The Rational Use of Intravenous Amiodarone in the Perioperative Period

Jeffrey R. Balser, M.D., Ph.D.*

AMIODARONE is an iodinated benzofuran derivative with demonstrated efficacy against a range of cardiac arrhythmias, including atrial fibrillation, paroxysmal supraventricular tachycardias, and life-threatening ventricular arrhythmias. Despite its many side effects, some of which may be serious, orally administered amiodarone has been widely used as a highly effective alternative to more conventional antiarrhythmic therapies in patients with refractory ventricular arrhythmias. Although oral amiodarone has been approved for this purpose since 1985, intravenous amiodarone had been available in the United States only through study protocols. With approval of intravenous amiodarone by the United States Food and Drug Administration (FDA; August 3, 1995) for management of refractory ventricular arrhythmias, anesthesiologists now possess a highly effective agent for treating patients with this life-threatening condition. It should be recognized, however, that anesthesia, surgery, and cardiopulmonary bypass may pose special risks to the patient receiving amiodarone, which should be carefully weighed when contemplating perioperative administration.

Pharmacodynamic Mechanisms

Amiodarone is an antiarrhythmic compound with multiple sites of action in the cardiovascular system. As a noncompetitive blocker of α- and β-adrenergic receptors, intravenous amiodarone induces arteriolar vasodilation and atrioventricular (AV) nodal suppression, prolongs the AV nodal refractory period, and slows AV nodal conduction. The negative chronotropic effects of amiodarone may be potentiated to some degree by calcium channel blockade, resulting from suppression of the slow inward current. Amiodarone also blocks cardiac sodium channels, producing a "class I" effect. This effect manifests as a reduced rate of upstroke of the cardiac action potential (fig. 1), which slows conduction in the ventricular myocardium and prolongs the QRS complex on the surface electrocardiograph (ECG). The effect of amiodarone on sodium channels is use-dependent, meaning that the drug has greater effects at faster heart rates, a feature of sodium channel blockade thought to underlie antiarrhythmic efficacy. It is postulated that amiodarone use-dependence results from preferential binding to the inactivated channel conformation, causing a delay in recovery of channels from this refractory state during diastolic repolarization.

Chronic oral amiodarone dosing lengthens the QT interval (its "class III effect") as a result of reduction in outward potassium current and consequent prolongation of the cardiac action potential (fig. 1). Although this effect may partly explain the high antiarrhythmic efficacy of oral and intravenous amiodarone, it also may paradoxically explain the potential for amiodarone to induce polymorphic ventricular arrhythmias. It is unknown whether amiodarone reduces potassium current through direct blockade of potassium channels or via modulation of channel regulatory pathways, such as the adrenergic second messenger systems. Also, although many antiarrhythmic agents with QT-prolonging activity suppress a rapidly activating component of the delayed rectifier potassium current, (IKr), amiodarone differs in its higher selectivity for the slowly activating component of delayed rectifier potassium current (IKs). The clinical implications of this unique electro-
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Physiologic profile remain uncertain but may partly underline the high efficacy of amiodarone and its low propensity, relative to other class III antiarrhythmic agents, to induce polymorphic ventricular arrhythmias (see Proarrhythmic effects of oral and intravenous amiodarone).

Although effects consistent with potassium channel blockade typically are apparent in the ventricular myocardium after chronic oral dosing (increased QT interval) and are occasionally seen in patients given large intravenous dosages (10 mg/kg), only AV nodal effects attributable to beta blockade are measurable after typical intravenous bolus dosages (5 mg/kg). However, acute in vitro exposure of canine ventricular muscle to amiodarone significantly prolongs the action potential. Therefore, although AV nodal suppression may be a significant antiarrhythmic mechanism of intravenous amiodarone, it also is possible that the arrhythmia substrate in ventricular muscle is susceptible to low amiodarone concentrations that may not dramatically prolong the QT interval. Therefore, a mechanistic role for sodium or potassium channel suppression by amiodarone during acute intravenous therapy cannot be excluded.

Pharmacokinetics and Dosing Regimens

Because of its high lipophilicity and poor oral bioavailability, onset of antiarrhythmic action may require weeks of oral amiodarone administration. Even when using high-dose loading regimens (800 - 1400 mg/day), a mean of 9 - 10 days is required to attain a therapeutic effect. Although intravenous administration circumvents the slow and variable absorption of oral amiodarone, serum concentrations after intravenous doses are highly variable and are not highly predictive of antiarrhythmic effects. Nonetheless, therapeutic effects are seen within 1 - 30 min after administration of a single intravenous dose, and efficacy in patients with refractory arrhythmias has been demonstrated in multicenter trials during the initial 12 h of therapy.

Table 1 provides general guidelines for intravenous amiodarone dosing. Intravenous administration may cause venous sclerosis, so infusion through a central vein is recommended. The current recommendations, based on recent dose-ranging studies, are to administer ~1000 mg during the first 24 h in three phases. After the initial 24 h, patients generally remain on the 'phase 3' infusion rate of 0.5 mg/min (720 mg/day) for 48 - 96 h before conversion to oral therapy. During this time, breakthrough arrhythmias may be effectively managed with supplemental 150-mg intravenous bolus infusions for a 10-min period to minimize hypotension. The adult dosing recommendations are based on recent multicenter dose-ranging trials and are given in milligrams per day without scaling to body size. A small pediatric trial has provided initial recommendations for effective dosing in children based on weight. Patients were given 5 mg/kg by infusing 1-mg/kg boluses for a 5- to 10-min period, each separated by 5- to 10-min intervals. During the infusions, transient decreases in blood pressure were easily managed with volume expansion. The patients then received continuous infusions at a rate of 10 mg·kg⁻¹·day⁻¹, with repeat 5 mg/kg loading doses as needed, up to a 15 mg·kg⁻¹·day⁻¹ total dose.

Partly because of its large volume of distribution

<table>
<thead>
<tr>
<th>Table 1. Intravenous Amiodarone Dosing Schedule</th>
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<tr>
<td><strong>Duration</strong></td>
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<td><strong>Day 1</strong></td>
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<td>Phase 1</td>
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<td>Phase 2</td>
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<td>Phase 3</td>
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<td>Subsequent days</td>
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<td>Breakthrough episodes</td>
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<td><strong>Breakthrough episodes</strong></td>
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 (>5000 l in adults), with cessation of therapy, the rate of elimination appears to depend heavily on the previous duration of therapy. After a single 400-mg intravenous dose, there is a rapid phase of elimination lasting 1–2 days, followed by a terminal elimination phase with a half-life lasting up to 40 days. The early, more rapid phase probably results from redistribution of drug from the central compartment into peripheral tissues. After longer dosing periods that allow accumulation in peripheral tissues, rapid redistribution contributes less to the elimination profile, and the slow terminal elimination rate predominates. The slow elimination rate largely eliminates the need to supplement such patients on chronic oral therapy with temporary intravenous doses peripherally. Because amiodarone serum levels are not highly predictive of therapeutic effects, patients should be monitored for arrhythmias while they are unable to take oral amiodarone; however, intravenous therapy need not be instituted peripherally unless arrhythmias reappear or the patient remains unable to take oral amiodarone for several weeks.

The slow phase of amiodarone elimination primarily reflects hepatic metabolism to the principal metabolite, N-desethylamiodarone; renal elimination of amiodarone and its known metabolites is negligible, and the ultimate pathway for elimination of amiodarone and its metabolites is unknown. Dosage adjustments for renal disease and hepatic disease appear to be unnecessary. N-desethylamiodarone has electrophysiologic properties analogous to the parent compound and may influence drug efficacy during prolonged therapy while also reducing the need to supplement patients with intravenous amiodarone when chronic oral therapy is interrupted for surgery. In contrast, levels of N-desethylamiodarone are very low in patients receiving intravenous amiodarone for only 2–4 days before conversion to oral therapy, so it is doubtful that metabolite-related antiarrhythmic effects are clinically relevant under these circumstances. In patients in whom longer periods of intravenous therapy are necessary, the recommended starting dosage for conversion to oral therapy is reduced. The manufacturer's guidelines for conversion to oral therapy are provided in Table 2. These recommendations are based on an oral bioavailability of 50%, which does not apply to all patients; therefore, close monitoring of the ECG is necessary.

| Table 2. Conversion from Intravenous to Oral Dosing |
|---------------------------------|---------------------|
| Duration of Intravenous Infusion | Initial Oral Daily Dosage |
| <1 week                         | 800–1600 mg         |
| 1–3 weeks                       | 600–800 mg          |
| >3 weeks                        | 400 mg              |

Nonperioperative Use of Intravenous Amiodarone for Ventricular Arrhythmias

Before recent FDA approval, intravenous amiodarone use in the United States was limited to controlled clinical trials. Three prospective multicenter studies evaluated intravenous amiodarone in patients with severe cardiac disease and refractory, hemodynamically destabilizing ventricular arrhythmias. Scheinman et al. examined 342 patients who were refractory or intolerant to three other agents: lidocaine, propranolol, and bretylium. Eighty percent of the patients had a previous myocardial infarction; 30% of the patients had incessant ventricular tachycardia (VT) at the start of amiodarone therapy, and 10% were receiving cardiopulmonary resuscitation. Overall, 78% of the patients survived 48 h, and 60% survived a 30-day follow-up period. Although the use of a placebo group was deemed unethical by the investigators, survival in similar patient groups has been estimated to be less than 20% despite aggressive therapy. In the absence of a placebo group, the 24-h dose–response relationship was evaluated as a means of establishing efficacy of intravenous amiodarone. The incidence of hemodynamically destabilizing ventricular arrhythmias decreased from 0.07 events/h for patients receiving a low dose (125 mg/24 h) to 0.02 events/h for patients receiving the highest dose (1000 mg/24 h). There also was a significant dose-related increase in the mean time to first recurrence of ventricular arrhythmia, from 9.8 h in those receiving the 125 mg/24-h dosage to 13.7 h in those receiving the 1000 mg/24-h dosage. After 48 h, 26% of patients in the 1000-mg dosage group remained arrhythmia-free versus only 16% of patients in the 125-mg group. Similarly, Levine et al. evaluated the dose–response relationship in 275 patients and found that the time to first arrhythmia recurrence in patients receiving 1.0–2.0 g/24 h was significantly greater than for those patients receiving only 500 mg/24 h. Although the conclusions of both studies are limited by the lack of a placebo group, the dose-dependent effects and impressive survival statistics strongly sug-
suggest that intravenous amiodarone therapy was benefi-
cial.

Although these dose-ranging trials examined intrave-
nous amiodarone only after failure of three other antiar-
rhythmic agents,\textsuperscript{22,25} a third trial compared intravenous amiodarone and intravenous bretylium for 48 h in 302 patients who were refractory to only two antiarrhythmic agents: lidocaine and procainamide.\textsuperscript{30} At a dosage of 1000 mg/24 h, intravenous amiodarone was equal-
to the standard intravenous bretylium dosage (2500 mg/
24 h) in arrhythmia event rate, the time to first arrhythmia recurrence, and the number of patients re-
quiring supplemental infusions for recurrent arrhyth-
mas. A smaller amiodarone dosage (125 mg/24 h) was significantly less effective. Survival rates for more than
48 h were similar between groups (86% overall). How-
ever, when compared with the 1000 mg/24 h amiodar-
one group, significantly more patients treated with bret-
ylium experienced hypotension (33% vs. 21%) or con-
gestive heart failure (5% vs. 0%). Many patients were
hemodynamically unstable at the time of study entry
because of either incessant ventricular tachycardia or
their underlying cardiac disease. Therefore, it is notable
that adverse hemodynamic effects with intravenous
amiodarone were less frequent in this setting than with
intravenous bretylium. This finding supports the con-
clusions of smaller studies suggesting that intravenous
amiodarone is well tolerated in patients receiving cate-
cholamine infusions for shock\textsuperscript{13} and in patients with
coronary artery disease and poor left ventricular func-
tion.\textsuperscript{34}

**Intravenous Amiodarone in Medical and Surgical ICU Patients with Supraventricular Arrhythmias**

Oral amiodarone has long-term efficacy in managing
refractory atrial arrhythmias, including paroxysmal
atrial tachycardia and atrial fibrillation.\textsuperscript{21} Because of the
slow onset of action with oral dosing regimens, intrave-
nous amiodarone has been evaluated for managing atrial
arrhythmias in patients in intensive care units (ICUs) in
whom a rapid antiarrhythmic effect is desirable. In one
uncontrolled study of critically ill patients on catechol-
amine infusions for shock (septic or cardiogenic), 8 of
10 patients loaded with intravenous amiodarone con-
verted to sinus rhythm within 12 h.\textsuperscript{22} Another uncon-
trolled study of 26 patients admitted to the ICU with
atrial fibrillation and a rapid ventricular response re-
ported a 24-h conversion rate of 81% with intravenous
amiodarone (1500 mg/24 h). Although no placebo-con-
trolled trials are available, two recent studies have
prospectively compared amiodarone with other therapies
for converting atrial tachyarrhythmias to sinus rhythm
in patients in ICUs. Chapman \textit{et al.}\textsuperscript{35} prospectively
studied a combination of 24 medical and surgical ICU pa-
tients who experienced a variety of supraventricular
rhythms including atrial fibrillation, atrial flutter, and
unspecified supraventricular tachycardias. The group
of patients receiving intravenous amiodarone (3-mg/kg bolus, then 10 mg/kg during a 24-h period) experienced
the same 70% rate of conversion by 12 h as the compari-
sion group receiving intravenous procainamide (10-mg/
kg bolus, then 2–4 mg/min). The two regimens were
equally well tolerated hemodynamically. Moran \textit{et al.}\textsuperscript{36}
compared high-dose intravenous magnesium therapy
with intravenous amiodarone in 42 medical and surgical
ICU patients with rapid supraventricular arrhythmias.
They reported a 50% rate of conversion to sinus rhythm
with intravenous amiodarone administration after 24 h,
but they found a surprising 78% conversion rate for
patients receiving intravenous magnesium. Like other
studies of intravenous amiodarone administration in
critically ill patients, both agents were well tolerated
hemodynamically.

After cardiac surgical procedures, atrial tachyarrhyth-
mias occur commonly (~30%) and are linked to cerebro-
vascular morbidity and a lengthened stay in the ICU.\textsuperscript{37}
In an uncontrolled study examining intravenous amio-
darone for management of a variety of arrhythmias after
cardiac surgery, 18 of 32 (56%) patients experiencing
postoperative atrial fibrillation or flutter converted to
sinus rhythm within 12 h after administration of intrave-
nous amiodarone.\textsuperscript{38} The lack of a placebo group com-
icates interpretation of these data because spontaneous
conversion is common in patients with atrial fibrilla-
tion.\textsuperscript{39} Trials comparing agents for converting atrial fibrilla-
tion to sinus rhythm after cardiac surgery have shown
that intravenous amiodarone is no more effec-
tive than digoxin\textsuperscript{40} and was slightly less effective than
oral quinidine.\textsuperscript{41} Further, although two European car-
diac surgery studies\textsuperscript{42,43} found that patients given intra-
venous amiodarone prophylactically after surgery expe-
rienced fewer supraventricular tachyarrhythmias, the
drug has not been compared with other effective pro-
phyllactic regimens for postoperative atrial arrhythmias,
such as procainamide.\textsuperscript{44} Intravenous amiodarone has
not been approved by the FDA for management of su-
praventricular arrhythmias, and its incremental value
over conventional agents for managing perioperative atrial arrhythmias remains unproven. Nonetheless, it appears to be hemodynamically well tolerated in ICU patients and may prove to be a useful adjunct in patients who fail to respond to alternative pharmacologic and nonpharmacologic therapies. 21

Use of Intravenous Amiodarone for Managing Perioperative Ventricular Arrhythmias

The recent approval of intravenous amiodarone provides an alternative to more traditional parenteral antiarrhythmic therapies. However, published experience with intravenous administration of amiodarone to surgical patients in the United States is minimal. There are no published trials that evaluate intravenous amiodarone for managing supraventricular or ventricular arrhythmias intraoperatively. However, the drug has been evaluated for management of ventricular arrhythmias after surgery. Two studies have examined the value of prophylactic intravenous amiodarone administration after cardiac surgery. In a prospective, randomized, placebo-controlled study of 77 patients after coronary artery bypass, Hohnloser et al. 22 found that the incidence of nonsustained VT (10 or more consecutive beats) was only 3% in amiodarone-treated patients compared with 16% in the control group. In another double-blind, randomized, placebo-controlled trial of 60 coronary artery bypass patients, Butler et al. 23 found that intravenous amiodarone administration reduced the incidence of nonsustained ventricular arrhythmias (three or more consecutive beats) from 33% to 15%. Lidocaine, the agent most commonly used for postoperative ventricular arrhythmia prophylaxis, also has been shown to reduce the incidence of sustained and nonsustained ventricular arrhythmias during the initial 24 h after cardiac surgery. 24 Nonetheless, no studies have demonstrated a survival benefit with prophylaxis for postoperative ventricular arrhythmias, and such prophylaxis is not standard therapy in many cardiac surgery centers. Further, although low cardiac output has proven to be an independent predictor of life-threatening ventricular arrhythmias after cardiac surgery, 25 the value of lidocaine prophylaxis in cardiac surgical patients with poor left ventricular function is questionable. A randomized, placebo-controlled trial of 100 cardiac surgery patients with a left ventricular ejection fraction less than 35% found no suppression of postoperative ventricular arrhythmias after intravenous lidocaine administration. 26 The efficacy of prophylactic amiodarone in postoperative patients with left ventricular dysfunction has not been specifically evaluated. A trend toward lower mortality from sudden cardiac death was noted in nonsurgical patients with nonischemic cardiomyopathy receiving chronic oral amiodarone, although overall outcome for patients with congestive heart failure was similar for patients receiving amiodarone or placebo. 27

There is sparse literature describing the use of amiodarone as an acute therapy for management of life-threatening ventricular arrhythmias after surgery. In a retrospective analysis from Belgium describing the use of intravenous amiodarone in 95 cardiac surgical patients with arrhythmias at the end of surgery, 28 recurrent postoperative ventricular tachycardia was suppressed in one of two patients, and intravenous amiodarone bolus injections of 2.5 mg/kg controlled the ventricular arrhythmias of three patients near the end of cardiac surgery, thereby facilitating use of an intraaortic balloon pump and separation from cardiopulmonary bypass. Another study examines a cohort of 12 patients collected during a 2.5-yr period who experienced recurrent, sustained ventricular tachycardia after cardiac surgery in the absence of ischemia. 29 These patients failed multiple antiarrhythmic regimens (procainamide, quinidine, lidocaine, and aprindine), and four patients required implantation of an automatic defibrillator; nonetheless, 7 of 12 were eventually treated successfully with amiodarone.

In another report of 10 pediatric patients experiencing life-threatening arrhythmias after surgery, intravenous amiodarone was effective after at least two other antiarrhythmic agents had failed. 30 Six of the 10 patients had undergone surgery to correct congenital heart defects; 7 of 10 were experiencing sustained VT, and 3 others had hemodynamically destabilizing supraventricular arrhythmias. Overall, 8 of 10 patients responded to intravenous amiodarone, and 6 of 10 had complete arrhythmia resolution (4 of 7 with VT). The investigators commented that intravenous amiodarone therapy was "truly lifesaving" in four patients in whom other modes of antiarrhythmic therapy had failed and who were experiencing myocardial ischemia and low cardiac output. Like all other available perioperative studies, the number of patients is too small to detect adverse outcomes, and there are no prospective, controlled trials evaluating intravenous amiodarone for management of postoperative ventricular arrhythmias in children or adults. Nonetheless, the rapidly accumulating evi-
dence,22,25,30 establishing the value of intravenous amiodarone for managing such arrhythmias in nonsurgical patients suggests that the drug should be considered as a viable alternative in surgical settings when traditional intravenous therapies fail. Special consideration should be given to potential risks associated with amiodarone use in patients undergoing anesthesia, surgery, or cardiopulmonary bypass.

The Potential for Amiodarone Toxicity in Perioperative Patients

Chronic oral amiodarone therapy is associated with a number of dose-related and duration-related side effects, including corneal microdeposits, interstitial pneumonitis, blue-gray skin discoloration, elevation of liver function tests, thyroid function abnormalities, and sleep disturbances.21 The incidence of these side effects approaches 50% when therapy is continued for 1 yr and may lead to discontinuation.50 In contrast, when intravenous amiodarone is used for short-term arrhythmia management, the long-term side effect profile of the oral drug is of less concern.25 Relevant side effects of short-term intravenous amiodarone therapy are limited to acute cardiovascular and pulmonary effects, which may be particularly serious in specific perioperative subgroups.

Acute Pulmonary Toxicity: Oral Amiodarone

A well-studied chronic pulmonary toxicity syndrome has been reported in 1–17% of patients receiving long-term oral amiodarone therapy;21 this drug-induced pneumonitis and fibrosis occurs primarily during the first 12 months of therapy, is dose-related and age-related, and may be fatal in up to 9% of patients.31 The symptoms usually are reversible on cessation of amiodarone therapy if detected early. In contrast, there is poorly understood postoperative adult respiratory distress syndrome (ARDS) described in patients taking oral amiodarone who undergo many types of surgery. These patients present 1–5 days after surgery with diffuse pulmonary infiltrates on chest radiography, severe hypoxemia (room air, P, < 60 mmHg), and normal pulmonary capillary wedge pressures.52 These patients often require prolonged intubation and have a high perioperative mortality rate.53,54 The literature characterizing this acute respiratory syndrome is summarized in Table 3; most of the studies to date consider small numbers of patients and are either retrospective analyses or case reports.

A majority of the reports linking preoperative oral amiodarone therapy to postoperative ARDS concern cardiac surgical procedures.55–57 In a recent retrospective analysis of patients given oral amiodarone who underwent surgery for ventricular arrhythmias,58 8 of 18 surgical survivors required prolonged intubation or reintubation because of postoperative hypoxemia and pulmonary infiltrates. Most of these patients underwent cardiopulmonary bypass for endocardial resection, although postoperative ARDS was described in one patient receiving only automatic implantable cardioverter/defibrillator (AICD) implantation. The duration of preoperative amiodarone therapy among the 18 treated patients was 12 ± 18 months (mean ± SD; range, 1 week to 48 months); however, 3 patients with postoperative ARDS received only 1–2 weeks of oral therapy. Two of the ARDS patients died, whereas no ARDS was detected in 44 similar patients who had not received amiodarone and underwent the same cardiothoracic procedures. In another retrospective analysis of 67 patients undergoing map-directed surgery for VT,59 17% of patients given oral amiodarone for at least 2 weeks developed acute respiratory failure, with a 50% mortality rate. Only one death (stroke-related) occurred in the group of patients not taking amiodarone.

Although some have suggested that amiodarone use should be avoided in arrhythmia patients deemed candidates for definitive surgical intervention,55,58 the long elimination half-life of amiodarone and the increased risk of malignant arrhythmias has limited the feasibility of stopping the drug preoperatively for most patients receiving chronic oral therapy.59 Further, the literature is not consistent regarding the risk associated with perioperative oral amiodarone therapy. A retrospective study evaluating 29 heart transplantation patients given amiodarone between 1986 and 1990 found that 2 amiodarone-treated patients developed postoperative symptoms consistent with ARDS, but the duration of postoperative intubation for these patients was less than 4 days, and the length of hospital stay and mortality rate were similar to a comparable group of recipients not taking amiodarone.53 Although additional studies are needed, it is intriguing to speculate as to whether the immunosuppressant drugs or aggressive preoperative diuresis may attenuate amiodarone-induced ARDS after transplantation.

The risk factors for development of postoperative ARDS when taking oral amiodarone are unknown. In a retrospective study evaluating an array of cardiac surgical procedures,56 4 of 28 (14%) patients receiving amio-
Table 3. Postoperative Adult Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis (Number of Patients)</th>
<th>Type of Surgery</th>
<th>Time, Route of Administration</th>
<th>ARDS Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuzcu et al., 1987&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Retrospective (56)</td>
<td>Cardiac</td>
<td>Preop and postop, oral</td>
<td>Preop, 4/28</td>
</tr>
<tr>
<td>Nalos et al., 1987&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Case report (4)</td>
<td>Cardiac, 3 AICD, 1</td>
<td>Preop, oral</td>
<td>Postop, 0/28</td>
</tr>
<tr>
<td>Kay et al., 1988&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Retrospective (33)</td>
<td>Cardiac and noncardiac</td>
<td>Preop, oral</td>
<td>4 patients</td>
</tr>
<tr>
<td>Greenspon et al., 1991&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Retrospective (67)</td>
<td>Cardiac and AICD</td>
<td>Preop, oral</td>
<td>Cardiac, 1/22</td>
</tr>
<tr>
<td>Chelimsky-Fallick et al., 1992&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Retrospective (58)</td>
<td>Heart transplantation</td>
<td>Preop, oral</td>
<td>All other, 3/11</td>
</tr>
<tr>
<td>Hawthorne et al., 1993&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Retrospective (99)</td>
<td>AICD</td>
<td>Preop, oral</td>
<td>Endocardial resection Amio, 7/13 Amio, 2/6 Control, 0/11</td>
</tr>
<tr>
<td>Mickleborough et al., 1994&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Retrospective (67)</td>
<td>Cardiac</td>
<td>Preop, oral</td>
<td>Control, 0/37</td>
</tr>
<tr>
<td>Van Mieghem et al., 1994&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Prospective (32)</td>
<td>Pneumonectomy</td>
<td>Preop, IV</td>
<td>Amio, 0/29 Amio, 10/39 Amio, 6/36 Control, 0/60</td>
</tr>
<tr>
<td></td>
<td>Retrospective (552)</td>
<td>Lobectomy and Pneumonectomy</td>
<td>Preop and postop, oral and IV</td>
<td>Amio, 3/11 Amio, 0/21 Control, 0/21</td>
</tr>
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</table>

ARDS = adult respiratory distress syndrome; preop = preoperatively; postop = postoperatively; AICD = automatic implantable cardioverter/defibrillator; amio = amiodarone; IV = intravenous.

darone preoperatively experienced postoperative respiratory failure, whereas no respiratory complications were noted in a similar group of 28 patients who did not begin amiodarone therapy until after surgery. It was noted that all four patients with postoperative respiratory failure had significantly lower preoperative \( P_aO_2 \) and higher \( (A - D)_{P_aO_2} \) values. However, a retrospective review of 99 patients receiving only AICD implantation at the Medical College of Virginia<sup>52</sup> found no identifiable risk factors for predicting postoperative ARDS in patients taking oral amiodarone. Although 10 of 39 amiodarone-treated patients developed ARDS compared with none of 60 similarly treated patients not taking the drug, the patients were similar regarding operative time, intraoperative \( F_{O_2} \), age, type of anesthesia, and the dosage or duration of amiodarone therapy.

The prevalence of extracorporeal oxygenation techniques in these studies suggests an interaction between amiodarone and cardiopulmonary bypass. Prolonged cardiopulmonary bypass has an independent association with postoperative ARDS<sup>56</sup>; exposure of blood elements to the nonphysiologic surfaces of the bypass circuit induces platelet aggregation, coagulation factor activation, and complement activation in the pulmonary circulation,<sup>60</sup> with resultant endothelial injury and pulmonary capillary leak. Therefore, it is possible that preoperative therapy with amiodarone somehow potentiates the endothelial injury related to cardiopulmonary bypass.<sup>57</sup> However, studies linking postoperative ARDS to preoperative oral amiodarone and procedures not involving cardiopulmonary bypass, such as AICD placement under general anesthesia,<sup>52,53,55</sup> suggest a multifactorial etiology. Postoperative ARDS also has been described in patients taking oral amiodarone who undergo noncardiac procedures, including general orthopedic and abdominal surgeries (Table 3).<sup>61</sup> Although previous amiodarone pulmonary toxicity,<sup>52</sup> congestive heart failure, superimposed infection, and high \( F_{O_2} (>0.9) \) have all been implicated,<sup>61,62</sup> the detailed mechanisms through which surgery and general anesthesia initiate respiratory compromise in patients taking oral amiodarone remain unknown.

Acute Pulmonary Toxicity: Intravenous Amiodarone

There are few published reports of intravenous amiodarone administration in the immediate preoperative period. However, one prospective trial wherein intrave-
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ous amiodarone was given for 3 days before pneumonectomy as prophylaxis for supraventricular tachycardia, the study was terminated prematurely because of a high incidence of postoperative ARDS in the amiodarone group.62 Three of 11 pneumonectomy patients receiving amiodarone before surgery developed ARDS 2 or 3 days after surgery. Right heart catheterization revealed normal pulmonary wedge pressures and cardiac outputs. Two of these patients died of intractable hypoxemia, with autopsies revealing a lymphocytic reaction and hyaline membranes typical of ARDS. At the time the study was interrupted, no ARDS had developed among the 10 control patients. A subsequent retrospective analysis by the same investigators revealed that the incidence of ARDS during a 3-yr period for pneumonectomies and lobectomies (552 total patients) was 11% among those treated with amiodarone versus 1.8% in those not treated (P < 0.0001). Although the incidence of postoperative ARDS was highest among right-sided pneumonectomy patients, the control (nonamiodarone) incidence of postoperative ARDS was greater for right-sided pneumonectomy patients than for left-sided pneumonectomy patients.62 It was unclear whether right-sided pneumonectomy patients had a greater incremental risk for postoperative ARDS as a result of amiodarone therapy than those having left-sided procedures.

Oral amiodarone may cause interstitial pneumonitis and fibrosis through direct and indirect mechanisms.62–65 The indirect pathway involves partitioning of inflammatory cells into the lung, similar to other pneumonitides related to exposure to organic antigens, such as farmers lung. The direct pathway involves injury to the lung parenchyma with a resultant fibrotic response. Reactive oxygen species, phospholipids, and the iodide molecule of amiodarone have been proposed as direct toxic mediators.65 The particular mechanisms responsible for ARDS after lung surgery in patients receiving amiodarone are less clear, but they may overlap with those involved in chronic toxicity. In particular, accumulation of phospholipids in lung macrophages was demonstrated in a 74-yr-old man who received intravenous amiodarone starting 4 days after surgery (1200 mg/day) after a total left-sided pneumonectomy for a left upper lobe carcinoma.66 The patient was experiencing ventricular arrhythmias after surgery refractory to lidocaine and bretylium; he developed ARDS 8 days after surgery (4 days after starting amiodarone) and underwent diagnostic bronchoscopy 10 days after surgery, which showed accumulation of phospholipids in the alveolar macrophages. The patient’s pulmonary infiltrates subsequently worsened; he developed sepsis and renal failure and eventually died. Phospholipid accumulation has been noted with high frequency in patients who experience pulmonary toxicity during chronic oral administration65; however, this report suggests that phospholipidosis may occur after relatively short courses of high-dose intravenous therapy.66 Although accumulation of phospholipids has been linked to pulmonary toxicity, it occurs in patients who do not experience toxicity.67 Thus, phospholipidosis may only be part of a constellation of factors that precipitate amiodarone-related toxicity. In pneumonectomy patients, such factors may include physiologic perturbations associated with lung removal. These include the loss of structural integrity of the alveolar capillary membrane as a result of increased blood flow and hyperinflation of the remaining lung, resulting in augmented filtration of fluid into the pulmonary interstitium.65,68 Further, because of the high lipid solubility of amiodarone, it has been postulated that the drug concentrates in the remaining lung of pneumonectomy patients, especially those who are thin.69

Although there are no data that specifically evaluate safety of administering intravenous amiodarone either before or during general surgical procedures or those that require cardiopulmonary bypass, a number of studies conducted outside the United States have evaluated intravenous amiodarone for either management or prophylaxis of arrhythmias occurring after cardiac operations (Table 4).38,40–43 Although the dosages used vary considerably, no acute respiratory complications were reported. In one of these studies, an amiodarone infusion was started before the end of surgery, immediately after removal of the aortic cross-clamp.45 Similar results were obtained when the incidence of respiratory failure in patients loaded with oral amiodarone after cardiac surgery (0 of 28) was compared with the incidence in those taking amiodarone before surgery (4 of 28, or 14%).60 These results contrast with those from patients who have undergone either lobectomy or pneumonectomy, in whom use of amiodarone 7 months after surgery has been associated with fatal ARDS.62,70 After nonpulmonary surgery, intravenous amiodarone use does not appear to be a risk factor for development of ARDS; however, large controlled studies are not yet available to confirm this impression.

Hemodynamic Manifestations

Chronic Oral Amiodarone and Cardiac Surgery. During noncardiac surgery, the hemodynamic conse-
Table 4. Intravenous Amiodarone after Cardiac Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis (Number of Patients)</th>
<th>Indication for Amiodarone</th>
<th>Time of Loading Dose</th>
<th>Amiodarone Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Installe et al., 1981</td>
<td>Retrospective (95)</td>
<td>Treatment of SVT and VT</td>
<td>Near the end of surgery or postop</td>
<td>SVT, 55/90 PVCs, 18/18 VT, 4/5</td>
</tr>
<tr>
<td>McColister et al., 1990</td>
<td>Prospective, randomized (80)</td>
<td>Treatment of VT</td>
<td>Postop</td>
<td>Quinidine, 25/39 (64%) Amiodarone, 17/41 (41%)</td>
</tr>
<tr>
<td>Hohnloser et al., 1991</td>
<td>Prospective, randomized (77)</td>
<td>SVT and VT prophylaxis</td>
<td>Postop</td>
<td>SVT Amio, 2/39 (5%) Control, 8/38 (21%) Nonsustained VT</td>
</tr>
<tr>
<td>Butler et al., 1993</td>
<td>Prospective, randomized (60)</td>
<td>SVT and VT prophylaxis</td>
<td>Removal of the aortic cross-clamp</td>
<td>SVT Amio, 5/60 (8%) Control, 12/60 (20%) Nonsustained VT</td>
</tr>
<tr>
<td>Cochrane et al., 1994</td>
<td>Prospective, randomized (30)</td>
<td>SVT treatment</td>
<td>Postop</td>
<td>Amio, 9/60 (15%) Control, 20/60 (33%)</td>
</tr>
</tbody>
</table>

SVT = supraventricular tachycardia; VT = ventricular tachycardia; postop = postoperatively; PVC = premature ventricular contraction.

quences of general anesthesia for patients chronically taking oral amiodarone usually are limited to mild hypotension.52 The cardiac surgical patient on chronic oral amiodarone may pose greater concern. The first case report describing adverse hemodynamic sequelae during cardiac surgery in a patient taking oral amiodarone preoperatively appeared in 1981.71 After a 96-min aortic cross-clamp period for coronary bypass grafts and left ventricular aneurysmectomy, a patient encountered difficulty separating from cardiopulmonary bypass. Although separation was eventually successful, the patient subsequently required cardiac pacing and epinephrine infusion for 5 days after surgery. An adverse hemodynamic profile after bypass surgery has been linked to chronic oral amiodarone use only in case reports58,72 and small retrospective studies.2,55,59 At least one retrospective analysis of cardiac surgery patients found the incidence of postoperative congestive heart failure and low cardiac index was not significantly increased by chronic oral amiodarone therapy.50 In general, three types of hemodynamic compromise have been reported after separation from cardiopulmonary bypass in patients on chronic amiodarone: AV nodal blockade requiring prolonged pacing; reduced left ventricular function requiring inotropic support and, occasionally, intraaortic balloon counterpulsation; and extreme systemic vasodilation requiring therapy with α agonists.

Hemodynamic Effects of Intravenous Amiodarone

Hemodynamic effects of acute intravenous amiodarone administration during general anesthesia and surgery are largely predictable despite the absence of published experience. Amiodarone and its intravenous vehicle (polysorbate 80) have vasodilatory and negative inotropic effects25,30 that cause hypotension in ~25% of patients. Although this side effect is dose-independent for daily intravenous dosages ranging from 125 mg to 2000 mg,22,25 it is most common during the initial rapid-loading infusion (phase I, Table 1). Although this hypotensive response usually is amenable to volume expansion or a decrease in the infusion rate, cessation of the infusion or use of intravenous pressor agents is sometimes required.25,25 Although more problematic in this regard than lidocaine, intravenous amiodarone at a 1000 mg/day dosage was significantly better tolerated hemodynamically in nonsurgical patients with refractory ventricular arrhythmias than intravenous bretylium.30 The adverse hemodynamic effects of intravenous ami-
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Amiodarone may be accentuated in critically ill patients. In the multicenter study by Levine et al., intravenous amiodarone loading induced hypotension requiring vasoconstrictor therapy in 14% of patients and led to death in 2%. Overall, 6% of the patients died of congestive heart failure, although many patients had preexisting heart failure; therefore, the extent to which intravenous amiodarone contributed to their symptoms is unknown. Nonetheless, particular difficulties have been encountered when intravenous amiodarone is rapidly infused into patients with congestive heart failure immediately after cardiac surgery. Patients with left ventricular stroke work indices less than 20 g·m·m⁻² have experienced worsening cardiogenic shock, requiring increased hemodynamic support with catecholamine infusions or intraaortic balloon counterpulsation. In contrast, when used prophylactically to prevent arrhythmias in postoperative cardiac surgery patients with preserved left ventricular function (mean cardiac indices > 2.3 l·min⁻¹·m⁻²), detrimental hemodynamic side effects were not observed. Similarly, when used to manage supraventricular arrhythmias in noncardiac surgery patients who were critically ill and pressor-dependent but had preserved left ventricular function (mean cardiac indices, 3.1 l·min⁻¹·m⁻²), cardiac index and mean arterial pressure were not significantly reduced by a standard intravenous loading regimen (3.7–5.0 mg/kg), and pressor dosage requirements were not altered.

It is likely that the vasodilatory and negative inotropic effects of intravenous amiodarone result from noncompetitive blockade at α- and β-adrenergic receptors, respectively. The clinically significant negative inotropic effect seen in postoperative cardiac surgery patients with poor left ventricular function may be potentiated by downregulation of myocardial β-adrenergic receptors resulting from cardiopulmonary bypass. It is interesting that in heart transplant recipients receiving amiodarone preoperatively, the duration of postoperative inotropic support was identical to matched control subjects. Although it is possible that the transplanted heart is less prone to amiodarone-induced hemodynamic sequelae, the mechanism is unknown.

Negative Chronotropic Effects of Intravenous Amiodarone

Bradycardia and atrioventricular block are side effects of intravenous amiodarone therapy that are related to noncompetitive β-adrenergic blockade. In nonsurgical populations, clinically significant bradycardia occurs in approximately 5% of patients, although high-grade atrioventricular block is uncommon, as is the need for pacing (0.7%). During noncardiac surgery, hemodynamically significant bradyarrhythmias have been described in patients taking oral amiodarone, and in vitro models have demonstrated an additive effect of amiodarone and volatile anesthetics in suppressing myocardial conduction. In cardiac surgical patients, conduction block is common immediately after surgery; although intravenous amiodarone therapy may enhance or complete atrioventricular block, hemodynamic repercussions are rare. Sinus bradycardia occasionally requires discontinuation of intravenous amiodarone after cardiac surgery, but the presence of epicardial pacing electrodes in many cardiac surgery patients renders this complication less troublesome.

Proarrhythmic Effects of Oral and Intravenous Amiodarone

Torsade de pointes, a ventricular tachycardia termed polymorphic because of its continuously changing QRS axis, is a life-threatening complication of therapy with all antiarrhythmic agents that prolong the QT interval, including amiodarone. Contributory predisposing factors include electrolyte disorders (hypokalemia, hypomagnesemia), diuretic therapy, female gender, and bradycardia. Whereas the estimated annual incidence of proarrhythmia because of oral therapy with class IA and class III antiarrhythmic agents ranges from 1.6% for quinidine to nearly 4.0% with sotalol, torsade de pointes occurs rarely with single agent oral amiodarone therapy, and the drug has been used safely in patients who experienced previous episodes of torsade de pointes with other antiarrhythmic agents. Although amiodarone is similar to other QT-prolonging agents in its ability to suppress outward potassium current and prolong the cardiac action potential, it differs somewhat in its potent effects on sodium and calcium channels, causing suppression of inward cationic currents. This effect on inward current would inhibit induction of early afterdepolarizations, which have been implicated as a triggering mechanism for torsade de pointes in a setting of prolonged repolarization. Alternatively, amiodarone appears to have greater selectivity for potassium channels that activate slowly during depolarization (Iₖ[A]), as opposed to most other antiarrhythmic agents with QT-prolonging activity that suppress a rapidly activating potassium current (Iₖ₅). This difference also may contribute to the relatively low propensity for amiodarone to induce torsade de pointes.

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less, like the other QT-prolonging antiarrhythmic compounds, amiodarone therapy generally is avoided in patients with acquired or congenital long-QT syndromes.

When used for acute therapy, intravenous amiodarone also has proarrhythmia potential. In the three randomized trials that have examined intravenous amiodarone for management of refractory ventricular arrhythmias, the incidence of new-onset torsade de pointes has been 0.5-1.5% during a 24- to 48-h period.22,25,30 Less than 20% of patients have experienced QT prolongation with short-term therapy, and this effect has not been a sensitive predictor of the likelihood of developing torsade de pointes.22 Intravenous amiodarone-related torsade de pointes has not been reported in the studies that examine postoperative use. Hohnloser et al.52 found significant QTc prolongation (>660 ms) after 75 h of therapy in two of 59 patients randomized to intravenous amiodarone administration after cardiac surgery for arrhythmia prophylaxis; in both patients, the amiodarone infusion was stopped, and no serious arrhythmias were noted. In addition to DC cardioversion and removal of the offending agent, acute therapy for drug-induced torsade de pointes includes intravenous magnesium sulfate and measures to increase the heart rate (atropine, isoproterenol, or pacing).93

Recommendations for Perioperative Administration of Intravenous Amiodarone

Supraventricular Tachycardias

The available trials evaluating pharmacologic management of atrial arrhythmias in medical and surgical ICUs35,36 and after cardiac surgery40,41 have not shown an incremental advantage of intravenous amiodarone over other antiarrhythmic agents. At present, intravenous amiodarone is not approved by the FDA for management of supraventricular arrhythmias. However, with the exception of cardiac surgical patients with severe left ventricular dysfunction,38 intravenous amiodarone has been hemodynamically well tolerated in ICU patients when used to treat supraventricular arrhythmias53 and may provide a useful alternative therapy in patients who are hemodynamically compromised and have failed to respond to other agents.21 Intravenous amiodarone also may be useful for extending therapy in patients on oral amiodarone for refractory preoperative atrial arrhythmias into the early postoperative period; however, in most patients who will return to oral therapy within a few days or weeks, the long half-life of chronic oral amiodarone eliminates the need to provide temporary intravenous therapy perioperatively.

Sustained Ventricular Arrhythmias

Intraoperative Ventricular Arrhythmias. Intravenous amiodarone is indicated for management of ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other agents. Although this indication could be interpreted broadly, in recent randomized controlled trials of nonsurgical patients, intravenous amiodarone was administered only after proven intolerance or therapeutic failure of two30 or three22,25 other antiarrhythmic agents. There are no studies, controlled or otherwise, that document either the safety or efficacy of intraoperative intravenous amiodarone administration in patients receiving general anesthesia. However, compelling results from controlled nonsurgical trials22,25,30 and from the limited published experience with postoperative surgical patients36,38,49 suggest that amiodarone can be life-saving under conditions where other antiarrhythmic agents fail. Therefore, recognizing the potential for hemodynamic and perhaps pulmonary sequelae, a rational approach is to use intravenous amiodarone in the operating room for managing refractory ventricular arrhythmias when other standard agents fail (lidocaine, bretylium, and procainamide) and when the patient is severely hemodynamically compromised.

Preoperative Ventricular Arrhythmias. In patients who are about to undergo surgery, evidence suggests that oral amiodarone therapy preoperatively may induce intraoperative hemodynamic complications for cardiac surgical patients and also may contribute to postoperative pulmonary complications (e.g., ARDS) in cardiac and general surgical patients (Table 3). Regarding pulmonary toxicity, the cumulative dose of amiodarone that places patients at risk is uncertain. Postoperative ARDS has been seen after only a few weeks of oral amiodarone therapy,53 and just 5 days of intravenous amiodarone therapy was implicated in postoperative ARDS among pneumonectomy patients.62 Nonetheless, the perceived risk of short-duration intravenous amiodarone therapy in the days before cardiac surgery or general (nonpneumonectomy) surgery is speculative because there are no published studies available. Therefore, as for the intraoperative period, it seems rational to avoid intravenous amiodarone therapy if possible and to use it when three other agents have failed. In pneumonectomy patients in whom postoperative ARDS has been reported,62 intravenous amiodarone should be re-
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served for life-threatening ventricular arrhythmias when all other antiarrhythmic therapeutic options have been exhausted.

Postoperative Ventricular Arrhythmias. With the exception of patients undergoing pneumonectomy and lobectomy, the studies available (Table 4) suggest that intravenous amiodarone therapy postoperatively does not precipitate ARDS; however, there are no large randomized controlled trials available to confirm this impression. Intravenous amiodarone was hemodynamically better tolerated than intravenous bretylium in a prospective analysis of nonsurgical critically ill patients with refractory ventricular arrhythmias.20 Given the hemodynamic instability of postoperative patients with sustained ventricular arrhythmias, it would seem prudent to consider intravenous amiodarone before intravenous bretylium for management of refractory ventricular arrhythmias. Bretylium infusions are often poorly tolerated for prolonged periods because of orthostatic hypotension, and a convenient oral therapy conversion is no longer available.

Although oral amiodarone may require days to achieve therapeutic efficacy, intravenous amiodarone administration has a rapid antiarrhythmic effect. The standard, three-phase 1050 mg/day dosing regimen recommended by the manufacturer (Table 1) is effective in most patients; breakthrough arrhythmias may be effectively managed with supplemental 150-mg infusions.22 Consultative assistance from a cardiology-electrophysiology service may be helpful when treating patients with intravenous amiodarone for extended periods. Such patients may be candidates for nonpharmacologic therapies (AICD) or for conversion to oral therapy.

Summary

Intravenous amiodarone is a potentially valuable therapy for perioperative patients experiencing life-threatening ventricular arrhythmias refractory to conventional antiarrhythmic agents perioperatively. Its potential for hemodynamic and pulmonary toxicity perioperatively suggests that it should remain an alternative therapy rather than a first-line option. However, because of its impressive efficacy in nonsurgical trials, its role in perioperative arrhythmia management will dramatically expand if clinical studies become available that clarify its safety in surgical populations.

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