Most antiarrhythmic drugs are potent compounds with a relatively narrow therapeutic index. When prescribed judiciously, they can have a key role in enhancing or prolonging the lives of patients with most common arrhythmias. But when misprescribed, through selection of an inappropriate drug or dosage regimen, the end result may range from inadequate control of the arrhythmia to a proarrhythmic effect. Ultimately, the optimal use of antiarrhythmic drug therapy depends in large part on understanding the pharmacodynamics and pharmacokinetics of each antiarrhythmic drug. Despite the common classification of antiarrhythmic drugs into class I, II, III, or IV, each drug has a unique pharmacological profile and must not be considered interchangeable with other members of its class. Likewise, each patient is unique with respect to the innumerable factors that can alter the pharmacokinetics of an antiarrhythmic drug, including coexisting diseases, concurrent drug therapies, and endogenous or age-related metabolic variations. This article provides an overview of the key pharmacodynamic and pharmacokinetic characteristics of the major antiarrhythmic drugs in use. It also offers specific examples that may be used to ensure that patients receive the most appropriate therapy.

The optimal prescribing of antiarrhythmic drug therapy is predicated on a thorough understanding of the pharmacodynamics and pharmacokinetics for that drug. Numerous antiarrhythmic drugs are available, each of which has a unique pharmacological profile. A substantial percentage of the putative treatment failures seen in a consulting practice occur in patients who have not received the correct dosage of an antiarrhythmic drug or were treated with the incorrect drug. This underscores the importance of individualizing therapy to achieve the desired therapeutic effect.

Many factors that must be considered when selecting an antiarrhythmic drug, including efficacy for the specific indication, relative toxicity, dosing convenience, and cost, apply to virtually any drug therapy. Other considerations that can influence the decision-making process are the familiarity of the practitioner with the drug, current treatment fads, previous exposure of the patient to the drug, and labeling concerns. However, the narrow therapeutic index of many antiarrhythmic drugs mandates careful consideration of such factors as whether the drug has active metabolites, whether coexisting diseases or concurrent drug therapy affect bioavailability, whether the drug is protein bound or undergoes first-pass (pre-systemic) metabolism, and potential drug-drug interactions (particularly with other antiarrhythmic drugs). These and other pharmacological properties of a drug can have profound implications for the clinical effectiveness and, more importantly, the clinical safety of a specific regimen. In some instances, lack of familiarity with the key pharmacodynamic and pharmacokinetic properties of an antiarrhythmic drug will not only compromise the therapeutic outcome but also can lead to serious, even life-threatening, proarrhythmic effects.
This article focuses on the general principles of pharmacology as they relate to antiarrhythmic drugs. In addition, it provides guidelines and recommendations for the use of antiarrhythmic drugs in the treatment of the overall patient population, elderly patients, and patients with implantable cardioverter-defibrillators (ICDs). This article describes the marked pharmacological differences among antiarrhythmic drugs and emphasizes the importance of careful evaluation of the pharmacodynamic and pharmacokinetic characteristics of each drug, not just the drug class, when prescribing antiarrhythmic drug therapy.

PHARMACODYNAMICS AND CLASSIFICATION

The pharmacodynamics of a drug refers to its mechanism of action and its effects at a specific site in the body. For antiarrhythmic drugs, the primary mechanism of action is based on their effects on certain ion channels and receptors located on the myocardial cell membrane. The pharmacodynamics of an antiarrhythmic drug determines not only the actions in specific arrhythmias but also the chronotropic, inotropic, and toxic effects. Thus, understanding the different pharmacodynamic properties of these drugs is important to predict the antiarrhythmic effects in a patient.

For almost a quarter of a century, antiarrhythmic drugs have been differentiated by their antiarrhythmic action according to the well-known classification system developed by Vaughan Williams1 and subsequently modified by Harrison2 (Table 1). Although numerous attempts have been made to revise and improve this classification system,4-6 it remains the clearest and most readily accessible method of categorizing the available antiarrhythmic drugs. The original system devised by Vaughan Williams1 includes 4 major groups of antiarrhythmic drugs: classes I, II, III, and IV. Class I drugs (later subclassified as IA, IB, and IC) primarily block the rapid inward sodium current, thereby slowing the rate of the rise of the action potential. Class II drugs (eg, propranolol hydrochloride and other β-adrenergic blocking agents) are β-adrenergic antagonists, which slow the sinus rhythm and slow atrioventricular nodal conduction without substantially changing the Q-T or QRS interval. Class III drugs (eg, sotalol hydrochloride and amioda-

<table>
<thead>
<tr>
<th>Class</th>
<th>Electrocardiographic Effect</th>
<th>Membrane Effect</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaughan Williams IA</td>
<td>↑ QRS and ↑ P-R interval</td>
<td>Sodium channel block; intermediate kinetics</td>
<td>Quinidine, Procainamide hydrochloride</td>
</tr>
<tr>
<td>IB</td>
<td>↓↑ Q-T interval</td>
<td>Sodium channel block; rapid kinetics</td>
<td>Lidocaine, Tocainide</td>
</tr>
<tr>
<td>IC</td>
<td>↑↑ QRS interval</td>
<td>Sodium channel block; slow kinetics</td>
<td>Mexiletine hydrochloride, Flecainide acetate, Propafenone hydrochloride</td>
</tr>
<tr>
<td>II</td>
<td>↓ Heart rate; ↑ P-R interval</td>
<td>β-adrenergic receptor inhibition</td>
<td>Propranolol hydrochloride and others</td>
</tr>
<tr>
<td>III</td>
<td>↑ Q-T interval</td>
<td>Potassium channel block; slow sodium channel facilitator</td>
<td>N-acetyl-procainamide, Sotalol hydrochloride</td>
</tr>
<tr>
<td>IV</td>
<td>↓ Heart rate; ↑ P-R interval</td>
<td>Calcium channel block</td>
<td>Verapamil, Diltiazem hydrochloride</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>P-R interval; ↓ Q-T interval</td>
<td>Na+, K+-ATPase inhibition</td>
<td>Digoxin, Digitoxin</td>
</tr>
<tr>
<td>Adenosine</td>
<td>↓ Heart rate; ↑P-R interval</td>
<td>Purinergic receptor agonist</td>
<td>Adenosine</td>
</tr>
</tbody>
</table>

*↑ indicates increased; ↓, decreased. Adapted with permission from Siddoway.3

The class I drugs are subclassified based on electrophysiologic effects, a refinement that has increased the general usefulness of the Vaughan Williams1 classification system. Drugs with class IA action (eg, quinidine gluconate, procainamide hydrochloride, and disopyramide phosphate) prolong the repolarization and the refractoriness of isolated myocardial tissue in addition to blocking the rapid inward sodium current. Hence, they may increase the duration of the QRS and QT intervals. Class IB drugs (eg, lidocaine hydrochloride, tocainide hydrochloride, and mexiletine hydrochloride) shorten the action potential but produce only modest inhibition of the rapid inward sodium current. In contrast to class IA drugs, class IB drugs have a minimal effect on the QRS, QT, or P-R interval. Drugs with class IC action (eg, flecainide acetate and propafenone hydrochloride) slow the conduction velocity but have little effect on repolarization. These potent sodium channel inhibitors increase the QRS interval more than the other class I drugs.

Although the Vaughan Williams1 classification system is a useful reference, it is not a comprehensive or definitive source for prescribing antiarrhythmic drugs, primarily because most antiarrhythmic drugs have more than one action. For example, quinidine sulfate has class I and, to a lesser extent, class III effects (ie, it blocks potassium and sodium channels), d,l-sotalol has class II and class III effects (ie, it blocks β-adrenergic receptors and potassium channels), and amiodarone exhibits the effects of all 4 classes. In addition, an antiarrhythmic drug may have primary and secondary (or indirect) effects, all of which can vary as a function of the site of action.
Table 2 lists some common arrhythmias and examples of drugs from the Vaughan Williams classification system that might be useful for each arrhythmia.

Many antiarrhythmic drugs have active metabolites (Table 3) for which the action may be distinct from that of the parent drug. For example, procainamide hydrochloride is a class IA drug because it blocks sodium channels, but its major metabolite, N-acetylprocainamide, is a class III drug because it blocks the outward potassium channels and has little or no effect on the sodium channels. Likewise, the class IC drug, propafenone, is metabolized to 5-hydroxypropafenone, which lacks the class II (β-adrenergic blocking) properties of the parent compound. On the other hand, virtually none of the class II and III drug, d,l-sotalol, is metabolized.

Thus, it is essential to know which drugs have active metabolites when prescribing antiarrhythmic drug therapy, although no method exists to predict which patients are genetically predisposed to extensive or poor metabolism of a specific drug. In addition, the presence of coexisting disorders, such as ischemia, acidosis, electrolyte imbalance, hypoxia, or high catecholamine levels, may also affect the pharmacodynamics of an antiarrhythmic drug. These and other factors illustrate why the pharmacodynamic properties of a specific antiarrhythmic drug, rather than the class to which it belongs, should be the primary considerations when prescribing antiarrhythmic drugs.

## PHARMACOKINETICS

The pharmacokinetic profile of a drug describes the plasma level at a specific time after the administration of a dose. The major factors that determine the plasma levels of a drug are the rate and extent of absorption, distribution to various body tissues, metabolism, and elimination. Although these are important factors in the prescribing decisions for any drug, they are particularly relevant in antiarrhythmic drug therapy, in which the pharmacokinetic variables can have a critical role in determining the therapeutic and undesirable effects of the drug.

Figure 1 shows the major pharmacokinetic events from the time of ingestion of an antiarrhythmic drug until elimination of the drug. Table 4 gives an overview of the pharmacokinetic properties of the major antiarrhythmic drugs.

### ABSORPTION

The bioavailability of a drug depends on the amount of the parent compound that reaches the systemic circulation. For example, the bioavailability of an intravenously administered drug is, by definition, 100%, whereas the bioavailability of...
an orally administered drug depends on factors related to absorption or to first-pass metabolism. Table 5 lists some of the factors that can affect the bioavailability of an orally administered drug. For example, the bioavailability of D,L-sotalol approaches 100%, whereas the oral bioavailability of verapamil (20%-35%), amiodarone (35%-50%), and propafenone (25%-75%) is low and variable.

The absorption of an antiarrhythmic drug can be reduced or the absorption time can be prolonged by the presence of certain foods (eg, milk) or drugs (eg, antacids or cholestyramine) that bind the drug in the gastric lumen. In addition, the presence of certain microflora in the gut can affect intraluminal drug degradation and thereby reduce the bioavailability of an antiarrhythmic drug. This effect has been reported in some patients who initially required higher-than-normal doses of digoxin; toxic effects of digoxin developed when broad-spectrum antibiotics were administered, eradicating the pathogen that had caused the reduced bioavailability, so increased serum levels of digoxin resulted.7

DISTRIBUTION

After absorption, a drug enters the plasma and is distributed to a highly perfused “central” compartment consisting of organs such as the heart, kidney, liver, and brain. From there, it is metabolized and eliminated or redistributed into a more slowly equilibrating, “deep” compartment composed of adipose tissue, muscle, skin, and other tissues. Many factors determine the volume of distribution of a drug, a theoretical concept that describes the relationship between the drug dose

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**Table 4. Pharmacokinetic Properties of Antiarrhythmic Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Daily Dosage, mg</th>
<th>No. of Doses per Day</th>
<th>Target Plasma Level, μmol/L†</th>
<th>Elimination Half-life, h‡</th>
<th>Major Route of Elimination</th>
<th>Protein Binding, %</th>
<th>Oral Bioavailability, %</th>
<th>Active Metabolites</th>
<th>Supplement After Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>200-400</td>
<td>1</td>
<td>1.6-3.9</td>
<td>~53 d</td>
<td>Hepatic</td>
<td>96</td>
<td>35-50</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bretylium*</td>
<td></td>
<td>Infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25</td>
<td>1</td>
<td>0.6-2.6 nmol/L</td>
<td>36-48</td>
<td>Renal</td>
<td>&lt;10</td>
<td>55-75</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.5</td>
<td>1-4</td>
<td></td>
<td>4</td>
<td>Hepatic</td>
<td>70-80</td>
<td>80-90</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>400-800</td>
<td>2-3</td>
<td>6-15</td>
<td>6-9</td>
<td>Renal and hepatic</td>
<td>50-65</td>
<td>80-90</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flecainide acetate</td>
<td>200-400</td>
<td>2</td>
<td>0.2-1.0 µg/mL</td>
<td>20</td>
<td>Renal</td>
<td>40</td>
<td>95</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ibutilide*</td>
<td>2</td>
<td>Infusion</td>
<td></td>
<td>6-9</td>
<td>Hepatic and renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine*</td>
<td>450-750</td>
<td>3</td>
<td>6.4-21.4</td>
<td>1.5-2.0</td>
<td>Hepatic</td>
<td>60-80</td>
<td>...</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mexiletine hydrochloride</td>
<td>600-900</td>
<td>2-3</td>
<td>0.5-2.0 µg/mL</td>
<td>8-17</td>
<td>Hepatic</td>
<td>70</td>
<td>90</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Meclozine</td>
<td>200-400</td>
<td>1</td>
<td>40-79</td>
<td>16-24</td>
<td>Hepatic</td>
<td>95</td>
<td>35-45</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>200-4000</td>
<td>2-6</td>
<td>17-42</td>
<td>3-5</td>
<td>Hepatic and renal</td>
<td>20</td>
<td>70-85</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Procainamide hydrochloride</td>
<td>450-900</td>
<td>2-3</td>
<td></td>
<td>3-8</td>
<td>Hepatic</td>
<td>90</td>
<td>25-75</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>Propafenone hydrochloride</td>
<td>600-1600</td>
<td>2-3</td>
<td>6.2-15.4</td>
<td>4-17</td>
<td>Hepatic</td>
<td>80</td>
<td>60-80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Quinidine</td>
<td>600-1800</td>
<td>3</td>
<td>16-57</td>
<td>8-20</td>
<td>Renal and hepatic</td>
<td>50</td>
<td>100</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tocainide</td>
<td>240-480</td>
<td>1-4</td>
<td></td>
<td>3-7</td>
<td>Hepatic</td>
<td>90</td>
<td>20-35</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Intravenous form approved for antiarrhythmic use. Adapted with permission from Siddoway.7
†Unless otherwise indicated. Levels for flecainide, mexiletine, and sotalol are given in traditional units rather than SI units.
‡Unless otherwise indicated.
and plasma level expressed as a function of body weight. These include the ability of the drug to enter various tissues, the lipophilicity, and the degree to which the drug is protein bound.

The issue of protein binding is particularly germane because many antiarrhythmic drugs are highly bound to plasma proteins, and it is the unbound drug that exerts an electrophysiologic effect. A complicating factor is the variable protein binding of antiarrhythmic drugs that can be influenced by the plasma level of the drug, interactions with other drugs, pH, and the plasma level of the binding protein. For example, the protein binding of disopyramide can vary, in a dose-dependent fashion, from 50% to 65% (Table 4). In contrast, D1-sotalol is devoid of protein binding. Protein binding can be increased or decreased, which may enhance or diminish the plasma level of the drug.

**METABOLISM**

The biotransformation (or metabolism) of most antiarrhythmic drugs occurs in the liver and is mediated by cytochrome P-450 isoenzymes, of which P4502D6 and P4503A4 are 2 of the most important. However, some rapidly eliminated drugs are also metabolized in the plasma, blood cells, vascular endothelium, and lungs. Antiarrhythmic drugs such as amiodarone (99%), propafenone (90%), and verapamil (90%) are almost completely metabolized, whereas drugs such as tocainide (10%), procainamide (15%), bretylium tosylate (<10%), and D1-sotalol (0%) are not. A number of antiarrhythmic drugs undergo extensive first-pass metabolism, which affects the dosage and route of administration. Lidocaine, for example, requires intravenous administration because of its extremely poor systemic bioavailability when taken orally, whereas propafenone, metoprolol tartrate, propranolol, and verapamil must be given in doses that are sufficiently high to compensate for their extensive first-pass metabolism.

Numerous other factors affect how an antiarrhythmic drug is metabolized. In many instances, the metabolic fate is determined by genetic factors. Evidence suggests that some persons have innately poor metabolic ability for specific drugs. The question of whether a drug possesses “saturable” kinetics must also be considered, because a nonlinear increase usually occurs in the plasma levels when the oral dosage of antiarrhythmic drugs is increased. For example, the plasma level of propafenone has been shown to increase 9-fold after only a 3-fold increase in dosage. Another factor that can have an important role in biotransformation is coexisting disease. For example, a patient with congestive heart failure is likely to have decreased hepatic blood flow, which may compromise hepatic metabolism and affect the elimination of hepatically metabolized drugs, such as propafenone and amiodarone. Coingestion of other drugs, including other antiarrhythmic drugs, may also affect the metabolism of a specific compound.

**Table 6** lists some common antiarrhythmic drugs and suggests dosing modifications for the treatment of patients with coexisting diseases or patients receiving digoxin or other commonly used drugs. It is interesting that most antiarrhythmic drugs used today, including quinidine, mexiletine, flecainide, propafenone, amiodarone, verapamil, and diltiazem, interact with other widely used drugs. This is particularly true for amiodarone, which interacts with virtually all drugs that are hydroxylated in the liver (eg, histamine2 blockers, anticoagulants, and β-adrenergic blocking agents). Another well-known and potentially serious interaction is the marked increase in serum digoxin levels produced by quinidine. In contrast, drugs such as D1-sotalol do not interact pharmacokinetically with any other drugs, which simplifies their use.

**ELIMINATION**

The 2 most common routes of antiarrhythmic drug elimination are renal and hepatic. Clearance (ie, the rate of removal of the drug from plasma) is the most dependable measure for determining the rates of drug metabolism and elimination. The elimination half-life is defined as the time needed for 50% of the drug to be eliminated from the body. However, the concept of half-life is complex because it reflects not only the half-life of the parent compound but also the half-life of any active metabolites. A dramatic illustration of this point was provided by the early clinical experience with encainide hydrochloride, which was initially reported to have a half-life of only 3 to 5 hours. As a result, the drug was prescribed for use up to 6 times daily. Investigators later discovered, however, that encainide had at least 2 active metabolites that not only were more potent than the parent compound in causing a widened QRS interval and proarrhythmic effects but also had longer half-lives. Consequently, many patients who took encainide every 4 or 6 hours experienced serious proarrhythmic events as a result of massive accumulation of the metabolites.

It is commonly believed that a steady state is achieved after approximately 5 half-lives—about the same number of half-lives needed for elimination of a drug from the body. However, steady-state levels can vary
Bioavailability is a particularly important concept in antiarrhythmic drug therapy, because many putative drug "failures" can be attributed to the premature assessment of the effectiveness of the antiarrhythmic drug. Consider, for example, a patient who has received a specific antiarrhythmic drug and will undergo an examination in the electrophysiology laboratory or ambulatory monitoring. The question of how much time must elapse from the time therapy is initiated until it is possible to determine effectiveness is dictated mainly by the time needed for the drug to reach steady-state levels.

As shown in Figure 2, this interval varies widely from one drug to another. For example, the effectiveness of procainamide can be assessed in 1 to 2 days compared with at least 7 days for amiodarone. Thus, many patients who are referred because of an inadequate response to an antiarrhythmic drug may have been treated for an insufficient time for the drug to achieve a steady-state level.

Other risks are possible when it is erroneously assumed that a drug has achieved steady-state levels. For instance, the assumption by clinicians that steady-state levels of flecainide can be attained within 48 hours may be an underestimate. In many cases, dosage escalation is initiated if an adequate antiarrhythmic effect has not been demonstrated within the estimated time needed to reach a steady state, often leading to extensive drug accumulation. Thus, for many antiarrhythmic drugs, waiting a "pharmacokinetically" appropriate period is essential before evaluating the response to treatment and changing the dosage.

Problems may also arise when the route of elimination is not fully understood. Most antiarrhythmic drugs are eliminated by the liver (eg, quinidine, lidocaine, and propafenone), whereas others are eliminated by the kidneys (eg, D.L-sotalol, flecainide, and digoxin). Other drugs undergo hepatic and renal elimination (eg, procainamide, disopyramide, and tocainide). For some drugs, the parent compound is eliminated by one route, whereas the active metabolite is eliminated by the other route. An example is procainamide, which is eliminated by the liver, while its metabolites are

![Figure 2. Time from initiation of therapy to possible determination of effectiveness. gid indicates 4 times a day; tid, 3 times a day; and bid, 2 times a day. Reprinted with permission from Eric N. Prystowsky, MD.](image-url)
eliminated by the kidneys. The elimination kinetics of sotalol are among the least complicated; it forms no metabolites and is eliminated exclusively by the kidneys.

**IMPORTANCE OF THE DRUG FORMULATION IN DETERMINING PHARMACOKINETIC EFFECTS**

A major concern when prescribing antiarrhythmic drugs is that the pharmacokinetics of a drug can vary as a function of the formulation. Problems are particularly apt to arise when a pharmacist substitutes a generic drug for a brand-name drug, because the antiarrhythmic properties or potential toxic effects of the 2 drugs may not be equivalent. Of equal concern are situations in which a therapeutic regimen is changed from an intravenous to an oral formulation of the same drug. By its very nature, intravenous dosing ensures that the patient receives primarily the parent compound; when the same drug is administered orally, the active metabolites are likely to have a more prominent role. Procainamide, for example, can be used to terminate monomorphic ventricular tachycardia (VT) in most patients when it is administered intravenously, but it is largely ineffective in preventing VT when administered orally. One reason for this dichotomy is that intravenous therapy produces excessive plasma levels of the parent compound, whereas orally administered procainamide is metabolized to N-acetyl-procainamide, which does not have the same antiarrhythmic effects.

Painstaking efforts have usually been made in the hospital to titrate the antiarrhythmic drug to achieve optimal therapeutic levels; a change in formulation not only affects bioavailability of the drug but also may alter metabolism and elimination. Furthermore, such substitutions may increase the risk of drug-drug or drug-device interactions. In all of the aforementioned situations, the end result is the same: there is no assurance that the patient is still receiving the same therapy that was successfully used to control the arrhythmia at the time of discharge from the hospital.

**PROS AND CONS OF MONITORING PLASMA LEVELS**

Considerable controversy surrounds the issue of monitoring plasma levels during administration of an antiarrhythmic drug. The main reasons for monitoring plasma levels are to confirm adherence to the therapeutic regimen, to avoid drug-related toxic effects, and to ascertain that the formulation of the drug prescribed produces the desired effect. There may be a discrepancy between the drug prescribed in the hospital and that dispensed by the pharmacist. For example, quinidine gluconate is commonly substituted for quinidine sulfate. Thus, there would be valid grounds for determining the plasma level if symptoms recur after discharge despite adequate control in the hospital. In addition, the comfort level of the prescribing physician with a specific antiarrhythmic drug regimen is often enhanced by tangible pharmacokinetic feedback, even if the relevance of this feedback is unclear.

However, legitimate reasons also exist for not monitoring plasma levels. Some adverse effects are unrelated to the plasma level of the drug, whereas others may be idiosyncratic or reflect variable individual susceptibility to a drug. Furthermore, the therapeutic range of most antiarrhythmic drugs is so wide that the concept of optimal plasma levels is virtually meaningless. For propafenone, for example, the therapeutic range for the plasma level of the parent compound is between 200 and 1500 ng/mL, a level that does not consider the additional activity of the active metabolite, 5-hydroxypropafenone. Last, the clinical relevance of plasma levels in the hospital setting is particularly doubtful, because most acute situations resolve long before the test results are provided by the laboratory.

**ANTIARRHYTHMIC DRUG THERAPY FOR THE ELDERLY**

The pharmacological characteristics of virtually all drugs are affected by aging. The pharmacokinetics of a drug are altered by age-related reductions in elimination by the kidneys, volume of distribution, and drug metabolism, whereas the pharmacodynamics of a drug are affected by factors such as reduced density of and sensitivity to the β-adrenergic receptors. Thus, the judicious use of drug therapy in the elderly is a unique challenge, particularly because of the widespread use of polypharmacy to treat an often bewildering array of coexisting diseases.

Many recommendations about antiarrhythmic drug therapy for the elderly apply to the use of any drug therapy in this age group. Because the pharmacokinetics of a drug are altered in elderly patients (primarily because of reduced renal and hepatic function and possibly reduced serum protein binding), lower dosages are required than would be used for younger patients. Lower dosages are especially important for antiarrhythmic drugs that are eliminated by the kidneys (e.g., D,L-sotalol, flecainide, bretylium, and digoxin), because the glomerular filtration rate is reduced substantially in elderly patients. Although specific guidelines have not been established for antiarrhythmic drug therapy in the elderly, generally advisable practices are initiating therapy at a lower-than-recommended dosage and gradually titrating upward based on the patient’s tolerance of the drug.

One of the primary pharmacodynamic changes associated with aging is a reduction in β-adrenoceptor sensitivity, which may lead to increased susceptibility to the effects of β-adrenergic blocking agents (ie, class II antiarrhythmic drugs), such as propranolol. Elderly patients also may be more susceptible to the effects of D,L-sotalol and amidarone, both of which are class III drugs that also have class II effects. However, there is no evidence that aging necessarily alters the number or function of cardiac ion channels.

**ANTIARRHYTHMIC DRUG THERAPY FOR PATIENTS WITH ICDs**

Reports about the percentage of patients with ICDs who are receiving concomitant antiarrhythmic drug therapy range from approximately 20% to 88%. Most studies, how-
ever, suggest that more than 50% of patients with ICDs also receive antiarrhythmic drugs.\textsuperscript{10,12} Thus, clinical experience suggests that even sophisticated third-generation ICDs do not obviate the need for antiarrhythmic drug therapy, especially in patients at risk for VT and atrial fibrillation.

For several reasons, antiarrhythmic drug therapy can be a useful adjunct for patients with ICDs. The concomitant use of antiarrhythmic drugs and ICDs can prevent recurrent VT and slow sustained VT, thereby decreasing the frequency of electric shocks and the amount of current required to terminate VT or ventricular fibrillation. The slowing of VT may also increase the hemodynamic tolerance of VT and ease pace termination.

However, 2 potentially important pharmacodynamic responses may occur when an antiarrhythmic drug is used with an ICD. First, some drugs have a marked effect on pacing thresholds, which is particularly prominent in class IC drugs, such as propafenone and flecaïnide. Second, many available antiarrhythmic drugs increase defibrillation thresholds (and the current required to terminate VT or ventricular fibrillation). The slowing of VT may also increase the hemodynamic tolerance of VT and ease pace termination.

Therefore, several recommendations are proposed for optimizing the use of antiarrhythmic drug therapy. First, use pharmacologically common sense when prescribing any antiarrhythmic drug. In other words, carefully evaluate the pharmacodynamics and pharmacokinetics of the antiarrhythmic drug and use objective criteria to determine the choice of therapies. Second, individualize therapy whenever possible. The patient and therapy must be “matched” as closely as possible, considering not only the pharmacological properties of a specific antiarrhythmic drug but also such factors as the patient’s age, coexisting disease, and whether the patient takes other drugs or has an ICD. Unlike many other classes of drugs (the members of which can be interchanged with relative impunity), the choice of antiarrhythmic drugs must be governed by due consideration of the unique characteristics of each drug, not by those of its class. Third, consider that multiple therapeutic options are available. Last, use drug combinations when appropriate and reasonable. By observing these recommendations, the clinical outcome of treatment with these potent drugs with potentially toxic effects should be positive.

More than 400 years ago, Paracelsus wrote, “A drug can be an inert substance, a poison, or a therapeutic agent dependent upon how it is used and the dosage in which it is given.” This maxim is particularly appropriate to the use of antiarrhythmic drugs, for which the potential for remedial and toxic effects mandates a close appraisal of their pharmacodynamic and pharmacokinetic properties. Clearly, antiarrhythmic drug therapy has an invaluable role in the treatment of most common arrhythmias, thus prolonging or improving the quality of life for many patients. In this age of managed care, an economic incentive to use antiarrhythmic drug therapy also exists; using antiarrhythmic drugs as a first-line approach generally costs less than using invasive procedures, such as ablation or the implantation of defibrillators. However, the beneficial effects of antiarrhythmic drug therapy can readily be offset by the potential toxic effects when the drugs are prescribed without due regard for the appropriateness of a specific drug for a specific patient.

REFERENCES