Rapid suppression of complex ventricular arrhythmias with high-dose oral amiodarone

NELSON D. MOSTOW, M.D., THOMAS R. VROBEL, M.D., DEBORAH NOON, AND LOUIS RAKITA, M.D.

ABSTRACT Although amiodarone is effective for the suppression of complex ventricular arrhythmias, a major problem with its use is the long delay between the initiation of therapy and the onset of effective suppression of arrhythmia. To test the hypothesis that rapid loading with oral amiodarone to a target serum concentration can overcome much of this delay, eight patients with refractory, sustained, hemodynamically compromising ventricular arrhythmias and 10 patients with potentially life-threatening ventricular arrhythmias were treated with a flexible, very high dose, oral loading protocol (800 to 2000 mg two to three times a day). Dosage was adjusted on the basis of amiodarone serum concentrations to maintain the trough serum concentrations between 2.0 and 3.0 μg/ml. Comparison of 24 hr Holter electrocardiograms obtained before and during therapy revealed statistically significant reductions in premature ventricular complexes (PVCs) and paired PVCs beginning the first day of therapy and a reduction in ventricular tachycardia (VT) beginning the second day. By day 2, four of eight patients with sustained VT and six of 10 patients with nonsustained VT showed no VT. Pulmonary arterial catheterization during the first 24 hr (mean amiodarone dose 3933 mg) revealed no significant hemodynamic alterations. Minor side effects were common (10 patients) but major side effects were rare (one patient). High-dose oral loading with amiodarone utilizing serum concentration guidelines is a safe and effective method of rapidly controlling life-threatening arrhythmias in selected patients.

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ALTHOUGH the efficacy of amiodarone for suppression of complex ventricular arrhythmias has been well documented,1–5 the long delay between initiation of therapy and the onset of suppression of arrhythmia remains an important problem. With conventional loading regimens, mean delays of 9.5 days have been reported.1 6 In patients with sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), such delays are life threatening. In all patients the wait is potentially dangerous, psychologically draining, and expensive.

The reason for the delay in onset of amiodarone’s antiarrhythmic effect is not known and may relate in part simply to the time required to achieve a “therapeutic” serum concentration.7 The purpose of this study was to explore this possibility by administering oral amiodarone in sufficiently high doses to quickly achieve and then maintain a target serum concentration of 2.0 to 3.0 μg/ml. Suppression of arrhythmia was evaluated by continuous electrocardiography and hemodynamic effects were examined by pulmonary arterial catheterization. The goal of this study was to establish the safety and efficacy of high-dose oral loading of amiodarone using serum concentration guidelines for suppression of sustained VT and complex ventricular ectopy.

Methods

Patients. Eighteen patients referred for therapy with amiodarone were studied. Eight patients had refractory, recurrent, sustained VT or VF requiring cardioversion, defibrillation, and/or short-term pharmacologic intervention for symptoms or signs of hemodynamic compromise. Ten patients who had refractory, asymptomatic, complex ventricular arrhythmias, including nonsustained VT, were considered to be at significant risk of sudden death. No arrhythmias were considered secondary to acute myocardial ischemia. Arrhythmias were considered refractory to standard therapy when they failed to be suppressed by procainamide, quinidine, and disopyramide (used individually) or when these agents were contraindicated because of known or potential side effects. Atherosclerotic coronary artery disease was present in 13 patients and congestive cardiomyopathy was present in five patients. Twelve patients had clinically evident congestive heart failure. None had severe, primary hepatic or renal disease. All patients gave written informed consent.
consent as approved by the Committee on Investigation in Humans.

**Study design.** All patients were studied in the coronary intensive care unit. At initiation of the study, all antiarrhythmic therapy was discontinued for four half-lives and two control 24 hr Holter electrocardiograms (ECGs) were obtained. If symptomatic arrhythmias precluded control recordings while the patients were off all antiarrhythmic therapy, amiodarone was initiated without control recordings. Concurrent antiarrhythmic therapy was administered as clinically indicated for symptomatic arrhythmias.

On the first day of therapy with amiodarone a Swan-Ganz catheter was inserted. After documentation of stable control hemodynamic variables, amiodarone was administered orally according to a flexible protocol (see below). Continuous electrocardiographic recordings were performed for 4 days after the initiation of therapy. Blood sampling was performed frequently during the first 24 hr of therapy to obtain peak and trough serum concentrations after the initial three doses. Blood samples were obtained at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 9, 10, 12, 14, 16, 20, and 24 hr. Thereafter, blood was obtained for analysis of amiodarone serum concentrations immediately before each dose of amiodarone. These were considered trough levels.

**Flexible amiodarone dosage regimen.** An oral regimen was designed to rapidly achieve and then maintain the trough serum amiodarone concentrations between 2.0 and 3.0 μg/ml. To accomplish this, an initial dose of 2000 mg was administered. The first patient received 1400 mg. Subsequent doses were given every 8 hr for the first 2 days and then twice daily. The amount given was based on frequently determined serum concentrations. When the serum concentrations were below the target range, the dose was 1200 mg. When the serum concentrations were 2.0 to 4.0 μg/ml the dose was 800 mg, and when the serum concentrations were above 4.0 μg/ml the dose was 600 mg. For the first 2 days meals were adjusted to allow two of the doses with meals (breakfast and supper) and the third dose was given with a middle-of-the-night snack. The twice daily doses were given with breakfast and supper.

**Data collection.** Electrocardiograms were recorded on Oxford two-channel cassette recorders (Oxford Co., Oxford, England). Cassettes were analyzed on a Marquette Series 8000 Holter Analysis System (Marquette Electronics, Milwaukee).

For validation, 48 half-hour ECG segments comprising the Massachusetts Institute of Technology–Beth Israel Hospital (MIT-BIH) arrhythmia database were analyzed on the Series 8000 system. The counts of premature ventricular complexes (PVCs), paired PVCs, and VT were within 10% of the database counts in 124 of 144 instances (86%). The majority of the discrepancies between counts obtained from the Series 8000 system and the published counts of the MIT-BIH database resulted from differences in classification rather than lack of detection. VT was defined as three or more ventricular ectopic complexes at a frequency greater than 100 beats/min. Serum was analyzed for amiodarone and a metabolite, desethyl amiodarone, by means of a high-pressure liquid chromatographic method developed in our laboratory. The minimum lag time from drawing a sample to reporting the result was approximately 1 hr with a dedicated research facility.

Blood pressure, heart rate, pulmonary capillary pressure, and cardiac output were recorded during the first 24 hr at the same time blood was drawn for determination of amiodarone concentrations. Cardiac output was measured by the thermodilution method and reported as the average of three measurements that varied by less than 10%.

**Statistical analysis.** Data are presented as mean (range) unless indicated. Data were analyzed with BMDP computer programs. Arrhythmia frequencies and the logs of the frequencies expressed as (frequency + 1) were tested for normality by tests for skewness and kurtosis, and their normal probability plots were examined. Repeated measures analysis of variance was performed to test for statistically significant differences in ec- topy and in hemodynamic variables over time. When significant differences were detected, a  t test was used to compare measurements obtained during therapy with control values. The Bonferroni multiple comparisons procedure was used to modify the t statistic to ensure an overall significance level of p < .05. All p values are reported after applying this procedure.

**Results**

**Pharmacokinetics.** The serum concentrations of amiodarone and desethyl amiodarone achieved by the high-dose oral loading protocol are shown in figure 1. The initial dose of 2000 mg resulted in serum concentrations within 20% of the target range by 6 hr in 15 of 18 patients. After the first 24 hr, individual patients' average serum concentrations were within 20% of the target range in all but one patient. Average trough serum concentrations during the 4 day period ranged from 2.08 to 2.80 μg/ml. The serum concentration of desethyl amiodarone increased from 0.29 μg/ml (0.14 to 0.43) on day 1 to 0.67 μg/ml (0.60 to 0.75) on day 4.

The cumulative 24 hr dose required to achieve and maintain the amiodarone serum concentration within the target range on day 1 was 3933 mg (2600 to 4400). The daily dose of amiodarone that was required to maintain the target serum concentration range was progressively lower over the next 3 days: day 2, 2367 mg (800 to 4400); day 3, 1767 mg (800 to 4000); and day 4, 1700 mg (800 to 2400).

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

**FIGURE 1.** Mean amiodarone (circles) and mean desethyl amiodarone (squares) serum concentrations. Oral amiodarone was administered two to three times a day by means of a flexible dosage regimen (see Methods). Dosage was adjusted for each patient based on the amiodarone serum concentration to achieve and maintain the target serum concentration range of 2.0 to 3.0 μg/ml (hatched area). For clarity, standard deviation bars are shown at 8 hr intervals during the first 24 hr.
The average peak amiodarone serum concentration after the initial dose of 2000 mg was 3.22 μg/ml (0.26 to 7.87) and the time to this peak was 5.2 hr (2.0 to 8.0). The peak amiodarone serum concentration after the second dose was 3.91 μg/ml (0.41 to 12.48). The peak after the third dose was 2.84 μg/ml (0.54 to 4.92). The troughs after the first three doses were 2.17 (0.26 to 5.09), 2.35 (0.62 to 5.21), and 2.42 μg/ml (0.43 to 4.04), respectively.

**Arrhythmia suppression.** Daily counts of PVCs (presented as mean per hour), paired PVCs, and VT for the two control tapes and the first 4 days of therapy were not normally distributed (see Methods). The logs of the arrhythmia counts (expressed as log [frequency + 1]) approximated a normal distribution and were used for statistical analysis. For all three arrhythmia categories, there were statistically significant differences among means over time (analysis of variance, p < .0001 for all).

Control recordings were obtained in 15 patients. There were no significant differences in the frequencies of arrhythmias between the two control days (p > .25 for all categories). Compared with each control period, the loading regimen was effective in reducing PVCs, paired PVCs, and VT (figure 2). For all three categories the reduction was progressive with time. The reduction in PVCs and paired PVCs was statistically significant by day 1. The reduction in VT was statistically significant beginning on day 2. The statistical comparisons of control and therapy were performed excluding the four patients who received concurrent therapy for symptomatic arrhythmias either during the control or therapy periods of the study. These analyses were also performed including these cases and the differences between control and therapy were more highly significant. No VT was present on 24 hr ECGs by day 2 in 10 of 18 patients (56%).

Before entering the study, all eight patients with recurrent, sustained, hemodynamically compromising VT or VF required therapy consisting of one or more cardioversions in six patients and short-term intravenous pharmacologic intervention in two patients. After the initiation of therapy with amiodarone, five patients had no sustained VT; two patients had two episodes each of sustained asymptomatic VT that terminated spontaneously, and one patient had several episodes of symptomatic VT requiring multiple cardioversions and concurrent bretylium and overdrive pacing therapy for several days before eventual complete suppression of VT with amiodarone alone.

To examine more precisely the time of onset of arrhythmia suppression, hourly PVC frequencies were examined (figure 3). For each patient, hourly counts of PVCs were expressed as a percentage of the patient’s mean hourly frequency during the 2 day control period. For statistical analysis, each hour of control day 2 and days 1 to 4 of therapy was compared with the same hour of control day 1. No hour of control day 2 was statistically different from the same hour of control day 1. The first hour of therapy that was statistically different from control day 1 was hour 6. Beginning with hour 13, the difference from control day 1 was statis-
typically significant for most hours of days 1 to 4 of therapy.

Hemodynamic and heart rate response. Hemodynamic variables and heart rate during the first 24 hr of therapy with amiodarone are shown in figure 4. There was no significant change in cardiac output (panel A), pulmonary capillary pressure (panel B), or blood pressure (panel C). The heart rate decreased from 82 to 69 beats/min by 16 hr (p < .05) (panel D).

Side effects. Mild side effects were common (table 1), but serious side effects were observed in only one patient who developed profound ataxia and weakness with inability to sit unassisted. These symptoms improved after several days off therapy and continued to improve after reinstitution of amiodarone at lower doses. The minor side effects responded sufficiently to symptomatic therapy so that the protocol could be maintained with minor dosage reductions. Orthostatic hypotension was observed in two patients. In both, it began when bretylium was initiated but persisted on amiodarone alone for 7 days after bretylium was discontinued. There was no correlation of side effects with amiodarone serum concentration (table 1).

Discussion

In this study we report the results of a very high dose, oral amiodarone loading regimen in which a target serum concentration of 2.0 to 3.0 μg/ml was rapidly achieved and then maintained by using frequent determinations of amiodarone serum concentration to guide dosing. The onset of arrhythmia suppression was noted within hours by this approach and by days 1 to 2 statistically significant reductions in the frequencies of PVCs, paired PVCs, and VT were observed. In spite of the large doses of amiodarone used, 3933 mg (2600 to 4400) over the first 24 hr, hemodynamic monitoring revealed no significant change in cardiac output, pulmonary capillary pressure, or blood pressure.

Comparison of amiodarone loading studies (table 2). When amiodarone first underwent investigation in the United States, initial oral dosage regimens of 200 to 800 mg daily were used and the time to suppression of ventricular arrhythmias was 16.9 days. Rakita and Sobol demonstrated that initial doses of 800 to 1400 mg daily could shorten this delay to an average of 9.5 days. A similar delay was noted by Kaski et al. in 23 patients with recurrent sustained VT receiving 600 to 2000 mg of oral amiodarone daily. Although these studies demonstrated more rapid suppression of arrhythmia with doses of up to 2000 mg daily than with doses of 200 to 800 mg daily, serum concentration monitoring was not used and the minimal time to suppression of arrhythmia was not defined.

In patients on long-term amiodarone therapy, improvement of arrhythmias has been associated with serum amiodarone concentrations above 1.0 to 2.0 μg/ml. At initiation of therapy with “loading” regimens of 800 mg of amiodarone daily, several days are required to achieve this level. Thus, regardless of the mechanism responsible for amiodarone’s antiarrhythmic actions (see below), part of the delay in onset of amiodarone’s antiarrhythmic effects in the past may have been due to submaximal loading. Recently, rapid suppression of arrhythmia was reported when intravenous amiodarone was used to treat 11 patients with life-threatening ventricular arrhythmias. The intravenous loading protocol rapidly achieved and then main-

![FIGURE 3. Time course of PVC reduction. For each patient, each hour's count of PVCs was expressed as a percentage of the mean hourly frequency during the 2 day control period. The average percentage of control frequency for all patients with control data is plotted with SD bars shown every 8 hr for clarity. Hours of Control Day 2 and days 1 to 4 of therapy were compared with the same hour of Control Day 1. *p < .05.](http://circ.ahajournals.org/DownloadedFrom/)
FIGURE 4. Hemodynamic and heart rate response during the first 24 hr of amiodarone therapy. Hemodynamic variables and heart rate were measured at the intervals indicated. Data are means with SD bars shown every 4 hr for clarity. Data during therapy were compared with control (t = 0) values. *p < .05. PCP = pulmonary capillary pressure.

Table 1: Side effects during high-dose oral amiodarone loading

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Amiodarone concentration at onset (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Accelerated junctional rhythm</td>
<td>1.92</td>
</tr>
<tr>
<td>Marked QT prolongation (&gt;0.60 sec)</td>
<td>3.13</td>
</tr>
<tr>
<td>Prolonged orthostatic hypotension</td>
<td>2.33, 3.44</td>
</tr>
<tr>
<td>(previously on bretylium)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4.35–3.01</td>
</tr>
<tr>
<td>Profound ataxia and weakness</td>
<td>2.39</td>
</tr>
<tr>
<td>Mild ataxia</td>
<td>2.32, 2.39</td>
</tr>
<tr>
<td>Tremor</td>
<td>1.73–3.44</td>
</tr>
<tr>
<td>Headache</td>
<td>2.56</td>
</tr>
</tbody>
</table>

Table 2: Comparison of amiodarone loading studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to first 24 hr</th>
<th>Daily dose (mg)</th>
<th>ECG with no VT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>1600–4400</td>
<td>800–2000</td>
<td>1000–2300</td>
</tr>
<tr>
<td>Conventional oral loading regimes</td>
<td>3.6</td>
<td>9.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Intravenous loading1</td>
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</table>
Short-term follow-up. The mean number of days to achieve 48 consecutive hours free of VT was 5.6 (1 to 16) and this was used as a major criterion in deciding when arrhythmias were sufficiently controlled to allow hospital discharge. After the first 4 days of therapy the patients were maintained on twice-a-day amiodarone therapy for at least 4 weeks and then once-a-day therapy. All patients were followed with frequent 24 hr ECGs and determinations of amiodarone serum concentration. In most cases, amiodarone doses were rapidly reduced to 400 mg twice a day and then reduced further more gradually. With this approach there were two sudden arrhythmic deaths after discharge within the first 6 weeks of therapy. One of these was a patient being treated for asymptomatic VT and one was a patient being treated for sustained symptomatic VT. In one case, a 24 hr ECG revealed the terminal arrhythmia to be torsades de pointes type VT. In both cases, weekly 24 hr ECGs for the 3 preceding weeks demonstrated adequate control of arrhythmias. For the sustained VT group, this relatively early sudden death frequency of 13% (1/8 patients) is similar to the 9% reported by Kaski et al. and the 12% fatal recurrence rate observed by Morady et al. at a mean of 1.6 months of therapy. Thus the high-dose oral loading protocol described here does not appear to increase the risk of sudden death over conventional loading regimens during the first several weeks of therapy.

Side effects. In spite of the large doses of amiodarone used, 3933 mg (2600 to 4400) over the first 24 hr, there were no significant effects on cardiac output, pulmonary capillary pressure, or blood pressure. Minor toxic effects were common and one instance of serious toxicity was encountered. This toxicity was seen in a 79-year-old man who received amiodarone for recurrent VT. Although technically asymptomatic, he had several runs of VT per minute, up to 30 beats in length, which were associated with a drop in blood pressure. At the time of transfer to our institution he was receiving bretylium. For the first several days of amiodarone therapy the patient was orthostatic and his side effects were unrecognized because he was kept flat in bed. Thus it was not until day 7 of therapy that his cerebellar ataxia was appreciated. The amiodarone was withheld 11 days, during which time his serum concentration fell from 1.67 to 0.53 μg/ml and his ataxia improved, although not to normal. After 11 days off amiodarone, VT recurred on 24 hr ECG and amiodarone was re-started at a reduced dose.

The protracted orthostatic hypotension noted in this and one other patient may have resulted from a drug interaction with bretylium. Three patients had received bretylium immediately before or concurrent with amiodarone. In two, orthostatic hypotension persisted for a week after bretylium was discontinued. Thus amiodarone may have delayed the recovery of vascular sympathetic tone that was initially depressed by bretylium. Because of the side effects encountered, we believe that this study defines the upper limit of serum levels that are likely to be tolerated during short-term oral loading and recommend that such high doses be reserved for patients with immediately life-threatening arrhythmias.

Hemodynamics. To our knowledge, a systematic evaluation of the short-term hemodynamic effects of high-dose oral amiodarone in humans has not previously been reported. Most studies examining the short-term hemodynamic effects of amiodarone have used the intravenous preparation, Cordarone injectable, produced by Labaz. This preparation uses polysorbate 80 as a wetting agent. Gough et al. have shown that polysorbate 80 in the concentrations used in injectable Cordarone possesses negative inotropic effects in dogs. Thus the short-term hemodynamic effects of amiodarone alone remain poorly characterized. Negative inotropic reactions have not been observed with long-term oral amiodarone therapy despite a large international experience in patients with severe left ventricular dysfunction. Our findings indicate that large doses of oral amiodarone can be administered without adverse hemodynamic effects to patients with severe left ventricular dysfunction provided that serum concentrations are maintained in the 2.0 to 3.0 μg/ml range.

Limitations of the study design. The protocol was designed to shorten the lag time between the initiation of therapy with amiodarone and the onset of effective suppression of arrhythmia by administering extremely large doses of oral amiodarone over the first few days of therapy. To protect patients from drug toxicity, a target serum concentration strategy was used to guide dosing. Although the protocol demonstrated that amiodarone can be more rapidly effective than was previously reported, the protocol is impractical because it is time consuming and most physicians do not have amiodarone serum concentrations immediately available. Now that this study has established that up to 4 g of amiodarone can be given over the first 24 hr of therapy, further work can be performed to determine the efficacy and safety of more practical fixed dosing regimens, such as 800 to 2000 mg initially followed by 800 mg two to three times a day.

Theoretical implications. One of the unique features of amiodarone is the reported delay between the initiation
of therapy and the onset of suppression of arrhythmia.\textsuperscript{3, 6} Although this has been attributed to a number of different mechanisms (see below), no study ever documented (with serum concentration monitoring) that the patients had received sufficient amiodarone to be considered adequately “loaded.” Our results provide clear documentation of adequate “loading.” The hastening of the onset of amiodarone’s antiarrhythmic effect by “loading” to a target serum concentration indicates that, in fact, part of the delay in onset reported by previous investigators was attributable to insufficient dosing regimens. However, with maintenance of the target serum concentration, a progressive increase in suppression of arrhythmia was noted over the first 4 days. Thus the data, by documenting serum concentrations, also prove that the mechanism of the pharmacodynamic response includes a component that requires time to “develop” even after the achievement of an adequate serum concentration. The mechanism of this response remains unclear and could relate to the concentration of desethyl amiodarone (which was noted to increase over the first 4 days of therapy), an effect mediated via thyroid hormone pathways, penetration of adequate amounts of amiodarone or desethyl amiodarone into subcellular organelles, or other causes.

In the context of discussing early dosing with amiodarone, the term “loading” has been used to refer to the achievement and maintenance of a target serum concentration. Because there are large tissue stores of amiodarone that may require several weeks to achieve steady state relative to a fixed serum concentration, the patients were not actually loaded in the classical pharmacokinetic sense of having achieved total body steady state. However, the achievement of total body steady state is not necessary to achieve a steady state between the serum concentration and the active site of action of the drug.\textsuperscript{14} For investigation of the relation of serum concentration to effect, it is critical to maintain a steady serum concentration and then to examine the time course of onset of the final effect, which in this case was suppression of arrhythmia.

**Clinical implications.** Although the basic mechanism or mechanisms of amiodarone’s effects have not been defined by this study, the data contained herein demonstrate that the achievement of a target amiodarone level of 2.0 to 3.0 \(\mu\)g/ml results in suppression of arrhythmia within several hours to a few days and that much larger doses of amiodarone than are currently in use are required to achieve this level. For patients with arrhythmias that are immediately life threatening, this more rapid onset of suppression of arrhythmia is of benefit and should result in less reluctance to use the drug. In the clinical setting, where rapid suppression of arrhythmia is required, our data demonstrate that patients can receive very high doses of amiodarone with relative safety. Because we used serum concentration guidelines in this study, it must be added that the safety of such high dosing regimens in the absence of serum concentration monitoring to keep the serum concentrations below 3.0 \(\mu\)g/ml is unknown. Finally, because minor side effects were common, high-dose loading should not be used for all patients requiring amiodarone. When clinical circumstances will allow several days for control of arrhythmias but when the risk of sudden death is still judged to be high enough to justify suppression of arrhythmia with amiodarone, the more widely used regimens of 800 to 2000 mg daily are recommended.

**References**


8. Biomedical Engineering Center for Clinical Instrumentation: MIT-BIH Arrhythmia Database (BMEC TR010). Boston, 1980, Massachusetts Institute of Technology Biomedical Engineering Center for Clinical Instrumentation


15. Rotmensh HH, Belchassen B, Swanson BN, Shoresh D, Spilerman

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