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Safety and Efficacy of Amiodarone*
The Low-Dose Perspective

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Amiodarone has been reported to be a remarkably safe and effective drug in the European and South American experience but American investigators have published conflicting data. Since this disparity may be explained by a different dosing schedule, we prospectively evaluated the safety and efficacy of a low dose regimen in a group of 68 patients with cardiac arrhythmia resistant to conventional therapy, of whom 57 had manifested either ventricular tachycardia or fibrillation. All were loaded either intravenously (17) or orally, and maintained on an oral dose of 200 to 600 mg/day (mean daily dose 317 ± 114 mg) and followed for 4 to 58 months (22 ± 11). Results indicated that amiodarone was a safe and effective antiarrhythmic drug when used in lower doses.

Amiodarone is a particularly potent agent for the treatment of serious cardiac arrhythmias. It has been shown to be effective in a variety of supraventricular and ventricular tachyarrhythmias resistant to conventional antiarrhythmic agents. Use of amiodarone in trials conducted in countries other than the United States has yielded an appreciable efficacy rate and an amazingly low incidence of side-effects, prompting considerable enthusiasm for the drug. However, more recent reports from American investigators have been significantly more bleak. For example, Mason et al recently compiled information obtained in 1,307 patients treated with the drug for a number of indications. They reported a 29 percent arrhythmia recurrence rate and a 19 percent incidence of severe side effects in the first year of therapy. The reasons for these disparate results can only be surmised. Inadequate data collection in the foreign experience could be invoked but seems implausible given the uniformity of the experience. Some unique susceptibility of American patients would seem a highly contrived explanation. A basic difference in how the drug has been used appears most likely. In fact, a careful review of studies to date indicates a significant difference in how amiodarone is employed. American investigators have consistently used higher doses of the drug long-term. For example, the average daily dose in the report of Mason et al was 443 ± 330 mg compared with 200 to 300 mg in the European literature.

The purpose of this study was to determine in a prospective fashion whether amiodarone is a safe and effective drug when administered in low doses.

**METHODS**

Patients referred to the Cardiac Arrhythmia Service at the Medical College of Pennsylvania were eligible for inclusion into the study. The protocol and consent form had been reviewed and approved by the Committee for the Protection of Human Subjects of the Medical College. The study entry criterion was a serious cardiac arrhythmia which had not responded to one or more conventional antiarrhythmic drugs. This was defined as persistent or recurrent spontaneous or induced supraventricular or ventricular tachyarrhythmia which, in the opinion of the patient's physician, constituted a significant impediment to the patient's health or well-being. Patients were excluded if the arrhythmia was deemed by the investigators to be not serious (not causing hemodynamic compromise or loss of consciousness), or if careful, long-term follow-up was precluded for any reason including poor general health or unreliability.

Preliminary cardiac testing was performed in all cases, and included ambulatory monitoring, and/or invasive electrophysiologic testing (using previously described techniques) to define the nature and extent of the cardiac arrhythmia. A battery of baseline laboratory testing was also obtained in each case and consisted of a hematologic profile, serum chemistries, hepatic, renal and thyroid function tests, antinuclear antibody test, chest x-ray, and slit-lamp eye examination. Patients then underwent either intravenous or oral loading. Intravenous loading consisted of 5 mg/kg infused over 30 minutes followed by a constant infusion of 900 mg/day for two days. Oral dosing was begun concomitantly with 800 mg for three days followed by 400 mg for three days. The oral program was decremental starting at 1,200 mg/day, and decreased by 400 mg every three days until a maintenance dose of 400 mg was achieved. Dose adjustments were permitted during the loading program if the QT interval did not show significant alteration (at least a 10 percent increase was expected by the end of the loading period). This loading program was used as a guideline but allowed physician discretion in the choice of the next daily dose.

At the end of the seven to ten day loading period and administration of an average loading dose of 7.2 g, repeat cardiac testing was carried out. Criteria for efficacy included abolition of nonsustained
ventricular tachycardia on monitoring and/or a significant slowing or noninducibility of a formerly inducible arrhythmia in the electrophysiology laboratory. Slowing of arrhythmia was considered significant if the cycle length increased to greater than 400 ms and was well tolerated hemodynamically while the patient was supine. If the arrhythmia was unaltered by amiodarone, an alternative treatment was selected. Those patients in whom a salutary response was obtained remained on the drug long-term. Patients with a partial response also remained on the drug, used either alone or in combination with another partially effective antiarrhythmic agent. Partial response was defined as rate slowing but poor hemodynamic tolerance or >75 percent but <100 percent abolition of nonsustained VT salvos. The usual daily dose used in the maintenance phase was the lowest that maintained antiarrhythmic efficacy and generally was 300 to 400 mg in patients with ventricular arrhythmia and 200 mg in patients with supraventricular arrhythmia. All patients were followed after hospital discharge by the investigators in conjunction with the private referring physicians. Patients were seen every three to six months, and an ECG was obtained at every visit. Twice annual testing consisted of a repeat of the laboratory testing obtained at baseline, together with a 24-hour ambulatory monitoring. Dose adjustments were made by the investigators and consisted only of down titration in those patients who had been discharged on a dose higher than the recommended maintenance amount because of a persistently foreshortened QT interval. Dose titration was not employed to treat tolerable or treatable side-effects. The drug was withdrawn if the patient developed intolerable side-effects or had a documented arrhythmia recurrence deemed serious by the investigator and/or private physician, or if a very rapid tachycardia remained inducible in the electrophysiology laboratory after the period of intravenous or oral loading.

**Results**

A total of 68 patients participated in the study, including 60 men and eight women with a mean age of 59 years. Fifty-seven patients had presented with hemodynamically significant VT or ventricular fibrillation (VF), six with supraventricular tachycardia (SVT), and five with atrial fibrillation or flutter. Seventeen of the patients underwent intravenous loading while the remaining 51 had oral loading only. Electrophysiologic testing was carried out in 58 patients both before and after amiodarone loading, and in the other ten, drug efficacy was gauged by the results of noninvasive testing. Patients studied noninvasively had greater than ten episodes of atrial fibrillation, greater than two episodes of supraventricular tachycardia, or >50 salvos of nonsustained VT on ambulatory monitoring on each of two baseline 24-hour ambulatory monitorings. The average daily dose of amiodarone was 317 ± 114 mg for the total group.

Patients were followed for four to 58 months (22 ± 11). Results of therapy are shown in Figure 1. Of the 11 patients with atrial flutter or fibrillation, eight (73 percent) had no recurrences including five who were treated with amiodarone alone and three who required another antiarrhythmic in combination. Of these eight, five had been studied invasively. One had been noninducible, while four had a slower tachycardia initiated (increase in cycle length of at least 100 ms in all cases) while on their discharge program. The other three patients were not studied invasively but had shown a >90 percent reduction in spontaneous arrhythmia frequency on ambulatory monitoring. There were three recurrences of supraventricular tachycardia, all well tolerated. Two of the three recurrences were heralded by the repeated provocation of a slower version of the clinical arrhythmia in the laboratory, while in one, a slower supraventricular arrhythmia was repeatedly observed on ambulatory monitoring. Of the 57 patients with VT/VF, 44 (77 percent) remained arrhythmia-free during the period of follow-up, including 11 who were treated with amiodarone in combination with another antiarrhythmic drug. Notably, only eight of these patients were rendered completely noninducible, while in the other 32 who underwent invasive testing, the induced

![Figure 1](https://www.chestjournal.org/Downloaded-from/www.chestjournal.org)
Table 1—Adverse Effects (Total 100)

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<th>Serious (drug continued)</th>
<th>8 (8 percent)</th>
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<tr>
<td>Hypothyroidism</td>
<td>2</td>
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<tr>
<td>Creatinine elevation</td>
<td>2</td>
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<tr>
<td>Tremor</td>
<td>2</td>
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<tr>
<td>Congestive heart failure</td>
<td>1</td>
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<tr>
<td>Intermittent junctional rhythm</td>
<td>1</td>
</tr>
<tr>
<td>Serious (drug discontinued)</td>
<td>4 (4 percent)</td>
</tr>
<tr>
<td>Pernicious vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>3 (2 deaths)</td>
</tr>
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</table>

Tachycardia was made significantly slower. Amiodarone failed in 13 patients, including five who were tested in the electrophysiology laboratory and were deemed failures because their same rapid tachycardia could be easily induced. Eight patients suffered a spontaneous recurrence of their ventricular arrhythmia, of whom six died (one receiving combination therapy; one had the drug stopped by the private physician two months earlier). The two who survived their recurrence were successfully converted to an alternative investigational antiarrhythmic program. Six of the eight patients who suffered a recurrence had electrophysiologic testing. The rate of the recurrent arrhythmia was accurately predicted in four of these six; that is, a slower VT was induced in the two survivors, and a faster VT was induced in two of the four nonsurvivors. Two of the patients who died were not studied, but their monitoring continued to show runs of nonsustained ventricular tachycardia.

Fifty-nine of the 68 patients had at least one side effect with amiodarone therapy. Adverse effects are shown in Table 1 and are divided into the following three categories: nonserious, serious but not precluding drug continuation, and serious for which the drug was discontinued. A total of 100 adverse effects were noted. Eighty-eight (88 percent) of these were nonserious, and included corneal microdeposits, transaminase level elevation, sun sensitivity dermatitis, and a positive antinuclear antibody test. Twelve (12 percent) of the complications were serious but in only four cases was drug withdrawal required. Two of the cases of pulmonary fibrosis led directly to the patients’ deaths from superinfection.

Overall, 11 patients died during the study period, including six who died suddenly, two whose deaths were not sudden but cardiac related, and three noncardiac deaths. Another ten patients were withdrawn for side-effects or for drug inefficiency demonstrated by a nonlethal recurrence or inducible arrhythmia in the electrophysiology laboratory. Figure 2 is an illustration of when drug discontinuation occurred in the course of treatment. Six of the deaths (two sudden) and all of the laboratory failures occurred in the first two months of therapy. One of the patients who failed testing and received an automatic implantable defibrillator remained on the drug and died later of a noncardiac cause. The remaining cases of drug withdrawal were scattered throughout the follow-up period, occurring as late as 52 months after the initiation of therapy.

**DISCUSSION**

Amiodarone was first investigated in South America as an antianginal agent. Although a coronary vasodilator, its antianginal effect was mild, but Rosennbaum et al. noted that it did suppress spontaneous atrial and ventricular ectopic activity. Early clinical investigation in South America and Europe disclosed a
remarkable efficacy rate together with good tolerance, and it was heralded as a “nearly ideal antiarrhythmic agent,” effective for a variety of cardiac arrhythmias. The initial American experience was somewhat disappointing. When used in higher doses and subjected to the rigors of invasive electrophysiologic testing, the drug appeared to have a substantially higher rate of toxicity and more modest efficacy. These differing results might be explainable on the basis of a number of factors. Because of important regulatory issues, American investigators used the drug in patients with more malignant arrhythmia. These patients, who also tend to have more severe heart disease, might also be more susceptible to side-effects that would limit treatment. It could also be argued that, since the drug was investigational, closer clinical surveillance was carried out in the United States, and thus, more cases of drug toxicity were uncovered. However, it would appear even more plausible that the important difference was dose. Investigators outside of the United States consistently used doses in the range of 200 mg daily, while American investigators have used much higher doses. For example, Waxman et al., Greene et al., and Rakita and Sobol used maintenance doses of 400 to 800 mg/day, 600 mg/day, and 500 mg/day, respectively. Conversely, Harris et al., in a retrospective study, used smaller doses (mean 360 mg/day) and reported a much lower incidence of side-effects, including pulmonary fibrosis, serious enough to warrant drug withdrawal. Since a general relationship between dose and toxicity had been constructed, we concluded that use of lower doses might be safer but that the key element was whether lower doses would continue to yield a satisfactory clinical response. We therefore embarked on a prospective study to examine the safety and efficacy of an amiodarone regimen in which a concerted effort was made to use the lowest possible dose of the drug in the maintenance phase.

The patient population studied, their arrhythmia treatment history, and their general medical condition were all similar to the profiles of patients who have received the drug in United States studies. Using an aggressive loading regimen, which in some cases included intravenous administration, standard invasive and noninvasive techniques of drug evaluation, and close clinical follow-up, we had an appreciable efficacy rate, defined by long arrhythmia-free intervals. As noted by other investigators, a beneficial effect of the drug could be defined in a number of ways. Reduction in the amount of ambient arrhythmia in those patients who had only noninvasive testing appeared to auger well. Although rendering the arrhythmia noninducible in the electrophysiology laboratory was a very useful endpoint, it happened rarely. Tachycardia slowing was much more common and usually indicated that the arrhythmia would not recur, but that if it did, the patient would tolerate it. Only two patients had a relatively well-tolerated arrhythmia provoked in the laboratory and subsequently had a sudden death. This occurred despite the fact that downward dose titration was carried out in every patient after hospital discharge.

Many of our patients experienced nonserious, and in most cases, only annoying side-effects. Corneal micro-deposits, transaminase level elevation, and sun sensitivity were ubiquitous complications of therapy, but none of these evolved into more important toxicity. For example, none of our patients developed a blue skin pigmentation, perhaps because we were alerted to this possibility and aggressively counseled them to use sun screens, or specifically because we used a lower dose. More serious complications were much less common, and in most cases, did not lead to withdrawal of the drug. In most cases, the patients responded to institution of appropriate medical therapy, such as thyroid replacement, and amiodarone could be continued. The complication that did cause discontinuation of the drug was pulmonary fibrosis of which we had three cases. Despite immediate cessation of the drug, two of our patients died as a direct result. In both cases, the patients had had a normal interim chest x-ray (in one, performed only two weeks before) and the onset of toxicity was fulminant.

A particularly intriguing finding was the time at which complications developed. Since dosing was uniform, the time at which side-effects developed in our study is directly proportional to the cumulative dose of drug. Some previous studies had suggested that development of toxicity was a function of duration of therapy and that it may correlate with cumulative dose. We observed adverse effects throughout the treatment period, not necessarily later in the course, despite a comparable follow-up period. Whether use of lower doses of amiodarone will be associated with an overall lower incidence of toxicity, or merely delays its inevitable occurrence remains to be defined with more prolonged follow-up studies of low-dose therapy.

The present study incorporated a careful clinical surveillance with frequent outpatient visits during which routine laboratory testing was performed. Pulmonary function tests and amiodarone blood levels were not routinely obtained. Carbon monoxide diffusion capacities have been shown to reflect subtle pulmonary toxicity and may presage the development of overt pulmonary fibrosis. In addition, it could be argued that pulmonary function tests are necessary to detect mild and perhaps transient cases of pulmonary toxicity. However, diffusion capacities can become abnormal in a number of disease states, including congestive heart failure, and transient cases of pulmonary toxicity have a questionable clinical significance. Since amiodarone was prescribed only in patients with
highly resistant cardiac arrhythmia, a subtle change in diffusion capacity, which occurs in many patients receiving the drug, would not constitute sufficient reason to discontinue it. Therefore, given its limited utility, this relatively expensive test was omitted from the laboratory follow-up program. Amiodarone blood levels have very limited use as well. They do not correlate with the development of toxicity, except perhaps neurologic, nor do they provide a useful therapeutic window.\(^29\) A much more meaningful index of biologic effect may be the repolarization time, measured as the QT interval. Two previous studies have, in fact, demonstrated a correlation between clinical effect and QT prolongation.\(^29,30\) We used that measurement as a gross dosing index both to guide our loading program and our long-term downward dose titration and found it to be easy, cheap, and accurate.

There were a number of factors which undoubtedly contributed to our good results and deserve emphasis. First, we were able to use electrophysiology studies in the majority of our patients and used rate slowing as an index of drug effect.\(^22,31\) Those patients who did not manifest rate slowing on initial study, either with amiodarone alone, or with another drug in combination, underwent implantation of an automatic cardioverter/defibrillator. This produces a strong selection bias but provides some information regarding the use of the drug in clinical practice. Second, we made liberal use of type 1 drugs in combination with amiodarone. These agents have been demonstrated to have an effect which is additive to that of amiodarone, and in many cases, provide further slowing of induced tachycardia or render the patient ininducible.\(^14,32\) In a few cases, patients were discharged on an effective combination and returned to the hospital two to three months later for repeat testing on amiodarone alone. In effect, use of a second drug allowed for successful outpatient completion of a long amiodarone loading period. In addition, patients were followed very carefully both by us and by the physicians who referred them to us. Consequently, we were able to detect and manage recurrences and side-effects promptly. Finally, dose titration was carefully supervised, and this may be the most important component of an effective amiodarone treatment program. All of these tactics have been employed by other investigators, and in fact, we were able to draw on their earlier experience and incorporate it into a prospective design which apparently improved the clinical application.

This study has a number of important limitations. Though prospective, in no way was it controlled or blinded. Inclusion of a high dose control group would have allowed for more definitive statements regarding these issues. The information which is currently available regarding dose and toxicity probably proscribes such a study on ethical grounds. The number of patients included in this study is relatively small and the period of follow-up may be inadequate to draw any firm conclusions. Since the drug has been approved in the United States, confirmatory or contradictory information may be forthcoming from larger postmarketing studies. The study group is heterogeneous in terms of arrhythmia diagnosis. However, our population is akin to that receiving the drug in the clinical setting. In addition, important safety information can be derived from all of the groups. We have been careful to segregate efficacy data to permit valid comparisons with previous studies.

In conclusion, low doses of amiodarone appear to be safe and effective when used in a very carefully supervised program which incorporates comprehensive arrhythmia testing and close clinical follow-up. Even under these circumstances, complications are frequent and potentially life-threatening, which justify current restrictions to use in patients with highly resistant and/or life-threatening cardiac arrhythmias.

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