Rational Choices in Antiarrhythmic Pharmacotherapy

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Cover Illustration by mb cunney
INTRODUCTION

Cardiac arrhythmias were responsible for approximately 20% of all deaths in the United States in 1999. Although device therapy with implanted cardiac defibrillators has supplanted drugs as the primary therapy for malignant ventricular arrhythmias, antiarrhythmic drugs frequently are used concurrently in patients with implanted defibrillators to suppress arrhythmias and their attendant device discharges and as primary therapy for supraventricular rhythms. Often, decisions regarding antiarrhythmic pharmacotherapy are made based on a combination of lore and familiarity. However, the efficacy of individual antiarrhythmic drugs varies across the different types of arrhythmia. In order to make informed decisions when initiating pharmacotherapy for cardiac arrhythmia, clinicians must understand the mechanism of cardiac arrhythmias and the action of antiarrhythmic drugs.

MECHANISMS OF ARRHYTHMIA

Classically, there are 3 mechanisms of arrhythmia: automaticity, triggered activity, and reentry. Two forms of enhanced automaticity are recognized: normal automaticity, which involves tissue for which impulse initiation is a normal property, and abnormal automaticity, which involves tissue that typically is not spontaneously active. An example of each form is sinus tachycardia and reperfusion arrhythmias, respectively. In triggered activity, abnormalities in the repolarization phase of one action potential cause subsequent membrane potential oscillations that reach threshold, prematurely triggering another action potential. Triggered arrhythmias are divided into 2 types based on when the oscillations start in relation to repolarization. With the early afterdepolarization (EAD) type, prolongation of the action potential (QT interval on the surface electrocardiogram [ECG]) causes oscillations before full repolarization has occurred. This mechanism is thought to initiate the polymorphic ventricular tachycardia known as torsades de pointes. The second type is delayed afterdepolarizations (DADs), in which oscillations occur after the action potential has repolarized. DADs seem to be related to cellular Ca²⁺ overload, as seen in digoxin toxicity. The third type of arrhythmia is reentry, which is a continuous short circuit of electrical activity rotating in the cardiac syncytium. A minimum requirement for this type of arrhythmia is a transient unidirectional conduction block. The rhythm is favored by slow conduction and tissue heterogeneity. Sodium channels and gap junctions are the main dynamic determinants of conduction velocity. The slowing of conduction velocity with the blocking of sodium channels leads to widening of the QRS interval, a property that is used to follow dosing of some antiarrhythmic drugs.

THE IONIC BASIS OF THE CARDIAC ACTION POTENTIAL

The surface ECG is a manifestation of the underlying cardiac electrical activity that is the result of cell depolarization initiating a cardiac action potential. The shape of this action potential is determined by a choreographed sequential activation and closure of various ion channels (Figure 1). Ion channels are transmembrane proteins that control the movement of ions across the cell membrane by opening and closing a central aqueous pore, a function called gating. The movement of ions through their respective channels changes the membrane potential. The extracellular current flow associated with the changes in membrane potential manifests as the ECG. A few channels are always open, while others open in response to stimuli such as ligand binding (ligand-gated), changes in voltage (voltage-gated), or mechanical forces (stretch-activated). The cardiac sodium and calcium channels as well as most potassium channels are voltage-gated ion channels. These channels are the targets of most available antiarrhythmic drugs.

Because arrhythmias are an electrical disorder, the ion channels are obvious targets for prevention and
treatment of arrhythmia. The classic antiarrhythmic drugs work by modulating this channel activity, mostly by preventing ion movement through the channels. A familiarity with the role of classes of channels in the generation of the action potential is essential to understanding the effects of antiarrhythmic drugs on arrhythmias and the ECG.

The resting membrane potential (phase 4 of the action potential or the TP interval on the ECG) of myocytes is set by a small leak of K⁺ out of cells down its electrochemical gradient through a channel known as I_{K1}. Thus, K⁺ is the major determinant of the cell’s resting membrane potential, which is approximately –70 mV in atrial myocytes and –90 mV in ventricular myocytes. When intracellular K⁺ is diminished, as occurs with cardiac glycoside toxicity or ischemia, the resting potential is depolarized. Thus, diminished K⁺ can lead a usually stable cell to show spontaneous phase 4 depolarizations, or abnormal automaticity.

Phase 0 of the action potential consists of cellular depolarization, or a shift in the cell’s membrane potential to a less negative value. Depolarization is brought about by the influx of Na⁺ through the rapidly opening, high-conductance, voltage-gated Na⁺ channels, resulting in an increase in intracellular Na⁺ concentration and depolarization of the cell membrane. In phase 4, Na⁺ channels are in the closed state until slight depolarization of the cell reaches threshold and causes the channels to open. The channels inactivate milliseconds after opening, preventing additional influx of Na⁺. The inactivated channels cannot be opened again until the cell is repolarized. The electrical current generated from the Na⁺ channel is one of the major determinants of conduction velocity for a given cell; thus, less Na⁺ current translates into slower conduction. The number of Na⁺ channels available to open is determined by the resting membrane potential, which is set by the K⁺ concentration gradient. The more depolarized a cell is, the less Na⁺ current it will be able to generate, meaning conduction will be slower. Such cells are apt to participate in reentry. Many classic antiarrhythmic drugs target the Na⁺ channel.

Phase 1, or early repolarization, is caused by inactivation of the depolarizing Na⁺ channels and activation of a particular class of repolarizing K⁺ channels, the transient outward current (I_{to}). Phase 1, the action potential notch on the ECG, is followed by a slower repolarization known as phase 2, or the plateau phase. Lasting 100 ms or more, this phase is a competition between depolarizing Ca²⁺ channels and repolarizing K⁺ channels. The almost equivalent inward current of Ca²⁺ and outward current of K⁺ results in a relatively stable depolarized potential, providing time for entry of Ca²⁺ into the cell that is necessary for muscle contraction. Inactivation of Ca²⁺ channels and increased K⁺ channel activity mark the onset of phase 3, rapid repolarization, which ends the action potential. Thus, repolarization is a function of K⁺ channels, including the delayed rectifier channel and the slowly activating K⁺ channel, I_{Ks} and I_{Kr}, respectively. Both of these channels are targets of antiarrhythmic drugs. Anything that shortens the duration of repolarization (ie, reducing the QT interval) reduces inotropy by inhibiting Ca²⁺ entry. Alternatively, anything that prolongs the duration of repolarization sets the stage for triggered activity.

**Figure 1.** Ion channels are the basis of the cardiac action potential and serve as a therapeutic target of various antiarrhythmic drugs.

**EFFECTS OF BLOCKING ION CHANNELS**

**SODIUM CHANNELS**

The main effect of Na⁺ channel blockers is a decrease in the conduction velocity, which is manifested as QRS widening on the ECG (Figure 2). This effect helps stop reentry but does so at the expense of creating new areas of slow conduction and possible reentry. In addition, the Na⁺ channel blockers increase the action potential threshold, resulting in decreased automaticity as well as increased pacing and defibrillation thresholds. The higher threshold tends to prevent abnormal automaticity. Na⁺ channel blockers can cause a slight decrease in action potential duration (QT interval) and negative inotropy through their actions on the Na⁺/Ca²⁺ exchanger. Reduced Na⁺ permeability through the channel means that less Na⁺ will enter the cell, which increases the driving force for the exchanger and leads to less intracellular Ca²⁺ and less contractility.

An important property of antiarrhythmic drugs is
use-dependency. As ion channels cycle between the closed (resting), activated (open), and inactivated states, they change conformations. Antiarrhythmic drugs, especially the Na+ channel blocking drugs, show marked differences in activity depending on the relative proportion of the channel states present. In tachycardia, increased channel cycling between the states results in more opportunity for the drugs to bind to their preferred channel state. This helps explain why antiarrhythmic drugs may be more active in tachycardia.

Use-dependency also may explain why certain Na+ channel drugs, such as lidocaine, work better for ventricular arrhythmias. Lidocaine likes to bind inactivated channels, which are more prominent during the longer ventricular action potential. In atrial arrhythmias, the shorter action potential duration of the atria leads to fewer inactivated channels and less drug activity.

**POTASSIUM CHANNELS**

Blocking of K+ channels increases the action potential duration, which results in increased refractoriness of the cell (Figure 3). This effects tends to stop reentry arrhythmias by making it harder for the short circuit to find tissue ready to conduct. If the short circuit reaches a refractory (electrically inexcitable) area, it will stop, thus terminating the tachycardia. By prolonging the action potential and refractory period, K+ channel blockers increase the likelihood that the wavefront will encounter its own refractory wake and be extinguished (Figure 4). The longer action potential translates into a longer QT interval on ECG. It also increases the risk of triggered activity. Theoretically, K+ channel blockade should enhance contractility because the longer action potential allows more Ca2+ to enter the cell, but unfortunately this effect generally is not seen clinically.
CALCIUM CHANNELS
Ca²⁺ channel blockers inhibit the sinoatrial node, atrioventricular (AV) node, and some tissue with abnormal automaticity that depends on Ca²⁺ channels to initiate the arrhythmia (eg, right ventricular outflow tachycardia). Generally, these agents have little effect on the action potential duration at clinical doses. Ca²⁺ channel blockers stop triggered activity due to EADs (because the oscillatory depolarizations are thought to be waves of Ca²⁺ channel reactivation) and DADs, which result from Ca²⁺ overload of the cell.

VAUGHAN WILLIAMS CLASSIFICATION
Antiarrhythmic drugs are commonly classified using the Vaughan Williams system (Table 1). This classification is based on the effect of drugs on conduction velocity (a Na⁺ channel-dependent effect) and action potential duration (a K⁺ channel-dependent effect). Class I drugs slow conduction velocity, or widen the QRS. Class II drugs are β-blockers. Class III drugs prolong action potential duration or QT interval. Class IV drugs are calcium channel blockers. Class I is further divided into Ia, Ib, and Ic. Class Ia agents (eg, quinidine and disopyramide) have additional K⁺ blocking activity and prolong the action potential. They are used most frequently for conversion of atrial flutter/fibrillation and maintenance of sinus rhythm. Class Ib agents (eg, lidocaine and mexiletine) have rapid channel binding kinetics and show use-dependent binding to the inactivated state. Because they unbind from channels rapidly in the TP interval, they cause minimal apparent change in conduction velocity and only a slight decrease in action potential duration. They are not useful for atrial arrhythmias but are used for ventricular arrhythmias, especially those associated with myocardial infarction (MI) and ischemia. Class Ic agents (eg, flecainide and moricizine) have slower Na⁺ channel blocking kinetics, and their effects are not relieved fully during the TP segment. They cause marked slowing of conduction velocity and are used for atrial and ventricular arrhythmias in patients with structurally normal hearts. Class III drugs are used in both atrial and ventricular rhythms.

CASE PATIENT PRESENTATIONS

CASE PATIENT 1
An asymptomatic 50-year-old woman with no significant past medical history, normal renal function, and a normal echocardiogram presents with atrial fibrillation.

- Which of the following drugs is not appropriate in the management of this patient’s atrial fibrillation?
  A) Procainamide  
  B) Lidocaine  
  C) Flecainide  
  D) Ibutilide  
  E) Dofetilide  

The correct answer is B. All these drugs except lidocaine can be used for conversion of sinus rhythm in atrial fibrillation. Because of its strong use-dependence favoring the inactivated state, lidocaine and other class Ib antiarrhythmic drugs have little effect on atrial arrhythmias. This class of antiarrhythmics is indicated for ventricular arrhythmias, especially in patients with acute MI. There is a low incidence of hemodynamic complications with use of lidocaine.² Predominant side effects are neurologic (eg, tremor, nystagmus, or delirium) and are thought to be the result of brain Na⁺ channel blocking activity (Table 2).

The class Ia agent procainamide is used in the treatment of atrial fibrillation, atrial flutter, and supra-
ventricular tachycardia (AV nodal reentrant tachycardia and AV reentrant tachycardia). It can increase the refractoriness of the accessory pathway in Wolff-Parkinson-White syndrome, preventing supraventricular tachycardia and slowing ventricular response over the accessory pathway in atrial flutter and atrial fibrillation.\(^3\) Because procainamide may facilitate AV nodal conduction, especially atrial flutter, the concomitant use of an AV nodal blocking agent is recommended. Limitations to the use of procainamide (class Ia) are its variable metabolism, its propensity to prolong the QT interval, and when given long term, to induce a lupus-like syndrome (30% of patients). Most patients (70%) develop antinuclear antibodies, especially those who are slow acetylators. Procainamide must be dose adjusted or avoided in renal failure patients.

Flecainide (class Ic) is a high-potency Na\(^+\) channel blocker that is used commonly in the treatment of atrial flutter and atrial fibrillation.\(^3\) Because procainamide may facilitate AV nodal conduction, especially atrial flutter, the concomitant use of an AV nodal blocking agent is recommended. Limitations to the use of procainamide (class Ia) are its variable metabolism, its propensity to prolong the QT interval, and when given long term, to induce a lupus-like syndrome (30% of patients). Most patients (70%) develop antinuclear antibodies, especially those who are slow acetylators. Procainamide must be dose adjusted or avoided in renal failure patients.

Flecainide (class Ic) is a high-potency Na\(^+\) channel blocker that is used commonly in the treatment of atrial flutter and atrial fibrillation. As with procainamide, an AV blocking agent is used concomitantly to prevent rapid ventricular rates with slowing atrial flutter rates. This step is not necessary with propafenone, however, because it has inherent β-blocking activity.\(^4\) The side effects of flecainide are rare and include blurred vision, headache, and ataxia. Class Ic agents are not used in patients with structural abnormalities of the heart, such as ischemic cardiomyopathy or more than mild left ventricular hypertrophy. This prohibition is based on results of the Cardiac Arrhythmia Suppression Trial (CAST).\(^5\) The trial was designed to test the hypothesis that suppression of ventricular ectopy with class Ic drugs after a MI reduces the incidence of sudden arrhythmic death.\(^6\) Patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. While highly efficacious at suppressing ventricular ectopy, the drugs caused excess mortality in treated patients. The risk was highest in those with structurally abnormal hearts.

Ibutilide (class III) is used intravenously for acute conversion of atrial flutter/fibrillation. Ibutilide blocks K\(^+\) channels and activates a prolonged Na\(^+\) current, prolonging the action potential, refractory period, and QT interval. It has a half-life of 6 to 9 hours and is metabolized by the liver. It is approximately 60% effective in cardioversion of atrial flutter and approximately 30% effective in atrial fibrillation; there is a small but significant incidence of torsades, which is increased in patients with low ejection fraction.\(^8\) Ibutilide works best in patients with new onset arrhythmias.

Dofetilide is a new, renally excreted, class III antiarrhythmic agent active in atrial and ventricular rhythms. Because of the risk of torsades, dofetilide therapy should be initiated in the hospital, where 72 hours of cardiac monitoring and serial ECGs is encouraged by the Food and Drug Administration.\(^10\) The Danish Investigators of Arrhythmia and Mortality on Dofetilide in CHF (DIAMOND-CHF)\(^11\) and DIAMOND-MI\(^12\) trials have demonstrated the safety of dofetilide in patients with structural heart disease.

### CASE PATIENT 2

A 60-year-old man with a history of MI, an ejection fraction of 0.25, and an implantable cardiac defibrillator presents with a complaint that he is receiving multiple shocks from the device. On device interrogation, he is noted to have several episodes of ventricular tachycardia. He shows no biochemical or ECG evidence of new ischemia/infarction.

- **Which antiarrhythmic medication is best to reduce the number of device discharges in this patient?**
  - A) Quinidine

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**Table 1. Vaughan Williams Classification of Antiarrhythmic Drugs**

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
<th>Representative Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Reduce V(_{max}); prolong repolarization and APD</td>
<td>Quinidine, procainamide, disopyramide</td>
</tr>
<tr>
<td>Ib</td>
<td>Do not reduce V(_{max}); shorten APD; shorten repolarization</td>
<td>Lidocaine, mexiletine, tocainide, phenytin</td>
</tr>
<tr>
<td>Ic</td>
<td>Reduce V(_{max}); slow conduction; little effect on repolarization</td>
<td>Flecainide, propafenone, moricizine</td>
</tr>
<tr>
<td>II</td>
<td>β-adrenergic blockade</td>
<td>Propranolol, esmolol, acebutolol, L-sotalol</td>
</tr>
<tr>
<td>III</td>
<td>Prolong repolarization and APD</td>
<td>Ibutilide, dofetilide, D,L-sotalol, amiodarone, bretylium</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium channel blockade</td>
<td>Verapamil, diltiazem, nifedipine</td>
</tr>
</tbody>
</table>

\(APD = \text{action potential duration.}\)
The best drug for preventing ventricular tachycardia and minimizing the number of shocks delivered in this patient would be amiodarone. Amiodarone has powerful and complex antiarrhythmic actions and is well tolerated in patients with reduced ejection fraction. Although amiodarone appears to have properties of all 4 classes of antiarrhythmic agents, its most obvious effects are K⁺ channel blockade, prolonging the action potential and increasing the QT interval. Also, it slows AV nodal conduction, presumably by β-blocker and Ca²⁺-channel-blocker activities. It can be used in suppression of a wide variety of ventricular and supraventricular arrhythmias and is the most effective drug for maintenance of sinus rhythm in patients with atrial fibrillation as well as for decreasing risk of ventricular tachyarrhythmias. It appears to have the least proarrhythmic side effects of the class III agents.

Several trials have been performed to evaluate the safety of amiodarone use in patients with MI and low ejection fraction. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), amiodarone reduced ventricular fibrillation and arrhythmic death after MI in patients with frequent or repetitive ventricular premature complexes (3.3% in amiodarone group versus 6.0% in placebo; \( P = 0.016 \)). The reduction was more prominent in patients with a previous MI and congestive heart failure. The European Amiodarone Myocardial Infarct Arrhythmia Trial (EMIAT) showed a 35% decrease in arrhythmic deaths in patients receiving amiodarone. However, neither trial showed an overall survival benefit with amiodarone therapy. The Grupo de la Sobredad en la Insufficiencia Cardiaca en Argentina (GESICA) trial compared low-dose amiodarone with placebo in patients with heart failure on standard therapy (including digoxin, diuretics, and angiotensin-converting enzyme [ACE] inhibitors) and found a 28% reduction in overall mortality with amiodarone. These results were not supported by the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) trial, which included patients with heart failure, premature ventricular contractions, and ejection fraction of 40% or less. The positive findings in the GESICA trial, which had a greater proportion of nonischemic cardiomyopathy patients compared to CHF-STAT, may suggest that amiodarone is more effective in nonischemic cardiomyopathy.

The correct answer is C. The best drug for preventing ventricular tachycardia and minimizing the number of shocks delivered in this patient would be amiodarone. Amiodarone has powerful and complex antiarrhythmic actions and is well tolerated in patients with reduced ejection fraction. Although amiodarone appears to have properties of all 4 classes of antiarrhythmic agents, its most obvious effects are K⁺ channel blockade, prolonging the action potential and increasing the QT interval. Also, it slows AV nodal conduction, presumably by β-blocker and Ca²⁺-channel-blocker activities. It can be used in suppression of a wide variety of ventricular and supraventricular arrhythmias and is the most effective drug for maintenance of sinus rhythm in patients with atrial fibrillation as well as for decreasing risk of ventricular tachyarrhythmias. It appears to have the least proarrhythmic side effects of the class III agents.

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Table 2. Adverse Effects of Antiarrhythmic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life (hr)</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>6–8</td>
<td>Gastrointestinal symptoms, hemolytic anemia, thrombocytopenia, hypotension, lupus--like syndrome</td>
</tr>
<tr>
<td>Procainamide</td>
<td>3–5</td>
<td>Lupus-like syndrome, hypersensitivity, gastrointestinal symptoms, leukopenia</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>4–8</td>
<td>Urinary retention, dry mouth, congestive heart failure exacerbation</td>
</tr>
<tr>
<td>Lidoine</td>
<td>1–4</td>
<td>Neurological and gastrointestinal symptoms</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>8–16</td>
<td>Neurologic and gastrointestinal symptoms, leukopenia</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>24</td>
<td>Neurologic and gastrointestinal symptoms, aplastic anemia, peripheral neuropathy, hyperglycemia, lymphadenopathy, Stevens-Johnson syndrome, hirsutism, osteomalacia</td>
</tr>
<tr>
<td>Flecaïnine</td>
<td>12–27</td>
<td>Neurologic and gastrointestinal symptoms, congestive heart failure exacerbation</td>
</tr>
<tr>
<td>Propafenone</td>
<td>2–4</td>
<td>Neurologic and gastrointestinal symptoms, metallic taste, β-blockade complications</td>
</tr>
<tr>
<td>Morcizine</td>
<td>2–6</td>
<td>Dizziness, nausea, headache, neurological symptoms</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>30–100 days</td>
<td>Pulmonary fibrosis, hypothyroidism, hyperthyroidism, corneal and skin deposits, hepatitis, bradycardia</td>
</tr>
<tr>
<td>D,L-Sotalol</td>
<td>7–18</td>
<td>Bradycardia, fatigue, exacerbation of congestive heart failure</td>
</tr>
<tr>
<td>Bretylium</td>
<td>5–10</td>
<td>Hypotension, nausea</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>2–12</td>
<td>Proarrhythmia, hypotension, bundle branch block, atrioventricular block, nausea, headache</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>10</td>
<td>Headache, chest pain, dizziness</td>
</tr>
</tbody>
</table>

B) Lidocaine
C) Amiodarone
D) D-Sotalol
Amiodarone has limitations, however. It contains iodine and can cause hypothyroid or rarely hyperthyroid symptoms. Its most serious adverse effect is irreversible, life-threatening pulmonary fibrosis, but this effect is unusual at doses used for treating atrial fibrillation (100–200 mg/day). A gallium lung scan and a reduction in diffusion capacity of lung for carbon monoxide of 30% are helpful in establishing a diagnosis of pulmonary fibrosis, but this approach has low specificity. Amiodarone is metabolized by the liver and can cause hepatotoxicity. It can be used in patients with renal failure, however. Other side effects include corneal deposits, myopathy, skin deposits that lead to photosensitivity as well as bluish tint, and neuropathy. It leads to increased levels of digoxin (50%–75%), warfarin (50%–100%), diltiazem, and cyclosporin. In view of these side effects, a baseline chest radiograph, pulmonary function tests, liver function tests, and thyroid function tests are recommended. Amiodarone can be given intravenously or orally. It is highly lipophilic, requires a loading dose, and has a half-life of weeks. The onset of action is between 2 days and 2 weeks, even when a loading dose is administered.

Quinidine is a class Ia agent with indications for use similar to procainamide. This class of antiarrhythmics can be used to suppress ventricular arrhythmias. However, a meta-analysis of 6 trials that used quinidine to treat atrial fibrillation showed that quinidine maintained patients in sinus rhythm longer compared with no antiarrhythmic therapy but was associated with an increase in total mortality. These results would argue against the use of quinidine in the case patient. Moreover, quinidine has significant side effects that complicate its use, including diarrhea (25%–50%), reversible thrombocytopenia, cinchonism (headache and tinnitus), hepatitis, bone marrow suppression, and lupus-like syndrome. Disopyramide (class Ia) also can be used in the treatment of ventricular arrhythmias, but it has a significant negative inotropic effect, making it an unsuitable choice for patients with ventricular dysfunction.

Class Ib agents are potentially useful for ventricular tachycardia, but lidocaine has significant first pass metabolism and has to be used intravenously. Mexiteline is a therapeutic alternative to amiodarone for this patient.

In addition to amiodarone, other class III agents could be useful. D,L-Sotalol is a racemic mixture of 2 compounds with differing activities on ion channels. The I-enantiomer is a nonselective β-blocker and K⁺ channel blocker while the D-enantiomer is a pure K⁺ channel blocker. Indications for use include ventricular tachyarrhythmias and prevention of recurrence of a wide variety of supraventricular arrhythmias. The most serious side effect of D-sotalol and D,L-Sotalol is QT prolongation leading to torsades. D,L-Sotalol should not be started in patients with QTc greater than 450 ms and should be stopped if the QTc exceeds 520 ms. D,L-Sotalol is also negatively inotropic because of its β-blocking activity. Renal dose adjustment is required. In the Survival with Oral D-Sotalol trial, D-sotalol increased mortality in patients with either left ventricular dysfunction and recent MI or with recent heart failure and remote MI, making it an inappropriate choice for our patient.

**CASE PATIENT 3**

A 60-year-old man is noted to be in persistent atrial fibrillation after coronary artery bypass surgery. He is started on intravenous amiodarone in the intensive care unit. On the second day postsurgery, he is noted to have an arrhythmia on the monitor (Figure 5).

- **What is the most likely cause of this arrhythmia?**
  - A) Hyperkalemia
  - B) Hypoxia
  - C) Amiodarone
  - D) Acidosis

**The answer is C.** This is an example of proarrhythmia associated with use of class Ia and III antiarrhythmic medications. Current ion channel blocking antiarrhythmic drugs have narrow therapeutic indices and have a tendency to cause new arrhythmias, especially in the presence of structural heart disease and a reduced ejection fraction. For this reason, it is prudent to start most antiarrhythmic drugs, with the exception possibly of amiodarone, in the inpatient setting with frequent monitoring of the ECG. The mechanism of class Ia and III-induced proarrhythmia is fairly well understood. K⁺ channel blockade prolongs the action potential and the QT interval, which increases the risk of EADs and torsades de pointes. Patients can be monitored for this effect by following the QT interval on ECG. The proarrhythmic risk of class Ic agents is not as easy to understand and predict. As shown in the CAST study, Class Ic drugs can cause life-threatening arrhythmias such as ventricular tachycardia and ventricular fibrillation, especially in patients with reduced ejection fraction. This effect could be a result of drug-induced Brugada syndrome, a genetic sudden death syndrome caused by reduced Na⁺ channel function. Neverthe less, the incidence of ventricular proarrhythmia with flecainide and propafenone is rare in the treatment of supraventricular arrhythmias in structurally normal...
hearts. In patients with an implantable cardioverter defibrillator, the device manages proarrhythmic risk of death, allowing a wider selection of antiarrhythmic drugs to be used.

**FUTURE DIRECTIONS OF ANTIARRHYTHMIC DRUG THERAPY**

The use of antiarrhythmic drugs has diminished considerably with the advent of catheter-based techniques in ablation of reentrant tachycardias, atrial fibrillation, and ectopic foci along with device therapy for ventricular tachycardia and fibrillation. Nevertheless, the future holds much promise for the rational use of classic and developing antiarrhythmic drugs.

One of the great promises of the genetic revolution is the use of pharmacogenomics. Individual variation in therapeutic response to antiarrhythmic drugs and in proarrhythmia caused by them can be attributed in part to the mutations and polymorphisms of genes encoding for ion channels or metabolic pathways. Some persons are known to have genetic proclivity to arrhythmias, such as the congenital long QT, short QT, and Brugada syndromes. More subtle mutations may determine arrhythmic risk and antiarrhythmic response. Understanding the genetic basis of drug action, pharmacokinetics, and pharmacodynamics may allow the safe and effective use of one particular drug for a specific arrhythmia in an individual. The genetic milieu may modulate the risk of proarrhythmia (eg, torsades de pointes) associated with the use of antiarrhythmic medications.

Antiarrhythmic drugs have a potential use in diagnosis, too. Antiarrhythmic drugs have been used in invasive electrophysiologic testing to suppress ventricular tachycardia. In the Multicenter Automatic Defibrillator Implementation Trial (MADIT) trial, procainamide response was used to help risk-stratify patients with asymptomatic nonsustained ventricular tachycardia, a prior MI, an ejection fraction of 0.35 or less, and an inducible ventricular tachyarrhythmia at electrophysiological testing. Sodium channel blockers, such as flecainide and ajmaline, also can be used to unmask concealed Brugada syndrome. Brugada syndrome is a genetic disorder that is caused by the loss of sodium channel function, causing ventricular fibrillation/tachycardia and potentially sudden death. Most of these patients have a distinct ECG pattern consisting of atypical right bundle branch block and right precordial ST-elevation, while others do not manifest changes on ECG. The use of sodium channel blockers can accentuate the defect, helping to identify concealed Brugada syndrome patients with high risk of sudden death, who can be treated with implantable defibrillator devices.

Last, new antiarrhythmic drugs as well as nontraditional antiarrhythmic drugs may be available for arrhythmia prevention and treatment as we explore the pathophysiology of arrhythmias further. Atrial fibrillation is a common and complex arrhythmia. A variety of genetic, metabolic, hemodynamic, and anatomical factors play a role in its initiation and maintenance. It is associated with anatomical and electrical remodeling of the atria that helps in maintenance of fibrillation and makes it resistant to cardioversion. Some of this remodeling is associated with angiotensin II, which causes mechanical remodeling of the atria by hypertrophy and leads to inhomogeneity of the mechanoelectrical substrate, maintaining the arrhythmia. There may be a
role for ACE inhibitors in prevention and reversal of this remodeling effect and hence in the treatment of atrial fibrillation. Recent investigation has shown that the local redox pathways involving nitric oxide and superoxide may be involved in atrial fibrillation and may serve as a novel therapeutic target. In addition, newly investigated chamber-specific potassium channels in the atrial myocardium (Kv1.5), which are responsible for ultra-delayed rectifier current in atria, are involved in electrical remodeling. Blocking these channels may lead to prolongation of the atrial action potential without alterations in the ventricle and may help in treating atrial fibrillation.

These exciting developments in genetics and the pathophysiology of arrhythmias may lead to new drugs and treatment strategies aimed at reducing the mortality and morbidity of cardiac arrhythmias.

**SUMMARY POINTS**

- The 3 mechanisms of arrhythmia are automaticity, triggered activity, and reentry.
- The surface electrocardiogram (ECG) is a manifestation of the underlying cardiac action potential. The action potential results from the coordinated opening of multiple ion channels.
- The classic antiarrhythmic drugs work by blocking ion channels or receptors.
- Antiarrhythmic drugs can be grouped into 4 classes that predominately correlate with Na+ channel, β-receptor, K+ channel, and Ca2+ channel blocking activities for classes I, II, III, and IV, respectively.
- Drugs that block K+ channels prolong the action potential and the QT interval.
- Class Ic drugs slow conduction velocity and prolong the QRS.
- Class Ib drugs do not work on atrial arrhythmias.
- Class I and III antiarrhythmic drugs can cause arrhythmias, a phenomenon known as proarrhythmia.

**REFERENCES**


