Amiodarone: clinical efficacy and toxicity in 96 patients with recurrent, drug-refractory arrhythmias

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ABSTRACT Ninety-six patients with recurrent, drug-refractory tachyarrhythmias were treated with amiodarone for 8.0 ± 7.5 months (range 1 day to 27 months); 77 for recurrent ventricular tachycardia or ventricular fibrillation (VT/VF), two for complex ventricular ectopy, and 17 for supraventricular tachyarrhythmias. The actuarial incidence of successful amiodarone therapy was 52 ± 7% at 12 months and 28 ± 9% at 24 months for patients with VT/VF. Neither patient with complex ventricular ectopy was successfully treated. Among the patients with supraventricular tachyarrhythmias, 64.7% were successfully treated for 7.7 ± 7.6 months (range 1 to 22 months). Amiodarone toxicity occurred in 66 of 91 patients (72.5%) treated for more than 1 week. Fourteen patients had therapy-limiting toxicity. Of these 14, six had pulmonary toxicity, four had arrhythmia exacerbation, one had hepatitis, one had renal toxicity, one had rash, and one had erythema nodosum. The actuarial incidence of therapy-limiting side effects was 27 ± 7% at 15 months. We conclude that amiodarone is useful in the treatment of refractory tachyarrhythmias but that the rate of efficacy in VT/VF is lower and the incidence of significant toxicity is higher than has been generally appreciated.


AMIODARONE, a benzofuran derivative structurally similar to thyroxine, is under investigation in the United States for treatment of supraventricular and ventricular tachyarrhythmias. Previous studies have stressed two major conclusions: amiodarone is extremely effective, even in patients with arrhythmias refractory to other drugs, and it has a very low incidence of significant toxicity.1–18

We report our experience with amiodarone in 96 patients who had recurrent arrhythmias previously refractory to drug therapy. Our results are at variance with both major conclusions of most previous studies.

Methods

Patients. We treated 96 patients with symptomatic, recurrent, previously drug-refractory arrhythmias not associated with acute myocardial infarction. Seventy-nine patients, whose clinical characteristics are summarized in table 1, had ventricular arrhythmias: 77 patients had recurrent ventricular tachycardia or ventricular fibrillation (VT/VF), and two patients had complex ventricular ectopy (CVE) without VT/VF. Seventeen patients had supraventricular tachyarrhythmias (SVT); 15 with recurrent paroxysmal atrial fibrillation or atrial flutter, and two with ectopic atrial tachycardia (ectopic AT).

Previous drug refractoriness. Patients were eligible for amiodarone therapy only if therapy with all standard antiarrhythmic agents had failed. Failure of a standard agent was defined as symptomatic arrhythmia recurrence during an empiric drug trial, inducible VT/VF during electrophysiologic testing, unacceptable side effects, or a major contraindication to the use of a specific drug. In addition, 48 of the patients with VT/VF had failed previous therapy with at least one experimental antiarrhythmic agent, and eight had failed previous VT/VF surgery guided by activation mapping. For patients with VT/VF, there were a total of 88 unsuccessful empiric trials plus electrophysiologic testing trials with procainamide, 85 with quinidine, 75 with lidocaine, 33 with disopyramide, 33 with propranolol, 30 with encainide, 19 with bretylium, 18 with lorcainide, 16 with phenytoin, 10 with Verapamil, 10 with tocainide, nine with mexiletine, and four with imipramine.

Amiodarone administration. Whenever possible, all antiarrhythmic agents, except for digitalis preparations, were discontinued at least 24 hr before amiodarone administration. A 12-lead electrocardiogram recording (ECG), 24 hr Holter monitor recording, plasma chemistry screening,* thyroid function tests, and an ophthalmologic evaluation were obtained in the

*Including sodium, chloride, potassium, bicarbonate, urea nitrogen, creatinine, glucose, calcium, phosphorus, uric acid, total protein, albumin, cholesterol, bilirubin, alkaline phosphatase, lactic dehydrogenase, SGOT, and complete blood count.

CIRCULATION
TABLE 1
Clinical characteristics in patients treated for ventricular arrhythmias

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>79</td>
<td>100%</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>81.0%</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>19.0%</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>59.1±9.8 yr (range 29 to 81)</td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heart disease</td>
<td>6 (7.6)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>60 (75.9)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>58 (73.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>9 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>6 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>66 (83.5)</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>11 (13.9)</td>
<td></td>
</tr>
<tr>
<td>CVE</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia-severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 or more episodes of VT/VF</td>
<td>72 (91.1)</td>
<td></td>
</tr>
<tr>
<td>Required emergent DC conversion</td>
<td>36 (45.6)</td>
<td></td>
</tr>
<tr>
<td>prior to amiodarone therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>19 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>21 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Mean empiric drug trials failed</td>
<td>3.6±1.7</td>
<td></td>
</tr>
<tr>
<td>Mean EP drug trials failed</td>
<td>2.0±1.6</td>
<td></td>
</tr>
</tbody>
</table>

EP = electrophysiologic; CAD = coronary artery disease; MI = myocardial infarction.

*Numbers in parentheses represent percent of total number of patients treated for ventricular arrhythmias.

baseline period; 66 of the patients who had VT/VF also underwent electrophysiologic testing by a previously described protocol. Thirty-three of these patients underwent electrophysiologic testing again after 2 or more weeks of amiodarone therapy. During the first 6 months of this study, inducibility of VT on amiodarone was used as a criterion to discontinue amiodarone. Thereafter, electrophysiologic testing was not used as a criterion for drug discontinuation.

Oral amiodarone was administered in divided doses of 600 to 1200 mg/day for 2 weeks (mean 800 ± 130 mg/day) to patients who had ventricular arrhythmias. Maintenance therapy of 400 mg/day, 5 days per week, to 800 mg/day (mean 628 ± 167 mg/day) was then continued. Patients who had SVT were treated with 400 to 600 mg/day (mean 500 ± 183 mg/day) without an initial loading period.

Doses were lowered if symptomatic but not life-threatening side effects occurred. Dosage was reduced to below 4 g/week in all patients unless a greater dosage was required to achieve efficacy. For patients who had VT/VF, doses were increased if VT (5 beats or more) was seen on ECG monitoring. If hemodynamically stable VT recurred on maximal maintenance doses, either quinidine or procainamide was added. For patients who had SVT, dosage was increased if no improvement in frequency or duration of symptoms occurred after at least 10 days of treatment.

Follow-up. Follow-up evaluations were made at the time of hospital discharge, at 1 week, 2 weeks, 1 month, 3 months, and at a minimum of 3 month intervals thereafter. These evaluations consisted of a physical examination, 12-lead ECG recording, 24 hr Holter monitor recording, plasma chemistry screening, thyroid function tests, and ophthalmologic evaluation. Digitalis levels and prothrombin times were monitored in patients taking digitalis preparations or anticoagulants.

Assessment of drug efficacy. Because amiodarone requires a prolonged loading period before its antiarrhythmic effect begins, we did not assess its efficacy until after 10 days of treatment. Amiodarone was considered to be effective in patients with VT/VF if all symptoms of recurrent VT were eliminated, if no VT longer than 5 beats was seen on ECG monitoring, and if sudden death did not occur. In patients who had CVE or SVT, drug efficacy was defined as a 90% reduction in frequency and duration of the arrhythmia, which was assessed by ECG monitoring and by symptoms.

Drug failure. Failure of amiodarone therapy was defined as either amiodarone inefficacy in patients on a standard maintenance dose, or as amiodarone withdrawal or dose reduction to ineffective levels necessitated by side effects.

Amiodarone pneumonitis. Amiodarone pneumonitis was diagnosed if (1) diffuse pulmonary infiltrates appeared after the use of amiodarone, (2) dyspnea and cough occurred, (3) congestive heart failure, infection, and collagen-vascular diseases were excluded by a therapeutic trial of diuretics and/or by measurement of pulmonary capillary wedge pressure, culture, or serologic study, and (4) either symptoms and pulmonary infiltrates resolved after discontinuation of amiodarone, or fibrosis consistent with amiodarone pneumonitis was seen on postmortem tissue examination.

Arrhythmia exacerbation. Amiodarone-induced arrhythmia exacerbation was diagnosed if a marked increase in arrhythmia frequency and duration occurred that was consistent with the expected onset of action of amiodarone as assessed by continuous in-hospital monitoring or by Holter monitoring.

Statistical analysis. Data are expressed as the mean ± 1 SD. Actuarial analysis was performed according to the method of Cutter and Ederer.20 Points on separate life-table curves were compared by the method of Greenwood,21 and are presented as percent ± SE.

Results

Seventy-six men and 20 women were treated with amiodarone. Their mean age was 58.0 ± 10.9 years (range 16 to 81) and the mean duration of therapy was 8 ± 7.5 months (range 1 day to 27 months).

Amiodarone efficacy

VT/VF. The 77 patients who had VT/VF had failed a mean of 3.6 ± 1.7 empiric drug trials and a mean of 2.0 ± 1.6 electrophysiologic testing drug trials before they began taking amiodarone. They were treated with amiodarone for a mean of 8.5 ± 8.4 months (range 1 day to 27 months). Seven patients (four who died within 1 week of beginning amiodarone treatment and three in whom amiodarone was discontinued during their first month of therapy because of inducible VT on electrophysiologic testing) are not considered to have failed therapy with amiodarone in our data analysis. No other patients had amiodarone discontinued because of inducible VT.

Figure 1 is an actuarial curve for amiodarone efficacy in patients with VT/VF. The actuarial incidence of drug efficacy was 52 ± 7% at 12 months and 28 ± 9% at 24 months.

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Thirty-two patients were successfully treated and 38 patients failed to respond to amiodarone. Three of those successfully treated required the addition of quinidine (one patient) or procainamide (two patients) for effective therapy with amiodarone. Of those who failed to respond, 14 had side effects requiring discontinuation of amiodarone, eight died suddenly, and 16 had recurrent VT. Of the 16 patients with recurrent VT, eight either had syncope or required emergency cardioversion with their recurrence, seven had lightheadedness or presyncope with their recurrence, and one had repeated asymptomatic runs of more than 5 beats of VT. If the patient with asymptomatic recurrence of VT were not considered to have failed with amiodarone, the actuarial incidence of amiodarone efficacy would be 53 ± 7% at 12 months and 31 ± 9% at 24 months.

Fourteen of the 38 drug failures occurred within the first month of therapy. Five had significant side effects (one with renal toxicity, one with hepatitis, one with rash, and two with toxic arrhythmias) and five were treated for at least 21 days before VT recurred. A total of 21 patients (14 with drug failure, four who died during the first week of therapy, and three who failed electrophysiologic testing) were treated with amiodarone for less than 1 month.

A separate actuarial curve is shown in figure 1 for patients treated successfully with amiodarone for 1 month or longer. There are no significant differences (p > .1) between points on this curve and those on the curve for all patients with VT/VF. Long-term drug efficacy (more than 24 months) is similar in these two groups.

Amiodarone was ineffective in both patients with CVE as judged by quantitative Holter monitoring.

SVT. Seventeen patients with SVT were treated with amiodarone; 12 male and five female patients with a mean age of 54.6 ± 9.9 years (range 16 to 81) were treated. They had failed a mean of 3.3 ± 0.9 empiric drug trials before they began taking amiodarone. On amiodarone therapy, 11 of the 17 patients with SVT (64.7%), 10 with paroxysmal atrial fibrillation or flutter, and one with ectopic AT had virtual elimination of their arrhythmias as assessed by Holter monitor study and by symptoms; they had no serious side effects for a mean of 7.7 ± 6.7 months (range 1 to 22). Five patients failed to respond to amiodarone, all within the first month of therapy. Three of these five did not improve, one improved without complete elimination of symptoms and discontinued the drug because of the financial cost of follow-up, and one experienced exacerbation of paroxysmal atrial fibrillation, which remitted when amiodarone was discontinued. A 16-year-old boy, with congenital transposition of the great vessels and ectopic AT, died suddenly in electromechanical dissociation after three doses of amiodarone. This event was not considered a failure of amiodarone.

Amiodarone toxicity (table 2). Sixty-six of the 91 patients (72.5%) treated with amiodarone for more than 1 week had evidence of toxicity. Fourteen (15.4%) had side effects necessitating the withdrawal of amiodarone, six had infiltrative pulmonary disease, four had exacerbation of the treated arrhythmia, one had severe hepatitis, one had suspected renal toxicity, one had rash, and one had erythema nodosum.

Figure 2 is an actuarial curve showing the cumulative proportion of therapy-limiting side effects. Significant side effects occurred in 27 ± 7% of our patients at 15 months.

Ocular. Twenty-seven patients (29.7%) had evidence of corneal microdeposits. These patients occasionally complained of halo vision or dry eyes, but no patient had to discontinue amiodarone because of ocular side effects.

Dermatologic. Twenty patients (22%) had dermatologic side effects: 11 had sun sensitivity, four had bluish discoloration, two had petechiae, two had nonspecific rash, and one had erythema nodosum. Amiodarone therapy was discontinued in one patient with nonspecific rash and the patient with erythema nodosum.

Thyroid. Thirteen patients (14.3%) developed chemical evidence of thyroid dysfunction. Ten were hypothyroid and three were hyperthyroid. None of the hypothyroid patients required treatment other than a reduction in the dose of amiodarone. Four hypothyroid

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Actuarial analysis of efficacy of amiodarone for all patients with VT/VF treated with amiodarone (●), for patients with VT/VF treated with amiodarone for at least 1 month (○), and of efficacy of encainide in a similar group of patients with VT/VF treated with encainide (△). The vertical bars represent SE.
TABLE 2
Amiodarone toxicity

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. patients with side effect</th>
<th>Patients on amiodarone &gt; 1 wk*</th>
<th>No. patients requiring drug withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal microdeposits</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun sensitivity</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bluish discoloration</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petechiae</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse interstitial infiltrates</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gl/hepatic</td>
<td></td>
<td>4.4/20.9</td>
<td></td>
</tr>
<tr>
<td>Severe hepatitis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transaminase elevation</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Creatinine elevation</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasthesias</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia exacerbation</td>
<td></td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>A. fib/flutter</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Accelerated junctional rhythm</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. fib/flutter = paroxysmal atrial fibrillation or flutter; GI = gastrointestinal.

*Total patients on amiodarone > 1 week = 91; total patients with toxicity = 66 (72.5%); total patients requiring amiodarone withdrawal = 14.

*Data expressed as percent total of patients on amiodarone > 1 week.

patients developed symptoms requiring thyroid replacement. Amiodarone was not discontinued in any patient because of thyroid toxicity.

Pulmonary. Six patients (6.6%) developed pulmonary toxicity. Three of these had complete resolution of pneumonitis when amiodarone was withdrawn and steroid therapy was begun. Two died of opportunistic infections that began during steroid therapy for amiodarone-induced pneumonitis. One died of myocardial infarction after a bronchoscopy and biopsy that showed fibrosis consistent with amiodarone pneumonitis. The mean duration of treatment with amiodarone for these six patients was 8.5 ± 4.9 months (range 3 to 14 months), and the dose of amiodarone ranged from 600 to 800 mg/day.

Gastrointestinal and hepatic. Four patients (4.4%) had minor gastrointestinal complaints (nausea, vomiting, epigastric fullness, or constipation) that did not require discontinuing amiodarone.

One patient developed severe hepatitis within the first month of treatment. Transaminase levels fell from the 3000 to 5000 IU/l range to normal within 14 days after stopping amiodarone. With amiodarone rechallenge, transaminase levels rose again to above 1000 IU/l within 3 days. Amiodarone was then discontinued, and a liver biopsy showed severe, nonspecific hepatitis. Eighteen additional patients (19.8%) had mild asymptomatic elevations in transaminase levels during amiodarone therapy.

Renal. Eight patients (8.8%) developed elevations in serum creatinine from normal levels to levels above normal during therapy with amiodarone. The mean increase was 0.81 ± 0.33 mg/100 ml (range 0.5 to 1.4 mg/100 ml). These creatinine elevations were sustained and no alternate explanations were evident. In one patient, amiodarone therapy was discontinued after 2 months because of a mild but progressive rise in creatinine level. His creatinine level subsequently returned to normal.

Neurologic system. Eighteen patients (19.8%) had neurologic side effects. Nine had significant tremor, six had ataxia, one had myoclonic jerks, one had restless legs syndrome, and one had paresthesias. These side effects frequently required a decrease in dosage.

Arrhythmia exacerbation. Four patients (4.4%) had ap-

FIGURE 2. Actuarial analysis of the incidence of side effects requiring amiodarone withdrawal for all patients treated with amiodarone. The vertical bars represent SE.
parent exacerbation of their underlying rhythm disturbances with amiodarone. Three of these patients, two with VT and one with atrial flutter, improved when amiodarone therapy was stopped. The fourth patient, whose VT became more rapid and hemodynamically unstable after 1 week of therapy with amiodarone, died of VT/VF that was newly refractory to cardioversion.

VT/VF newly refractory to cardioversion. VT/VF newly refractory to cardioversion was seen in five of the 77 patients with VT/VF who were treated with amiodarone. All had had several previous successful cardioversions before therapy with amiodarone. One of these patients is described above. In addition, two otherwise stable, hospitalized patients with VT/VF died of recurrent VT refractory to cardioversion after 3 days and 1 month of therapy, respectively. Two more patients, who were critically ill and who were receiving multiple antiarrhythmic drugs, died of VT refractory to cardioversion within 48 hr of starting amiodarone therapy. Since it was impossible to prove that amiodarone caused refractoriness to cardioversion in these patients, we did not consider VT/VF newly refractory to cardioversion as a side effect in our data analysis.

Other. One patient developed a symptomatic accelerated junctional rhythm related to amiodarone that required frequent dosage adjustments. One patient developed symptomatic bradycardia that required placement of a permanent pacemaker.

Discussion

Several investigators have reported that amiodarone is extremely safe and effective in the treatment of a wide variety of tachyarrhythmias. Rosenbaum et al. described efficacy in 82% of 145 patients who had ventricular arrhythmias and in 92.4% of 106 patients who had SVT. No serious side effects occurred. Groh et al. reported over 70% efficacy in 14 patients who had VT refractory to conventional drugs, with no therapy-limiting side effects. Haffajee et al. reported success in 14 of 17 patients who had ventricular arrhythmias and in eight of nine who had SVT with "minimal" side effects. Kaski et al. reported that in 23 patients who had sustained, recurrent, symptomatic VT, 65% had no recurrence during a mean follow-up of 21.5 months, and none had significant side effects. Nademanee et al. reported successful treatment in 18 of 19 patients who had refractory ventricular tachyarrhythmias and described amiodarone as "extremely potent and safe." Heger et al. found amiodarone effective in 57% of 45 patients with recurrent VT/VF and stated that side effects were "frequent but do not usually limit therapy." Sobol and Rakita noted that voluminous literature showed amiodarone to be "extremely effective and remarkably safe," and stated that the safety of amiodarone "is unapproached by any antiarrhythmic agent available."

The results of this study do not support either of the major conclusions of these previous reports. We find that amiodarone is less efficacious than previously reported in treating refractory ventricular arrhythmias and causes a significant incidence of serious side effects. Findings more similar to ours were recently reported by Waxman et al., although their incidence of therapy-limiting side effects was lower than in our study.

Clinical efficacy. Our results in treating patients who had SVT are similar to those reported in other studies, but our actuarial success rate of 28% ± 9% for patients with VT/VF treated for 2 years is lower than the 65% to 95% rate reported in other studies. Our predicted 2 year drug efficacy rate is similar to that seen in a similar group of patients with refractory VT/VF treated with encainide at our institution (figure 1), which suggests that amiodarone may not be vastly superior to other experimental antiarrhythmic agents in patients with refractory arrhythmias.

There are several possible reasons for the discrepancy between our results and those of other investigators. First, our group of 77 patients with VT/VF is substantially larger than most groups in previous studies. Second, our patients' arrhythmias may have been more refractory to therapy than those in other studies; for example, eight of our patients had previous ineffective VT/VF surgery guided by activation mapping. Third, a substantial number of our patients developed side effects requiring the discontinuation of amiodarone. Our high rate of inefficacy with amiodarone cannot be ascribed to excessively rigid criteria for efficacy, since all but one of our patients with amiodarone failure had severe side effects, sudden death, or symptomatic recurrence of VT.

Although 14 of our 38 drug failures occurred during the first month of therapy, it is unlikely that a substantial number of these were due to an "inadequate" trial of amiodarone, since five drug failures were caused by serious toxicity and five other patients were treated for at least 21 days. Further, the actuarial curve of drug efficacy for patients treated successfully for the first month does not differ significantly from the curve for all patients with VT/VF. Finally, a long delay before a therapeutic effect is attained is a disadvantage in patients with frequent, life-threatening arrhythmias. It is practical to consider amiodarone ineffective when a long delay cannot be tolerated.
Toxicity. Our high incidence of mild ocular, thyroidal, and gastrointestinal side effects is similar to that in previous reports. However, neurologic side effects, seen in almost 20% of our patients, have been reported only rarely in previous studies. These symptoms, especially tremor and gait disturbance, frequently required a decrease in dosage of amiodarone, but did not lead to its discontinuation.

Amiodarone was withdrawn because of side effects in 15.4% of the patients treated for more than 1 week. Further, by actuarial analysis, only 73% ±7% of our patients were free of treatment-limiting side effects at 15 months.

Two patients with cutaneous toxicity required discontinuation of amiodarone, one for rash and one for erythema nodosum, which is a previously reported complication of amiodarone. Six patients had pulmonary complications because of amiodarone. Amiodarone-induced pneumonitis was first reported by Rotmensch et al. in 1980, and several other cases have since been reported. Sobol and Rakita reported six patients with pneumonitis and pulmonary fibrosis associated with amiodarone; two of these died of pneumonitis. In our study, 9.1% of patients treated for more than 1 month developed serious pulmonary toxicity. This incidence is similar to that reported in a recent study by Heger et al., in which three of 45 patients developed biopsy-proven pulmonary fibrosis.

One patient developed severe hepatitis that, by time course and response to rechallenge, appeared to be caused by amiodarone. Until very recently, amiodarone-induced clinical hepatitis had not been reported.

One patient discontinued amiodarone because of a progressive rise in creatinine level, which fell to normal within 2 weeks of withholding amiodarone. Significant amiodarone-related nephrotoxicity has not been reported previously.

One of the more distressing toxic reactions observed was exacerbation of the underlying rhythm disturbance in four patients, one of whom died. In addition, amiodarone may have produced refractoriness to cardioversion in five patients treated for VT/VF. It is impossible to be sure that refractoriness to cardioversion was related to amiodarone. If it was, the problem appears to occur soon after the drug is started, since all five patients died within the first month and three died within 4 days of beginning treatment. In any event, it is clear that at least 4.2%, and perhaps as many as 8.3%, of our patients experienced exacerbation of their arrhythmia with amiodarone. Although this incidence has not been previously reported with amiodarone, it is similar to the incidence of arrhythmia exacerbation seen with other antiarrhythmic agents. Because of long half-life of amiodarone, an amiodarone-induced arrhythmia exacerbation could be difficult to manage.

Conclusion

This study of 96 patients with recurrent, drug-refractory arrhythmias treated with amiodarone supports the findings of previous investigators, which showed that amiodarone is useful for treating supraventricular and ventricular arrhythmias. However, in our study, the efficacy of amiodarone in the treatment of drug-refractory ventricular tachyarrhythmias is much lower than reported in most previous studies. In addition, amiodarone causes a higher incidence of serious toxicity than has been generally accepted. Pulmonary toxicity and arrhythmia exacerbation are potentially lethal side effects.

Although it offers realistic hope in the treatment of previously drug-refractory arrhythmias, amiodarone is not an "ideal" antiarrhythmic agent. Amiodarone may be more efficacious and less toxic than reported here if it is used as a first-line agent in lower doses. However, we recommend that it be reserved for patients with truly refractory, symptomatic arrhythmias and that careful observation for side effects be made during its use.

References

12. Haafajee C, Alpert J, Lesko L, Canada A, Ascdoridian G: Amioda-
rame for refractory symptomatic tachyarrhythmia. Circulation 62 (suppl III): III-152, (abst)
Amiodarone: clinical efficacy and toxicity in 96 patients with recurrent, drug-refractory arrhythmias.
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