Antiarrhythmic Drugs
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Principles of Antiarrhythmic Therapy

Benefit Should Exceed Risk

The benefits of antiarrhythmic drug therapy are clearly evident in the acute setting, when a patient presents with a highly symptomatic, often sustained, arrhythmia that drug therapy terminates within minutes. In this setting, symptomatic benefits are obvious, and risk is minimized because patients are monitored and exposed to drug only for brief periods of time.

By contrast, with chronic therapy, the balance between risk and benefit is more difficult to evaluate. Chronic therapy in a patient with heart disease may be effective at one point in time, but efficacy may be lost later due to a changing substrate. Chronic antiarrhythmic therapy is incompletely effective in the best-controlled clinical trials, the consequences of arrhythmia recurrence are clinically important (varying from recurrent hospitalization to death), and the risk of serious adverse effects appears to grow over time. Therefore, in contemporary antiarrhythmic therapy, drugs retain a primary role in acute termination and in selected chronic arrhythmia settings, notably atrial fibrillation (AF), in which arrhythmia recurrence may not be catastrophic. By contrast, ablative and device-based therapies are more desirable from a risk-benefit point of view in other settings, where drugs have assumed a secondary role. Should ablative therapies for AF continue to evolve, drugs may assume a secondary role here as well. On the other hand, the development of new drug therapies for AF that are highly effective and safe during chronic therapy would also be desirable.

Choosing a Specific Drug

Mechanism-Based Approaches

A general pharmacologic principle is that the best treatment is one targeted specifically to disease mechanisms. In arrhythmia therapy, a good example is cure of arrhythmias in the Wolff-Parkinson-White syndrome by bypass tract ablation. As our understanding of the molecular and cellular basis of arrhythmias has evolved, so too has a list of arrhythmias for which specific mechanisms have been defined, and therefore specific antiarrhythmic drug therapies may be indicated (Table 99.1). Thus, the role of adrenergic triggering in right ventricular outflow tract tachycardia makes beta-blockers an appropriate mechanism-based therapy. Recognition of the critical role of slow conduction within the atrioventricular (AV) node in AV nodal reentrant tachycardia or orthodromic reciprocating tachycardias makes adenosine an appropriate, mechanism-based choice for therapy for the acute termination of these arrhythmias. The delineation of molecular mechanisms in specific rare genetic syndromes, discussed further below, may also prompt consideration of specific mechanism-based therapies, although frequently the numbers of patients evaluated are small and the agents available are not specific.

In most settings, the choice of drugs is not yet mechanism-driven. Unfortunately, for most common arrhythmias, such as ventricular tachycardia (VT) in myocardial disease or AF, arrhythmia mechanisms have been more difficult to define, and so the choice of drug therapy remains “empiric.” In such settings, drugs shown by clinical experience to be effective often turn out to target multiple aspects of the abnormal electrophysiology, including modifying the
TABLE 99.1. Mechanism-based antiarrhythmic drug therapy

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Mechanism-based therapy</th>
<th>Mechanism targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV nodal reentry</td>
<td>Adenosine</td>
<td>Macro-reentry utilizing the AV node</td>
</tr>
<tr>
<td>AV reentry</td>
<td>Verapamil</td>
<td>Adrenergically driven</td>
</tr>
<tr>
<td>Outflow tract VT</td>
<td>Beta-blockers</td>
<td>Reentry within the His-Purkinje system</td>
</tr>
<tr>
<td>Fascicular VT</td>
<td>Beta-blockers</td>
<td>Reentry within the His-Purkinje system</td>
</tr>
<tr>
<td>Torsades de pointes due to drugs or bradyarrhythmias</td>
<td>Pacing</td>
<td>I&lt;sub&gt;r&lt;/sub&gt; block leading to bradyarrhythmias</td>
</tr>
<tr>
<td>Congenital long QT syndrome, type 1</td>
<td>Isoproterenol</td>
<td>Abnormal action potential prolongation and heterogeneity due to loss of I&lt;sub&gt;Kr&lt;/sub&gt; function</td>
</tr>
<tr>
<td>Congenital long QT syndrome, type 2</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; supplementation to 4.5–5 mEq/L</td>
<td>Abnormal action potential prolongation and heterogeneity due to decreased inward sodium current during the action potential plateau</td>
</tr>
<tr>
<td>Congenital long QT syndrome, type 3</td>
<td>Sodium channel block (mexiletine, flecainide)</td>
<td>Abnormal action potential prolongation and heterogeneity due to increased inward sodium current during the action potential plateau</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>I&lt;sub&gt;to&lt;/sub&gt; block [possibly quinidine]</td>
<td>Increased heterogeneity of action repolarization due to loss of sodium channel function and maintained I&lt;sub&gt;to&lt;/sub&gt;</td>
</tr>
<tr>
<td>AF, VF, or T-wave oversensing in short QT syndrome</td>
<td>Quinidine, sotalol</td>
<td>Increased outward current, leading to shortened action potentials</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic VT</td>
<td>Beta-blockers</td>
<td>“Leaky” SR leading to afterdepolarization-mediated arrhythmias with heart rate increases due to adrenergic stimulation</td>
</tr>
</tbody>
</table>

*aOther therapies may be effective (e.g., magnesium for torsades de pointes) but are not listed here because their mechanisms of action are not clearly defined.*

*bOther mechanisms may be operative (e.g., conduction slowing in the Brugada syndrome) but these are not yet amenable to specific drug therapies.*

AF, atrial fibrillation; AV, atrioventricular; SR, sarcoplasmic reticulum; VF, ventricular fibrillation; VT, ventricular tachycardia.

Arrhythmia-prone substrate or inhibiting known or putative trigger[s] of arrhythmias. The expectation that all patients with AF or VT will respond to therapy in a similar fashion makes the assumption that underlying mechanisms are similar across patients; however, as genetic, molecular, and cellular studies continue to demonstrate, this assumption is largely unwarranted. As a result, the incomplete efficacy of drugs in these arrhythmias, that in fact seem to represent a spectrum of many different arrhythmia ‘‘diseases,’’ should come as no surprise.

Large clinical trials provide the best evidence for choosing among drug therapies and dosages in settings like AF and VT. The use of evidence-based principles should be complemented by consideration of patient-specific characteristics that may make one drug more or less desirable compared to others. Thus, the presence of chronic pulmonary disease argues against the use of amiodarone because drug-related toxicity may be accordingly more difficult to diagnose (and perhaps more likely to occur). Certain drugs may predispose to particular forms of proarrrhythmia and thus should be avoided in certain subsets; sodium channel blockers in patients with remote myocardial infarction is one example. Other disease-specific relative drug contraindications are listed in Table 99.2.

**Classification of Drugs and Target Arrhythmias**

Schemes to group drugs into classes are useful if class members share efficacies or toxicities. Some antiarrhythmic drugs share important electrophysiologic properties, notably block of sodium channels or of the potassium current I<sub>Kr</sub> (the common mechanism underlying QT prolongation), and these can provide the basis for predicting shared or “class” actions including toxicities (Table 99.3). Block or enhancement of other ionic currents, such as the slow component of the delayed rectifier (I<sub>Ks</sub>), the transient outward current (I<sub>to</sub>), or acetylcholine-activated current (I<sub>ACH</sub>), may also contribute to clinical drug actions in some cases.

An alternative approach is to classify not drugs but rather key electrophysiologic mechanisms involved in arrhythmogenesis, thereby allowing specific drugs to be chosen to target these mechanisms. This is the approach adopted by the “Sicilian gambit” investigators and is nicely exemplified by the definition of new molecular mechanisms in congenital arrhythmia syndromes and the way in which these then lead naturally to mechanism-based therapies. An evolving understanding of the molecular and cellular basis of arrhythmias should allow a more appropriate choice of key molecule[s] whose targeting is likely to be safe and effective in the therapy of a particular arrhythmia.

The term antiarrhythmic drugs has traditionally been taken to include drugs targeting ion channels in cardiac myocytes (sodium channel blockers, calcium channel blockers, and QT prolonging agents [generally potassium channel blockers]), β-adrenergic receptor blockers, and a series of other drugs used primarily for the therapy of arrhythmias, such as digoxin, magnesium, and adenosine.
### TABLE 99.2. Disease-specific relative drug contraindications

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relatively contraindicated drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Disopyramide</td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td>Other sodium channel blockers: quinidine, procainamide, disopyramide, propafenone, cibenzoline . . .</td>
</tr>
<tr>
<td>Manifest preexcitation</td>
<td>Digitalis</td>
</tr>
<tr>
<td></td>
<td>Verapamil, diltiazem</td>
</tr>
<tr>
<td>Preexcited AF</td>
<td>Digitalis</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>Adenosine</td>
</tr>
<tr>
<td>Vagally mediated AF</td>
<td>Digitalis</td>
</tr>
<tr>
<td>Lung disease</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Asthma</td>
<td>Adenosine</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
</tr>
<tr>
<td></td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Sodium channel blockers: flecainide, quinidine, procainamide, disopyramide, propafenone, cibenzoline . . .</td>
</tr>
<tr>
<td>Prostatism, glaucoma</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Tremor</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Constipation</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Sotalol</td>
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<tr>
<td></td>
<td>Dofetilide</td>
</tr>
</tbody>
</table>

### TABLE 99.3. Expected effects of blocking antiarrhythmic drug targets in the heart

<table>
<thead>
<tr>
<th>Ionic target</th>
<th>Blocking drugs</th>
<th>Effect of therapeutic doses on normal ECG</th>
<th>Cardiac toxicity of excess block</th>
<th>Extracardiac toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channel</td>
<td>Amiodarone</td>
<td>QRS prolongation, exaggerated at high concentration or fast sinus rates; PR prolongation</td>
<td>Slow atrial flutter, occasionally with 1:1 AV conduction</td>
<td>Exacerbation of myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td></td>
<td>Bradyarrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td></td>
<td>Increased energy requirement for defibrillation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td></td>
<td>More frequent episodes of reentrant VT or SVT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cibenzoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pilsicainide</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Propafenone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Mexiletine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-type calcium channels</td>
<td>Verapamil</td>
<td>Sinus rate slowing; PR interval prolongation</td>
<td>Bradyarrhythmias</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td></td>
<td>AV nodal block</td>
<td></td>
</tr>
<tr>
<td>Rapid component of the delayed rectifier potassium current</td>
<td>Amiodarone</td>
<td>QT interval prolongation (sinus bradycardia may also occur)</td>
<td>Torsades de pointes</td>
<td></td>
</tr>
<tr>
<td>[I_K]</td>
<td>Quinidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pilsicainide</td>
<td></td>
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<tr>
<td></td>
<td>Propafenone</td>
<td></td>
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<tr>
<td></td>
<td>Flecainide</td>
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<td></td>
<td>Mexiletine</td>
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<td></td>
<td>Sotalol</td>
<td></td>
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<tr>
<td></td>
<td>Dofetilide</td>
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<tr>
<td></td>
<td>Ibutilide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>β-adrenergic receptors</td>
<td>Beta-blockers, including sotalol</td>
<td>Sinus rate slowing; PR interval prolongation</td>
<td>Bradyarrhythmias</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td></td>
<td>AV nodal block</td>
<td>Sleep difficulties</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td></td>
<td>Depressed contractility (acutely)</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>

* Lidocaine and mexiletine have faster rates of onset and offset of binding to the channel, and so tend to exhibit fewer of the effects (such as QRS prolongation) listed for other blockers.

* Many other drugs, notably dihydropyridines like nifedipine and amlodipine, block L-type calcium channels but not in myocardium, their effects on cardiac electrophysiology generally reflect sympathetic activation (e.g., sinus tachycardia) due to peripheral vasodilation.

* I<sub>K</sub> block is also the mechanism whereby many noncardiovascular drugs prolong QT interval and cause torsades de pointes. Other drugs (e.g., flecainide, verapamil) also block I<sub>K</sub> but have such potent effects on inward currents (sodium or calcium) that the clinical effects of I<sub>K</sub> block—QT prolongation and torsades de pointes risk—are not seen. Similarly, torsades de pointes is rare with amiodarone.

* QT prolongation during procainamide therapy is often due to accumulation of the active metabolite N-acetylprocainamide [NAPA], which does not block cardiac sodium channels.

* The beta-blocking properties of propafenone are most evident clinically at high concentrations of the parent drug seen in individuals deficient in CYP2D6 activity on a genetic basis or due to concomitant drug therapy. Unlike other drugs that competitively block β-receptors, amiodarone exhibits antiadrenergic properties by noncompetitive blockade, reducing the number of receptors available for occupancy by agonists like adrenaline.
Recent studies have demonstrated that other widely used cardiovascular therapies, including anti-angiotensin drugs and hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors may also exert important antiarythmic effects. Such effects may include not only reductio of sudden cardiac death (an arrhythmic event that represents the culmination of many potential disease pathways) but also prevention of AF. These studies not only provide potential new tools for arrhythmia treatment, but also implicate new signaling pathways in the genesis of arrhythmias and therefore as potential new targets for the development of effective antiarrhythmic interventions. The pharmacologic properties of these agents are discussed in other chapters.

Atrial fibrillation is the commonest arrhythmia for which drugs remain the primary therapy, but the efficacy of currently available drugs is disappointing. As a result, the role of nonpharmacologic therapies for AF continues to evolve, and new drugs are currently in development. Some [like azimilide or dronedarone] seem similar to available agents in that they target multiple potassium channels including 

![insert equation here]

I_{Ks}." Others are reported to target atrial-specific channels [including a potassium current termed I_{Kur}] or receptors. Experimental studies have suggested that manipulation of activated phosphorylation pathways or of abnormal intracellular calcium homeostasis could also provide antiarrhythmic effects. It is possible that new drugs targeting these mechanisms could affect overall management for AF.

**Drug—Channel Interactions**

Experimental studies prior to the cloning era indicated that ion channels, the targets of many antiarrhythmics, have specific drug binding sites. Further, drug binding to these receptor sites on the channels to modify their function was found to be modulated by the state of the channel (open, closed, or inactivated); these observations led to formulation of the modulated receptor hypothesis to analyze drug—channel interactions. More contemporary studies have demonstrated molecular correlates of this approach. There are specific sites on ion channel proteins to which drugs bind, and the interactions of drugs with these sites can be modulated by channel protein conformation (or "state"). In some cases, ion currents are blocked by direct binding in the pore region (a common mechanism for most I_{Ks} blockers), whereas in others, drug binding to other regions of the protein alters its function (an "allosteric" effect).

Most sodium channel blocking drugs inhibit open or inactivated states of the channel; hence, during each cardiac cycle, they associate with and block channels, and then dissociate during diastole, ultimately reaching a steady-state level of block. If the heart rate is increased, there is less time for dissociation, so channel block is enhanced. In addition, the rate of dissociation from the channel varies among drugs. For "fast-off" drugs like lidocaine, very little block accumulates even at fast rates. For "slow-off" drugs like flecainide, block accumulates even at physiologic rates. Since sodium channel block slows intraventricular conduction, QRS interval prolongation is seen on the surface electrocardiogram (ECG); this explains why QRS widening is evident at normal heart rates during flecainide [but not lidocaine] therapy, and widens further if the heart rate is increased. In addition, since conduction slowing promotes reentry, conduction slowing by the drug at faster rates may explain cases of flecainide-induced VT during exercise.

**Choosing a Dose**

A range of dosages likely to be effective is derived from clinical experience [with older drugs] and from controlled clinical trials [with newer drugs]. In the acute setting, the goal is to deliver effective therapy rapidly enough to generate an antiarrhythmic effect without causing side effects, and this often mandates intravenous doses. However, extremely rapid intravenous administration of highly effective drugs such as amiodarone or lidocaine will cause adverse effects. An exception here is adenosine, which must be delivered as a very rapid intravenous bolus in order to achieve its antiarrhythmic actions.

The important general pharmacokinetic principle is that administration of a loading dose in the acute situation does not abbreviate or otherwise alter the time required to achieve steady-state plasma concentrations. This is determined solely by the elimination half-life; steady state is achieved during initiation of therapy, a change in therapy, or discontinuation of therapy [when the steady state is zero] after four to five elimination half-lives.

When chronic therapy is initiated with any drug, there is by definition no urgency to produce a rapid therapeutic effect, and so loading doses are generally unnecessary. Chronic drug therapy, therefore, is usually best initiated at the lowest dose likely to produce a clinical effect. If a clinical effect is not observed and toxicity is absent once steady state is achieved, the dose may be increased. An exception to this general approach is amiodarone because its elimination half-life is so long. Here, initiation of therapy with higher dosages is appropriate, to avoid the extraordinarily long periods that are required for the drug to actually come to steady state.

Occasional patients escalate to high dosages of a drug and display no sign of efficacy or of dose-related toxicity. Such patients may represent the upper extreme of a normal population distribution. On the other hand, this clinical scenario should also raise the possibilities of incomplete absorption, genetically determined rapid metabolism, or drug interactions enhancing drug elimination or blunting drug effect. Similarly, the observation of unusual efficacy or toxicity at very low drug dosages should prompt consideration of analogous underlying mechanisms.

**Pharmacokinetic Principles**

One common mechanism underlying variability in response to antiarrhythmic drugs is variability in pharmacokinetics, the result of the processes of drug absorption, distribution, metabolism, and elimination. As a general rule, variability in pharmacokinetics contributes substantially to variability in drug efficacy or toxicity when two conditions are met: [1] there is a narrow “therapeutic window,” the margin between dosages and plasma concentrations associated with efficacy and those associated with toxicity; and [2] the drug is metab-
Drug metabolism and elimination is accomplished by specific gene products, drug metabolizing enzymes [primarily members of the cytochrome P-450 (CYP) superfamily] and drug transport molecules. DNA variants that alter the activity of these proteins are increasingly well recognized; some exert only subtle effects on protein function, whereas in other cases, an individual may totally lack enzymatic activity. As discussed above, this becomes especially important if the affected pathway is critical for elimination of a narrow therapeutic margin drug. In addition, concomitant drug therapy can modulate the activity of drug metabolizing and transport molecules. Most such drug interactions result in inhibition of the elimination pathway, occasionally, concomitant drug therapy can induce expression of drug metabolism and thus accelerate elimination. Under this circumstance, an increase in drug dosage may be required to maintain a therapeutic effect.

The major drug metabolizing enzymes for antiarrhythmic drugs are CYP2D6, CYP2C9, and CYP3A4/5. Approximately, 5% to 10% of Caucasians and African Americans are homozygous for loss of function alleles in CYP2D6; these individuals totally lack enzymatic activity and are designated “poor metabolizers” (PMs). CYP2D6 PMs have markedly decreased propafenone clearance, and accumulate the parent drug to plasma concentrations high enough to produce clinically significant beta-blockade, as a result, asthma can be a risk in these patients. Similarly, CYP2D6 PMs also have higher concentrations of timolol and metoprolol. Many nonantiarrhythmic drugs are metabolized by CYP2D6, including the analgesic codeine and a number of tricyclics. Propafenone and quinidine are CYP2D6 inhibitors, and therefore may alter the effects of CYP2D6 substrates.

CYP2C9 is the enzyme primarily responsible for the metabolism of warfarin’s active S-enantiomer. Reduction of function CYP2C9 alleles have been described, and homozygous individuals appear to be at very high risk for bleeding complications, even at very low dosages. Amiodarone is a potent CYP2C9 inhibitor, and dosages of warfarin therefore must be adjusted downward with amiodarone therapy.

CYP3A4 and CYP3A5 are two closely related enzymes that are the most abundant cytochromes in the liver and are responsible for the metabolism of the majority of currently used drugs. Individuals totally lacking CYP3A activity have not been described, although there is substantial variability in the activity. However, CYP3A activity can be nearly totally inhibited by concomitant drug therapy, notably with certainazole antifungals [ketoconazole], macrolide antibiotics [erythromycin], HIV protease inhibitors [ritonavir], amiodarone, diltiazem, verapamil, and large doses of grapefruit juice. CYP3A activity can also be induced by rifampin, phenytoin, and St. John’s wort; reduction in plasma concentrations and loss of drug effects can occur under these conditions. Inhibition of CYP3A-mediated elimination by these drug interactions was the major cause of terfenadine accumulation in plasma, leading to cases of torsades de pointes that eventually prompted the drug’s withdrawal from the market.

N-acetyltransferase (NAT) activity is responsible for the elimination of procainamide. There are two NAT genes, NAT1 and NAT2. NAT1 is expressed in all individuals, but loss of functional alleles has been reported in NAT2. As a result, patients can be divided into rapid and slow acetylators [although there are no “nonacetylators”]. Slow acetylators have a higher incidence of procainamide-induced lupus syndrome during chronic therapy.

Specific drug transport molecules mediate drug uptake into and efflux from specific intracellular sites. The most widely studied drug transport molecule is P-glycoprotein, which is responsible for the elimination of digoxin. Many drugs inhibit P-glycoprotein activity, and their use with digoxin can lead to increased digoxin plasma concentrations.
and toxicity; amiodarone, quinidine, verapamil, itraconazole, cyclosporine, and erythromycin are examples.\textsuperscript{16,27}


guidelines have now been published for acute and chronic therapy of supraventricular arrhythmias, particularly if the arrhythmia has been present for a short duration. These guidelines include very extensive literature annotation and discussion of the rationale for the choice of therapy in each situation.

Managing Drug Therapy

Therapeutic ranges for individual drugs delineate plasma concentrations below which a therapeutic effect is unlikely and above which the risk of dose-related toxicity increases. Some drug toxicity is unrelated to dosage and is thus not prevented by maintaining therapeutic plasma concentrations. The fundamental premise of plasma drug concentration monitoring is that concentration of drug in plasma is an accurate guide to plasma concentration in peripheral tissues where drugs often act. In some conditions, this parallelism may not hold, and monitoring plasma concentrations is not necessarily more or less desirable. Each recommendation is accompanied by a level of evidence ranging from A, for evidence derived from many controlled clinical trials, to B, for anecdotal evidence and expert opinion. Joint American College of Cardiology (ACC)/European Society of Cardiology (ESC)/Heart Rhythm Society (HRS) guidelines have now been published for acute and chronic therapy of supraventricular tachycardia (SVT) and of atrial fibrillation (AF).\textsuperscript{28,29} Recently a guideline for management of ventricular arrhythmias and sudden death was published. The major points of these documents are summarized in this chapter; the documents themselves include very extensive literature annotation and discussion of the rationale for the choice of therapy in each situation.

Guidelines for Drug Therapy of Supraventricular Tachycardia\textsuperscript{28}

Most regular narrow-complex SVT responds to intravenous administration of AV nodal-blocking drugs, and adenosine is preferred over calcium channel blockers (verapamil or diltiazem) or beta-blockers (esmolol, metoprolol, or propranolol) because of its rapid onset and offset of action. Failure to terminate a regular narrow-complex tachycardia with these agents suggests an alternate diagnosis, such as inappropriate sinus tachycardia or atrial tachycardia. Other drugs whose intravenous administration can be useful include amiodarone and digoxin. In patients with wide-complex regular tachycardia, efforts should be made to distinguish SVT from VT. In most settings, it is prudent to treat wide QRS tachycardia of unknown origin as VT; procainamide, sotalol, amiodarone, and lidocaine can be used in this setting. Options may be different in children in whom SVT is more likely. In patients with poor left ventricular performance, amiodarone or lidocaine is preferred.

Many patients go on to catheter ablation for curative therapy of SVT. For those in whom chronic drug therapy is entertained, many agents have been used with success: verapamil, diltiazem, beta-blockers, sotalol, amiodarone, and, in patients with relatively preserved left ventricular function, flecainide and propafenone. Digoxin is also occasionally effective. However, digoxin, verapamil, and diltiazem are contraindicated in patients with manifest preexcitation, as they increase the risk of ventricular rate acceleration and ventricular fibrillation (VF). In this situation, flecainide, propafenone, sotalol, amiodarone, and beta-blockers are preferred.

There is little well-controlled clinical trial evidence to support strong recommendations in other less common forms of SVT such as focal atrial tachycardia or in appropriate sinus tachycardia. The drugs listed above may all be tried.

Atrial flutter can also present as regular narrow-complex tachycardia. Rate control (with beta-blockers, verapamil, diltiazem, amiodarone, or digitalis—all generally administered intravenously) may be attempted as initial management. Pharmacologic conversion can be achieved by ibutilide, sotalol, or amiodarone. Flecainide, propafenone, and procainamide can occasionally be tried, although slowing of the flutter rate and paradoxically increased ventricular rate is also possible; when these drugs are used, an AV nodal blocking agent (verapamil, diltiazem, or a beta-blocker) is added. Long-term pharmacologic management of atrial flutter can be accomplished by many potassium or sodium channel blocking drugs: dofetilide, amiodarone, sotalol, flecainide, quinidine, propafenone, procainamide, and disopyramide.

Guidelines for Drug Therapy of Atrial Fibrillation\textsuperscript{29}

As discussed in greater detail elsewhere (Chapter 92), management strategies in AF include rate control and rhythm control, as well as anticoagulation. For intravenous rate control, verapamil, diltiazem, or beta-blockers are the drugs of choice. Digoxin is generally less effective, and is most useful in the setting of concomitant heart failure. Oral therapy for rate control includes the same drugs. Amiodarone can also be used.

Drugs can be used to convert AF to sinus rhythm, especially if the arrhythmia has been present for a short duration.
fl ecainide, propafenone, and sotalol are the drugs of first choice. By history, physical examination, ECG, and echocardiogram, the arrhythmia can be confirmed. In patients with no heart disease, generally assessed with history, physical examination, ECG, and echocardiogram, flecainide, propafenone, and sotalol have been used quite successfully to effect pharmacologic cardioversion. In patients who have responded under monitored conditions to this approach, the patient may then be prescribed the drugs to be used for acute termination of further episodes of AF. Risks include hypotension and precipitation of atrial flutter with 1:1 AV conduction; these are small in appropriately selected populations. Asymptomatic ventricular arrhythmias are not an indication for chronic therapy, regardless of the etiology. Patients with symptomatic ventricular ectopy may occasionally be considered for chronic therapy, regardless of the etiology. Patients with outflow tract tachycardia or fascicular tachycardia can be managed with beta-blockers or calcium channel blockers, although ablation is increasingly the preferred primary approach.

In patients with heart failure, the strongest evidence supports the use of amiodarone or dofetilide. In patients with coronary disease, sotalol, amiodarone, or dofetilide is preferred, followed by consideration of disopyramide, procainamide, or quinidine; flecainide and propafenone are contraindicated in patients with coronary disease. Patients with hypertension present a particular management problem as this is a very common coexisting condition in AF. If hypertension has resulted in severe left ventricular hypertrophy, amiodarone is the drug of choice and there are few other pharmacologic options for maintenance of sinus rhythm. If left ventricular hypertrophy (LVH) is mild (LV wall thickness <1.4 cm), some authorities entertain the use of flecainide and propafenone, although this is controversial.

Ventricular Arrhythmias and Cardiac Arrest

Acute management of patients with cardiac arrest follows structured flowcharts and cardiac life support guidelines, including confirmation of the arrhythmia, airway management, and cardiopulmonary resuscitation. Drugs that may be useful in pulseless electrical activity or asystole include epi nephrine, atropine, and sodium bicarbonate. For VF or pulseless VT, prompt defibrillation is the first intervention. If this fails, intubation and cardiopulmonary resuscitation are initiated. Drugs of first choice in this setting include epinephrine (1 mg intravenously repeated every 3 to 5 minutes) or vasopressin 40 units, once. If further defibrillating shocks are ineffective, epi nephrine, sodium bicarbonate, and/or antiarrhythmics can be attempted; antiarrhythmics that are useful in this situation may include amiodarone, lidocaine, magnesium, or procainamide. Randomized trials, survival to hospitalization is superior with amiodarone compared to lidocaine, although survival to hospital discharge is different.

Another situation in which ventricular ectopy or nonsustained VT can be symptomatic is the patient with structural heart disease or primary cardiac ion channelopathy. In this situation, implantable cardioverter/defibrillators (ICDs) are used to manage the problem of sudden death risk, but drugs may be required to manage symptoms, and are often needed if ICD shocks are frequent. In patients with coronary disease, amiodarone or sotalol are the drugs of choice, and flecainide and propafenone are contraindicated. Randomized, controlled trials have shown reduced ICD discharges with sotalol and with the investigational agent azimilide, but not with dofetilide.

Another situation in which antiarrhythmic drugs may be considered is in a patient in whom an ICD would ordinarily be used, but for some reason (age, concomitant disease, ICD infection, etc.) is not. In this setting, amiodarone has been used as a gold standard, although well-controlled clinical trial data attesting to its efficacy are lacking. A metaanalysis of its effects in placebo-controlled trials in the post-myocardial infarction setting suggests modest benefit, and this may add to long-recognized benefits of beta-blockers in this setting. By contrast, in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), amiodarone appeared to increase mortality compared to placebo among patients with...
class III heart failure. Nevertheless, amiodarone continues to be used in this setting, in part, because alternate therapies appear at least equally ineffective.

The increasing recognition of individual syndromes of genetically determined arrhythmias, and elucidation of their potential mechanisms at the molecular and cellular levels, has, in turn, led to proposals for unusual therapies in some of these settings. In the congenital long QT syndrome, beta-blockers continue to be recommended as first-line therapy for patients known to be mutation carriers, although some data suggest that beta-blockers are less effective in the LQT2 and LQT3 forms of the disease. In the LQT3 form of the disease, sodium channel block with mexiletine or flecainide may be a useful adjunct, although flecainide may also increase risk if Brugada syndrome-type physiology is also present. Similarly, I_to block using quinidine may be useful in patients with Brugada syndrome, particularly in the setting of ICD “storm.” Quinidine has also been used in the short QT syndrome, where it appears to normalize QT duration and to reduce the amplitude of very peaked T waves. The latter action may be especially useful in patients with the short QT syndrome and ICDs, in whom double counting of the peaked T waves may lead to inappropriate ICD discharges. Patients with catecholaminergic polymorphic VT are best treated with beta-blockers. Among those with hypertrophic cardiomyopathy, amiodarone has frequently been used both to reduce the incidence of nonsustained VT as well as to prevent AF with rapid ventricular responses.

**Proarhythmia**

Multiple syndromes of drug-induced arrhythmia have been described, each with specific culprit drugs, risk profiles, and clinical features. Proarhythmia can arise with drugs intended for noncardiovascular indications; examples include VT with tricyclic antidepressants and torsades de pointes with a wide range of drugs, including antihistamines, antibiotics, and antipsychotics. Proarhythmia appears much more commonly with antiarrhythmic drugs than with other agents, and advanced heart disease, concomitant drug therapy interfering with drug elimination, or electrolyte abnormalities are common exacerbating features. Management consists of recognition of the specific syndrome, withdrawal of any offending agents, correction of any underlying exacerbating factors (electrolyte abnormality, transient myocardial ischemia, poor oxygenation), and subtype-specific therapies if needed. Common forms of proarhythmia, culprit drugs, clinical features, and management are summarized in Table 99.5. Electrocardiograms of examples of proarhythmia are shown in Figure 99.2.

<table>
<thead>
<tr>
<th>TABLE 99.5. Proarhythmia syndromes and their management</th>
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</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td>Digitalis intoxication</td>
</tr>
<tr>
<td>Torsades de pointes</td>
</tr>
<tr>
<td>Sodium channel blocker toxicity</td>
</tr>
<tr>
<td>Beta-blocker withdrawal</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>Calcium channel blocker toxicity</td>
</tr>
</tbody>
</table>

*Treatment in all cases consists of recognition, withdrawal of offending agents, correction of any other potential exacerbating conditions [hypokalemia, hypoxia, transient myocardial ischemia], and immediate resuscitation if needed. “Mild” refers to minimally symptomatic patients with no/few recurrences, while “serious” refers to those with recurrent destabilizing arrhythmias. ATPase, adenosine triphosphatase; AV, atrioventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation, VT, ventricular tachycardia.*
Prolonged episodes of torsades de pointes require resuscitation and cardioversion. Initial therapy for recurrent episodes is intravenous magnesium and, if the arrhythmia recurs, isoproterenol or pacing (to prevent pause-dependent initiations).51,52 Torsades de pointes in the congenital long QT syndrome may be managed similarly, although isoproterenol may in fact provoke further episodes especially in the LQTI form of the disease. Serious arrhythmias related to digitalis excess require antidigitalis antibodies, which are highly effective even in advanced intoxication.53 Sodium channel blockers, such as flecainide and propafenone, and quinidine, can generate a number of distinct proarrhythmia syndromes. When used for AF, atrial flutter with slowed flutter rate a 1:1 AV conduction is possible. In this setting, the sodium channel blocking properties of these agents lead to rate-dependent QRS widening, and the misdiagnosis of VT is frequent.54 The commonest ECG manifestation of tricyclic antidepressant overdose is sinus tachycardia with wide QRS complexes due to the drug’s sodium channel blocking properties; VT and, more rarely, torsades de pointes can occur. After recognition, AV nodal blocking drugs should be administered.

Increased thresholds for pacing and for defibrillation are a common manifestation of sodium channel blockers, including amiodarone. Repositioning leads or drug withdrawal may be required. Prior to widespread ICD use, sodium channel blocking drugs were used as primary treatment for sustained VT, and occasionally, patients would develop an increase in frequency or be resistant to defibrillation, which could be fatal; this form of toxicity is much less common now that these drugs are used much more rarely in these settings. Sodium channel blockers can also provoke an increase in SVT frequency. Many drugs have been associated with very rare instances of VF or sudden death; these include dietary supplements (ephedra), certain anticancer agents [5-fluorouracil (5-FU)], and antimigraine therapies. Management here consists of recognition and withdrawal of the drug.

**Summary of Important Properties of Individual Drugs**  [see also Table 99.6]

**Adenosine**

**Pharmacology**

Adenosine is a naturally occurring nucleoside whose actions are mediated by interaction with specific adenosine receptors. In the heart, this action produces calcium channel block and activation of an adenosine-dependent potassium channel, likely the same channel as that activated by acetylcholine [IK,ACh]. The net result of these actions is action potential shortening in atrium and AV nodal block.

**Pharmacokinetics**

Adenosine is eliminated from the circulation in seconds by rapid uptake into cells, and inactivation by adenosine deaminase. Dipyridamole inhibits uptake and thus exaggerates adenosine effects. Methylxanthines, including theophylline and caffeine, block adenosine receptors and so may inhibit the drug’s effects.

**Use**

Rapid bolus intravenous administration of adenosine produces transient AV nodal block, which terminates arrhythmias using the AV node as a portion of their circuit (AV nodal reentry, AV reentry). In atrial arrhythmias, transient AV nodal block may be useful in exposing the underlying rhythm and establishing the diagnosis. Outflow tract and fascicular tachycardias, occurring in the normal heart, may also be terminated by adenosine. However, common forms of VT in myocardial disease are adenosine-resistant; occasionally, induction of VA block by adenosine may be useful in establishing the diagnosis.

Because of its extremely rapid elimination rate, adenosine is unique among antiarrhythmic (and most other) drugs in that it must be administered as a very rapid intravenous bolus, preferably through a large or central line. Slower intravenous infusions of adenosine are used in other settings (e.g., neurosurgery) to produce controlled hypotension. Adenosine triphosphate (ATP) is also available in some countries for intravenous administration to terminate SVT, and acts by rapid degradation to adenosine.

**Adverse Effects**

Adenosine has supplanted other pharmacotherapy for acute termination of SVT because its actions dissipate so rapidly, making side effects only transient. Most patients feel a sense of air hunger and nonspecific chest discomfort with administration of adenosine; bronchospasm can occur.55 Asystole that follows administration of the drug and termination of the arrhythmia may last several seconds; prolonged asystole...
TABLE 99.6. Pharmacokinetics of antiarrhythmic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination half-life(^1)</th>
<th>Active metabolites(^2)</th>
<th>Major route of clearance</th>
<th>Major pharmacokinetic interactions(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-12 hours</td>
<td>Long</td>
<td>Hepatic</td>
<td>Renal</td>
</tr>
<tr>
<td>Adenosine</td>
<td>X (seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Weeks</td>
<td>X</td>
<td>X (CYP3A4)</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>36 hr</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>12–18 hr</td>
<td>X</td>
<td>X (CYP2D6)</td>
<td>X</td>
</tr>
<tr>
<td>Flunitrile</td>
<td>2 hr</td>
<td>X</td>
<td>X (CYP3A4)</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2 hr</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>3 hr</td>
<td>X</td>
<td>X (NAT2)</td>
<td>X</td>
</tr>
<tr>
<td>Propafenone</td>
<td>2–32</td>
<td>X</td>
<td>X (CYP2D6)</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Elimination half-life determines the time to steady state (4 to 5 elimination half-lives), the actual steady state achieved is determined by clearance. Propafenone elimination half-life is highly variable due to genetic factors (see text). NAT, \(N\)-acetyltransferase.

\(^2\) Drugs for which variability in clinical actions have been attributed to active metabolites are indicated.

\(^3\) Antiarrhythmics, beta-blockers, and calcium channel blockers interact to depress cardiac output, and sinus and AV nodal function.
requiring resuscitation has been reported after cardiac transplant. By activating potassium current in the atrium, adenosine shortens atrial refractory period, and may thereby precipitate AF. This is unusual, but if the patient has an accessory pathway, very rapid ventricular responses can ensue. Amiodarone

**Pharmacology**

Amiodarone is certainly the “dirtiest” antiarrhythmic, interacting with multiple ion channels, cell surface receptors, and other molecules to block their function. The drug is unusually lipophilic, and this accounts for its unusual pharmacologic effects, including its very slow uptake and elimination. However, while the onset of many of the drug’s effects are slow, other actions can be manifest on acute exposure; antiadrenergic actions tend to be prominent early, while changes in refactoriness may take longer to be apparent. In animal experiments, amiodarone administration appears to alter steady-state transcript levels of messenger RNAs (mRNAs) encoding multiple ion channels. Thus, the drug likely produces both acute and chronic effects by interacting with ion channels and other molecular targets, and may, in addition, “remodel” the heart through an effect on transcription.

Amiodarone is a sodium channel blocker, interacting primarily with inactivated states of the channel. This effect, and its calcium channel blocking effect, may underlie its ability to inhibit afterdepolarizations in vitro. The drug is also a blocker of multiple potassium channels, including \( I_{C} \). It has antiadrenergic effects. However, unlike traditional beta-blockers, the drug acts as a noncompetitive antagonist, the number of \( \beta \) receptors available during chronic amiodarone therapy is reduced, but the drug does not compete for access to those receptors with agonists such as norepinephrine. Amiodarone is a potent inhibitor of many drug metabolizing and drug transport systems, notably CYP3A4, CYP2C9, and P-glycoprotein.

**Pharmacokinetics**

Amiodarone is 30% to 50% bioavailable, so intravenous doses are smaller than oral ones. The drug undergoes CYP3A4-mediated metabolism to desethylamiodarone, an active metabolite. Amiodarone is eliminated extraordinarily slowly with a terminal phase elimination half-life measured in weeks or months. Thus, the time for the drug to achieve true steady state may be as long as a year. It is for this reason that loading regimens are required when amiodarone is initiated, and that dosages can often be reduced progressively during long-term therapy.

**Use**

Intravenous amiodarone has emerged as a drug of choice for a wide range of arrhythmias. It is superior to comparator drugs (procainamide or bretylium, an older drug that is no longer available) in life-threatening recurrent VT or VF, and may be especially useful in VT caused by active myocardial ischemia. Its marginal superiority over lidocaine out of hospital cardiac arrest is discussed above. Its effects in AF are less clear; in some studies it does improve conversion of the arrhythmia to sinus, but this effect may be delayed. Intravenous amiodarone also may be useful to slow the ventricular response rate in AF, and has been used successfully for rate control in postoperative junctional ectopic tachycardia in children.

Chronic amiodarone is used as adjutantive therapy in patients with ICD firings, as primary therapy for ventricular arrhythmias, and as therapy for AF and flutter. In each setting, the goal of therapy is to achieve an early drug effect by administration of relatively large doses (800 to 1200 mg daily) and to taper these over several days or weeks to maintenance dosages. Thus, in a patient with very frequent ICD discharges, a reasonable regimen might start with 1200 mg daily for several days, and taper to 400 mg daily over several weeks. On the other hand, in patients with AF where the indication is less pressing, one regimen is 800 mg daily for a week, and then chronic therapy with 200 mg (or eventually less) daily.

**Adverse Effects**

Intravenous amiodarone can cause phlebitis and severe cellulitis if extravasated. For this reason, it is preferable to administer the drug through a large-bore or central line. Hypotension is common. Marked QT prolongation and torsades de pointes can occur.

During chronic therapy, PR, QRS, and QT intervals are all prolonged. Despite QT prolongation, torsades de pointes is exceedingly unusual during amiodarone therapy, the likely explanation is that the drug includes among its many pharmacologic actions block of inward currents that prevent torsades initiation. Amiodarone does not generally produce major depression of ventricular performance, an advantage compared to other drugs.

The major forms of amiodarone toxicity during chronic therapy are extracardiac. The most feared toxicity is pulmonary; pulmonary fibrosis is the commonest manifestation, although atypical forms (that may, for example, be localized) can also occur. The cardinal laboratory manifestation of amiodarone toxicity is reduced diffusion capacity for carbon monoxide (DLCO). Pulmonary toxicity does appear to be dose related, although it can occur during chronic therapy with doses at or below 200 mg daily. Routine surveillance with chest x-rays and pulmonary function studies has been advocated as a method to detect early amiodarone toxicity, but the efficacy of these maneuvers is not established. Once pulmonary toxicity is suspected, further diagnostic workup may include biopsy, right heart catheterization (to eliminate a role for concomitant heart failure), and gallium scanning. None of these is specific, and biopsy often reveals foam cells, but cannot make a definitive diagnosis of toxicity. If toxicity is strongly suspected, the drug should be withdrawn. Corticosteroids have been used, but their efficacy is not certain. Death from pulmonary insufficiency can occur. Underlying pulmonary disease may be a risk factor, and patients often seem to manifest amiodarone pulmonary toxicity following a separate incident of lung injury, due to heart failure exacerbation, pneumonia, or general anesthesia.

Corneal microdeposits are ubiquitous during chronic amiodarone therapy, but rarely interfere with vision; halos
around lights at night may be one complaint. Much more rarely, the drug has been associated with optic neuritis. Liver function is often abnormal, and rarely may progress to cirrhosis. Peripheral neuropathy can be severe. Photosensitivity is common, and patients should be warned to use sunscreen and broad-brimmed hats. Both hypothyroidism and hyperthyroidism can occur, and hyperthyroidism—which can present as worsened arrhythmias—may require thyroid ablation or withdrawal of amiodarone. Because of the potential for toxicity, chest x-rays, thyroid function studies, and liver functions tests have been recommended every 6 to 12 months even in the absence of symptoms. 

**Disopyramide**

**Pharmacology**

Disopyramide is a sodium channel blocker with onset and offset kinetics similar to those of quinidine. It also prolongs QT interval. Disopyramide exerts prominent anti-inotropic and anticholinergic effects at clinical dosages.

**Pharmacokinetics**

Disopyramide is eliminated by hepatic metabolism and renal excretion. The pathways are induced by phenytoin, suggesting participation by CYP3A4 and P-glycoprotein. The drug is administered as a racemate; the enantiomers are equally potent as sodium channel blockers, but only one, S-disopyramide, prolongs action potentials in vitro. The drug is variably bound to plasma proteins within the therapeutic range, and its binding is saturable; as a result, monitoring plasma concentrations of total drug is not useful.

**Use**

Disopyramide is used as second- or third-line therapy for atrial arrhythmias. Its anticholinergic actions make it suitable for patients with vagally-mediated AF. Its negative inotropic effects also may be useful in management of patients with hypertrophic cardiomyopathy and outflow tract obstruction, and it may occasionally be used in patients with neurocardiogenic syncope.

**Adverse Effects**

Torsades de pointes, exacerbation of heart failure, and anticholinergic effects (constipation, urinary retention, glaucoma, dry eyes and mouth) can all occur. In a postmyocardial infarction prophylaxis trial in the mid-1980s [prior to the Cardiac Arrhythmia Suppression Trial [CAST]], disopyramide tended to increase mortality. 

**Dofetilide**

**Pharmacology**

Dofetilide is a potent and specific blocker of \( \mathrm{I}_{\text{Kr}} \), with no other significant pharmacologic actions. As a result, the drug produces QT prolongation, and torsades de pointes is its only significant toxicity.

**Pharmacokinetics**

Dofetilide is eliminated largely by renal excretion, and to a small extent by CYP3A4-mediated metabolism. Its elimination half-life (10 hours) allows twice-daily dosing. Certain drugs appear to inhibit dofetilide elimination, such as cimetidine, verapamil, ketoconazole, trimethoprim-sulfamethoxazole, and hydrochlorothiazide, and they are contraindicated because they may thereby increase the extent of QT prolongation and risk of torsades de pointes.

**Use**

Oral administration of dofetilide is effective in pharmacologic conversion of AF in about 30% of cases at 0.5 mg twice daily, the highest dose, with less efficacy at lower doses. The drug also reduces recurrence of AF following restoration of sinus rhythm. Dofetilide reduces rehospitalization for heart failure, an effect that may be attributable to maintenance of sinus rhythm in patients with AF.

Placebo-controlled trials have failed to demonstrate efficacy of the drug in reducing the frequency of episodes of paroxysmal AF, or of reducing episodes of VT or ICD discharges.

**Adverse Effects**

Data on torsades de pointes incidence are available from large trials in which the drug was initiated with in-hospital monitoring. In the Danish Investigations of Arrhythmia and Mortality on Dofetilide [DIAMOND] studies, dofetilide was compared to placebo in patients convalescing from myocardial infarction and in patients with recent hospitalization for heart failure. In the heart failure arm, the incidence of torsades de pointes was 3%, and some cases were fatal. In the postmyocardial infarction group the incidence was lower, 1%. Because of the risk of torsades de pointes, the drug can only be prescribed in the United States by practitioners who have been certified in its use. The drug is initiated in the hospital, and is unique among antiarrhythmics in that the starting dose, 0.5 mg twice daily, is the highest allowable dose; downward dose adjustments are made if the QT interval is excessively long or if renal function is impaired. The drug should not be used in patients with advanced renal failure.

**Flecainide**

**Pharmacology**

Flecainide is a potent sodium channel blocker, with slow onset and offset kinetics; PR and QRS widening are usual. It also blocks \( \mathrm{I}_{\text{Kr}} \), although reports of torsades de pointes are exceedingly rare.

**Pharmacokinetics**

Flecainide is eliminated with a half-life of 10 to 17 hours by hepatic metabolism by CYP2D6 and by renal excretion. Defects in either pathway are generally well tolerated, if the alternate pathway is unperturbed. Occasional patients with CYP2D6 deficiency (due to genetic factors or interactions with inhibiting drugs) and concomitant renal failure can develop flecainide toxicity. Flecainide is usually administered twice daily. In children 1 to 12 years of age [but not
Flecainide is effective in restoring and maintaining sinus rhythm in patients with AF and SVT.

**Adverse Effects**

Flecainide increased mortality following myocardial infarction in CAST, and therefore, is generally contraindicated in patients with coronary artery disease, and by extension, in patients with advanced structural heart disease. The drug can depress left ventricular performance, and precipitate or exacerbate heart failure. Flecainide can produce atrial flutter, can depress left ventricular performance, and precipitate or exacerbate heart failure. Flecainide can produce atrial flutter with 1:1 AV conduction, increased pacing and defibrillating thresholds, and exacerbation of VT.

**Pharmacokinetics**

The drug is administered as an intravenous “bolus” (1 mg over 10 minutes, that can be repeated 10 minutes later) and is subsequently eliminated by hepatic metabolism. Peak pharmacologic effects coincide roughly with the end of the infusion. The elimination half-life is 4 to 6 hours, and so patients should be observed for at least 4 hours after administration of the drug.

**Use**

Flecainide can be safely used in patients receiving chronic amiodarone therapy. Flecainide is also effective in patients with AF and rapid ventricular responses due to antegrade accessory pathway conduction, in this setting, it not only can convert AF, but also slows conduction down the bypass tract.

**Adverse Effect**

The major adverse effect is torsades de pointes.

**Mexiletine**

Mexiletine is a lidocaine analogue that can be administered orally. It is occasionally useful when added to other drugs (amiodarone, quinidine, sotalol) in patients with symptomatic VT. Mexiletine tended to increase mortality in a post-MI trial. In addition, mexiletine has been used in the congeni-
tal long QT syndrome, notably in the LQT3 (sodium channel-linked) subtype, where it may directly block the plateau sodium current that causes QT prolongation.81

Mexiletine is eliminated by hepatic metabolism, and is generally administered three times daily. Side effects such as tremor and nausea are common, and may be reduced by administering the drug with food, which decreases the peak plasma concentrations without affecting overall absorption. Another lidocaine analogue, tocainide, has very similar electrophysiologic effects, undergoes elimination primarily by renal excretion, and is no longer available because of bone marrow depression.

Procainamide

**Pharmacology**

The major effect of procainamide is sodium channel block, with relatively rapid onset and offset kinetics. QT prolongation is also evident during procainamide therapy, and at least some of this effect reflects generation of an active metabolite, N-acetylprocainamide (NAPA), which is a weak I\(\text{Kr}\) blocker that does not block sodium channels. PR, QRS, and QT prolongation are seen during procainamide therapy. The drug has ganglionic blocking properties, so hypotension during intravenous infusion is common.

**Pharmacokinetics**

Procainamide is eliminated by renal excretion and by N-acetylation to NAPA, as discussed above, this metabolism is in part genetically determined. Its elimination half-life is short, 3 to 4 hours, while that of NAPA is somewhat longer [8 to 12 hours]. As a result of this rapid elimination, and a narrow margin between concentrations required to produce efficacy and those producing toxicity, chronic oral therapy requires very frequent dosing or the use of sustained release formulations. N-acetylprocainamide is eliminated by renal excretion. In renal failure, accumulation of either parent or metabolite can occur, depending in part on acetylator phenotype.

Monitoring procainamide plasma concentrations should be used to ensure that concentrations of the parent drug remain in the 4- to 8-µg/mL range. N-acetylprocainamide concentrations >20µg/mL appear to carry a higher risk of torsades de pointes. Procainamide concentrations above 10µg/mL appear to carry a risk of marked QRS widening and potential arrhythmia exacerbation.

**Use**

Intravenous procainamide can be effective in suppressing symptomatic or life-threatening ventricular arrhythmias. It can also be effective in converting AF to sinus rhythm, and can slow the ventricular rate in patients presenting with preexcited AF and rapid ventricular responses. Procainamide is administered as an intravenous loading dose; one reasonable regimen is 15mg/kg (approximately 1g in an adult), administered over 50 minutes. Maintenance infusion rates are 30 to 60µg/kg/min (1–4mg/min in an adult). The drug is not well tolerated during chronic therapy, although very occasionally, patients (e.g., those with highly symptomatic and drug-resistant ventricular arrhythmias) may be considered for therapy.

**Adverse Effects**

During intravenous administration, the major adverse effect of procainamide is hypotension. Marked QRS widening and QT prolongation with torsades de pointes can also occur, particularly if plasma concentration of parent drug or metabolite is elevated, respectively. Adverse effects during chronic therapy are common, and include anorexia, nausea, electrocardiographic toxicity discussed above, agranulocytosis, and the drug-induced lupus syndrome.

Propafenone

**Pharmacology**

Propafenone is a potent sodium channel blocker with slow onset and offset kinetics. Propafenone is also a beta-blocker in vitro, and this effect can be observed at high plasma concentrations in human subjects.85

**Pharmacokinetics**

Propafenone is eliminated by CYP2D6. As a result, PMs and individuals receiving CYP2D6 inhibitors develop high plasma concentrations and increased risk of adverse effects, including bronchospasm and bradycardia. A sustained release formulation allows twice daily dosing.85

**Use**

Propafenone is effective in restoring and maintaining sinus rhythm in patients with AF and SVT.

**Adverse Effects**

Propafenone has not been formally tested in patients following myocardial infarction, but it seems reasonable to assume that it may exert adverse effects in this population like other sodium channel blocking drugs.2,66,80,83 Therefore, it is generally contraindicated in patients who have coronary disease and in those with advanced structural heart disease. Other adverse effects include depressed left ventricular performance, exacerbation of heart failure, atrial flutter with 1:1 AV conduction, and increased pacing and defibrillation thresholds.

Quinidine

**Pharmacology**

Quinidine is a component of an antimalarial extract from the bark of the cinchona plant, and was developed as an antiarrhythmic by Wenckebach just after the First World War. It blocks the sodium current channel and multiple potassium currents, including I\(\text{Kr}\), I\(\text{Ks}\), and I\(\text{To}\). Its kinetics of interaction with the sodium channel are intermediate. I\(\text{Kr}\) block can occur at very low concentrations; in vitro, action potential prolongation by quinidine is blunted at higher concentrations, likely reflecting an additional effect of sodium channel block.84
Quinidine is an alpha-blocker, and can thereby produce hypotension when administered intravenously. It has vaso-lytic actions, which make the drug occasionally useful in vasovagal syncope, and can also enhance AV nodal conduction during atrial flutter. It is a very potent inhibitor of CYP2D6, exerting this pharmacologic action at dosages as low as 5 mg; low-dose quinidine has actually been used in combination with CYP2D6 substrates to increase and make more uniform the plasma concentrations. Quinidine is also an inhibitor of P-glycoprotein, and as a result, decreases digoxin clearance and increases its serum concentrations.

Pharmacokinetics
Quinidine is eliminated by CYP3A4-mediated hepatic metabolism, with a half-life of 6 to 12 hours. Metabolites have some pharmacologic activity, but none is more potent than the parent drug. Maintaining plasma concentrations between 1.5 and 5 μg/mL has been a useful way of reducing dose-related toxicity.

Quinidine reduces clearance of many other drugs by its effect on CYP2D6 and P-glycoprotein. In addition, quinidine metabolism is subject to variability due to coadministration of drugs that inhibit or enhance CYP3A4 activity (Table 99.6).

Use
Quinidine can be effective in atrial and ventricular arrhythmias. It has also been used in unusual congenital arrhythmia syndromes discussed above (Brugada syndrome, short QT syndrome).

Adverse Effects
Quinidine is not well tolerated and so is not used as first-line therapy. It frequently causes gastrointestinal upset (diarrhea or nausea), the mechanism is unknown. Torsades de pointes occurs in 1% to 5% of patients in most series. Quinidine causes a number of immunologic adverse effects, notably thrombocytopenia.

Sotalol
Pharmacology
Sotalol is a nonselective beta-blocker with additional Iₖₕ-blocking effects. As a result, sinus bradycardia, PR, and QT prolongation occur.

Pharmacokinetics
Sotalol is eliminated by renal excretion of unchanged drug, with a half-life of 6 to 12 hours.

Use
Sotalol is effective in atrial and ventricular arrhythmias. The drug is available for oral administration in the U.S., and an intravenous formulation is available in other parts of the world.

Adverse Effects
Excessive bradycardia and torsades de pointes can occur. Dosages must be adjusted downward in renal failure.

Beta-Blockers as Antiarrhythmic Agents
Pharmacology
Epinephrine and norepinephrine are the physiologic agonists at α- and β-receptors. Available beta-blockers compete with these physiologic agonists for access to the receptors, and thereby blunt agonist activity. During chronic therapy, receptor upregulation can occur. β₁-receptors mediate tachycardia and increased contractility in normal hearts, although in heart failure there may be an increased contribution by β₂-receptors. β₁-agonists produce arterial vasodilatation. Acute antiarrhythmic effects are mediated primarily by β₁-receptor antagonism, although during chronic therapy, especially in patients with advanced heart disease, beta-blockers produce multiple beneficial effects, not all of whose underlying physiologic mechanisms are yet understood; many available beta-blockers produce a number of other effects such as alpha-blockade, antioxidant effects, and “membrane stabilization” (sodium channel block) that may contribute to antiarrhythmic actions. Beta-blockade inhibits VF due to acute myocardial ischemia in animal models. Most available beta-blockers are administered once or twice a day. Some undergo predominant hepatic metabolism (e.g., propranolol), while others are eliminated by renal excretion of unchanged drug (e.g., nadolol, atenolol). Metoprolol, timolol, and carvedilol are metabolized by CYP2D6, and so excess pharmacologic effects can be observed in subjects with defective CYP2D6 activity on a genetic basis or due to drug interactions.

Use
Beta-blockers are useful in termination of SVT, rate slowing in AF or flutter, and occasionally, patients with VT, notably those with “idiopathic” forms, as well as those with active ischemia. Beta-blockers reduce the incidence of sudden death when used in patients convalescing from acute myocardial infarction. Beta-blockers are first-line therapy for all forms of the congenital long QT syndrome, and some data suggest they may be especially useful in the LQT1 form.

Adverse Effects
Beta-blockers can produce excess bradycardia and AV block in susceptible individuals. Exacerbation of heart failure can occur, although beta-blockers are beneficial when appropriately titrated in patients with heart failure.

Antiarrhythmic Effects of Calcium Channel Blockers
Verapamil and diltiazem block L-type calcium channels and are used in termination of SVT, rate control in AF and flutter, and in rare patients with idiopathic ventricular arrhythmias in structurally normal hearts. The drugs can be administered intravenously for acute arrhythmia management, and
orally for long-term therapy. With intravenous administration, hypotension and bradycardia can occur, especially in young children. During chronic oral therapy, constipation is common with verapamil, and peripheral edema can occur with both agents. Calcium channel blockers, such as amlo
dipine used in other settings such as hypertension, are not useful as antiarrhythmics.

Digoxin

Pharmacology

Digoxin is a high potency inhibitor of sodium potassium adenosine triphosphatase (ATPase). In heart cells, this action, in turn, increases sodium–calcium exchange, and increases intracellular calcium concentration. These actions are responsible for the drug’s positive inotropic effects, and likely also mediate some of its proarrhythmic actions. A second major effect produced by digoxin is increased vagal activity, which underlies the drug’s sinus and AV nodal slowing properties.

Pharmacokinetics

Digoxin is eliminated slowly primarily by renal excretion. With an elimination half-life of 36 hours in normal individuals, steady state is approached in 7 to 10 days. Intravenous loading doses transiently produce very high plasma concentrations, but distribution into peripheral tissues is required for the drug to produce its effect, and this can be delayed for several hours. Other forms of digitalis glycoside have been, and continue to be, used in some parts of the world, and these may be eliminated by other routes, digitoxin is eliminated primarily by hepatic metabolism.

Adverse Effects

The hallmark of excess digitalis is arrhythmias, which often have features of both enhanced automaticity, as well as inhibition of sinus and AV nodal function, junctional tachycardia or paroxysmal atrial tachycardia with AV block are characteristic, as are isolated ventricular arrhythmias. Neurologic symptoms, such as confusion and visual disturbances, occur during chronic toxicity, particularly in the elderly. With suicidal ingestion, digoxin produces striking and difficult-to-manage hyperkalemia, with accompanying asystole. Management of mild digoxin toxicity consists of drug withdrawal and observation of the patient; temporary pacing may occasionally be required. With more serious forms of toxicity, antidigoxin antibodies are indicated. These can be highly effective, even in patients presenting with cardiac arrest. Serum digoxin concentrations are artifactualy elevated after administration of the antibody.

Use

Digoxin is used as adjunctive therapy for rate control of AF, particularly in patients with heart failure. Addition of a second agent (beta-blocker or calcium channel blocker) is frequently required to maintain rate control during exertion.

Magnesium

Use

When serum magnesium is low, arrhythmias (including torsades de pointes) can occur and can be effectively suppressed by restoring normal magnesium. Intravenous magnesium sulfate can also be effective for some arrhythmias (torsades de pointes, digitalis toxicity) even in the absence of hypomagnesemia. Excess magnesium causes hypermagnesemia with areflexia and respiratory suppression.

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