Evidence-Based Analysis of Amiodarone Efficacy and Safety

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Amiodarone was initially developed 3 decades ago for angina. On the basis of the number of prescriptions filled in retail pharmacies, amiodarone was the most-often-prescribed antiarrhythmic agent, accounting for 24.1% of the total antiarrhythmic prescriptions in 1998. Amiodarone accounted for 34.5% of prescriptions in Europe, 32.8% in North America, 73.8% in Latin America, and 0.3% in Japan and the Philippines. Amiodarone use has increased globally in 1998 at a rate greater than that of the whole antiarrhythmic market, with striking growth in North America, a 20.0% increase from 1997 to 1998 (according to International Medical Statistics, Medical Data Index, and Scott Levin drug and diagnosis audit, obtained with the assistance of J. Jones, Sanofi Pharma Inc, Paris, France). Amiodarone is used to manage virtually all forms of supraventricular and ventricular tachycardia. This review focuses on the arrhythmias most commonly requiring antiarrhythmic therapy—sustained ventricular tachycardia (VT), ventricular fibrillation (VF), and atrial fibrillation (AF)—because they are the most clinically significant and have been the focus of most studies published. This review will analyze the evidence that amiodarone is a safe and effective antiarrhythmic drug.

Pharmacokinetics

To exploit the antiarrhythmic properties of amiodarone fully, the clinician needs to be familiar with its pharmacokinetics, because they differ markedly from those of other cardiac drugs. Amiodarone is markedly lipophilic, which may account for some of its unusual pharmacokinetic features. It is incompletely absorbed (35% to 65%) after oral administration. It is taken up very extensively by tissue, with marked interindividual variation. Estimates of the elimination half-life of amiodarone vary, depending on how it has been measured. The relatively short half-life for disappearance of amiodarone from plasma after intravenous administration is likely a measure of drug redistribution from vascular space into tissue and not true body elimination. After long-term oral therapy, amiodarone has a true elimination half-life of up to 60 days. Slow distribution to tissue results in a requirement of very long loading periods, up to several months, before reaching steady-state tissue concentrations. Large loading doses of oral therapy, typically 800 to 1600 mg/d in 3 to 4 divided doses, can accelerate the onset of activity. However, even with loading, arrhythmia recurrence during

the first months of therapy does not necessarily predict long-term inefficacy. Amiodarone plasma concentration measurements are of marginal clinical utility for several reasons. Amiodarone is deethylated to an active metabolite desethyl-amiodarone, concentrations of which exceed those of the parent compound during long-term therapy. There is also marked intersubject variability in plasma concentrations of amiodarone and desethyl-amiodarone concentrations associated with arrhythmic suppression. Plasma concentrations >2.5 mg/L have been associated with increased risk of toxicity. The optimal dose of amiodarone has not been systematically studied. Generally doses of 200 to 400 mg/d have been used during long-term therapy of supraventricular and ventricular arrhythmias, but doses as low as 100 mg/d have been shown to be effective in some patients.

Electrophysiology

The electrophysiological actions of amiodarone are complex and incompletely understood. Amiodarone has generally been classified as a Vaughan-Williams class III agent, prolonging repolarization by inhibition of outward potassium channels. It has also been shown to have use-dependent class I activity, inhibition of the inward sodium currents, and class II activity. The antiadrenergic effect of amiodarone, however, is different from that of b-blocker drugs because it is noncompetitive and additive to the effect of b-blockers.

Amiodarone depresses automaticity of the sinoatrial node, resulting in slowing of the heart rate in sinus rhythm. It both slows conduction and increases refractoriness of the AV node, properties useful in the management of supraventricular arrhythmias. Its class III activity results in increases in atrial and ventricular refractoriness and in prolongation of the QTc interval. Amiodarone prolongs VT cycle length by 20% to 25% during long-term therapy. The effects of oral amiodarone on sinoatrial and AV nodal function are maximal within 2 weeks, whereas the effects on VT and ventricular refractoriness tend to emerge more gradually during oral therapy, becoming maximal at 10 weeks.

Ventricular Tachyarrhythmias

Amiodarone has been widely used to control symptomatic ventricular arrhythmias, primarily to prevent recurrence of VT and VF. Although amiodarone is accepted as effective against VT and VF, there is little supportive evidence from
placebo-controlled studies. Nonetheless, amiodarone is approved for use against VT and VF by most regulatory agencies worldwide and has a high profile as a useful drug. Its high rate of use against VT or VF is based largely on considerable clinical experience and concern about the safety of other drugs.

Amiodarone suppresses ventricular premature depolarizations (VPDs) and episodes of nonsustained VT. This is clearly demonstrated in several of the primary prevention trials of amiodarone in post–myocardial infarction and congestive heart failure (CHF) patients in whom baseline and follow-up 24-hour ambulatory ECGs were performed. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) pilot study, which enrolled patients with CHF eligible patients by means of left ventricular ejection fraction assessment, Holter ECG, or both to identify a particularly high-risk group. Only 3 of the trials reported a statistically significant reduction of all-cause death. A recently reported meta-analysis of the 3 trials has shown that they are consistent and that there is a statistically significant mortality reduction of 27% with the ICD compared with amiodarone.

**Prophylaxis Against Sudden Death**

Over the decade from 1985 to 1995, many trials were done to assess the effect of amiodarone in the prevention of death in patients who had never had a sustained ventricular arrhythmia but were nonetheless at high risk of death from arrhythmia. Several randomized trials, varying in size from 34 to 1486 patients, were performed. Eight studies enrolled patients with recent myocardial infarction, and 5 enrolled patients with CHF. Most of the trials screened potentially eligible patients by means of left ventricular ejection fraction assessment, Holter ECG, or both to identify a particularly high-risk group. Only 3 of the trials reported a statistically significant reduction of all-cause mortality with amiodarone. Several others observed statistically significant reductions in arrhythmic death but without a significant (or in some cases any) reduction in all-cause mortality. A meta-analysis of these trials based on individual patient data yielded a relative risk reduction in all-cause mortality of 13% to 15%, which was of borderline statistical significance ($P=0.03$ or $0.06$, VT/VF, or syncopal ICD shock, was significantly reduced by amiodarone. At 4 years of follow-up, event-free survival was 52% for amiodarone and 36% for conventional care, a 44% increase. Cardiac death and all-cause mortality rates were also lower on amiodarone. Although small, this study provides considerable support for a benefit of amiodarone over class I drugs. There is evidence from other sources, however, that class I drugs are proarrhythmic and may increase all-cause mortality. Accordingly, the observed difference in outcomes in the CASCADE study may have been due to harmful effect of conventional therapy, a beneficial effect of amiodarone, or most likely, their combination. In summary, the direct evidence that amiodarone prevents recurrent VT and VF is based mostly on clinical experience and not on randomized trials.

The general view that amiodarone is the most useful drug for VT and VF, notwithstanding the rather modest evidence from randomized trials, led to its being adopted as the standard medical therapy in several recent randomized secondary prevention trials evaluating the ICD. In the Canadian Implantable Defibrillator Study (CIDS) and Antiarrhythmics Versus Implantable Defibrillators (AVID) study, patients with either VF or sustained VT were randomized to receive an ICD or medical therapy. In CIDS, medical therapy was amiodarone; in AVID, it was amiodarone or sotalol. (In practice, however, virtually all AVID study patients received amiodarone, mostly because of physician preference.) Amiodarone was I of 3 drugs that were randomly compared with the ICD in the Cardiac Arrest Study, Hamburg (CASH), which enrolled only cardiac arrest survivors. All 3 studies observed improved survival with the ICD compared with amiodarone, with relative risk reductions ranging from 20% to 40%. In the AVID study, all-cause mortality was statistically significantly reduced by ICD therapy, whereas in both CASH and CIDS, ICD therapy was associated with nonsignificant reductions in all-cause death. A recently reported meta-analysis of the 3 trials has shown that they are consistent and that there is a statistically significant mortality reduction of 27% with the ICD compared with amiodarone.
depending on analytical method used). The reduction in all-cause death was due to a relative 29% decrease in arrhythmic deaths ($P < 0.003$), which accounted for somewhat less than half of all deaths. There was no effect of amiodarone on nonarrhythmic deaths. The Figure shows the individual trial results and overall treatment effect for the outcomes of all-cause mortality and arrhythmic/sudden death. The 13% relative risk reduction in all-cause mortality is entirely consistent with a 29% reduction in arrhythmic deaths and with no effect on the nonarrhythmic deaths. The treatment benefit was uniform across the CHF and post–myocardial infarction trial patients and was independent of major prognostic variables, such as left ventricular function.

Because there is good evidence that β-blocking drugs reduce sudden death after myocardial infarction, it is tempting to attribute the prophylactic benefit of amiodarone against sudden death to its antiadrenergic effect. However, the available data indicate that this is unlikely because amiodarone interacts positively with β-blocker therapy in post–myocardial infarction patients. In both the European Myocardial Infarction Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), 2 of the large randomized trials of amiodarone after myocardial infarction, patients receiving β-blockers at baseline had a statistically significantly better effect from amiodarone than those not receiving a β-blocker. This significant interaction remains even after adjustment for differences in baseline prognostic variables. This finding suggests that the amiodarone effect in reducing arrhythmic death is separate from and complementary to the effect of β-blockers in these patients.

Widespread clinical experience indicates that amiodarone is useful against VT and VF; thus, it was used in 3 major multicenter trials as best medical therapy for these lethal conditions. Yet hard evidence that amiodarone is effective against VT and VF is scant. The initial acceptance of amiodarone was based almost entirely on uncontrolled clinical experience. Subsequently, several randomized trials were performed, but in these, amiodarone was compared with other questionable drug treatments or evaluated as primary prophylaxis against arrhythmic death. Nonetheless, 3 decades of clinical experience worldwide and a clear-cut reduction in arrhythmic death in the randomized placebo-controlled prophylactic trials provide somewhat indirect but convincing evidence that amiodarone is effective against VT/VF recurrence, although the degree of benefit remains imprecise. On the other hand, it is now clear from randomization trials that amiodarone is not as effective as the ICD for prevention of lethal arrhythmia. What is the proper role of amiodarone in the prevention of recurrent VT and VF? Amiodarone will surely continue to be useful for control of VT/VF both as an adjunct to ICD therapy and as primary therapy when there are economic constraints on ICD use. The potential benefits of amiodarone in ICD patients require more careful evaluation in randomized studies. Amiodarone has not lived up to the expectation that it would be a highly effective prophylactic
agent in post-myocardial infarction or heart failure patients. The primary prevention trials have shown quite clearly that amiodarone reduced arrhythmic death, but the beneficial effect on all-cause mortality is too small to justify routine prophylactic use.

**Short-Term Control of VT/VF**

Intravenous amiodarone is available for rapid control of recurrent VT or VF, and its effectiveness has recently been evaluated in 3 randomized controlled trials.\(^5\) The target patient populations of these trials were identical: patients with recurrent in-hospital, hemodynamically unstable VT or VF with \(\geq 2\) episodes within the past 24 hours. Additionally, patients were required to have failed to respond to or be intolerant of lidocaine, procarainamide, and (in 2 of the trials) bretylium. Study patients were severely ill; about a quarter were on a mechanical ventilator or intra-aortic balloon pump before enrollment, and 10% were undergoing cardiopulmonary resuscitation at the time of enrollment.

One study compared 3 doses of intravenous amiodarone: 525, 1050, and 2100 mg/d, a 4-fold difference between high and low doses.\(^6\) Because of the use of investigator-initiated, intermittent, open-label amiodarone boluses for recurrent VT, the actual mean amiodarone doses received by the 3 groups were 742, 1175, and 1921 mg/d. There was no statistically significant difference in the number of patients without VT/VF recurrence during the 1-day study period: 32 of 86 (37%), 36 of 92 (45%), and 42 of 92 (53%) for the low-, medium-, and high-dose groups, respectively. The number of supplemental amiodarone 150-mg bolus infusions given by blinded investigators was statistically significantly less in those randomized to higher dose of amiodarone (\(P=0.0043\)).

A wider range of amiodarone doses (125, 500, and 1000 mg/d) was evaluated by Sheinman et al,\(^6\) including a low dose that was expected to be subtherapeutic. This stronger study design, however, was also confounded by open-label bolus amiodarone injections given by study investigators. There was, however, a trend toward a relationship between intended amiodarone dose and VT/VF recurrence rate (\(P=0.067\)). After adjustment for baseline imbalances, the median 24-hour recurrence rates of VT/VF, from lowest to highest doses, were 1.68, 0.96, and 0.48 events per 24 hours (\(P=0.043\)).

The third study compared 2 amiodarone doses (125 and 1000 mg/d) to bretylium (2500 mg/d).\(^6\) Once again, the target amiodarone dose ratio of 8 to 1 was compressed to 1.8 to 1 as a result of open-label boluses. There was no significant difference in the primary outcome, which was median VT/VF recurrence rate over 24 hours. For low-dose amiodarone, high-dose amiodarone, and bretylium, these rates were 1.68, 0.48, and 0.96 events per 24 hours, respectively (\(P=0.237\)). There was no difference between high-dose amiodarone and bretylium; however, >50% of patients had crossed over from bretylium to amiodarone by 16 hours.

The failure of these studies to provide clear evidence of amiodarone efficacy may be related to the “active-control” study design used, a lack of adequate statistical power, high rates of supplemental amiodarone boluses, and high crossover rates. Nonetheless, these studies provide some evidence that IV amiodarone (1 g/d) is moderately effective during a 24-hour period against VT and VF.

Recently, the Amiodarone in the Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST) study was presented.\(^6\) In patients with out-of-hospital cardiac arrest still in VT or VF after 3 direct-current shocks, amiodarone was evaluated in a randomized, placebo-controlled trial of 504 patients. With amiodarone added to the advanced cardiac life support protocol, the number of patients admitted to hospital alive increased from 35% to 44% (\(P<0.03\)). Other planned or ongoing trials, including a randomized comparison against lidocaine, are evaluating intravenous amiodarone in the management of acute VF.

Although amiodarone appears useful in short-term management of VT and VF, its role vis-à-vis other antiarrhythmic drugs is unclear. On the basis of a meta-analysis of class I and III drugs,\(^6\) the proarrhythmic potential of amiodarone probably is lower than that of lidocaine or procarainamide; however, its use as a primary agent probably should wait until the results of direct comparative trials become available. Amiodarone is a reasonable alternative to bretylium.

**Amiodarone for AF**

Although amiodarone is widely used to control AF, it is not approved in North America for any supraventricular arrhythmia. Pharmacological control of AF is a useful clinical goal and a reasonable clinical trial outcome. Management of AF entails a variety of approaches in different patients and at different times. These include maintenance of sinus rhythm, conversion of AF to sinus rhythm, control of ventricular rate, and primary prevention of AF. Amiodarone has been evaluated with randomized trials in all of these settings (see the Table).

All randomized trials of amiodarone for long-term maintenance of sinus rhythm in patients with recurrent AF have used active-control groups. Three studies compared amiodarone with quinidine.\(^6\) One brief report indicated improved maintenance of sinus rhythm at 1 month after cardioversion in a randomized comparison of amiodarone 200 mg/d with quinidine (32.5% vs 13.3%, \(P=0.042\)). Vitolo et al\(^6\) found amiodarone to be superior to quinidine in a study of 54 patients randomly allocated to either therapy after cardioversion. After 6 months, the percentage of patients in sinus rhythm was 79% for amiodarone and 46% for quinidine (\(P=0.014\)). However, Zehender et al,\(^6\) in a randomized trial of amiodarone against the quinidine/verapamil combination in 40 patients, found no difference in either the conversion rate of AF to sinus rhythm or in long-term maintenance of sinus rhythm during up to 2 years of follow-up. Kochiakakis et al\(^6\) recently reported the results of a small study comparing amiodarone with sotalol for maintenance of sinus rhythm in paroxysmal AF. During follow-up of slightly <1 year, amiodarone outperformed sotalol, with 10 of 35 amiodarone patients developing AF compared with 21 of 35 sotalol patients (\(P=0.008\)). It is therefore likely that amiodarone is effective for maintenance of sinus rhythm in the patient with recurrent AF, and there is modest evidence of superiority over other agents.

Several studies evaluated intravenous amiodarone for conversion of acute AF to sinus rhythm. There are 6 trials with
nonactive control groups: 2 that formally compared intravenous amiodarone to digoxin, 66,67 3 that were placebo controlled with digoxin use in all patients, 68 –70 and 1 that compared amiodarone with intravenous verapamil. 71 Digoxin and verapamil have little efficacy for conversion of AF. Three of these trials observed a significantly higher rate of acute conversion to sinus rhythm with amiodarone: 67% versus 90%, \( P<0.029 \) 66; 71% versus 92% \( P=0.0048 \) 65; and 77% versus 0% \( P=0.001 \). 71 The other 3 showed nonsignificant trends to better conversion with amiodarone: 56% versus 59%, \( P=\text{NS} \) 68; 60% versus 68%, \( P=0.532 \) 65; and 75% versus 83%, \( P=\text{NS} \). 64 Control of ventricular rate in AF was evaluated in 2 placebo-controlled studies, both of which reported significantly lower ventricular rates with amiodarone.69,70 Thus, amiodarone is effective for acute conversion of AF and has a beneficial effect on heart rate in AF.

Several active-control short-term conversion studies have been reported. Two of these compared intravenous amiodarone with oral quinidine for management of acute AF. In an 80-patient study of postoperative AF, the 8-hour conversion rate was superior with quinidine (64%) compared with amiodarone (41%), \( P=0.04 \).72 In another 75-patient study of conversion of acute AF, amiodarone and quinidine were both highly effective, with conversion rates of 92% and 100% for intravenous amiodarone and oral quinidine, respectively.73 Conversion of chronic AF (lasting >3 weeks) was evaluated in a 32-patient randomized study.74 There was no significant difference between intravenous amiodarone and oral quinidine in 24-hour conversion rates or control of ventricular response.

Amiodarone has been compared with class 1C drugs for acute AF conversion. In 1 of these studies, amiodarone and flecainide had similar rates of conversion.70 Two studies of intravenous amiodarone and propafenone in postoperative AF of 40 and 84 patients, respectively, observed little difference between drugs, although there was a small trend in each study in favor of amiodarone at 24 hours with conversion rates of 67% versus 77% \( (P=\text{NS}) \)75 and 68% versus 83% \( (P=\text{NS}) \).76 Interestingly, in both studies, early (1 hour) conversion rates were significantly better with propafenone, suggesting a more delayed onset of action with amiodarone. Other small, randomized studies of acute AF conversion have found intravenous amiodarone to be similar to intravenous procainamide,77 and in 1 trial, significantly less effective than magnesium sulfate.78

<table>
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<tr>
<th>Trial</th>
<th>Control</th>
<th>Patients, n</th>
<th>Primary Outcome</th>
<th>Time Period</th>
<th>Odds of SR With Amiodarone</th>
<th>( P )</th>
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<tr>
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<td>4 y</td>
<td>1.05</td>
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SR indicates sinus rhythm. *Sinus rhythm achieved in 77% of amiodarone and 0% of verapamil patients.
Primary prevention of AF is a worthwhile goal that has been studied in 1 heart failure trial and extensively in patients recovering from open-heart surgery, in whom AF occurs in about 30% of patients. Four placebo-controlled trials of amiodarone have been published. Redle et al\(^9\) reported a nonsignificant, modest reduction in postoperative AF in a study of 127 patients after CABG surgery receiving oral amiodarone beginning 1 to 3 days before surgery. In a study of 120 patients, Butler et al\(^80\) reported a significant reduction in postoperative AF with amiodarone. Hohnloser et al\(^81\) observed a significant reduction in postoperative AF (from 21% to 5%, \(P<0.05\)) with intravenous amiodarone started postoperatively. Another study of 124 patients using oral amiodarone at least 7 days preoperatively reported a reduction in postoperative AF from 53% to 25% (\(P=0.003\)).\(^82\) Finally, in a subanalysis of Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHF-STAT), a mortality trial of prophylactic amiodarone in heart failure, patients on amiodarone were significantly less likely to develop AF than those on placebo, and patients with AF at baseline were also more likely to convert to sinus rhythm if they received amiodarone.\(^83\)

In summary, there is reasonable evidence from many rather small, randomized controlled trials that amiodarone is effective for conversion of AF and maintenance of sinus rhythm. However, the available active-control studies provide little evidence that it is superior to other effective drugs. It should be noted that active-control studies inherently pose a greater challenge to the demonstration of efficacy than do placebo-controlled trials, because the differences one can expect to observe in comparison with other effective agents are usually small. Thus, active-control studies need to be more rigorously designed and include larger numbers of patients. The Canadian Trial of Atrial Fibrillation (reported in March 1999), a trial of 400 patients with AF, reported a significant reduction in AF recurrence with amiodarone compared with either sotalol or propafenone (personal communication, D. Roy, Institute of Cardiology, Montreal, Canada). In addition, a large substudy of the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) is comparing amiodarone to other drugs for control of AF.

**Cardiac Safety of Amiodarone**

There is good evidence that amiodarone is effective against a variety of arrhythmias and that it possibly is superior to other drugs in some settings. These benefits do not explain why amiodarone has become the most used antiarrhythmic drug. Clinical decision making balances assessment of effectiveness against risk of adverse outcomes, and amiodarone has been shown to be a relatively safe drug, especially in patients with serious heart disease. Amiodarone can result in severe toxicity of lung, liver, thyroid, nerves, and skin. However, early concern about its noncardiac side effects\(^24\)–\(^31\) has been replaced by appreciation of its low cardiovascular toxicity.\(^36\)\(^,\)\(^55\) To help understand the evidence that amiodarone is relatively safe, one should understand the safety concerns regarding other antiarrhythmic drugs. On the basis of the results of several clinical trials and subsequent meta-analysis, considerable evidence accumulated in the early 1990s that many antiarrhythmic drugs increase the risk of death in the very patients who could benefit most from effective arrhythmia prevention, those with serious underlying myocardial and coronary artery disease.\(^22\)\(^,\)\(^38\)\(^,\)\(^56\)\(^,\)\(^84\) Although the mechanism of this adverse effect is unclear, proarrhythmic and adverse hemodynamic actions are the most likely culprits.

The cardiovascular safety of amiodarone can be assessed from various case series and from randomized trials. Assessment of the risk of proarrhythmic effects of drugs can be difficult because few features distinguish a proarrhythmic effect from breakthrough of the underlying arrhythmia. The 1 finding that is virtually diagnostic of drug-induced arrhythmia is torsade de pointes, polymorphic VT in the presence of marked QT interval prolongation. Even so, QT prolongation occurs in virtually all amiodarone-treated patients, and polymorphic VT can occur spontaneously; thus, there is some lack of reliability even from case studies and follow-up studies reporting torsade de pointes. Ultimately, the most reliable safety data come from randomized, controlled trials.

There have been many case reports of amiodarone-induced torsade de pointes.\(^85\)–\(^88\) In most, the typical arrhythmia occurred in the presence of marked QT prolongation, with resolution in many cases after drug discontinuation and/or heart rate acceleration.\(^86\)\(^,\)\(^88\) The incidence of this complication appears to be low (<0.5%). Many large follow-up studies have reported no cases,\(^8\)\(^,\)\(^29\)\(^,\)\(^31\) including the 2 largest (with 462 and 589 patients, respectively).\(^35\)\(^,\)\(^36\)

Use of programmed electrical stimulation can define a different type of potential proarrhythmic effect of antiarrhythmic drugs. Whereas amiodarone usually slows the rate of VT, faster VT has been reported after amiodarone in some cases.\(^89\)–\(^91\) Other studies have shown conversion of nonsustained to sustained VT or induction of VT with fewer extrastimuli with amiodarone and other drugs.\(^19\)\(^,\)\(^91\)\(^,\)\(^92\) No study has used a placebo-controlled approach to evaluate this risk. Furthermore, the results of programmed electrical stimulation and the spontaneous occurrence of VT can vary over time, making clinical interpretation of these data problematic.

The results of randomized, controlled studies in high-risk patients are a more reliable way to assess the potential of amiodarone to worsen outcomes. In several of these trials of amiodarone, there was a reduction in arrhythmic death.\(^44\)\(^,\)\(^45\) and in the meta-analysis\(^55\) summarizing all these trials, the risk of arrhythmic death was significantly reduced by 29%. Thus, while it is possible that in individual patients amiodarone might cause death by proarrhythmia or bradycardia, the net effect in groups of patients is beneficial. Therefore, the clinician should be watchful because the individual patient receiving amiodarone may have an adverse arrhythmic event. He or she can be confident that these are rare and that the overall risk of death from arrhythmia or any cause with amiodarone is likely reduced.

Amiodarone is generally well tolerated in patients with CHF, although 1 intravenous study demonstrated depression of contractility in patients with compromised left ventricular function.\(^93\) Several randomized trials of amiodarone in patients with severe left ventricular dysfunction have reported that it is well tolerated. Doval et al\(^51\) reported that amiodarone significantly reduced admission to hospital for CHF and
improved functional class in a trial of 516 heart failure patients randomized to amiodarone or usual care. In CHF-STAT, a randomized placebo-controlled trial of amiodarone in 674 patients with heart failure, there was significant improvement in left ventricular ejection fraction with amiodarone compared with placebo. In 2 small, randomized trials of amiodarone in heart failure, there was either no significant effect on left ventricular ejection fraction or significant improvement compared with placebo.54

Amiodarone may induce severe bradycardia requiring a permanent pacemaker, but reports of severe complications caused by bradycardia induced by amiodarone are not common.35,36 The 1-year risk of bradycardia requiring medication discontinuation in the meta-analysis of double-blind, placebo-controlled, primary prevention trials was 2.4% on amiodarone and 0.8% on placebo.55

Some case series have reported an increased risk of marked bradycardia and hypotension immediately after cardiac surgery in patients already on amiodarone at the time of surgery.95,96 Other case-control studies, however, have not reproduced this finding.97,98 None of the placebo-controlled trials of prophylactic amiodarone for perioperative AF prevention found any adverse cardiovascular effects of the drug.81–84 Thus, it is relatively unlikely that amiodarone poses a serious cardiovascular risk to the postoperative patient. Case reports and case series of postoperative acute pulmonary toxicity are similarly lacking in the rigor of randomized controlled methodology.95–99

Several animal and human studies have reported the effects of long-term oral amiodarone on the energy required for cardiac defibrillation. Animal studies have been somewhat contradictory, with some studies reporting an increase in defibrillation threshold and others noting an increase.100–102 In human studies,104–106 have mostly indicated an increase in defibrillation threshold in patients receiving long-term oral amiodarone, although 1 study found no change.107 These studies are methodologically weak, because amiodarone therapy was not allocated randomly. It is possible that the same factors resulting in amiodarone use also increase defibrillation threshold. This area requires further study.

In summary, there is considerable evidence that amiodarone has less cardiovascular toxicity than other antiarrhythmic drugs. This is based largely on an analysis of the results of several placebo-controlled trials of both amiodarone and other drugs and on meta-analysis of these trials. These trials indicate increased cardiovascular mortality from several class I drugs and with 1 class III drug.84 With amiodarone, there is neutral or slightly improved mortality.55 Large follow-up studies of amiodarone confirm this view.35,36

Noncardiac Toxicity

Amiodarone may result in serious noncardiac toxicity, particularly pulmonary infiltrates, hepatic dysfunction, thyroid dysfunction, and peripheral neuropathy. Pulmonary toxicity can be severe and occasionally fatal.97 The diagnosis is most often made by observing patchy interstitial infiltrates on chest x-ray, usually associated with a subacute presentation of dyspnea. Typically, once the differential diagnosis of pulmonary edema has been excluded, amiodarone discontinuation is indicated. Estimates of the risk of pulmonary toxicity during long-term oral therapy vary and may be dose related. The most reliable estimate of the 1-year risk of this complication comes from double-blind, placebo-controlled, randomized trials, because there is a tendency to overdiagnose the condition in patients receiving open-label amiodarone. Meta-analysis of the double-blind trials indicates an absolute 1% net risk (amiodarone rate less placebo rate) of this complication during 1 year, with some fatal cases reported.55

The same meta-analysis also reported that the 1-year net risk of events (severe enough to cause study drug discontinuation) was 0.6% for hepatic toxicity, 0.3% for peripheral neuropathy, and 0.9% for hyperthyroidism. Hypothyroidism was quite common, occurring in 6% during the first year of treatment, but usually it is easily managed by thyroid hormone replacement concurrent with continuation or discontinuation of amiodarone. During long-term management of patients on amiodarone, routine toxicity screening is required. This includes periodic (usually every 6 months) measurement of thyroid (sensitive serum T4), hepatic (AST), and pulmonary function (chest x-ray), as well as clinical evaluation.

Conclusions

Amiodarone is currently the leading antiarrhythmic drug because of proven efficacy and safety. There is reasonable evidence of effectiveness against several clinical important arrhythmias. However, good randomized trials evaluating the efficacy of amiodarone are still needed, especially comparative studies against other drugs for control of AF and a placebo-controlled trial against VT. Amiodarone is particularly useful because its safety has been clearly demonstrated by a large body of evidence, including several randomized trials. Compared with many other antiarrhythmic drugs, amiodarone causes few cardiovascular adverse effects; however, its overall tolerance is limited by considerable noncardiac toxicity.

Although amiodarone will continue to give way to the ICD as primary therapy for many patients presenting with sustained VT or VF, it is likely that amiodarone use will continue in ICD patients to prevent ICD discharges. Evaluation of combined use of amiodarone and the ICD may provide the first opportunity to do a placebo-controlled trial of amiodarone efficacy against VT recurrence. Pharmacological therapy remains the major approach to management of AF, and use of amiodarone is likely to increase in future years.

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References


83. Keren A, Tzivoni D, Gottlieb S, Benhorin S, Stern S. Atypical ventricular tachycardia (torsades de pointes) induced by amiodarone: arrhyth-

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