Cardiovascular Drugs and the Management of Heart Disease

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Preface

The recent introduction of new cardiac drugs and new applications of standard drugs has brought about rapid and significant changes in the clinical management of cardiovascular disorders. New pharmaceuticals, as well as other therapeutic advances, have altered dramatically the once standard treatment of such common problems as angina, hypertension, dysrhythmias, congestive heart failure, and acute myocardial infarction. This comprehensive text summarizes this information and experience and presents it in a readable and practical fashion for use by the busy physician.

Most chapters in the first half of the book deal with current information on individual cardiac drugs and groups of cardiac drugs. In order to provide rapid and easy access to the guidelines for the clinical application of these agents, each chapter is introduced by a summary providing the specific major therapeutic indications and dosages as well as important clinical pharmacology, side effects, drug interactions, and contraindications. In this way, if a cardiac drug is to be administered, the chapter summary may be used as a ready reference to the information necessary for rapid clinical decision making. Also included are concise tables that summarize loading and maintenance dosages of intravenous agents and dose-related hemodynamic effects and toxicities. The text of each drug chapter provides detailed and well-referenced justification for the recommendations in the summary and can be read at leisure for more specific background information.

The remainder of the book covers the management of the cardiovascular disorders most often seen in the clinical practice of medicine. These chapters reflect practical information derived both from the scientific literature and from the clinical experience of the authors. Because of the ever expanding, complex, and sometimes contradictory results of medical research, it is not surprising that alternative clinical management approaches can be offered and frequently remain controversial. For example, it took days for a group of board certified cardiologists to agree on the best set of routine admission orders for a patient with an acute myocardial infarction. These new guidelines are presented in the summary of the chapter of the management of such patients. Indeed, an attempt to offer recommendations representing practical clinical consensus has been made for each cardiovascular disorder addressed.

As is evident from the table of contents, the major emphasis of this book is on the medical management of cardiovascular disease. An additional, but at times difficult, aspect of therapeutics is to know when to consider surgical intervention. The indications for surgery in valvular and ischemic heart disease, as well as temporary and permanent pacemaker therapy, are covered in detail. Although surgery may be an integral and necessary part of the management of an individual patient with cardiovascular disease, in the adult patient surgery is rarely curative. The medical management of such patients remains as important after surgery as before.

This volume is designed as both a therapeutic handbook and a reference text that can be used equally well in the wards of the hospital, in the physician's office, or in the medical library. It is anticipated that this form of presentation will be of interest to all physicians who care for patients with cardiovascular disorders.

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Chapter 1

Principles of Drug Therapy

Kenneth A. Conrad

Most drugs that are used to treat cardiovascular disorders have a narrow therapeutic range. When plasma concentrations fall below this range, efficacy is unlikely, and when they exceed it, toxicity becomes more frequent. To achieve this therapeutic range, an understanding of basic pharmacokinetic principles is essential. In this chapter, these principles will be presented, and an approach to drug dosing based on these concepts will be suggested.

DRUG DISTRIBUTION

To exert its pharmacologic effect, a drug must reach the site at which that effect is initiated. This is usually accomplished via the systemic circulation. When a drug is given intravenously, it reaches the systemic circulation instantly. The magnitude of the increase in plasma concentration depends on several factors: the rate of infusion, the volume of the "central compartment" (usually the blood volume), and the rate at which the drug leaves the central compartment (either via distribution into peripheral compartments such as muscle, fat, etc. or via hepatic or renal elimination). The concept of compartments is represented diagrammatically in Fig. 1.

Rapid intravenous administration of certain drugs can produce extraordinarily high plasma drug concentrations, resulting in therapeutic efficacy, toxicity, or both. For instance, administration of 100 mg of lidocaine intravenously to a 70-kg person will produce high therapeutic levels and will suppress ventricular ectopic beats in many patients. However, because drug distribution and elimination occur rapidly, the plasma levels will usually fall to subtherapeutic levels within minutes. Rapid administration of 200 mg of lidocaine will produce potentially toxic levels for the first few minutes. A compromise that will minimize the toxicity and maximize the therapeutic effects of the drug would be to administer two separate boluses. In practice, the initial bolus of 100 mg is accompanied by an intravenous infusion, and a second bolus of 50 mg is given 15 or 20 min later (1).

On the other hand, distribution of digoxin to its active site in the myocardium proceeds more slowly. Therefore, although plasma levels after intravenous administration of a "loading" dose may be severalfold above the "toxic" range for the first few hours, no untoward effects usually occur (2).

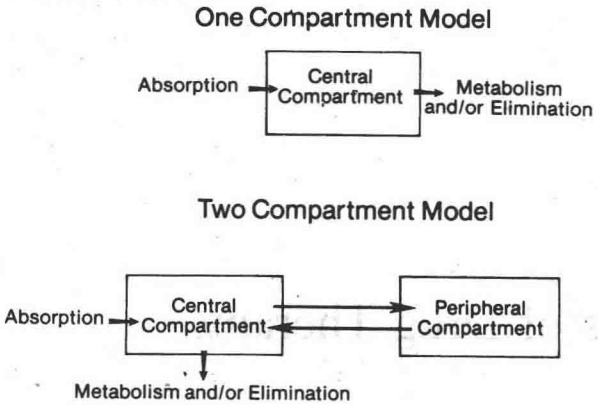

FIG. 1. Compartment models. The disposition of drugs is illustrated for drugs that have one- or two-compartment characteristics.

TABLE 1. *Volume of distribution of several drugs*

Drug	V_d (liters/kg)
Digoxin	10
Propranolol	3
Quinidine	3
Procainamide	2
Lidocaine	0.5 (Central) 1.6 (Apparent)
Diazepam	1.3
Digitoxin	0.6
Warfarin	0.1

The rate and extent of drug distribution depend on several factors, including tissue blood flow (usually high in kidney, liver, heart, brain), the presence of drugs or disease states that may alter blood flow, plasma protein binding, and the rate of uptake of drug by tissues.

The concept of an apparent volume of distribution (V_d) is useful in understanding the way in which any given drug is distributed in the body, although the term itself may not necessarily relate to any physiologic space.

The V_d expresses a relationship between the amount of drug in the body and the drug concentration in the plasma (3). For a drug that has one-compartment characteristics, the V_d is that volume in which the drug appears to be distributed if the drug existed in that volume in the same concentration as in plasma. The volume of distribution (V_d) may be very high if the drug binds avidly to the tissues. This is the case for digoxin, which has a distribution volume of 10 liters/kg. On the other hand, a drug that remains primarily in the blood will have a low V_d. Warfarin, whose V_d is 0.1 liter/kg (Table 1), is an example of such a drug.

EFFECTS OF DISEASE STATES ON DRUG PROTEIN BINDING AND DISTRIBUTION

Changes in drug distribution in patients with renal and hepatic disease occur primarily as a result of changes in drug protein binding. Tissue uptake of basic drugs may be reduced and that of acidic drugs increased in the presence of acidosis, particularly if it is acute.

Acidosis may lead to increased toxicity of drugs such as salicylates since uptake by the brain is increased.

The volume of distribution of several drugs, including lidocaine (4), procainamide (5), and quinidine (6), is reduced in congestive heart failure. This is presumably a result of the poor perfusion of peripheral tissues. As a consequence of this reduction in distribution, plasma drug levels will be higher than expected, and toxicity may result from delivery of the drug to more adequately perfused tissues—especially the heart and brain.

The binding of drug to tissue and serum proteins can influence drug distribution, the rate at which the drug reaches its active site(s), and the rate at which it is eliminated from the blood.

A drug that is bound to plasma proteins is usually pharmacologically inactive. Only unbound drug diffuses into tissue, since the protein–drug complex cannot penetrate cell membranes. Similarly, metabolism and elimination of the drug usually involve the unbound drug.

Albumin is the protein to which most drugs are bound in serum. Albumin is present in serum in concentrations of 40 g/liter and is able to bind most drugs in concentrations of up to 100 mg/liter (100 μg/ml) without changes in the percent binding. However, drugs whose therapeutic concentration exceeds 100 μg/ml, such as salicylate and phenylbutazone, may saturate available binding sites, and a larger fraction of free drug may be present when plasma concentrations exceed 100 μg/ml (7).

Most drug assays measure total drug (bound plus free) in plasma. Estimates of apparent V_d will be higher if there is less plasma protein binding of a drug, as less of the drug will be present in the plasma:

$$V_d \text{ (increased)} = \frac{\text{Amount of drug in body (unchanged)}}{\text{Concentration in plasma (decreased)}} \quad (1)$$

Disease states and drug interactions can have clinically important effects on drug protein binding and on the pharmacologic effects of drugs. Protein binding of drugs may be reduced in the elderly and in patients with the nephrotic syndrome or chronic liver disease as a result of reduced serum albumin concentrations. In patients with renal failure, the binding of acidic drugs such as phenytoin (8), warfarin (9), and salicylate (10) is reduced. Therefore, the therapeutic concentration of phenytoin and salicylate (as measured by assays of total drug plasma) will be lower in patients with such disease states. A total serum level of 15 μg/ml (usual therapeutic range 10–20 μg/ml) of phenytoin may well be "toxic" in a patient whose phenytoin protein binding is reduced as a result of uremia.

DRUG ABSORPTION

Most drugs are administered orally in tablet or capsule form. Before these drugs can be absorbed through the gastrointestinal tract, the tablet or capsule must disintegrate, and the drug must dissolve in the gastrointestinal fluids. In the newer, sustained-release-type preparations of certain drugs (e.g., Procan SR®, Slow K®), the medication is embedded in a wax matrix or is film coated. Differences in dosage formulation because of differences in stabilizing materials, binders, lubricants, etc. may alter disintegration and dissolution rates and account for large differences in rate, and perhaps extent, of drug absorption. For most drugs used in the treatment of cardiovascular disease, the extent of drug absorption is the

most important consideration. This is true because most drugs are given chronically, and a constant, steady state of concentration is desirable. To be more specific, it is the extent of bioavailability or the amount of drug that reaches the systemic circulation that is most important. Bioavailability depends on absorption, gastrointestinal drug metabolism, and the extent of drug metabolism as it passes through the liver in the portal blood (the so-called "first-pass" metabolism—see Drug Metabolism). Some drugs with low bioavailability also tend to have more variable availability and therefore may be associated with fluctuations in plasma concentration and effects.

After drug dissolution has occurred, the drug will be available for absorption. Drugs that are weakly acidic or basic and are lipid soluble are absorbed well through the stomach. Strong bases such as ephedrine will not be absorbed by the stomach at all. However, because of the large surface area of the small intestine, most drug absorption occurs there regardless of the acidic or basic nature of the drug.

Gastric emptying may vary as a consequence of drug therapy or disease. Any process that prolongs gastric emptying time will tend to reduce the overall absorption rate of a drug but may not affect the extent of drug absorption. Gastric emptying is slowed by exercise, by excitement, by anticholinergic drugs, and in patients with gastric ulcers (11).

Changes in peristalsis in the small intestine have variable effects on drug absorption. Reduced peristalsis will slow the dissolution and absorption rate of drugs, but because the drug is in contact with the absorbing surface for a longer period, more of the drug may be absorbed (12).

Interactions between drugs or between drugs and food sometimes alter the absorption of drugs (13). Food may enhance the bioavailability of propranolol, metoprolol, hydrochlorothiazide, phenytoin, carbamazepine, erythromycin stearate, and dicoumarol. Food may reduce the bioavailability of isoniazid, rifampin, penicillin, and ampicillin. Tetracycline binds with iron, calcium in food (milk products), or antacids. Antacids reduce gastric emptying. Aluminum and magnesium antacids reduce the absorption of digoxin (14). Kaolin products bind tetracycline and anticholinergics; cholestyramine reduces absorption of chlorothiazide, phenobarbital, digitalis preparations, and anticoagulants by binding to them (15).

Sublingual Administration

Absorption of drugs from the oral mucosa is generally good and has the advantage over oral dosing that the liver is bypassed so that "first-pass" metabolism is avoided. Similarly, interactions with food and degradation by intestinal enzymes are also avoided.

Sublingual administration of nitroglycerin and other organic nitrates is often desirable because of the rapidity with which the liver metabolizes these drugs. Oral dosage forms of nitrates may be effective if a dose is large enough to enable a portion of the drug to escape metabolism in the liver on the first pass through that organ.

Rectal Administration

Drugs may be absorbed by the rectal mucosa. An advantage to this route is that drugs absorbed this way also avoid the hepatic first-pass metabolism. However, rectal absorption is often erratic and incomplete, and, therefore, this route of administration is discouraged.

Parenteral Injection

Intravenous administration of drugs insures complete bioavailability of the drug given. This route is useful to rapidly attain serum drug levels that are "therapeutic." It is desirable

in patients who cannot tolerate oral medications and in patients in shock who would absorb oral, subcutaneous, or intramuscular drugs poorly. However, risks of adverse responses to some intravenous drugs are also high, particularly if the drug is given too rapidly.

The subcutaneous route of drug administration is acceptable only for nonirritating drugs and for those where a rapid rate of absorption is not necessary. Insulin and heparin are two drugs that are often administered subcutaneously.

Intramuscular injection of drugs is sometimes employed when oral intake is restricted. Drugs in aqueous solutions are rapidly absorbed after intramuscular injection. Absorption is faster from the deltoid than from the thigh muscle, presumably because of the increased vascularity of the former (16). However, when solutions of relatively insoluble drugs are injected, absorption may be slow and incomplete (e.g., quinidine, digitalis, phenytoin). Furthermore, intramuscular injection of such drugs may cause a considerable amount of pain.

DRUG ELIMINATION (METABOLISM AND EXCRETION)

Elimination of drugs from the body proceeds primarily by either renal excretion or by hepatic metabolism. For a few drugs, elimination through the bile is significant. Most lipid-soluble drugs are reabsorbed from the renal tubules, so that elimination of the drugs requires metabolism to more polar compounds.

Metabolism

Drug metabolism takes place primarily in the liver, but drug-metabolizing enzymes are also present in the gastrointestinal mucosa, the placenta, the kidney, and the plasma itself.

Drug metabolism usually produces metabolites that are less active than the parent compound, but, in some cases, metabolites are active, whereas the parent compound is not. Several metabolic steps may occur before a drug is ready for elimination by the kidney. Some metabolites are toxic (metabolites of acetaminophen and lidocaine) and may contribute to or be solely responsible for the major adverse effects of a drug.

Drug biotransformation may occur by conjugation of the drug to a carbohydrate, an amino acid, or other compound (Table 2) (17). Glucuronide conjugation is a very common process and occurs within the hepatic microsomes. Drug oxidation also occurs within hepatic microsomes, whereas reduction and hydrolysis are mediated by microsomal and by nonmicrosomal enzymes. Lipid solubility of a drug favors metabolism by microsomal enzymes, since this allows the drug to penetrate into the endoplasmic reticulum and to bind to cytochrome P-450.

An important group of enzymes within the hepatic endoplasmic reticulum are the mixed-function oxidases. These are involved in the metabolism of many drugs through *N*- and *O*-dealkylation, ring and side chain hydroxylation, deamination, and *N*-hydroxylation. The cytochrome system (cytochrome P-450) is extremely important in these reactions: the drug binds with oxidized cytochrome P-450, and this complex is then reduced. The reduced complex then combines with molecular oxygen; an electron and hydrogen ions (donor: NADPH) are donated, resulting in the formation of an oxidized metabolite and regenerated cytochrome.

Induction of microsomal enzymes by phenobarbital and by polycyclic hydrocarbons such as those found in cigarette smoke may drastically increase the metabolism of several drugs. Phenobarbital increases the metabolism of warfarin; smoking increases the metabolism of theophylline. Cessation of phenobarbital will result in a decreased rate of warfarin metabolism

TABLE 2. *Metabolic processes of drugs*

Reaction	Substrate
Hydroxylation	Phenytoin
	Propranolol
	Quinidine
Dealkylation	Theophylline
	Lidocaine
Oxidation	Chlorpromazine
Reduction	Chloramphenicol
	Chloral hydrate
Hydrolysis	Procaine, succinylcholine
Conjugations	
Glycine conjugation	Nicotinic acid
Glucoronidation	Oxazepam
	Sulfisoxazole
	Meprobamate
Methylation	Histamine, epinephrine
Acetylation	Isoniazid
	Hydralazine
	Procainamide

which may produce toxicity (hypoprothrombinemia) if the warfarin dose is not reduced. Quinidine metabolism may be enhanced by phenytoin and phenobarbital (18).

Drug metabolism may also be inhibited. Allopurinol inhibits metabolism of azathioprine and mercaptopurine. Phenytoin metabolism may be reduced by isoniazid. Propranolol reduces antipyrine (19), lidocaine (19a), and theophylline (20) elimination. Cimetidine reduces metabolism of warfarin (21).

As drug passes through the liver in the circulation, a portion (ranging from 0 to 100%) is eliminated. For those drugs that are highly extracted (percent eliminated > 50%), drug clearance will be significantly altered by changes in hepatic blood flow (22). Although only unbound drug diffuses across membranes to reach metabolic sites, if a drug is avidly metabolized by the liver, more drug will dissociate from proteins and become available for metabolism. For this type of avidly extracted drug (e.g., lidocaine, morphine), oral administration will often not produce adequate serum concentrations, since the drug passing through the liver via the hepatic portal system will be almost 100 percent metabolized before it reaches the systemic circulation. Although some drugs (morphine, propranolol) may be given in doses high enough to allow some drug to reach the systemic circulation, others such as lidocaine cannot be given in very high doses because of the production of toxic metabolites.

Drug metabolism may be reduced in patients with advanced liver disease. Lidocaine elimination is reduced in patients with severe chronic liver disease. There are few well-controlled studies of the effects of chronic liver disease on hepatic clearance of other cardioactive drugs. Congestive heart failure and reduced liver blood flow will reduce the metabolism of lidocaine and other highly extracted drugs (23).

Excretion

Renal excretion of water-soluble or polar drugs and the water-soluble metabolites of other drugs is an important mechanism by which many exogenous compounds are eliminated. Glomerular filtration, active tubular secretion, and tubular reabsorption may all be involved in renal handling of drugs.