Amiodarone Drug Interactions

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Amiodarone, a class III antiarrhythmic, has become the drug of choice for the management of supraventricular and ventricular arrhythmias.\(^1,2\) Although not an FDA-approved indication, the use of amiodarone to treat atrial fibrillation is supported by practice guidelines from the American College of Cardiology/American Heart Association (AHA) and the European Society of Cardiology.

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A HIGH-RISK AGENT

Although amiodarone is widely used, it must be considered a high-risk agent. The drug has an extensive adverse-effect profile, including thyroid, hepatic, and pulmonary toxicities.\(^5,6\) Before therapy is initiated, baseline thyroid, liver, and pulmonary function tests are recommended. In addition, a baseline chest radiograph and eye examination should be performed. Because of the extremely long half-life of amiodarone, its effects can persist long after it has been discontinued. Furthermore, amiodarone is associated with significant drug interactions, which require prudent monitoring and dosage adjustments. Our emphasis here is on the clinically relevant interactions; in Tables 1 through 5, we provide strategies to minimize risk.

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**Table 1 — Amiodarone and CV agents: examples of clinically significant interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment/management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Significant increase in INR. Onset may be seen within 1 to 2 weeks. Peak effect is at 7 weeks. Decrease warfarin dose by 20% to 30%. Higher maintenance doses of amiodarone may require adjustments.</td>
</tr>
</tbody>
</table>
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- Even greater reductions in warfarin dose. Closely monitor INR.
- Simvastatin, lovastatin, atorvastatin increases risk of myopathy and rhabdomyolysis. Onset may be seen within 2 weeks. Simvastatin dosage should not exceed 20 mg/d. Lovastatin dosage should not exceed 40 mg/d. No specific recommended dosage of atorvastatin. Ask patients about muscle pain and weakness.
- Digoxin: Serum digoxin concentrations can increase by up to 104%. Onset can be as early as 2 days. Monitor for GI, neurologic, and cardiac toxicities. Reduce digoxin dose by 50%.
MECHANISMS OF INTERACTION

Cytochrome P-450 enzyme system. Amiodarone is metabolized hepatically and serves as a substrate primarily for cytochrome P-450 (CYP) 3A4. In addition, it is a potent inhibitor of CYP 3A4, 2C9, 2D6, and 1A2. As a result, concurrent use of CYP 3A4 inhibitors can cause levels of amiodarone to increase and the use of CYP 3A4 inducers can result in decreased concentrations of amiodarone. Numerous amiodarone drug interactions are associated with the inhibition of CYP 3A4 and other CYP isoenzymes by amiodarone, resulting in increased serum concentrations of the other medications (see Tables 1 through 5 for examples).

Transporter proteins. P-glycoproteins act as energy-dependent transmembrane efflux pumps that play a role in the distribution of medications such as digoxin, cyclosporine, and protease inhibitors. These proteins are widely distributed in the intestines, but they are also located among the endothelial cells of the blood-brain barrier, kidneys, liver, and other organs. Amiodarone can inhibit P-glycoprotein expression, which results in supratherapeutic levels of agents absorbed via this pathway.

Pharmacodynamic interaction. This interaction occurs when the pharmacologic response to a given agent is changed by the actions of another drug. An example of this type of interaction would be 2 drugs that produce additive effects.
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Amiodarone prolongation and de pointes. Effects can be rapid. Withhold amiodarone for at least 3 half-lives before administering dofetilide or sotalol. Withhold amiodarone for 5 half-lives before and 4 hours after administering ibutilide. Quinidine concentrations can increase by 33% with concurrent amiodarone use; decrease quinidine dose by 30% to 50%.

Lidocaine, procainamide, flecainide, propafenone

Amiodarone increases serum levels of each agent. Monitor for lidocaine-induced CNS toxicity and adjust lidocaine dose. Monitor for procainamide-induced hypotension and arrhythmias; procainamide-induced hypotension and arrhythmias;
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- Flecainide: Monitor for flecainide-induced proarrhythmias; reduce flecainide dose by 50%.
- Propafenone: Monitor for propafenone-induced GI and CNS effects; reduce propafenone dose as needed.

CV, cardiovascular; INR, international normalized ratio; AV, atrioventricular.
*These are examples only. See current texts and reviews for further information.

Table 2 — Amiodarone and antimicrobial agents: examples of clinically significant interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment/management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolones</td>
<td>Additive effect, which increases risk of QT prolongation and torsades de pointes.</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Delayed onset. Consider another antibacterial agent.</td>
</tr>
<tr>
<td>Ketolides</td>
<td>Delayed onset.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
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Elevated amiodarone levels. Delayed onset. Concomitant administration with ritonavir and nelfinavir is contraindicated. Monitor for amiodarone toxicity, and reduce dose as needed.

*These are examples only. See current texts and reviews for further information.

Table 3 — Amiodarone and GI agents: examples of clinically significant interactions*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment/manage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Decreased amiodarone levels Monitor amiodarone efficacy; increase dose as needed.</td>
</tr>
</tbody>
</table>
Additive effect, which increases risk of QT prolongation and torsades de pointes. Increased cisapride levels. Avoid concomitant use. Use metoclopramide as an alternative. Monitor cardiac function if concurrent use of 5-HT3 antagonists and amiodarone cannot be avoided.

Cimetidine can increase amiodarone levels by about 40%. Avoid concomitant use. Use another H2-blocker.

*These are examples only. See current texts and reviews for further information.

### Table 4 — Amiodarone and neurologic agents: examples of clinically significant interactions*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment/manage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Torsades additive effect, which increases risk of QT prolongation and torsades de pointes. Increased cisapride levels. Avoid concomitant use. Use metoclopramide as an alternative. Monitor cardiac function if concurrent use of 5-HT3 antagonists and amiodarone cannot be avoided. Cimetidine can increase amiodarone levels by about 40%. Avoid concomitant use. Use another H2-blocker. *These are examples only. See current texts and reviews for further information.</td>
</tr>
</tbody>
</table>
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**Phenytoin, fosphenytoin**

Increases serum phenytoin concentrations or decreases amiodarone concentrations. Delayed onset.

Monitor for CNS toxicity and amiodarone clinical efficacy. Adjust doses accordingly.

*These are examples only. See current texts and reviews for further information.

Table 5 - Amiodarone and miscellaneous agents: examples of clinically significant
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment/Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Elevated cyclosporine levels; levels can increase 2- to 3-fold. Delayed onset. Monitor levels and adjust dose accordingly.</td>
</tr>
<tr>
<td>Grapefruit/grapefruit juice</td>
<td>Increased amiodarone levels. Can occur with 200 - 300 mL of juice or with whole fruit segments. Avoid concomitant use.</td>
</tr>
<tr>
<td>Anesthetic agents</td>
<td>Additive effect, which increases risk of hypotension and bradycardia. Close monitoring is necessary.</td>
</tr>
</tbody>
</table>

*These are examples only. See current texts and reviews for further information.*
References:


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