Amiodarone: Guidelines for Use and Monitoring
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Amiodarone is a potent antiarrhythmic agent that is used to treat ventricular arrhythmias and atrial fibrillation. The drug prevents the recurrence of life-threatening ventricular arrhythmias and produces a modest reduction of sudden deaths in high-risk patients. Amiodarone is more effective than sotalol or propafenone in preventing recurrent atrial fibrillation in patients for whom a rhythm-control strategy is chosen. When long-term amiodarone therapy is used, potential drug toxicity and interactions must be considered. The dosage of amiodarone should be kept at the lowest effective level. In patients who also are taking digoxin and warfarin, physicians must pay close attention to digoxin levels and prothrombin time, keeping in mind that the effects of interaction with amiodarone do not peak until seven weeks after the initiation of concomitant therapy. Laboratory studies to assess liver and thyroid function should be performed at least every six months. (Am Fam Physician 2003;68:2189-96. Copyright 2003© American Academy of Family Physicians.)

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See page 2113 for definitions of strength-of-evidence levels.

Amiodarone (Cordarone) is a complex antiarrhythmic agent with multiple electrophysiologic effects, unusual pharmacokinetics, and numerous potentially harmful drug interactions and adverse effects. Although the U.S. Food and Drug Administration (FDA) has labeled amiodarone only for the treatment of life-threatening ventricular arrhythmias, the drug also is used to treat atrial fibrillation. Because of the complexity and widespread use of this agent, other treatment decisions often are affected. This article reviews the pharmacology, indications, adverse effects, and drug interactions of amiodarone, and outlines a strategy for surveillance of patients who are taking this drug.

Clinical Pharmacology

PHARMACOKINETICS

Amiodarone is an iodine-containing compound with some structural similarity to thyroxine. The drug’s high iodine content likely is a factor in its effects on the thyroid gland. The bioavailability of amiodarone is variable but generally poor, ranging from 22 to 95 percent. Absorption is enhanced when the drug is taken with food. Amiodarone is highly lipid soluble and is stored in high concentrations in fat and muscle, as well as in the liver, lungs, and skin. Amiodarone crosses the placenta and reaches measurable levels in breast milk.

The major metabolite of amiodarone is desethylamiodarone (DEA), which is known to have antiarrhythmic properties. Grapefruit juice can inhibit amiodarone metabolism and lead to elevated drug levels, but the impact of this interaction on the long-term efficacy and toxicity of amiodarone is not known.

The elimination half-life of amiodarone is highly variable and unusually long, averaging about 58 days. The long half-life is thought to be a result of the drug’s slow release from lipid-rich tissues.

ELECTROPHYSIOLOGIC EFFECTS

Amiodarone is considered to be a class III drug (Vaughan Williams classification), which indicates that it prolongs the QT interval. However, the drug has many other effects: it slows heart rate and atrioventricular nodal conduction (via calcium channel and beta-receptor blockade), prolongs refractoriness (via potassium and sodium channel blockade), and slows intracardiac conduction (via sodium channel blockade).

The relationship between plasma amiodarone concentrations and effect, as well as
the contribution of the metabolite DEA, is not well established.² Routine monitoring of the amiodarone plasma level is not recommended.⁴ [Evidence level C, consensus/expert guidelines]

Indications

LONG-TERM TREATMENT

Amiodarone is approved for use in the secondary prevention of life-threatening ventricular arrhythmias. The North American Society for Pacing and Electrophysiology (NASPE) recommends amiodarone as the antiarrhythmic agent of choice in patients who have survived sustained ventricular tachyarrhythmias, particularly those with left ventricular dysfunction.⁴

Studies on the use of amiodarone for the primary prevention of sudden death in high-risk patients have had mixed results. One meta-analysis of 13 studies of patients with congestive heart failure or recent myocardial infarction showed a small reduction in total annual mortality, from 12.3 percent to 10.9 percent (absolute risk reduction [ARR], 2.4 percent; number needed to treat [NNT], 42).³ [Evidence level A, meta-analysis] The benefit of amiodarone therapy was more pronounced in the patients who had congestive heart failure, with treatment reducing the annual mortality rate from 24.3 percent to 19.9 percent (ARR, 4.4 percent; NNT, 23). Because implantable cardioverter-defibrillators (ICDs) are more effective than amiodarone in reducing mortality in high-risk patients with previous myocardial infarction, primary treatment should be an ICD.⁶-⁹ [Reference 6—Evidence level A, meta-analysis] In these patients, amiodarone may be used as an adjunct to reduce the frequency of ICD shocks or to control atrial fibrillation in selected highly symptomatic patients. The relative efficacy of amiodarone and ICDs in preventing sudden death in patients without coronary disease is under investigation.

Amiodarone is used in the treatment of atrial fibrillation, although the FDA has not approved this indication. Various practice guidelines recommend amiodarone as a second-line drug in the long-term treatment of atrial fibrillation in patients with structural heart disease and in highly symptomatic patients without heart disease.¹⁰ Several smaller studies have shown that amiodarone is similar to quinidine and sotalol in the treatment of atrial fibrillation in these patients.¹¹,¹² In one randomized controlled trial (RCT),¹² sinus rhythm was maintained successfully for 16 months in 65 percent of patients treated with amiodarone, compared with 37 percent of patients treated with sotalol or propafenone (ARR, 28 percent; NNT, 3.6). However, recent studies have shown that aggressive attempts to maintain sinus rhythm using amiodarone or other drugs do not improve outcomes in relatively asymptomatic patients.¹³,¹⁴ Therefore, long-term amiodarone therapy, with its potential for toxicity, does not appear to be justified in patients who are taking anticoagulant drugs if rate-control strategies can provide satisfactory symptomatic improvement.

ACUTE TREATMENT

Intravenously administered amiodarone is effective for the emergency treatment of ventricular tachyarrhythmias. Onset of the antiar-
rhythmic effect of intravenous amiodarone occurs in less than 30 minutes.\textsuperscript{15}

In the Advanced Cardiac Life Support (ACLS) guidelines published in 2000, amiodarone and procainamide are recommended for the initial treatment of hemodynamically stable wide-complex tachycardia.\textsuperscript{16} However, these guidelines list amiodarone as being only “possibly effective” for the treatment of refractory pulseless ventricular tachycardia or ventricular fibrillation. In contrast, a recent study comparing the use of amiodarone and lidocaine in patients with shock-resistant, out-of-hospital ventricular fibrillation showed that amiodarone therapy substantially improves survival and hospital admission rates.\textsuperscript{17} \textit{[Evidence level A, RCT]}

Typical amiodarone dosages in the ACLS setting are provided in Table 1.\textsuperscript{2,10} In patients who require long-term treatment, intravenous dosing should be switched to oral dosing. Patients who received intravenous amiodarone for less than one week should take 800 to 1,600 mg oral amiodarone per day.\textsuperscript{2} Patients who received intravenous amiodarone for one to three weeks should take 600 to 800 oral amiodarone per day, and patients who received intravenous amiodarone for more than three weeks should take 400 mg oral amiodarone per day.

Intravenously administered amiodarone is being used with increasing frequency in the acute treatment of atrial fibrillation. In a meta-analysis of 18 RCTs, amiodarone was similar to other antiarrhythmic drugs in its ability to convert patients to normal sinus rhythm (72.1 percent for amiodarone compared with 71.9 percent for other antiarrhythmic drugs).\textsuperscript{18} \textit{[Evidence level A, meta-analysis]} The meta-analysis did not address the effect of antiarrhythmic drugs on mortality and other clinical outcomes. Use of these drugs would be most appropriate in patients with recurrent hemodynamically unstable atrial fibrillation.\textsuperscript{19} Amiodarone may be particularly beneficial in patients with rapid ventricular rates or impaired renal function.

### Adverse Effects

Amiodarone has been associated with toxicity involving the lungs, thyroid gland, liver, eyes, skin, and nerves (Table 2).\textsuperscript{2,5,11,19} The frequency of most adverse effects is related to the total amiodarone exposure (i.e., dosage and duration of treatment). Therefore, physicians must use the lowest possible dosage of amiodarone and, if possible, discontinue treatment if adverse effects occur.

### PULMONARY TOXICITY

The most serious potential adverse effect of amiodarone therapy is pulmonary toxicity, which may result from direct drug-induced phospholipidosis or immune-mediated hypersensitivity.\textsuperscript{19} The most common clinical presentation is subacute cough and progressive dyspnea, with associated patchy interstitial infiltrates on chest radiographs and

<table>
<thead>
<tr>
<th>Table 1: Dosage Guidelines for Amiodarone (Cordarone)</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
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<tr>
<td>Atrial fibrillation</td>
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</table>

\textit{IV = intravenous; GI = gastrointestinal. Information from references 2 and 10.}
reduced diffusing capacity on pulmonary function tests. A much less common presentation is adult respiratory distress syndrome.

In early studies, the frequency of pulmonary toxicity in amiodarone therapy was 2 to 17 percent. More recent studies have shown a lower incidence in patients receiving dosages of 300 mg per day or less. A meta-analysis of double-blind trials found the frequency of adult respiratory distress syndrome to be 1 percent annually.

Routine screening for adult respiratory distress syndrome is of limited value, because pulmonary toxicity can develop rapidly with no antecedent abnormalities on chest radiographs or pulmonary function tests. Any report from the patient of worsening dyspnea or cough should elicit a prompt assessment for pulmonary toxicity. Congestive heart failure can mimic amiodarone pneumonitis and, thus, must be ruled out early in the evaluation. High-resolution computed tomographic scanning can be helpful in making a diagnosis.

The primary treatment for pulmonary toxicity is withdrawal of amiodarone and provision of supportive care and, in some cases, corticosteroids. In most instances, the toxicity is reversible.

**THYROID TOXICITY**

Thyroid toxicity is the most common complication that requires intervention. Thyroid abnormalities have been described in up to 10 percent of patients receiving amiodarone. The frequency of thyroid abnormalities has been described as follows: hyperthyroidism in 2 percent, hypothyroidism in 6 percent, and liver toxicity in 1 percent. Optic neuropathy has been identified in 1 percent of patients. Proarrhythmia (less than 1 percent), bradycardia (2 to 4 percent), and photosensitivity (4 to 9 percent) are minor effects.

### TABLE 2

**Adverse Effects of Amiodarone (Cordarone)**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Frequency (%)</th>
<th>Method of diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>2 to 17(^2)</td>
<td>Chest radiograph; pulmonary function tests, including DLco</td>
<td>Stop amiodarone; initiate corticosteroid therapy.</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2(^2)</td>
<td>Free T(_4) level, TSH level</td>
<td>Initiate antithyroid drug therapy; consider stopping amiodarone.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6(^5)</td>
<td>Free T(_4) level, TSH level</td>
<td>Administer thyroid hormone supplementation.</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>1(^5)</td>
<td>Liver enzyme levels three times higher than normal</td>
<td>Consider stopping amiodarone.</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>Unknown(^19)</td>
<td>Ophthalmologic examination</td>
<td>Consider stopping amiodarone; causal relationship is uncertain.</td>
</tr>
<tr>
<td>Proarrhythmia</td>
<td>&lt;1(^11)</td>
<td>ECG</td>
<td>Stop amiodarone.</td>
</tr>
<tr>
<td>Bradyarrhythmia</td>
<td>2 to 4(^2)</td>
<td>Physical examination, ECG</td>
<td>If severe, stop amiodarone or insert pacemaker.</td>
</tr>
<tr>
<td><strong>Minor effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, anorexia</td>
<td>30(^2)</td>
<td>History, physical examination</td>
<td>Reduce dosage.</td>
</tr>
<tr>
<td>Corneal microdeposits</td>
<td>&gt;90(^2,19)</td>
<td>Slit-lamp examination</td>
<td>None</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>4 to 9(^2)</td>
<td>History, physical examination</td>
<td>Use sunblock.</td>
</tr>
<tr>
<td>Blue discoloration of skin</td>
<td>&lt;9(^3)</td>
<td>Physical examination</td>
<td>Reduce dosage.</td>
</tr>
</tbody>
</table>

DLco = diffusing capacity of lung for carbon monoxide; T\(_4\) = thyroxine; TSH = thyroid-stimulating hormone; ECG = electrocardiogram.

Information from references 2, 5, 11, and 19.
percent of patients receiving long-term amiodarone therapy. Hyperthyroidism may result from an excess of iodine or acute thyroiditis. Hypothyroidism is two to four times more common than hyperthyroidism.

In hypothyroid patients with a strong clinical indication for amiodarone, the drug may be continued with appropriate thyroid hormone supplementation. Treatments of amiodarone-induced hyperthyroidism include the withdrawal of amiodarone (if this can be done safely), the addition of antithyroid medications or prednisone, and surgical thyroidectomy.

LIVER TOXICITY
Liver toxicity, manifested by elevation of liver transaminase levels, is common in patients who are receiving long-term amiodarone therapy. This adverse effect occurs at a rate of 0.6 percent annually.

Patients with liver toxicity are rarely symptomatic. If liver enzyme levels are three times higher than normal, amiodarone should be discontinued unless a patient is at high risk for recurrence of life-threatening arrhythmia.

GASTROINTESTINAL ADVERSE EFFECTS
Gastrointestinal side effects of amiodarone include nausea, anorexia, and constipation. These symptoms often are dosage related and usually improve when the dosage is reduced.

OCULAR ADVERSE EFFECTS
Corneal microdeposits are visible on slit-lamp examination in nearly all patients treated with amiodarone. These deposits seldom affect vision and rarely necessitate discontinuation of the drug.

Optic neuropathy and optic neuritis, sometimes progressing to total blindness, have been described in a small number of patients treated with amiodarone. A causal relationship is not well established. Any patient who notes changes in visual acuity or peripheral vision should be referred for ophthalmologic evaluation.

The most serious potential adverse effect of amiodarone therapy is pulmonary toxicity. The most common clinical presentation is subacute cough and progressive dyspnea, with associated patchy interstitial infiltrates on chest radiographs and reduced diffusing capacity on pulmonary function tests.

DERMATOLOGIC ADVERSE EFFECTS
Photosensitivity is common in patients receiving amiodarone therapy. Therefore, all patients should be cautioned to use sunblock and, whenever possible, to cover exposed skin when they are outdoors.

In patients with extended and recurrent sun exposure, bluish skin discoloration may develop in exposed areas. The discoloration resolves over several months after amiodarone is discontinued.

**TABLE 3 Important Amiodarone (Cordarone) Drug Interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Result of interaction</th>
</tr>
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<tbody>
<tr>
<td>Digoxin&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Elevated digoxin plasma concentration</td>
</tr>
<tr>
<td>Warfarin (Coumadin)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Elevated prothrombin time</td>
</tr>
<tr>
<td>Simvastatin (Zocor)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Increased incidence of myopathy when simvastatin dosage is higher than 20 mg per day</td>
</tr>
<tr>
<td>Sildenafil (Viagra)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Increased sildenafil plasma concentration</td>
</tr>
<tr>
<td>Cyclosporine (Sandimmune)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Increased cyclosporine plasma concentration</td>
</tr>
<tr>
<td>Antiarrhythmic drugs&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Additive effects: possible elevated plasma concentrations of quinidine, disopyramide (Norpace), flecainide (Tambocon), propafenone (Rythmol), and dofetilide (Tikosyn)</td>
</tr>
<tr>
<td>Quinolones&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Additive QT effect: possible increased risk of proarrhythmia</td>
</tr>
<tr>
<td>Antidepressants&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Increased plasma concentration of hepatically metabolized drugs: possible increased risk of proarrhythmia</td>
</tr>
</tbody>
</table>

Information from references 4 and 21 through 25.
Neurologic toxicity associated with amiodarone therapy can include ataxia, paresthesias, and tremor. These conditions often are dosage related and improve when the dosage is reduced. Peripheral neuropathy has been reported to occur at a rate of 0.3 percent annually.11

Bradycardia and heart block occur in 1 to 3 percent of patients receiving amiodarone.2 Amiodarone-induced proarrhythmia occurs at an annual rate of less than 1 percent.11 Although almost all patients treated with the drug have prolongation of the QT interval, polymorphic ventricular tachycardia (i.e., torsades de pointes) is rare. Amiodarone therapy is contraindicated in patients with second- or third-degree heart block who do not have a pacemaker.

Intravenously administered amiodarone causes heart block or bradycardia in 4.9 percent of patients and hypotension in 16 percent.2 If these conditions occur, infusion of the drug should be discontinued, or the rate of infusion should be reduced.

Drug Interactions

Amiodarone is a potent inhibitor of the hepatic and renal metabolism of several drugs (Table 3).4,21-25 Amiodarone inhibits metabolism through several cytochrome P450 pathways, including CYP 2C9 (which metabolizes warfarin [Coumadin]), CYP 2D6 (which metabolizes several beta blockers and narcotics), and CYP 3A4 (which metabolizes cyclosporine [Sandimmune] and calcium channel blockers). Interactions with warfarin and digoxin are the most clinically important.

Amiodarone reduces warfarin clearance and can lead to sudden and pronounced increases in the prothrombin time and International Normalized Ratio.21 The peak effects of interaction occur approximately seven weeks after initiation of therapy.

Digoxin levels predictably double after coadministration with amiodarone.22 This increase occurs because of the inhibition of digoxin secretion from renal tubules and...
the inhibition of the P-glycoprotein membrane transporter system. The digoxin dosage should be reduced by 50 percent when amiodarone is started, and plasma digoxin levels should be monitored closely. Patients taking amiodarone should not eat grapefruit or drink grapefruit juice because it can inhibit the conversion of amiodarone to an active metabolite.

**Dosage and Administration**

In patients receiving oral amiodarone therapy, there may be a delay of two weeks or more before antiarrhythmic effects are noted. A loading regimen (i.e., use of a relatively high dosage at the beginning of therapy) can shorten the delay.

Typical dosing regimens are provided in Table 1. Because dosages below 300 mg per day are associated with a reduced incidence of pulmonary adverse effects, physicians should aim for a long-term maintenance dosage of 200 mg per day or less.

**Monitoring**

Patients treated with amiodarone should be followed regularly to assess ongoing need for amiodarone, efficacy of the drug, appropriateness of dosage, adverse effects, and potential drug interactions. Consensus follow-up recommendations from the NASPE are summarized in Table 4. A form to guide patient monitoring is provided in Figure 1.

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Amiodarone

REFERENCES


