often display differing distributions among ethnic groups. This finding may have importance for drug use among ethnic groups, as well as in drug development.

GENETICALLY DETERMINED DRUG DISPOSITION AND VARIABLE EFFECTS The concept that genetically determined variations in drug metabolism might be associated with variant drug levels, and hence effect, was advanced at the end of the nineteenth century, and the first examples of familial clustering of unusual drug responses due to this mechanism were noted in the mid-twentieth century. Clinically important genetic variants have been described in multiple molecular pathways of drug disposition (Table 3-1). These variants are identified either by directly establishing DNA sequence (genotyping) or by phenotyping: exposing a large group of otherwise healthy subjects to a specific probe substrate for the metabolizing enzyme under study and observing the distribution of activity (Fig. 3-6). A distinct multimodal distribution argues for a predominant effect of variants in a single gene in the metabolism of that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed *poor metabolizers* (PM phenotype); many variants can produce such a loss of function, complicating the use of genotyping in clinical practice. Individuals with one functional allele make up a second (*intermediate metabolizers*), and those with two functional alleles a third (*extensive metabolizers*, EMs). On the other hand, a unimodal distribution of activity argues against the presence of important single loss-of-function alleles in the population under study.

Transferase Variants Of the variants in genes encoding drug-metabolizing enzymes that have been described to date, one, in the *TPMT* gene, has been adopted as routine clinical practice in some specialized centers. *TPMT* bioinactivates the antileukemic drug 6-mercaptopurine. Further, 6-mercaptopurine is itself an active metabolite of the immu-

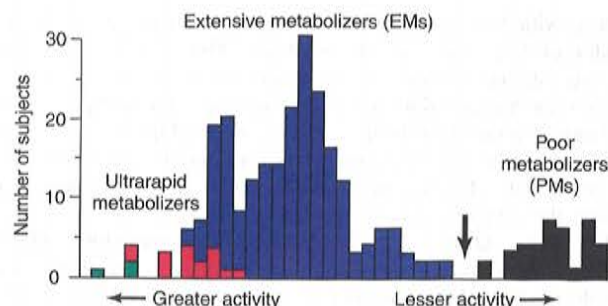


FIGURE 3-6 CYP2D6 metabolic activity was assessed in 290 subjects by administration of a test dose of a probe substrate and measurement of urinary formation of the CYP2D6-generated metabolite. The heavy arrow indicates a clear antimode, separating poor metabolizer subjects (black), with two loss-of-function CYP2D6 alleles. Individuals with one or two functional alleles are grouped together as extensive metabolizers (blue). Also shown are ultrarapid metabolizers, with 2 to 11 functional copies of the gene (red) and 12 functional copies (green), displaying the greatest enzyme activity. (Adapted by permission from M-L Dahl et al: *J Pharmacol Exp Ther* 274:516, 1995.)

nosuppressive azathioprine. Homozygotes for alleles encoding the inactive *TPMT* (1 in 300 individuals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-mercaptopurine. On the other hand, homozygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with the drugs. These data illustrate the potential power of a genomic approach to optimize therapy, especially in the setting of high-risk pharmacokinetics.

N-acetylation is catalyzed by hepatic *N*-acetyl transferase (*NAT*), which actually represents the activity of two genes, *NAT-1* and *NAT-2*. Both enzymes transfer an acetyl group from acetyl coenzyme A to the drug; *NAT-1* activity is generally constant, while polymorphisms in *NAT-2* result in individual differences in the rate at which drugs are acetylated and thus define "rapid acetylators" and "slow acetylators." Slow acetylators make up ~50% of European- and African-derived populations but are less common among Asians.

Slow acetylators have an increased incidence of the drug-induced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid. Induction of CYPs (e.g., by rifampin) also increases the risk of isoniazid-related hepatitis, likely reflecting generation of reactive metabolites of acetylhydrazine, itself an isoniazid metabolite.

Polymorphisms that reduce transcription of uridine diphosphate glucuronosyltransferase (*UGT1A1*) cause benign hyperbilirubinemia (Gilbert's disease; Chap. 284). These have also been associated with diarrhea and increased bone marrow depression with the antineoplastic irinotecan, whose active metabolite is normally detoxified by this pathway.

CYP Variants CYP3A4 is the most abundant hepatic and intestinal CYP and is also the enzyme responsible for metabolism of the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but the distribution is unimodal, suggesting that the variability does not arise from variants in the *CYP3A4* gene. The mechanisms underlying this variability are not yet well understood. A closely related gene, encoding CYP3A5 (which shares substrates with CYP3A4), does display loss-of-function variants, especially in African-derived populations. CYP3A refers to both enzymes.

CYP2D6 accounts for very little total hepatic CYP by weight but is second to CYP3A4 in the number of commonly used drugs that it metabolizes. CYP2D6 is polymorphically distributed, with about 7% of European- and African-derived populations (but very few Asians) displaying the PM phenotype (Fig. 3-6). Over 70 loss-of-function variants in the *CYP2D6* gene have been described; the PM phenotype arises in individuals with two such alleles. In addition, individuals with multiple functional copies of the *CYP2D6* gene (ultrarapid metabolizers) have been identified, particularly among northern Africans. CYP2D6 represents the main metabolic pathway for a number of drugs

(Table 3-1). Codeine is biotransformed by CYP2D6 to the potent active metabolite morphine, so its effects are blunted in PMs and exaggerated in ultrarapid metabolizers. With beta blockers metabolized by CYP2D6 (including ophthalmic timolol and the antiarrhythmic propafenone), PM subjects display greater signs of beta blockade (including bradycardia and bronchospasm) than EMs. Further, in EM subjects, propafenone elimination becomes nonlinear at higher doses so, for example, a tripling of the dose may lead to a tenfold increase in drug concentration. The oral hypoglycemic agent phenformin was withdrawn because it occasionally caused profound lactic acidosis; this likely arose as a result of high concentrations in CYP2D6 PMs. Ultrarapid metabolizers may require very high dosages of tricyclic antidepressants to achieve a therapeutic effect, and with codeine may display transient euphoria and nausea due to very rapid generation of morphine.

The PM phenotype for CYP2C19 is common (20%) among Asians, and rarer (3 to 5%) in European-derived populations. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with "standard" dosages were markedly lower in EM patients (29%) than in PMs (100%). Thus, understanding the importance of this polymorphism would have been important in developing the drug, and knowing a patient's CYP2C19 genotype should improve therapy.

There are common allelic variants of CYP2C9 that encode proteins with loss of catalytic function. These variant alleles are associated with a requirement for lower maintenance dose of warfarin. In rarer (<2%) individuals homozygous for these variant alleles, maintenance warfarin dosages may be difficult to establish, and the risk of bleeding complications appears increased. Similarly, patients with loss-of-function CYP2C9 alleles display increased rates of neurologic complications with phenytoin and of hypoglycemia with glipizide.

VARIABILITY IN THE MOLECULAR TARGETS WITH WHICH DRUGS INTERACT As molecular approaches identify specific gene products as targets of drug action, polymorphisms that alter the expression or function of these drug targets—and thus modulate their actions in patients—are also being recognized. For example, genome-wide searches in families with premature Alzheimer's disease have associated variants in the APOE locus with the disease (Chap. 350). The E4 allele of the gene has been associated with a worse prognosis, a finding that has been attributed to reduced expression of choline acetyltransferase. Further, this polymorphism is also linked to response to the acetylcholinesterase inhibitor tacrine; a beneficial response appears to be more common in patients with the prognostically more benign APOE2 or APOE3 alleles (in which the target molecule is expressed more abundantly).

Multiple polymorphisms identified in the β_2 -adrenergic receptor appear to be linked to specific phenotypes in asthma and congestive heart failure, diseases in which β_2 -receptor function might be expected to determine prognosis. Polymorphisms in the β_2 -receptor gene have also been associated with response to inhaled β_2 -receptor agonists, while those in the β_1 -adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering. Similarly, response to the 5-lipoxygenase inhibitor zileuton in asthma has been linked to polymorphisms that determine the expression level of the 5-lipoxygenase gene. Herceptin, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the herceptin receptor; thus, "genotyping" the tumor is a mechanism to avoid potentially toxic therapy in patients who would derive no benefit.

Drugs may also interact with genetic pathways of disease, to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks (Chap. 337). Deficiency of glucose-6-phosphate dehydrogenase (G6PD), most often in individuals of African or Mediterranean descent, increases risk of hemolytic anemia in response to primaquine and a number of other drugs that do not cause hemolysis in patients with adequate quantities of this enzyme (Chap. 93). Patients with mutations in the ryanodine

receptor that controls intracellular calcium in skeletal muscle and other tissues may be asymptomatic until exposed to certain general anesthetics, which trigger the syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes (Chap. 214), and in some patients this adverse effect represents unmasking of previously subclinical congenital long QT syndrome.

POLYMORPHISMS THAT MODULATE THE BIOLOGIC CONTEXT WITHIN WHICH THE DRUG-TARGET INTERACTIONS OCCUR The interaction of a drug with its molecular target is translated into a clinical action in a complex biologic milieu that is itself often perturbed by disease. Thus, polymorphisms that determine variability in this biology may profoundly influence drug response, although the genes involved are not themselves directly targets of drug action. The common insertion/deletion (I/D) polymorphism in the ACE gene determines prognosis in many types of heart disease, including heart failure. In patients with heart failure treated with β -adrenergic blockers, the best response to therapy has been associated with the DD genotype, the group with the worst prognosis. The mechanism underlying this outcome is uncertain, but a direct effect of beta blockers on ACE seems unlikely; rather the I/D genotype likely affects the biology of heart failure to allow an improved response to beta blockers. Similarly, polymorphisms in genes important for lipid homeostasis (such as the ABCA1 transporter and the cholesterol ester transport protein) modulate response to HMG-CoA reductase inhibitors. In one large study, the combination of diuretic use combined with a variant in the adducin gene (encoding a cytoskeletal protein important for renal tubular sodium absorption) decreased stroke or myocardial infarction risk, while neither factor alone has an effect. Common polymorphisms in ion channel genes that are not themselves the target of QT-prolonging drugs may nevertheless influence the extent to which those drugs affect the electrocardiogram and produce arrhythmias.

PROSPECTS FOR INCORPORATING GENETIC INFORMATION INTO CLINICAL PRACTICE These and many other examples of associations between specific genotypes and drug responses raise the tantalizing prospect that patients will undergo routine genotyping for loci known to modulate drug levels or response prior to receiving a prescription. The twin goals are to identify patients likely to exhibit adverse effects and those most likely to respond well. Obstacles that must be overcome before this vision becomes a reality include replication of even the most compelling associations, demonstrations of cost-effectiveness, development of readily useable genotyping technologies, and ethical issues involved in genotyping. While these barriers seem daunting, the field is very young and evolving rapidly. Indeed, one major result of understanding of the role of genetics in drug action has been improved screening of drugs during the development process to reduce the likelihood of highly variable metabolism or unanticipated toxicity (such as torsades de pointes).

INTERACTIONS BETWEEN DRUGS

Drug interactions can complicate therapy by adversely increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels. *Interactions must be considered in the differential diagnosis of any unusual response occurring during drug therapy.* Prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A meticulous drug history should include examination of the patient's medications and, if necessary, calls to the pharmacist to identify prescriptions. It should also address the use of agents not often volunteered during questioning, such as over-the-counter (OTC) drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. The practicing physician cannot be expected to memorize these. How-

TABLE 3-2 Drugs with a High Risk of Generating Pharmacokinetic Interactions

Drug	Mechanism	Examples
Antacids; bile acid sequestrants	Reduced absorption	Antacids/tetracyclines; cholestyramine/digoxin
Proton pump inhibitors; H ₂ -receptor blockers	Altered gastric pH	Ketoconazole absorption decreased
Rifampin; carbamazepine; barbiturates; phenytoin; St. John's wort; glutethimide	Induction of hepatic metabolism	Decreased concentration and effects of: warfarin; quinidine; cyclosporine; losartan
Tricyclic antidepressants; fluoxetine; quinidine	Inhibitors of CYP2D6	Increased beta blockade; decreased codeine effect
Cimetidine	Inhibitor of multiple CYPs	Increased concentration and effects of: warfarin; theophylline; phenytoin
Ketoconazole, itraconazole; erythromycin, clarithromycin; calcium channel blockers; ritonavir	Inhibitor of CYP3A	Increased concentration and toxicity of: some HMG-CoA reductase inhibitors; cyclosporine; cisapride, terfenadine (now withdrawn)
		Increased concentration and effects of: indinavir (with ritonavir);
		Decreased clearance and dose requirement for: cyclosporine (with calcium channel blockers)
Allopurinol	Xanthine oxidase inhibitor	Azathioprine and 6-mercaptopurine toxicity
Amiodarone	Inhibitor of many CYPs and of P-glycoprotein	Decreased clearance (risk of toxicity) for: warfarin; digoxin; quinidine
Gemfibrozil (and other fibrates)	CYP3A inhibition	Rhabdomyolysis when co-prescribed with some HMG-CoA reductase inhibitors
Quinidine; amiodarone; verapamil; cyclosporine; itraconazole; erythromycin	P-glycoprotein inhibition	Risk of digoxin toxicity
Phenylbutazone, probenecid; salicylates	Inhibition of renal tubular transport	Salicylates → increased risk of methotrexate toxicity

ever, certain drugs consistently run the risk of generating interactions, through mechanisms that are well understood; examples (not an exhaustive listing) are presented below and in Table 3-2. When such drugs are started or stopped, prescribers must be especially alert to the possibility of interactions.

PHARMACOKINETIC INTERACTIONS CAUSING DIMINISHED DRUG DELIVERY TO TARGET SITES ■ Impaired Gastrointestinal Absorption Aluminum ions, present in antacids, can form insoluble chelates with the tetracyclines, preventing their absorption. Kaolin-pectin suspensions bind digoxin, and when the substances are administered together, digoxin absorption is reduced by about one-half. Resins that sequester bile acids in the gut can bind other drugs, such as digoxin. Ketoconazole is a weak base that dissolves well only at acidic pH. Histamine H₂ receptor antagonists and proton pump inhibitors reduce gastric acidity and thus impair the dissolution and absorption of ketoconazole.

Induction of CYP or Transporter Activity Expression of some genes responsible for drug elimination, notably *CYP3A* and *MDR1*, can be markedly increased by "inducing" drugs, such as rifampin, carbamazepine, phenytoin, St. John's wort, and glutethimide and by smoking, exposure to chlorinated insecticides such as DDT (*CYP1A2*), and chronic alcohol ingestion. One mechanism for this coordinate induction of multiple pathways is increased expression of common transcription factors (e.g., hepatocyte nuclear factor 4 α). Administration of inducing agents lowers plasma levels over 2 to 3 weeks as gene expression is increased. This alters the effects of many drugs, including warfarin, quinidine, mexiletine, verapamil, ketoconazole, itraconazole, cyclosporine, dexamethasone, methylprednisolone, prednisolone (the active metabolite of prednisone), oral contraceptive steroids, methadone, and metronidazole. These interactions all have obvious clinical significance. Further, if a drug dose is stabilized in the presence of an inducer which is subsequently stopped, major toxicity can occur as clearance returns to preinduction levels and drug concentrations rise. This is a particular problem with narrow-therapeutic-ratio drugs such

as warfarin and some antiarrhythmics. Individuals vary in the extent to which drug metabolism can be induced, likely through genetic mechanisms.

Inhibition of Cellular Uptake or Binding Tricyclic antidepressants, doxepin, and chlorpromazine are potent inhibitors of norepinephrine uptake into adrenergic neurons and prevent the uptake of the guanidinium antihypertensive agents (such as guanethidine and guanadrel), thereby abolishing their antihypertensive effects. Similarly, the antihypertensive effect of clonidine is partially antagonized by tricyclic antidepressants.

PHARMACOKINETIC INTERACTIONS CAUSING INCREASED DRUG DELIVERY TO TARGET SITES ■ Inhibition of Drug Metabolism Inhibition of drug metabolism can lead to reduced clearance, prolonged half-life, accumulation of drug during maintenance therapy, and thus adverse effects. In contrast to induction, new protein synthesis is not involved, and the effect develops as drug and any inhibitor metabolites accumulate (a function of their elimination half-

lives). Since shared substrates of a single enzyme can compete for access to the active site of the protein, many CYP substrates can also be considered inhibitors. However, some drugs are especially potent as inhibitors (and occasionally may not even be substrates); it is in the use of agents of the latter type that clinicians must be most alert to the potential for interactions.

Cimetidine (but not other H₂-receptor blockers) is a potent inhibitor of the oxidative metabolism of many drugs, including warfarin, quinidine, nifedipine, lidocaine, theophylline, and phenytoin. Severe adverse reactions can develop as a consequence.

The antifungal agents ketoconazole and itraconazole are potent inhibitors of enzymes in the CYP3A family. When fluconazole levels are elevated as a result of higher doses and/or renal insufficiency, this drug can also inhibit CYP3A. The macrolide antibiotics erythromycin and clarithromycin inhibit CYP3A4 to a clinically significant extent, but azithromycin does not. Some of the calcium channel blockers, including diltiazem, nifedipine, and verapamil can also inhibit CYP3A, as can some of the enzyme's substrates, such as cyclosporine. Examples of CYP3A substrates also include quinidine, lovastatin, simvastatin, atorvastatin, nifedipine, lidocaine, erythromycin, methylprednisolone, carbamazepine, midazolam, and triazolam.

Phenytoin, an inducer of many systems including CYP3A, inhibits CYP2C9. CYP2C9 metabolism of losartan to its active metabolite is inhibited by phenytoin, with potential loss of antihypertensive effect.

Accumulation of the prokinetic drug cisapride and the antihistamine terfenadine due to CYP3A inhibition led to QT prolongation and torsades de pointes. Measures to prevent co-prescription of these agents with CYP3A inhibitors were unsuccessful, and alternative safer agents were developed, so these drugs were eventually withdrawn.

Cyclosporine can cause serious toxicity when its metabolism via CYP3A4 is inhibited by erythromycin, ketoconazole, diltiazem, nifedipine, or verapamil. The risk of myopathy with some HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin) is thought to be increased by CYP3A4 inhibition. One agent in this class, cerivas-

tatin, was withdrawn because of an especially high incidence of this adverse effect, although cellular studies suggest inhibition of other pathways may have also contributed in this case. The antiviral ritonavir is a very potent CYP3A4 inhibitor that is often added to anti-HIV regimens not because of its antiviral effects but because it decreases clearance, and hence increases efficacy, of other anti-HIV agents. Grapefruit (but not orange) juice inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.

CYP2D6 is markedly inhibited by quinidine and is also blocked by a number of neuroleptic drugs, such as chlorpromazine and haloperidol, and by fluoxetine. The analgesic effect of codeine depends on its metabolism to morphine via CYP2D6. Thus, quinidine reduces the analgesic efficacy of codeine in EMs. Since desipramine is cleared largely by metabolism via CYP2D6 in EMs, its levels are increased substantially by concurrent administration of quinidine, fluoxetine, or the neuroleptic drugs that inhibit CYP2D6. Clinical consequences of fluoxetine's interaction with CYP2D6 substrates may not be apparent for weeks after the drug is started, because of its very long half-life and slow generation of a CYP2D6-inhibiting metabolite.

6-Mercaptopurine, the active metabolite of azathioprine, is metabolized not only by TPMT but also by xanthine oxidase. When allopurinol, a potent inhibitor of xanthine oxidase, is administered with standard doses of azathioprine or 6-mercaptopurine, life-threatening toxicity (bone marrow suppression) can result.

Inhibition of Drug Transport The best studied example is P-glycoprotein (Fig. 3-4). Quinidine inhibits P-glycoprotein function in vitro, and it now appears that the long-recognized doubling of plasma digoxin when quinidine is coadministered reflects this action in vivo, particularly since the effects of quinidine (increased digoxin bioavailability and reduced renal and hepatic secretion) occur at the sites of P-glycoprotein expression. Many other drugs also elevate digoxin concentrations (e.g., amiodarone, verapamil, cyclosporine, itraconazole, and erythromycin), and a similar mechanism seems likely. Reduced CNS penetration of multiple HIV protease inhibitors (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein-mediated exclusion of the drug from the CNS; thus inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS.

A number of drugs are secreted by the renal tubular transport systems for organic anions. Inhibition of these systems can cause excessive drug accumulation. Salicylate, for example, reduces the renal clearance of methotrexate, an interaction that may lead to methotrexate toxicity. Renal tubular secretion contributes substantially to the elimination of penicillin, which can be inhibited (to increase its therapeutic effect) by probenecid.

Inhibition of the tubular cation transport system by cimetidine decreases the renal clearance of dofetilide and of procainamide and its active metabolite NAPA.

DRUG INTERACTIONS NOT MEDIATED BY CHANGES IN DRUG DISPOSITION Drugs may act on separate components of a common process to generate effects greater than either has alone. For example, although small doses of aspirin (<1 g daily) do not alter the prothrombin time appreciably in patients who are receiving warfarin therapy, aspirin nevertheless increases the risk of bleeding in these patients because it inhibits platelet aggregation. Thus the combination of impaired functions of platelets and of the clotting system, while useful in some patients, also increases the potential for hemorrhagic complications. Similarly, the use of other antithrombotic agents (heparin, glycoprotein IIb/IIIa inhibitors, clopidogrel) with aspirin improves outcomes in acute coronary syndromes, while exacerbating this bleeding tendency.

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastric ulcers, and, in patients treated with warfarin, the risk of bleeding from a peptic ulcer is increased almost threefold by concomitant use of a NSAID. Indomethacin, piroxicam, and probably other NSAIDs antagonize

the antihypertensive effects of β -adrenergic receptor blockers, diuretics, ACE inhibitors, and other drugs. The resulting elevation in blood pressure ranges from trivial to severe. This effect is not seen with aspirin and sulindac but has been found with cyclooxygenase-2 inhibitors (celecoxib, rofecoxib).

Torsades de pointes during administration of QT-prolonging antiarrhythmics (quinidine, sotalol, dofetilide) occur much more frequently in those patients receiving diuretics, probably reflecting hypokalemia. In vitro, hypokalemia not only prolongs the QT interval in the absence of drug but also potentiates drug block of ion channels that results in QT prolongation. Also, some diuretics have direct electrophysiologic actions that prolong QT.

The administration of supplemental potassium leads to more frequent and more severe hyperkalemia when potassium elimination is reduced by concurrent treatment with ACE inhibitors, spironolactone, amiloride, or triamterene.

The pharmacologic effects of sildenafil result from inhibition of the phosphodiesterase type 5 isoform that inactivates cyclic GMP in the vasculature. Nitroglycerin and related nitrates used to treat angina produce vasodilation by elevating cyclic GMP. Thus, coadministration of these nitrates with sildenafil can cause profound hypotension, which can be catastrophic in patients with coronary disease.

Sometimes, combining drugs can increase overall efficacy and/or reduce drug-specific toxicity. Such therapeutically useful interactions are described in chapters dealing with specific disease entities, elsewhere in this text.

ADVERSE REACTIONS TO DRUGS

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these untoward effects often present diagnostic problems because they can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Major advances in the investigation, development, and regulation of drugs ensure in most instances that drugs are uniform, effective, and relatively safe and that their recognized hazards are publicized. However, prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials, and the selected nature of these patients, rare adverse effects may not be detected prior to a drug's approval, and physicians therefore need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized adverse events. Often, these adverse reactions are rare, such as hematologic abnormalities, arrhythmias, hepatitis, or renal dysfunction. In these cases, often (but inappropriately) labeled "idiosyncratic," elucidating underlying mechanisms can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure. National adverse reaction reporting systems, such as those operated by the U.S. Food and Drug Administration (suspected adverse reactions can be reported online at <http://www.fda.gov/medwatch/report/hcp.htm>) and the Committee on Safety of Medicines in Great Britain, can prove useful. The publication or reporting of a newly recognized adverse reaction can in a short time stimulate many similar such reports of reactions that previously had gone unrecognized.

Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients led to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. These examples further reinforce the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

The large number and variety of drugs and herbal remedies available OTC as well as by prescription make it impossible for patient or physician to obtain or retain the knowledge necessary to use all drugs well. It is understandable, therefore, that many OTC drugs are used unwisely by the public and that restricted drugs may be prescribed incorrectly by physicians.

Some 25 to 50% of patients make errors in self-administration of prescribed medicines, and these errors can be responsible for adverse drug effects. Elderly patients are the group most likely to commit such errors, perhaps in part because they consume more medicines. One-third or more of patients also may not take their prescribed medications. Similarly, patients commit errors in taking OTC drugs by not reading or following the directions on the containers. Physicians must recognize that providing directions with prescriptions does not always guarantee compliance.

In hospital, drugs are administered in a controlled setting, and patient compliance is, in general, ensured. Errors may occur nevertheless—the wrong drug or dose may be given or the drug may be given to the wrong patient—and improved drug distribution and administration systems are addressing this problem. On the other hand, there are no easy means for controlling how ambulatory patients take prescription or OTC drugs.

EPIDEMIOLOGY Patients receive, on average, 10 different drugs during each hospitalization. The sicker the patient, the more drugs are given, and there is a corresponding increase in the likelihood of adverse drug reactions. When <6 different drugs are given to hospitalized patients the probability of an adverse reaction is ~5%, but if >15 drugs are given, the probability is >40%. Retrospective analyses of ambulatory patients have revealed adverse drug effects in 20%. Serious adverse reactions are also well recognized with “herbal” remedies and OTC compounds: examples include kava-associated hepatotoxicity, L-tryptophan-associated eosinophilia-myalgia, and phenylpropanolamine-associated stroke, each of which has caused fatalities.

A 2000 Institute of Medicine report indicated that 7000 Americans die annually because of medication errors, that 2 to 3% of hospital admissions are for illnesses attributed to drugs, that the in-hospital cost was >\$2 billion, and that this represents a tiny fraction of the overall problem of medication errors and its costs. A small group of widely used drugs accounts for a disproportionate number of reactions. Aspirin and other NSAIDs, analgesics, digoxin, anticoagulants, diuretics, antimicrobials, glucocorticoids, antineoplastics, and hypoglycemic agents account for 90% of reactions, although the drugs involved differ between ambulatory and hospitalized patients.

ETIOLOGY Most adverse drug reactions are preventable, and recent studies using a systems analysis approach suggest that the most common system failure associated with an adverse drug reaction is the failure to disseminate knowledge about drugs to individuals who prescribe and administer them. Most adverse reactions may be classified in two groups. The most frequent ones result from exaggeration of an intended pharmacologic action of the drug, and the underlying mechanisms have been discussed above. Other adverse reactions ensue from toxic effects unrelated to the intended pharmacologic actions. The latter effects are often unpredictable and frequently severe, and result from recognized as well as undiscovered mechanisms.

TOXICITY UNRELATED TO A DRUG'S PRIMARY PHARMACOLOGIC ACTIVITY ■ Cytotoxic Reactions Drug or more commonly reactive metabolites generated by CYPs can covalently bind to tissue macromolecules (such as proteins or DNA) to cause tissue toxicity. Because of the reactive nature of these metabolites covalent binding often occurs close to the site of production; this is typically the liver, although CYPs are found in other tissues as well.

The most common cause of drug-induced hepatotoxicity is acetaminophen overdosage. Normally, reactive metabolites are detoxified by combining with hepatic glutathione. When glutathione becomes exhausted, the metabolites bind instead to hepatic protein, with re-

sultant hepatocyte damage. The hepatic necrosis produced by the ingestion of acetaminophen can be prevented, or at least attenuated, by the administration of substances such as *N*-acetylcysteine that reduce the binding of electrophilic metabolites to hepatic proteins. The risk of hepatic necrosis is increased in patients receiving drugs such as phenobarbital or phenytoin that increase the rate of drug metabolism or ethanol that exhaust glutathione stores. Such toxicity has even occurred with therapeutic dosages, so patients at risk through these mechanisms should be warned.

Immunologic Mechanisms Most pharmacologic agents are small molecules with low molecular weights (<2000) and thus are poor immunogens. Generation of an immune response to a drug therefore usually requires *in vivo* activation and covalent linkage to protein, carbohydrate, or nucleic acid.

Drug stimulation of antibody production may mediate tissue injury by several mechanisms. The antibody may attack the drug when the drug is covalently attached to a cell, and thereby destroy the cell. This occurs in penicillin-induced hemolytic anemia. Antibody-drug-antigen complexes may be passively adsorbed by a bystander cell, which is then destroyed by activation of complement; this occurs in quinine- and quinidine-induced thrombocytopenia. Heparin-induced thrombocytopenia arises when antibodies against complexes of platelet factor 4 peptide and heparin generate immune complexes that activate platelets; thus the thrombocytopenia is accompanied by “paradoxical” thrombosis and is treated with thrombin inhibitors. Drugs or their reactive metabolites may alter a host tissue, rendering it antigenic and eliciting autoantibodies. For example, hydralazine and procainamide (or their reactive metabolites) can chemically alter nuclear material, stimulating the formation of antinuclear antibodies and occasionally causing lupus erythematosus. Autoantibodies can be elicited by drugs that neither interact with the host antigen nor have any chemical similarity to the host tissue; for example, the antihypertensive α -methyl-dopa frequently stimulates the formation of antibodies to host erythrocytes, yet the drug neither attaches to the erythrocyte nor shares any chemical similarities with the antigenic determinants on the erythrocyte. Drug-induced pure red cell aplasia (Chap. 94) is due to an immune-based drug reaction. Red cell formation in bone marrow cultures can be inhibited by phenytoin and purified IgG obtained from a patient with pure red cell aplasia associated with phenytoin.

Serum sickness (Chap. 298) results from the deposition of circulating drug-antibody complexes on endothelial surfaces. Complement activation occurs, chemotactic factors are generated locally, and an inflammatory response develops at the site of complex entrapment. Arthralgias, urticaria, lymphadenopathy, glomerulonephritis, or cerebritis may result. Foreign proteins (vaccines, streptokinase, therapeutic antibodies) and antibiotics are common causes. Many drugs, particularly antimicrobial agents, ACE inhibitors, and aspirin, can elicit anaphylaxis, with production of IgE, which binds to mast cell membranes. Contact with a drug antigen initiates a series of biochemical events in the mast cell and results in the release of mediators that can produce the characteristic urticaria, wheezing, flushing, rhinorrhea, and (occasionally) hypotension.

Drugs may also elicit cell-mediated immune responses. Topically administered substances may interact with sulfhydryl or amino groups in the skin and react with sensitized lymphocytes to produce the rash characteristic of contact dermatitis. Other types of rashes may also result from the interaction of serum factors, drugs, and sensitized lymphocytes.

DIAGNOSIS AND TREATMENT OF ADVERSE DRUG REACTIONS The manifestations of drug-induced diseases frequently resemble those of other diseases, and a given set of manifestations may be produced by different and dissimilar drugs. Recognition of the role of a drug or drugs in an illness depends on appreciation of the possible adverse reactions to drugs in any disease, on identification of the temporal relationship between drug administration and development of the illness, and on familiarity with the common manifestations of the drugs. Many associations between particular drugs and specific reactions have been

described, but there is always a "first time" for a novel association, and any drug should be suspected of causing an adverse effect if the clinical setting is appropriate.

Illness related to a drug's intended pharmacologic action is often more easily recognized than illness attributable to immune or other mechanisms. For example, side effects such as cardiac arrhythmias in patients receiving digitalis, hypoglycemia in patients given insulin, and bleeding in patients receiving anticoagulants are more readily related to a specific drug than are symptoms such as fever or rash, which may be caused by many drugs or by other factors.

Electronic sources of adverse drug reactions can be useful (e.g., <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/cadrnwsletter.html>). However, exhaustive compilations often provide little sense of perspective in terms of frequency and seriousness, which can vary considerably among patients.

Eliciting a drug history from patients is important for diagnosis. Attention must be directed to OTC drugs and herbal preparations as well as to prescription drugs. Each type can be responsible for adverse drug effects, and adverse interactions may occur between OTC drugs and prescribed drugs. Loss of efficacy of oral contraceptives or cyclosporine by concurrent use of St. John's wort are examples. In addition, it is common for patients to be cared for by several physicians, and duplicative, additive, counteractive, or synergistic drug combinations may therefore be administered if the physicians are not aware of the patients' drug histories. Every physician should determine what drugs a patient has been taking, at least during the preceding 30 days, before prescribing any medications. A frequently overlooked source of additional drug exposure is topical therapy; for example, a patient complaining of bronchospasm may not mention that an ophthalmic beta blocker is being used unless specifically asked. A history of previous adverse drug effects in patients is common. Since these patients have shown a predisposition to drug-induced illnesses, such a history should dictate added caution in prescribing drugs.

Laboratory studies may include demonstration of serum antibody in some persons with drug allergies involving cellular blood elements, as in agranulocytosis, hemolytic anemia, and thrombocytopenia. For example, both quinine and quinidine can produce platelet agglutination in vitro in the presence of complement and the serum from a patient who has developed thrombocytopenia following use of this drug. Biochemical abnormalities such as G6PD deficiency, serum pseudocholinesterase level, or genotyping may also be useful in diagnosis, often after an adverse effect has occurred in the patient or a family member.

Once an adverse reaction is suspected, discontinuation of the suspected drug followed by disappearance of the reaction is presumptive evidence of a drug-induced illness. Confirming evidence may be sought by cautiously reintroducing the drug and seeing if the reaction reappears. However, that should be done only if confirmation would be useful in the future management of the patient and if the attempt would not entail undue risk. With concentration-dependent adverse reactions, lowering the dosage may cause the reaction to disappear, and raising it may cause the reaction to reappear. When the reaction is thought to be allergic, however, readministration of the drug may be hazardous, since anaphylaxis may develop. Readministration is unwise under these conditions unless no alternative drugs are available and treatment is necessary.

If the patient is receiving many drugs when an adverse reaction is suspected, the drugs likeliest to be responsible can usually be identified. All drugs may be discontinued at once or, if this is not practical, they should be discontinued one at a time, starting with the one that is most suspect, and the patient observed for signs of improvement.

The time needed for a concentration-dependent adverse effect to disappear depends on the time required for the concentration to fall below the range associated with the adverse effect; that, in turn, depends on the initial blood level and on the rate of elimination or metabolism of the drug. Adverse effects of drugs with long half-lives take a considerable time to disappear.

SUMMARY

Modern clinical pharmacology aims to replace empiricism in the use of drugs with therapy based on in-depth understanding of factor(s) that determine an individual's response to drug treatment. Molecular pharmacology, pharmacokinetics, genetics, clinical trials, and the educated prescriber all contribute to this process. No drug response should ever be termed "idiosyncratic"; all responses have a mechanism whose understanding will help guide further therapy with that drug or successors. This rapidly expanding understanding of variability in drug actions makes the process of prescribing drugs increasingly daunting for the practitioner. However, fundamental principles should guide this process:

- The benefits of drug therapy, however defined, should always outweigh the risk.
- The smallest dosage necessary to produce the desired effect should be used.
- The number of medications and doses per day should be minimized.
- Although the literature is rapidly expanding, accessing it is becoming easier; tools such as computers and hand-held devices to search databases of literature and unbiased opinion will become increasingly commonplace.
- Genetics play a role in determining variability in drug response and may become a part of clinical practice.
- Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse reactions.
- Prescribers should use only a limited number of drugs, with which they are thoroughly familiar.

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