9 Principles of Drug Therapeutics, Pharmacogenomics, and Biologics

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In 2018 the total cost of health care in the United States was approximately $3.6 trillion, 17.7% of the Gross Domestic Product, and more than 10% was spent on prescription drugs.[1] Cardiovascular disease makes up the largest subcategory in this spending: in 2020 the American Heart Association estimated that the cost of care for cardiovascular disease in 2015 was $351.3 billion/year.[2]

Not every patient responds to drug therapy in the same way; efficacy varies, and adverse drug reactions (ADRs) range from minor to potentially fatal. Multiple mechanisms can result in this variability, such as poor compliance, variable impact of diverse disease mechanisms on drug actions, drug interactions, and the increasingly well-recognized role of genomic variation. Indeed, ADRs across all therapeutic categories are estimated to be the fourth to sixth most common cause of death in the United States, costing over $30 billion annually and accounting directly for 3% to 6% of all hospital admissions.[3,4]

RISK VERSUS BENEFIT OF DRUG THERAPY

The fundamental assumption underlying administration of any drug is that the real or expected benefit exceeds the anticipated risk. The benefits of drug therapy are initially defined in small clinical trials, perhaps involving several thousand patients, before a drug's marketing and approval. Ultimately, the efficacy and safety profiles of any drug are determined after the compound has been marketed and used widely in hundreds of thousands of patients. Occasionally, unexpected drug actions detected during or after a development program can result in new indications: PDE5 inhibitors for pulmonary hypertension or SGLT-2 inhibitors for heart failure are examples.

When a drug is administered for the acute correction of a life-threatening condition, the benefits are often self-evident; insulin for diabetic ketoacidosis and nitroprusside for hypertensive encephalopathy are examples. However, extrapolation of such immediately obvious benefits to other clinical situations may not be warranted.

Clinical Trials Can Define Unexpected Adverse Drug Reactions

Randomized clinical trials (RCTs) have proven invaluable both to demonstrate the efficacy of drug therapy and to identify rare but serious ADRs. One of the first examples of an RCT identifying an unexpected serious ADR was the Cardiac Arrhythmia Suppression Trial (CAST), which tested the hypothesis that suppression of ventricular ectopic activity, a recognized risk factor for sudden death after myocardial infarction (MI), would reduce mortality; this notion was highly ingrained in cardiovascular practice in the 1970s and 1980s. In CAST, sodium channel–blocking antiarrhythmic drugs did suppress ventricular ectopic beats but also unexpectedly increased mortality threefold. The use of ectopic beat suppression as a surrogate marker did not produce the desired drug action—reduction in mortality—probably because the underlying pathophysiology was incompletely understood.

Similarly, drugs with positive inotropic activity augment cardiac output in patients with heart failure but also are associated with an increase in mortality, probably because of drug-induced arrhythmias. Nevertheless, clinical trials with these agents suggest symptom relief. Thus the prescriber and the patient may elect therapy with positive inotropic drugs to realize this benefit while recognizing the risk. This complex decision making is at the heart of the broad concept of personalized medicine, which incorporates into the care of an individual patient not only genomic (or other) markers of variable drug responses, but also factors such as patients' understanding of their disease, presence of other diseases, willingness to tolerate minor or serious risks of treatment, and sociocultural factors which impact key health determinants such as exposure to pollution, ability to pay for care, and literacy and numeracy.

Classes of Adverse Drug Reactions

The risks of drug therapy may be a direct extension of the pharmacologic actions for which the drug is actually being prescribed. Hypoglycemia in a patient taking an antidiabetic agent and bleeding in a patient taking an anticoagulant are examples; sodium channel block in CAST is another. T cell activation by immune checkpoint inhibitors, with resultant myocarditis, may in this sense also be "on-target."[5]

In other cases, ADRs develop as a consequence of pharmacologic actions that were not appreciated during a drug's initial development and use in patients. Examples include rhabdomyolysis occurring with 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins), angioedema developing during angiotensin-converting enzyme (ACE) inhibitor therapy, and torsades de pointes during treatment with noncardiovascular drugs such as methadone or hydroxychloroquine.[6] Of importance, these rarer but serious effects generally become evident only after a drug has been marketed and extensively used. Even rare ADRs can alter the overall perception of risk versus benefit and can prompt removal of the drug from the market, particularly if alternate therapies thought to be safer are available or the benefits of drug therapy are modest or difficult to demonstrate. For example, withdrawal of the first insulin sensitizer, troglitazone, after recognition of hepatotoxicity was further spurred by the availability of other new drugs in this class.

The recognition of multiple cyclooxygenase (COX) isoforms led to the development of specific COX-2 inhibitors to retain aspirin's analgesic effects but reduce gastrointestinal side effects. However, one of these, rofecoxib, was withdrawn because of an apparent increase in cardiovascular mortality. The events surrounding the withdrawal of rofecoxib have important implications for drug development and utilization. First, specificity achieved by targeting a single molecular entity may not necessarily reduce ADRs; one possibility is that by inhibiting COX-2, the drug removes a vascular protective effect of prostacyclin. Second, drug side effects may

include not only readily identifiable events such as rhabdomyolysis or torsades de pointes but also an increase—that may be difficult to detect—in events such as MI that are common in the general population.

PHARMACOKINETICS AND PHARMACODYNAMICS

Two major processes determine how the interaction between a drug and its target molecule(s) can generate variable drug actions in a patient.The first, *pharmacokinetics* (Fig.9.1), describes drug delivery to and removal from the target molecule and includes the processes of absorption, distribution, metabolism, and excretion—collectively termed *drug disposition.* The second process, *pharmacodynamics* (Fig 9.2), describes how the interaction between a drug and its molecular target(s) generates downstream molecular, cellular, whole-organ, and whole-body effects.

Genes encoding drug-metabolizing enzymes and drug transport molecules determine pharmacokinetics. Genes encoding drug targets and the molecules modulating the biology in which the drug-target interaction occurs (including those causing the disease being treated) determine pharmacodynamics. *Pharmacogenetics* describes the concept that individual variants in the genes controlling these processes contribute to variable drug actions. *Pharmacogenomics* is often used to describe the way in which variability across multiple genes, up to whole genomes, explains differences in drug response among individuals and populations. The following overview of broad principles of pharmacokinetics, pharmacodynamics, and pharmacogenomics is followed by more detailed discussion of the specific genes, their function, and important variants influencing cardiovascular drug responses.

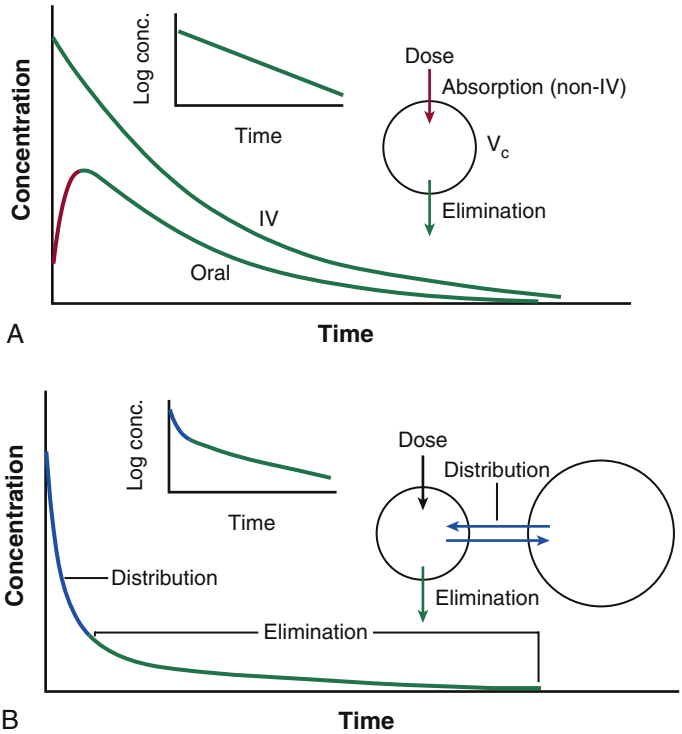

FIGURE 9.1 Models of plasma concentrations as a function of time after a single dose of a drug. **A,** The simplest situation is one in which a drug is administered as a rapid intravenous (IV) bolus into a volume (V_c), where it is instantaneously and uniformly distributed. Elimination then takes place from this volume. In this case, drug elimination is monoexponential; that is, a plot of the logarithm of concentration versus time is linear *(inset)*. When the same dose of drug is administered orally, a distinct absorption phase is required before drug entry into V_c. Most absorption (shown here in *red*) is completed before elimination (shown in *green*), although the processes overlap. In this example, the amount of drug delivered by the oral route is less than that delivered by the IV route, assessed by the total areas under the two curves, indicating reduced bioavailability. **B,** In this example, drug is delivered to the central volume, from which it is not only eliminated but also undergoes distribution to the peripheral sites. This distribution process *(blue)* is more rapid than elimination, resulting in a distinct biexponential disappearance curve *(inset)*.

PHARMACOKINETIC PRINCIPLES

Administration of an intravenous (IV) drug bolus results in maximal drug concentrations at the end of delivery of the bolus, followed by a decline in plasma drug concentrations over time (Fig. 9.1A), generally because of drug elimination. In the simplest case this decline occurs monoexponentially over time. A useful parameter to describe this decline is the half-life ($t_{1/2}$), the time in which 50% of the drug is eliminated; for example, after two half-lives, 75% of the drug has been eliminated, and after three half-lives, 87.5%. A monoexponential process can be considered almost complete in four or five half-lives. In some cases the decline of drug concentrations after administration of an IV bolus dose is multiexponential. The most common explanation is that the drug is not only eliminated (represented by terminal portion of time-concentration plot) but also undergoes more rapid distribution to peripheral tissues. Just as elimination may be usefully described by a half-life, distribution half-lives also can be derived from curves such as those shown in Figure 9.1B.

The plasma concentration measured immediately after a bolus dose can be used to derive a volume into which the drug is distributed. When the decline of plasma concentrations is multiexponential, multiple distribution compartments can be defined; these volumes of distribution can be useful in considering dose adjustments in cases of disease but rarely correspond exactly to any physical volume, such as plasma or total body water. With drugs that are highly tissue bound (e.g., some antidepressants), the volume of distribution can exceed total body volume by orders of magnitude.

Drugs are often administered by non-IV routes, such as oral, sublingual, transcutaneous, or intramuscular. Such routes of administration differ from the IV route in two ways (see Fig. 9.1A). First, concentrations in plasma demonstrate a distinct rising phase as the drug slowly enters plasma. Second, the total amount of drug that actually enters the systemic circulation may be less than that achieved by the IV route. The relative amount of drug entering by any route, compared with the same dose administered intravenously, is termed *bioavailability,* calculated as the ratio of the area under the time-concentration curves, as shown in Figure 9.1A. Some drugs undergo extensive metabolism before entry into the systemic circulation, and as a result the amount of drug required to achieve a therapeutic effect is much greater (and often more variable) than that required for the same drug administered intravenously. Thus small doses of IV propranolol (5 mg) may achieve heart rate slowing equivalent to that observed with much larger oral doses (80 to 120 mg). Propranolol is actually well absorbed but undergoes extensive metabolism in the intestine and liver before entering the systemic circulation. Another example is amiodarone; its physicochemical characteristics make it only 30% to 50% bioavailable when administered orally. Thus an IV infusion of 0.5 mg/min (720 mg/day) is equivalent to 1.5 to 2 g/day orally.

Drug elimination occurs by metabolism followed by the excretion of metabolites and unmetabolized parent drug, generally by the biliary tract or kidneys. This process can be quantified as *clearance,* the volume that is cleared of drug in any given period. Clearance may be organ specific (e.g., renal clearance, hepatic clearance) or whole-body clearance. Drug metabolism is conventionally divided into phase I oxidation and phase II conjugation, both of which enhance water solubility and, consequently, biliary or renal elimination.

The most common enzyme systems mediating phase I drug metabolism are those of the cytochrome P-450 superfamily, termed *CYPs.* Multiple CYPs are expressed in human liver and other tissues. A major source of variability in drug action is variability in CYP expression and/or genetic variants that alter CYP activity. Table 9.1 lists CYPs and other proteins important for pharmacokinetics of cardiovascular drugs. Excretion of drugs or their metabolites into the urine or bile is accomplished by glomerular filtration or specific drug transport molecules, whose level of expression and genetic variation are only now being explored. One widely studied transporter is *P-glycoprotein,* the product of expression of the *MDR1* (or *ABCB1*) gene. Originally identified as a factor mediating multiple drug resistance in patients with cancer, P-glycoprotein expression is now well recognized in normal enterocytes, hepatocytes, renal tubular cells, the endothelium of the capillaries forming the blood-brain barrier, and the testes. In each of these sites, P-glycoprotein expression is restricted to the apical aspect of polarized cells, where it acts to enhance drug efflux. In the intestine, P-glycoprotein pumps substrates back into the lumen, thereby limiting bioavailability. In the liver and kidney, it promotes drug excretion into bile or urine. In central nervous system capillary endothelium, P-glycoprotein–mediated efflux is an important mechanism limiting drug access to the brain. Transporters also play a role drug uptake into many cells. One example is OATP1B1, which is responsible for simvastatin uptake into hepatocytes; variants in *SLCO1B1*, which encodes the transporter, have been associated with an increased risk for simvastatin-induced muscle toxicity.

Pharmacodynamic Principles

Drugs can exert variable effects, even in the absence of pharmacokinetic variability. This can arise as a function of variability in the molecular targets with which drugs interact to achieve their beneficial and adverse effects, as well as variability in the broader biologic context within which the drug-target interaction takes place (see Fig. 9.2). Variability in the number or function of a drug's target molecules can arise because of genetic factors (see later) or because disease alters the number of target molecules or their state (e.g., changes in extent of phosphorylation). Simple examples of variability in the biologic context are high dietary salt, which can inhibit the antihypertensive action of beta blockers, and hypokalemia, which increases the risk for drug-induced QT prolongation. In addition, disease itself can modulate drug response. For example, the effect of lytic therapy in a patient with no clots is manifestly different from that in a patient with an acute coronary syndrome, or the vasodilating effects of nitrates, beneficial in patients with coronary disease with angina, can be catastrophic in patients with aortic stenosis. These examples highlight the requirement for precision in diagnosis to avoid situations in which risk outweighs potential benefit. One hope is that emerging genomic or other molecular approaches can add to this precision.

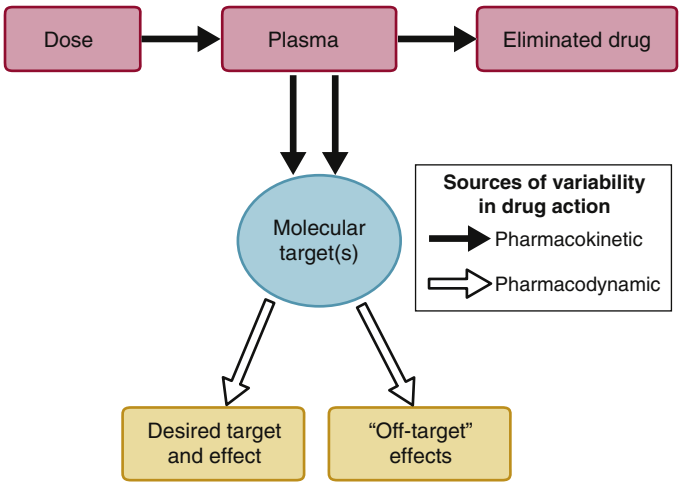

FIGURE 9.2 Pharmacokinetic and pharmacodynamic sources of variability in drug action. Pharmacokinetic processes determine drug concentration at molecular targets that through multiple mechanisms broadly termed pharmacodynamics transduce beneficial and undesirable drug effects. (From Roden DM, Van Driest SL, Wells QS, et al. Opportunities and challenges in cardiovascular pharmacogenomics: from discovery to implementation. *Circ Res*. 2018;122[9]:1176–1190)

TABLE 9.1 Proteins Important in Drug Metabolism and Elimination

PROTEIN	SUBSTRATES
Cytochrome P-450s (CYPs)	
CYP3A4, CYP3A5*	Erythromycin, clarithromycin; quinidine, mexiletine; many benzodiazepines; cyclosporine, tacrolimus; many antiretrovirals
	HMG-CoA reductase inhibitors: atorvastatin, simvastatin, lovastatin; not pravastatin
	Many calcium channel blockers; apixaban, rivaroxaban
CYP2D6*	Some beta blockers: propranolol, timolol, metoprolol, carvedilol
	Propafenone; desipramine and other tricyclics; codeine†; tamoxifen†; dextromethorphan
CYP2C9*	Warfarin, phenytoin, tolbutamide, losartan,† rosuvastatin
CYP2C19*	Omeprazole, clopidogrel†
Other Drug-Metabolizing Enzymes	
N-acetyltransferase*	Procainamide, hydralazine, isoniazid
Thiopurine methyltransferase*	6-Mercaptopurine, azathioprine
Pseudocholinesterase*	Succinylcholine
Serine esterase 1 (CES1)	Clopidogrel, dabigatran
Uridine diphosphate-glucuronosyltransferase*	Irinotecan,† atazanavir
Drug Transporters	
P-glycoprotein	Digoxin, dabigatran
SLCO1B1*	Simvastatin, atorvastatin; methotrexate; troglitazone; bosentan

HMG-CoA, 3-Hydroxy-3-methylglutaryl–coenzyme A.
*Clinically important genetic variants described.
†Prodrug bioactivated by drug metabolism.

Drug Targets

The targets with which drugs interact to produce beneficial effects may or may not be the same as those with which drugs interact to produce ADRs. Drug targets may be in the circulation, at the cell surface, or within cells. Many drugs widely used in cardiovascular therapeutics (e.g., digoxin, amiodarone, aspirin) were developed when the technology to identify specific molecular targets was not available. Some drugs (e.g., amiodarone) have many drug targets. In other cases, however, even older drugs are found to have rather specific molecular targets. The actions of digitalis glycosides are mediated primarily by the inhibition of sodium/potassium–adenosine triphosphatase (Na^+,K^+-ATPase). Aspirin permanently acetylates a specific serine residue on the COX enzyme, an effect that is thought to mediate its analgesic effects and its gastrointestinal toxicity. Most newer drugs have been developed to interact with a specific drug target identified in the course of basic mechanistic studies; examples of such targets are HMG-CoA reductase, ACE, G protein–coupled receptors (GPCRs; e.g., alpha, beta, angiotensin II, histamine), and platelet P2Y12 receptors.

An emerging approach is to use modern genetic techniques to identify loss-of-function DNA variants that are tolerated throughout life and associated with a desired phenotype, such as greatly reduced MI risk. Inhibitors of the corresponding gene products are thus predicted to exert a beneficial effect and lack serious on-target ADRs. PCSK9 inhibitors are an excellent example (see Chapter 27), and other potential drug targets are now being identified using this approach.[7,8] Furthermore, an emerging understanding of the way in which genetic variation produces mendelian diseases such as cystic fibrosis is leading to new, mechanism-based therapies.[9] Cardiovascular diseases such as hypertrophic cardiomyopathy appear ripe for such development (see Chapter 54).[10]

Time Course of Drug Effects

With repeated doses, drug levels accumulate to a *steady state,* the condition under which the rate of drug administration is equal to the rate of drug elimination in any given period. Drug accumulation to steady state is near-complete in four to five elimination half-lives (Fig. 9.3). For many drugs, the target molecule is in plasma or readily accessible from plasma, so this time course also describes the development of pharmacologic effects. In other cases, however, although steady-state plasma concentrations are achieved in four to five elimination half-lives, steady-state drug effects take longer to achieve; there are several possible explanations for this. First, an active metabolite may need to be generated to achieve drug effects. Second, time may be required for translation of the drug effect at the molecular site to a physiologic endpoint. For example, inhibition of HMG-CoA reductase ultimately leads to a desired lowering of low-density lipoprotein (LDL) cholesterol, but the development of this desired effect may take days or weeks after the drug is started. Third, penetration of a drug into intracellular or other tissue sites of action may be required before development of a drug effect. One mechanism underlying such penetration is the variable function of the drug uptake and efflux transport proteins (discussed earlier) that control intracellular drug concentrations.

Pharmacogenomic Principles (see Chapter 7)

A range of experimental techniques have been used to establish a role for both common and rare DNA polymorphisms in pharmacokinetic and pharmacodynamic pathways as mediators of variable drug actions. Rare variants associated with mendelian diseases such as familial hypercholesterolemia and long-QT syndrome are traditionally termed *mutations,* whereas the term *polymorphism* is used more generically to describe variants that may or may not be associated with any human trait. Polymorphism frequency often varies strikingly by ancestry, and with the

advent of inexpensive sequencing, it is apparent that the vast majority of DNA polymorphisms in any individual are actually rare (minor allele frequency [MAF] < 1%) across a large population of individuals of the same ancestry. The most common type is a single nucleotide polymorphism (SNP or single nucleotide variant [SNV]); SNPs that change the encoded amino acid are termed *nonsynonymous*. Other types are short insertions or deletions (indels) or copy number variations (CNVs), in which large segments of DNA are deleted or duplicated (or more).

One of the great success stories of modern cardiovascular genetics has been the use of linkage analysis in large families to identify disease-causing rare variants (mutations) in familial syndromes with highly unusual clinical phenotypes, such as familial hypercholesterolemia (see Chapter 27), hypertrophic cardiomyopathy (see Chapter 54), and the ion channelopathies (see Chapter 63). Linkage analysis has not been widely applied to study pharmacogenomics because large kindreds with multiple individuals having clearly defined drug-response phenotypes generally are not available.

DNA variation contributes importantly to variability in common human traits, such as laboratory values or susceptibility to common disease. Methods are available to establish the extent to which that variability includes a heritable component, often by examining twins, large families, or groups of families; evidence for heritability provides strong justification for pursuing studies to identify contributing genetic variation. Indeed, this general approach has established that common phenotypes such as LDL cholesterol, blood pressure, and susceptibility to atrial fibrillation are highly heritable. The extent to which rare and common variants contribute to this variability is only now being addressed. Across populations, individual common (MAF > 5%) DNA polymorphisms rarely account for more than even 1% of variability in common traits. Variability in response to drug exposure presents a striking exception to this general rule, where even single common DNA polymorphisms may contribute substantially, 10% or more in many cases, to overall variability in drug response. It has been speculated that common variants with large effects on drug response can persist in a population because there is no evolutionary pressure against such variants because drug exposure is a recent event in human history.

One mechanism accounting for this large effect is that common SNPs in drug metabolism pathways can result in extremely large fluctuations in drug concentration and corresponding effects. Examples of specific cardiovascular phenotypes in which common SNPs have been associated with risk are presented in Table 9.2 and discussed later. Of note, rarer variants in these (or other) genes are only now being described, so their role in mediating drug response is much less well understood. In addition, virtually all studies to date have focused primarily on populations of European ancestry, and data are only now being generated on specific polymorphisms mediating variable drug actions in other ancestries.

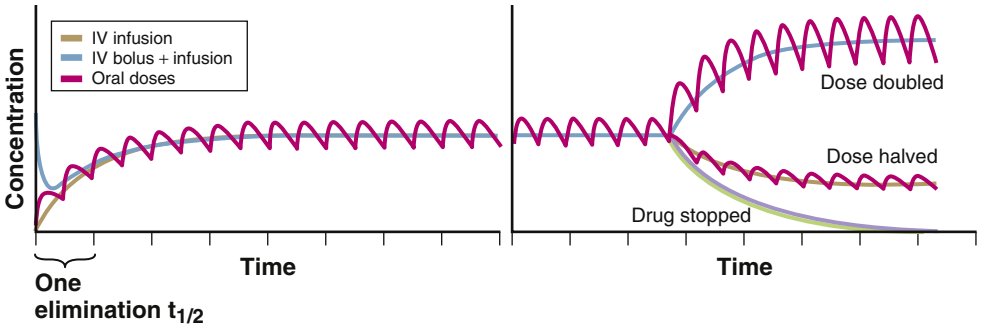

FIGURE 9.3 Time course of drug concentrations when treatment is started or dose changed. *Left,* The *hash lines* on the abscissa each indicate one elimination half-life ($t_{1/2}$). With a constant-rate intravenous (IV) infusion *(gold)*, plasma concentrations accumulate to steady state in four or five elimination half-lives. When a loading bolus is administered with the maintenance infusion *(blue)*, plasma concentrations are transiently higher but may dip, as shown here, before achieving the same steady state. When the same drug is administered by the oral route, the time course of drug accumulation is identical *(magenta)*; in this case the drug was administered at intervals of 50% of a $t_{1/2}$. Steady-state plasma concentrations during oral therapy fluctuate around the mean determined by IV therapy. *Right,* This plot shows that when dosages are doubled, or halved, or the drug is stopped during steady-state administration, the time required to achieve the new steady state is four or five half-lives and is independent of the route of administration.

The Candidate Gene Approach. One technique to identify associations between DNA polymorphisms and drug response (or other traits) uses an understanding of the physiology of the trait under question to identify candidate genes modulating the trait. Thus, for example, an investigator interested in variability in the PR interval might invoke

TABLE 9.2 Examples of Common Single Nucleotide Polymorphisms Mediating Variable Drug Actions

DRUG EFFECT	PATHWAY	GENE	SNP*	DBSNP ID NUMBER	COMMENTS
Adverse outcomes during clopidogrel treatment for acute coronary syndrome	PK	*CYP2C19*	*CYP2C19*2, CYP2C19*3:* loss-of-function (LOF) variants *CYP2C19*17*	rs4244285	*2 and *3 result in defective clopidogrel bioactivation and decreased antiplatelet activity. About 3% of European- and 15% of Asian-ancestry individuals carry two LOF alleles. *17 increases *CYP2C19* activity and has been associated with increased bleeding during clopidogrel.
Excess beta blocker effect: metoprolol, timolol	PK	*CYP2D6*	Many variants		
Warfarin steady-state dose	PK	*CYP2C9*	*CYP2C9*2, *3* (European ancestry); **5, *6, *8* (African ancestry)	rs1799853 rs1057910	*VKORC1* and *CYP2C9* variants account for ~50% of variability in warfarin steady-state dose. *VKORC1* promoter variant frequency varies by ancestry. Bleeding risk has been associated with *CYP2C9*3* and variant *CYP4F2*.
	PD	*VKORC1*	Promoter variant: −1639G>A	rs9923231	
	PD	*CYP4F2*	V433M	rs2108622	
Statin myotoxicity	PK	*SLCO1B1*	*SLCO1B1*5:* V174A	rs4149056	Risk of simvastatin myotoxicity is increased 20-fold in homozygotes and 4-fold in heterozygotes.
Response to beta blockers for hypertension, heart failure	PD (target)	*ADRB1*	S49G	rs1801252	
		ADRB2	R389G	rs1801253	
Beta blocker therapy in heart failure	PD (target)	*GRK5*	G41L	rs17098707	
Torsades de pointes	PD	*KCNE1*	D85N	rs1805128	8% allele frequency in patients with torsades versus ~2% in control subjects (odds ratio ~10)

dbSNP, National Center for Biotechnology Information's SNP database; *PD,* pharmacodynamic; *PK,* pharmacokinetic; *SNP,* single nucleotide polymorphism.
*Trivial name (e.g., *2, *3) and amino acid change provided.

polymorphisms in calcium channel genes, or an investigator interested in blood pressure might invoke variation in the ACE gene. The association between polymorphisms in these candidate genes and the phenotype under study is then examined in persons with well-characterized phenotypes. The candidate gene approach is intuitively appealing because it takes advantage of what is known about underlying physiology. Despite this appeal, however, the method is now recognized to carry with it the great potential for false-positive associations, especially when small numbers of participants are studied. An important exception has been in pharmacogenomics, where the candidate gene approach has yielded important and clinically reproducible associations between single common polymorphisms and drug response. This exception probably reflects the unusually high contribution of SNPs to overall variability in drug response previously mentioned.

Unbiased Approaches, Such as Genome-Wide Association. Another approach to identifying polymorphisms contributing to variable human traits is the genome-wide association study (GWAS). Here, study participants are genotyped at hundreds of thousands or millions of sites known to harbor common SNPs across the genome. Because the GWAS platforms focus on common SNPs, effect sizes for individual SNPs are often small and difficult to identify and validate unless large numbers of participants, thousands or more, are studied. In addition, the SNPs associated with the trait usually are not themselves functional but rather serve as markers for loci that harbor truly functional variants. The great advantage of the method is that it is unbiased, in that it makes no assumptions about underlying physiology, and one of its major accomplishments has been to identify entirely new pathways underlying variability in human traits.[11] The GWAS approach has been applied to study drug response phenotypes,[12] and even in relatively small sets, it has occasionally been successful in identifying associated common variants. Sometimes these are known from candidate gene studies. In other cases, notably drug hypersensitivity reactions,[13] GWASs in relatively small numbers (tens or hundreds of patients) have identified very strong signals that have then been replicated. More recently, methods have been developed to combine multiple trait-associated SNPs into a single polygenic risk score, and these scores are showing promise in identifying patients at risk for disease and their potential to identify patients at risk for unusual drug responses is being investigated.[14,15]

The GWAS paradigm is enabled by technology to generate the dense genotype datasets. New technologies being developed to generate other types of high-dimensional data similarly hold the promise of elucidating new biologic pathways in disease and drug response. Rapid, extremely high-throughput and increasingly inexpensive sequencing technologies are detecting rare DNA sequence variants whose contribution to disease or drug response is only now being appreciated.[7] RNA sequencing ("RNA-Seq") has replaced microarray analysis as the method of choice for cataloging RNA transcript profiles and abundance by specific cellular subtype and disease, and the extension of this technique to single cells is providing important new insights into our view of common and rare diseases. Advances in mass spectrometry are similarly enabling development of catalogs (proteomic and metabolomic profiling) of all proteins or of small-molecule metabolites of cellular processes, including drug metabolites, by cell and disease. Other sources of high-dimensional data include electronic health record (EHR) systems, as discussed later, and high-density digital images. Integrating these diverse data types into a comprehensive picture of the perturbations that result in disease or variable drug responses is the goal of the evolving discipline of *systems* biology and pharmacology. It has been proposed that future drug development would be better served by a focus on pathways identified by systems approaches rather than single targets.[16]

MOLECULAR AND GENETIC BASIS FOR VARIABLE DRUG RESPONSE

Many factors contribute to variable drug responses, including the patient's age, severity of the disease being treated, presence of disease of excretory organs, drug interactions, and poor compliance. This section describes major pathways leading to variable drug responses.

High-Risk Pharmacokinetics

When a drug is metabolized and excreted by multiple pathways, absence of one of these pathways, because of genetic variants, drug interactions, or dysfunction of excretory organs, generally does not affect drug concentrations or actions. By contrast, if a single pathway plays a critical role, the drug is more likely to exhibit marked variability in plasma concentration and associated effects, a situation that has been termed *high-risk pharmacokinetics* (Fig. 9.4).

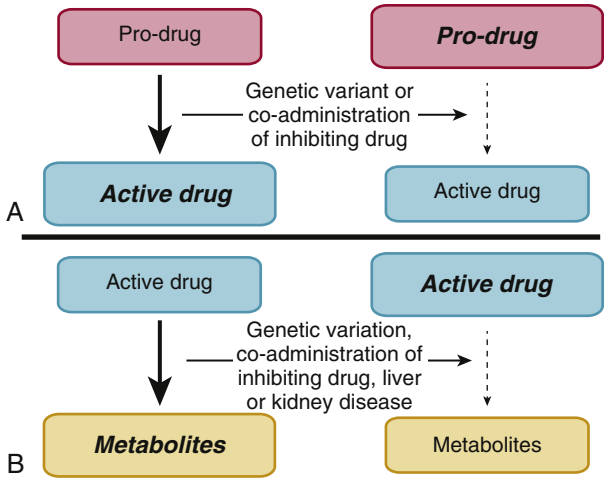

FIGURE 9.4 Two high-risk pharmacokinetic scenarios. **A,** Pro-drug activated by a single drug-metabolizing pathway. In this case, loss of function genetic variants or co-administration of a drug that inhibits the pathway will lead to failure of bioactivation and loss of drug effect. **B,** Active drug metabolized by a single pathway. In this case, loss of function genetic variants, co-administration of a drug that inhibits the pathway, or the presence of liver or kidney disease can inhibit drug elimination and thus lead to exaggerated drug action. This occurs because clinically important alternate pathways for drug elimination are absent, and increases in plasma parent drug concentrations can translate into serious drug toxicity. Note also that gain-of-function genetic variants or co-administered drugs that increase the rate of elimination will lead to decreased drug action. The overall effect is also modulated by the activity of the metabolites.

One high-risk scenario (Fig. 9.4A) involves bioactivation of a drug—that is, metabolism of the drug to active and potent metabolites that mediate pharmacologic action. Decreased function of such a pathway reduces or eliminates drug effect. Bioactivation of clopidogrel by CYP2C19 is an example; persons with reduced CYP2C19 activity (caused by genetic variants or possibly by interacting drugs; see Tables 9.1 and 9.2) have an increased incidence of cardiovascular events following coronary stent placement.[17] Similarly, the widely used analgesic codeine undergoes CYP2D6-mediated bioactivation to an active metabolite, morphine, and patients with reduced CYP2D6 activity ("poor metabolizers" [PMs]) display reduced analgesia. A small group of individuals with multiple functional copies of *CYP2D6*, and thus increased enzymatic activity ("ultrarapid metabolizers" [UMs]), has been identified; in this group, codeine may produce respiratory depression because of rapid morphine generation. In 2013 the U.S. Food and Drug Administration (FDA) label for codeine was revised to contraindicate its use in children after tonsillectomy, because deaths in UMs had been reported. A third example is the angiotensin receptor blocker losartan, which is bioactivated by CYP2C9; reduced antihypertensive effect is a risk with common genetic variants that reduce CYP2C9 activity or with co-administration of CYP2C9 inhibitors such as phenytoin.

In a second high-risk pharmacokinetic scenario (Fig. 9.4B), a drug is eliminated by only a single pathway. In this case, absence of activity of that pathway will lead to marked accumulation of drug in plasma, and for many drugs, such accumulation results in a high risk of drug toxicity. A simple example is the dependence of sotalol or dofetilide elimination on renal function; failure to decrease the dosage in a patient with renal dysfunction leads to accumulation of these drugs in plasma and an increased risk for drug-induced QT prolongation and torsades de pointes. Similarly, administration of a wide range of P-glycoprotein inhibitors will predictably elevate plasma concentration of digoxin, which is eliminated primarily by P-glycoprotein–mediated efflux into bile and urine (see Table 9.2). Propafenone is metabolized by CYP2D6 to a metabolite that has some sodium channel–blocking actions but lacks the weak beta-blocking effect of the parent drug. Administration of propafenone to PMs, or co-administration of CYP2D6 inhibitors (e.g., some SSRI antidepressants) to EMs, can lead to parent drug accumulation, bradycardia, and bronchospasm.

Other Important Pharmacogenetic Effects

Administration of CYP2D6-metabolized beta blockers, including metoprolol and carvedilol, to patients with defective enzyme activity may produce exaggerated heart rate slowing. Some antidepressants are CYP2D6 substrates; for these drugs, cardiovascular adverse effects are more common in CYP2D6 PMs, whereas therapeutic efficacy is more difficult to achieve in UMs.

The risk of aberrant drug responses caused by CYP variants is greatest in persons who are homozygous (i.e., PMs). However, for drugs with very narrow therapeutic margins (e.g., warfarin, clopidogrel), even heterozygotes may display unusual drug sensitivity. Although PMs make up a minority of persons in most populations, many drugs in common use can inhibit these enzymes and thereby "phenocopy" the PM trait. Omeprazole blocks CYP2C19 and in some studies has been associated with an increase in cardiovascular events during clopidogrel therapy; however, this effect is controversial and may not extend to other proton pump inhibitors.[18] Similarly, specific inhibitors of CYP2D6 and CYP2C9 can phenocopy the PM trait when co-administered with substrate drugs (Table 9.3).

TABLE 9.3 Drug Interactions: Mechanisms and Examples

MECHANISM	DRUG	INTERACTING DRUG	EFFECT
Decreased bioavailability	Digoxin	Antacids	Decreased digoxin effect secondary to decreased absorption
Increased bioavailability	Digoxin	Antibiotics	By eliminating gut flora that metabolize digoxin, some antibiotics may increase digoxin bioavailability. NOTE: Some antibiotics also interfere with P-glycoprotein (expressed in the intestine and elsewhere), another effect that can elevate digoxin concentration.
Induction of hepatic metabolism	*CYP3A/P-glycoprotein substrates:*	Phenytoin	Loss of drug effect secondary to increased metabolism
	Quinidine	Rifampin	
	Mexiletine	Barbiturates	
	Verapamil	St. John's wort	
	Cyclosporine		
	Apixaban		
	Rivaroxaban		
Inhibition of hepatic metabolism	*CYP2C9:*	Amiodarone	Decreased warfarin requirement
	Warfarin	Phenytoin	Diminished conversion of losartan to its active metabolite, with decreased antihypertensive control
	Losartan		
	CYP3A substrates:	Ketoconazole	Increased risk for drug toxicity
	Quinidine	Itraconazole	
	Cyclosporine	Erythromycin	
	HMG-CoA reductase inhibitors: lovastatin, simvastatin, atorvastatin; not pravastatin	Clarithromycin	
		Some calcium blockers	
	Apixaban	Some HIV protease inhibitors (especially ritonavir)	
	Rivaroxaban		
	CYP2D6 substrates:	Quinidine (even ultralow dose), fluoxetine, paroxetine	Increased beta blockade
	Beta blockers (see Table 9.2)		Increased adverse effects
	Propafenone		Decreased analgesia (due to failure of biotransformation to active metabolite morphine)
	Desipramine		
	Codeine		
	CYP2C19:	Omeprazole, possibly other proton pump inhibitors	Decreased clopidogrel efficacy
	Clopidogrel		
Inhibition of drug transport	*P-glycoprotein transport:*	Amiodarone, quinidine, verapamil, cyclosporine, itraconazole, erythromycin, dronedarone	Increased digoxin or dabigatran plasma concentrations, with toxicity
	Digoxin, dabigatran		
	Renal tubular transport:	Verapamil	Slightly increased plasma concentration and QT effect
	Dofetilide		
	Monoamine transport:	Tricyclic antidepressants	Blunted antihypertensive effects
	Guanadrel		
Pharmacodynamic interactions	Aspirin + warfarin		Increased therapeutic antithrombotic effect; increased risk of bleeding
	Nonsteroidal anti-inflammatory drugs	Warfarin	Increased risk of gastrointestinal bleeding
	Antihypertensive drugs	Nonsteroidal anti-inflammatory drugs	Loss of blood pressure lowering
	QT-prolonging antiarrhythmics	Diuretics	Increased torsades de pointes risk secondary to diuretic-induced hypokalemia
	Supplemental potassium and/or spironolactone	ACE inhibitors	Hyperkalemia
	Sildenafil	Nitrates	Increased and persistent vasodilation; risk of myocardial ischemia

ACE, Angiotensin-converting enzyme; *HIV,* human immunodeficiency virus; *HMG-CoA*, 3-hydroxy-3-methylglutaryl–coenzyme A.

The widely used antirejection drug tacrolimus is bioinactivated by CYP3A5. A variant common in persons of European ancestry reduces enzyme activity. This variant is rare in patients of African ancestry, who therefore often require higher doses to avoid transplant rejection.[19]

A common nonsynonymous SNP in *SLCO1B1* has been associated with increased risk for simvastatin-induced myopathy by candidate studies with variability in simvastatin pharmacokinetics and by GWAS.[20]

The heart rate slowing and blood pressure effects of beta blockers and beta agonists have been associated with polymorphisms in the *drug targets*, the $beta_1$ and $beta_2$ receptors. A common variant in *ADRB1*, encoding the $beta_1$ receptor, has been implicated as a mediator of survival and prevention of atrial fibrillation[21] during therapy with the beta blocker bucindolol in heart failure. Variability in warfarin dose requirements has been clearly associated with variants in both *CYP2C9*, which mediates elimination of the active enantiomer of the drug, and *VKORC1*, part of the vitamin K complex that is the drug target. Indeed, these common variants account for up to half of the variability in warfarin dose requirement, illustrating the large impact that common SNPs can exert on drug response phenotypes. Furthermore, allele frequencies vary strikingly by ancestry, probably accounting for warfarin dose requirements being low in Asian patients and high in African patients compared with white patients.[22] Rosuvastatin plasma concentrations are higher in East Asian subjects, and variants in multiple genes have been implicated; as a result, lower doses are suggested.

Torsades de pointes during QT-prolonging drug therapy has been linked to polymorphisms not only in the ion channel that is the target for most QT-prolonging drugs (Kv11.1, encoded by *KCNH2*, also known as *HERG*) but also to other ion channel genes. A large candidate gene survey reported that a nonsynonymous SNP in *KCNE1*, a subunit for the slowly activating potassium current I_{Ks}, conferred an odds ratio of approximately 10 for torsades risk. In addition, in approximately 20% of cases, this ADR occurs in patients with clinically latent congenital long-QT syndrome, emphasizing the interrelationship among disease, genetic background, and drug therapy. Interestingly, a polygenic risk score constructed from a GWAS of baseline QT intervals was able to separate patients with drug-induced torsades de pointes and those tolerating QT-prolonging drugs.[14] Similarly, sodium channel–blocking drugs also can bring out latent Brugada syndrome. Patients with congenital long-QT syndrome or Brugada syndrome and their practitioners should be aware of websites that list potentially dangerous drugs (www.crediblemeds.org for long QT; www.brugadadrugs.org for Brugada syndrome).

The anticancer drug trastuzumab is effective only in patients with cancers that do not express the Her2/neu receptor. Because the drug also potentiates anthracycline-related cardiotoxicity, toxic therapy can be avoided in patients who are receptor negative (see also Chapters 56 and 57). More recently, rare truncating SNPs in titin, implicated in dilated cardiomyopathy, have also been associated with chemotherapy-induced cardiomyopathy.[23] Indeed, anticancer drugs and in particular newer "targeted" agents are increasingly recognized to cause diverse cardiovascular ADRs, including arterial and venous thrombosis, cardiomyopathy, myocarditis, and arrhythmias. Understanding the pathways leading to these effects could inform new approaches to prevent and treat cardiovascular disease more broadly.[24]

OPTIMIZING DRUG DOSES

The goals of drug therapy should be defined before the initiation of drug treatment. These may include acute correction of serious pathophysiology, acute or chronic symptom relief, or changes in surrogate endpoints (e.g., blood pressure, serum cholesterol, INR) that have been linked to beneficial outcomes in target patient populations. However, the lessons of CAST and of positive inotropic drugs should make prescribers skeptical about such surrogate-guided therapy in the absence of controlled clinical trials.

When the goal of drug therapy is to correct acutely a disturbance in physiology, the drug should be administered intravenously in doses designed to achieve a therapeutic effect rapidly. This approach is best justified when benefits clearly outweigh risks. Large boluses of IV drugs carry a risk of enhancing drug-related toxicity; therefore, even with the most urgent medical indication, this approach is rarely appropriate. An exception is adenosine, which must be administered as a rapidly delivered bolus because it undergoes extensive and rapid elimination from plasma by uptake into almost all cells. As a consequence, a slow bolus or infusion rarely achieves sufficiently high concentrations at the desired site of action (the coronary artery perfusing the atrioventricular node) to terminate arrhythmias. Similarly, the time course of anesthesia depends on anesthetic drug delivery to and removal from sites in the central nervous system.

The time required to achieve steady-state plasma concentrations is determined by the elimination half-life (see earlier). The administration of a loading dose may shorten this time, but only if the kinetics of distribution and elimination are known beforehand in an individual patient and the correct loading regimen is chosen. Otherwise, overshoot or undershoot during the loading phase may occur (see Fig. 9.3). Thus the initiation of drug therapy by a loading strategy should be used only when the indication is acute.

Two dose-response curves describe the relationship between drug dose and the expected cumulative incidence of a beneficial effect or an ADR (Fig. 9.5). The distance along the *x* axis describing the difference between these curves, often termed the *therapeutic ratio* (or index, or window), provides an index of the likelihood that a chronic dosing regimen that provides benefits without ADRs can be identified. Drugs with especially wide therapeutic indices often can be administered at infrequent intervals, even if they are rapidly eliminated (Fig. 9.5A,C).

When anticipated ADRs are serious, the most appropriate treatment strategy is to start at low doses and reevaluate the necessity for increasing drug dosages once steady-state drug effects have been achieved. This approach has the advantage of minimizing the risk of dose-related ADRs but carries with it a need to titrate doses to efficacy. Only when stable drug effects are achieved should increasing drug dosage to achieve the desired therapeutic effect be considered. An example is sotalol: because the risk of torsades de pointes increases with drug dosage, the starting dose should be low.

In other cases, anticipated toxicity is relatively mild and manageable. It may then be acceptable to start at dosages higher than the minimum required to achieve a therapeutic effect, accepting a greater-than-minimal risk of ADRs; some antihypertensives can be administered in this way. However, the principle of using the lowest dose possible to minimize toxicity, particularly toxicity that is unpredictable and unrelated to recognized pharmacologic actions, should be the rule.

Occasionally, dose escalation into the high therapeutic range results in no beneficial drug effect and no side effects. In this circumstance the prescriber should be alert to the possibility of noncompliance or drug interactions at the pharmacokinetic or pharmacodynamic level. Depending on the nature of the anticipated toxicity, dose escalation beyond the usual therapeutic range may occasionally be acceptable but only if anticipated toxicity is not serious and is readily manageable.

Plasma Concentration Monitoring

For some drugs, curves such as those shown in Figure 9.5A and B, relating drug concentration to cumulative incidence of beneficial and adverse effects, can be generated. With such drugs, monitoring plasma drug concentrations to ensure that they remain within a desired therapeutic range (i.e., greater than a minimum required for efficacy and less than a maximum likely to produce ADRs) may be a useful adjunct to therapy. Monitoring drug concentrations also may be useful to ensure compliance and to detect pharmacokinetically based drug interactions that underlie unanticipated efficacy and/or toxicity at usual dosages. Samples for measurement of plasma concentrations generally should be obtained just before the next dose, at steady state. These trough concentrations provide an index of the minimum plasma concentration expected during a dosing interval.

On the other hand, patient monitoring, whether by plasma concentration or other physiologic indices, to detect incipient toxicity is best accomplished at the time of anticipated peak drug concentrations.

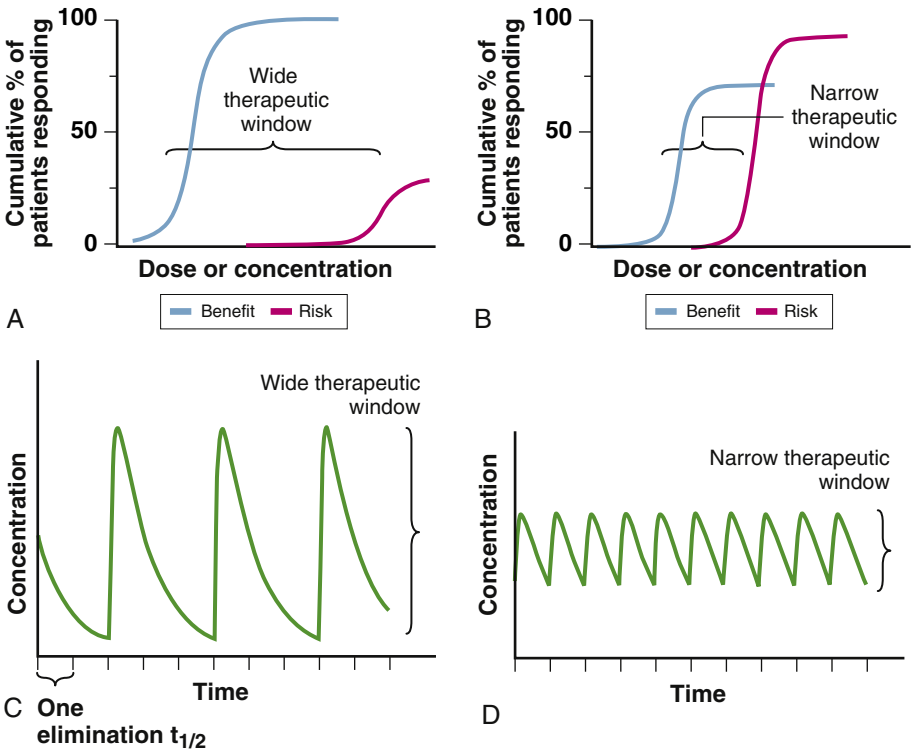

FIGURE 9.5 The concept of therapeutic ratio. **A** and **B,** Two dose-response (or concentration-response) curves. The *blue* lines describe the relationship between dose and cumulative incidence of beneficial effects, and the *magenta* lines depict the relationship between dose and dose-related adverse effects (risk). **A,** A drug with a wide therapeutic ratio displays separation between the two curves, a high degree of efficacy, and low degree of dose-related toxicity. Under these conditions, a wide therapeutic ratio can be defined. **B,** Conversely, the curves describing cumulative efficacy and cumulative incidence of adverse effects are positioned near each other, the incidence of adverse effects is higher, and the expected beneficial response is lower. These characteristics define a narrow therapeutic ratio. **C** and **D,** Steady-state plasma concentrations with oral drug administration as a function of time with wide *(left)* and narrow *(right)* therapeutic ratios. The *hash marks* on the abscissae each indicate one elimination half-life ($t_{1/2}$). **C,** When the therapeutic window is wide, drug administration every three elimination half-lives can produce plasma concentrations that are maintained above the minimum for efficacy and below the maximum beyond which toxicity is anticipated. **D,** The opposite situation is illustrated. To maintain plasma concentrations within the narrow therapeutic range, the drug must be administered more frequently.

Thus patient surveillance for QT prolongation during therapy with sotalol or dofetilide is best timed for 1 to 2 hours after the administration of a dose of drug at a steady state.

A lag between the time courses of drug in plasma and drug effects may exist (see earlier). In addition, monitoring plasma drug concentrations relies on the assumption that the concentration measured is in equilibrium with that at the target molecular site. Of note, it is only the fraction of drug not bound to plasma proteins that is available to achieve such equilibration. Variability in the extent of protein binding can therefore affect the free fraction and anticipated drug effect, even in the presence of apparently therapeutic total plasma drug concentrations.

Dose Adjustments in Disease

Polypharmacy is common in patients with varying degrees of specific organ dysfunction. Although treatment with an individual agent may be justified, the practitioner should also recognize the risk of unanticipated drug effects and interactions, particularly drug toxicity, during therapy with multiple drugs.

The presence of renal disease mandates dose reductions (or choosing alternate therapies if renal dysfunction is severe) for drugs eliminated primarily by renal excretion. Examples include dabigatran, rivaroxaban, edoxaban, digoxin, dofetilide, and sotalol. Apixaban can be used even in patients undergoing dialysis, with reduced doses in certain subgroups (e.g., older patients, those weighing <60 kg). A requirement for dose adjustment in cases of mild renal dysfunction is dictated by available clinical data and the likelihood of serious toxicity if drug accumulates in plasma because of impaired elimination. Renal failure reduces the protein binding of some drugs (e.g., phenytoin); in this case a total drug concentration value in the therapeutic range may actually represent a toxic value of unbound drug.

Advanced liver disease is characterized by decreased hepatic drug metabolism and portacaval shunts that decrease clearance, particularly first-pass clearance. Moreover, affected patients frequently have other profound disturbances of homeostasis, such as coagulopathy, severe ascites, and altered mental status. These pathophysiologic features of advanced liver disease can affect not only the dose of a drug required to achieve a potentially therapeutic effect but also the perception of risks and benefits, thereby altering the prescriber's assessment of the actual need for therapy.

Heart disease is similarly associated with several disturbances of drug elimination and drug sensitivity that may alter the therapeutic doses or the practitioner's perception of the desirability of therapy based on evaluation of risks and benefits. Patients with left ventricular hypertrophy often have baseline QT prolongation, so risks associated with use of QT-prolonging antiarrhythmics may increase; most guidelines suggest avoiding QT-prolonging antiarrhythmics in such patients (see Chapters 67 and 99).

In heart failure (see Chapter 50), hepatic congestion can lead to decreased clearance with a corresponding increased risk for toxicity with usual doses of certain drugs, including some sedatives, lidocaine, and beta blockers. On the other hand, gut congestion can lead to decreased absorption of oral drugs and decreased effects. In addition, patients with heart failure may demonstrate reduced renal perfusion and require dose adjustments on this basis. Heart failure also is characterized by a redistribution of regional blood flow, which can lead to reduced volume of distribution and enhanced risk for drug toxicity. Lidocaine probably is the best-studied example; loading doses of lidocaine should be reduced in patients with heart failure, because of altered distribution, whereas maintenance doses should be reduced in both heart failure and liver disease, because of altered clearance.

Age also is a major factor in determining drug doses, as well as sensitivity to drug effects. Doses in children generally are administered on an mg/kg body weight basis, although firm data to guide therapy are often not available. Variable postnatal maturation of drug disposition systems may present a special problem in the neonate. Older persons often have reduced creatinine clearance, even those with a normal serum creatinine level, and dosages of renally excreted drugs should be adjusted accordingly (see Chapters 90 and 101). Diastolic dysfunction with hepatic congestion is more common in older adults, and vascular disease and dementia often occur, which can lead to increased postural hypotension and risk of falling. Therapies such as sedatives, tricyclic antidepressants, or anticoagulants should be initiated only when the practitioner is convinced that the benefits of such therapies outweigh this increased risk.

Drug Interactions

As a result of therapeutic successes not only in heart disease but also in other disease areas, cardiovascular physicians are increasingly encountering patients receiving multiple medications for

cardiovascular and noncardiovascular indications. Table 9.3 summarizes mechanisms that may underlie important drug interactions. Drug interactions may be based on altered absorption, distribution, metabolism, or excretion. In addition, drugs can interact at the pharmacodynamic level. A trivial example is the co-administration of two antihypertensive drugs, leading to excessive hypotension. Similarly, co-administration of platelet inhibitors and anticoagulants leads to an increased risk for bleeding, although benefits of such combinations also can be demonstrated.

The most important principle in approaching a patient receiving polypharmacy is to recognize the high potential for drug interactions. A complete medication history should be obtained from each patient at regular intervals; patients will often omit topical medications such as eye drops, health food supplements, and medications prescribed by other practitioners unless specifically prompted. Each of these, however, carries a risk of important systemic drug actions and interactions. Even high dosages of grapefruit juice, which contains CYP3A and P-glycoprotein inhibitors, can affect drug responses. Beta blocker eye drops can produce systemic beta blockade, particularly with CYP2D6 substrates (e.g., timolol) in patients with defective CYP2D6 activity. St. John's wort induces CYP3A and P-glycoprotein activity (similar to phenytoin and other drugs) and thus can greatly lower plasma concentrations of substrate drugs such as cyclosporine. As with many other interactions, this may not be a special problem provided both drugs are continued. However, if a patient stabilized on cyclosporine stops taking a concomitantly administered CYP3A inducer, plasma concentrations of the drug can rise dramatically, and toxicity can ensue. Similarly, initiation of an inducer may lead to greatly lowered cyclosporine concentrations and a risk of organ rejection. A number of natural supplements have been associated with serious drug toxicity (e.g., phenylpropanolamine-associated stroke) that has resulted in their withdrawal from the market.

Incorporating Pharmacogenetic Information into Prescribing

The identification of polymorphisms associated with variable drug responses naturally raises the question of how these data could or should be used to optimize drug doses, avoid drugs likely to be ineffective, and avoid drugs likely to produce major toxicities. Indeed, in 2007 the FDA began systematically including pharmacogenetic information in drug labels,[25] and the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides in-depth reviews of the effects of specific genetic variants on drug responses.[26] Despite the intuitive appeal of a pharmacogenetically guided approach to drug therapy, however, practitioners wanting to adopt genetic testing to guide drug therapy encounter substantial practical barriers, including reimbursement and cost, varying levels of evidence supporting a role for genetics, and implementation issues such as how fast and accurately a genetic test result can be delivered. The nature of pharmacogenetic variation is that most patients will display average responses to most drugs, so systematically testing every patient in the hopes of finding the minority likely to display aberrant responses is cumbersome and seems inefficient in terms of time and cost unless the benefit for individual patients is large.[22] An example of a large benefit is that routine genotyping of all patients receiving the antiretroviral agent abacavir is now the standard of care because it avoids a potentially life-threatening skin reaction in 3% of patients. By contrast, RCTs suggest either no effect or a modest effect on time within therapeutic range when genotype information is incorporated into warfarin dosing.[22,27,28] Many of these trials were underpowered to examine bleeding risk, which has been associated with variants in *CYP4F2* or *CYP2C9* in population- or EHR-based studies.[22] Two large RCTs have compared thrombosis and bleeding risk with clopidogrel versus other platelet inhibitors (ticagrelor, prasugrel): one showed a significant benefit of using clopidogrel in patients who do not carry *CYP2C19* loss-of-function varaints,[29,30] whereas the other (not yet reported in full) trended to such a benefit but did not achieve its targeted endpoint.[31]

A difficulty with such drug-specific approaches is that the benefit of the genotype data must be large to justify the cumbersomeness and cost of testing all exposed individuals. Although the probability is small that genetic variation plays an important role in predicting the response of an individual patient to a specific drug, when many drugs are prescribed for a population of patients, each patient will display genetically determined aberrant responses to some drugs. This reasoning underlies the concept of *preemptive genotyping,* in which many genetic variants relevant to many variable drug responses are assayed in patients who have not yet been exposed to the drugs.[32,33] These data are then stored in EHR systems with advanced point-of-care decision support capabilities that deliver instantaneous advice when a drug is prescribed to a patient with known genomic variants.[34] Several technologic developments enable this vision, including advanced EHRs and multiplexed inexpensive genotyping assays or sequencing that interrogate many polymorphisms for the same cost as a handful relevant to one drug. The concept is now being tested at a few medical centers, with the goals of establishing cost and benefit, understanding how health care providers react, and optimizing decision support to integrate pharmacogenomic information seamlessly into health care.[22,34,35]

FUTURE PERSPECTIVES

The past 25 years have seen dramatic advances in the treatment of heart disease, in no small part because of the development of highly effective and well-tolerated drug therapies such as HMG-CoA reductase inhibitors, ACE inhibitors, and beta blockers. These developments, along with improved nonpharmacologic approaches, have led to dramatically enhanced survival of patients with advanced heart disease. Thus polypharmacy in an aging and chronically ill population is becoming increasingly common. In this milieu, drug effects become increasingly variable, reflecting interactions among drugs, underlying disease and disease mechanisms, and genetic backgrounds. Furthermore, despite advances in the Western world, cardiovascular disease is emerging as an increasing problem worldwide as smoking and the metabolic syndrome are increasing. Understanding how genetic background plays into disease susceptibility and responses to drug therapy, concepts largely tested in only European-ancestry populations to date, represents a major challenge in cardiovascular medicine.

More generally, genomic medicine—the application of genetic variant information in health care—is still in its infancy, so reported associations require independent confirmation and assessment of clinical importance and cost-effectiveness before they can or should enter clinical practice. Importantly, most pharmacogenomic studies reported to date have focused on common variants, and we now recognize that the vast majority of polymorphisms in any gene, including CYPs and other "pharmacogenes," are uncommon (MAF < 1%). Developing approaches to establish the clinical impact of such rare variants on drug responses, and a potential role for polygenic risk scores, is an emerging challenge.

This challenge is all the more acute because the cost of sequencing has fallen drastically since the completion of the first-draft human genome in 2000, and the less-than-$1000 whole-genome sequence is now a reality. This may be enabling for the preemptive pharmacogenomic strategy just outlined, as well as a broader vision of genome-guided health care, but presents major challenges in data storage and mining.

The relationship between the prescriber and the patient remains the centerpiece of modern therapeutics. An increasingly sophisticated molecular and genetic view of response to drug therapy should not change this view but rather complement it. Each initiation of drug therapy represents a new clinical experiment. Prescribers must always be vigilant regarding the possibility of unusual drug effects, which could provide clues about unanticipated and important mechanisms of beneficial and adverse drug effects.

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