Intravenous Amiodarone for Recurrent Sustained Hypotensive Ventricular Tachyarrhythmias

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Objectives. We sought to determine the response rate and safety of intravenous amiodarone in patients with ventricular tachyarrhythmias refractory to standard therapies.

Background. Numerous small retrospective reports suggest a response of refractory ventricular tachyarrhythmias to intravenous amiodarone, yet no controlled prospective trials exist.

Methods. Two hundred seventy-three patients with recurrent hypotensive ventricular tachyarrhythmias refractory to lidocaine, procainamide and bretylium were randomized to receive one of three doses of intravenous amiodarone: 525, 1,050 or 2,100 mg/24 h (mean [±SE] dose 743.7 ± 418.7, 1,175.2 ± 483.7, 1,921.2 ± 688.8 mg, respectively) by continuous infusion over 24 h.

Results. Of the 273 patients, 110 (40.3% response rate) survived 24 h without another hypotensive ventricular tachyarrhythmic event while being treated with intravenous amiodarone as a single agent (primary end point). A significant difference in the time to first recurrence of ventricular tachyarrhythmia (post hoc analysis) over the first 12 h was observed when the combined 1,050- and 2,100-mg dose groups were compared with the 525-mg dose group (p = 0.046). The number of supplemental (150 mg) infusions of intravenous amiodarone (given for breakthrough destabilizing tachyarrhythmias) during hours 0 to 6 (prespecified secondary end point) was significantly greater in the 525-mg dose group than in the 2,100-mg dose group (1.09 ± 1.57 vs. 0.51 ± 0.97, p = 0.0043). However, there was no clear dose-response relation observed in this trial with respect to success rates (primary end point), time to first recurrence of tachyarrhythmia (post hoc analysis) or mortality (secondary end point) over 24 h.

Conclusions. Intravenous amiodarone is a relatively safe therapy for ventricular tachyarrhythmias refractory to other medications.

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Amiodarone is associated with a significant antiarrhythmic effect, even in patients with refractory ventricular arrhythmias (1–5). Because it has a relatively slow onset of action when administered orally, maximal effect is not reached until 2 to 4 weeks after the initiation of therapy despite aggressive oral loading (6). In contrast, intravenous administration has a rapid antiarrhythmic effect in patients with recurrent, sustained ventricular tachyarrhythmias (7–11).

Previously published reports of intravenous amiodarone have been either retrospective reviews or the results of uncontrolled studies with relatively small numbers of patients who were often treated concomitantly with other antiarrhythmic medications. Therefore, the present prospective, controlled, randomized, double-blind, dose-range study was undertaken to determine definitively the response to intravenous amiodarone (Cordarone Intravenous, Wyeth-Ayerst Research, Radnor, Pennsylvania) in patients with life-threatening ventricular arrhythmias.

Methods

Patient selection. A total of 273 patients with sustained hypotensive ventricular tachycardia or fibrillation refractory to standard therapy were enrolled in this study at 39 medical centers in the United States. *Hypotensive ventricular tachycardia* was defined as ventricular tachycardia causing systolic blood pressure to decrease <80 mm Hg with clinical signs or

Table 1. Baseline Clinical Characteristics

	Amiodarone Dose Group			
	500 mg (n = 88)	1,000 mg (n = 92)	2,000 mg (n = 93)	Total (n = 273)
Male	61 (69)	67 (73)	70 (75)	198 (73)
Female	27 (31)	25 (27)	23 (25)	75 (27)
Age (yr)	63 ± 10	63 ± 12	63 ± 11	63 ± 11
LVEF (%)	33 ± 14	31 ± 12	33 ± 16	32 ± 14
NYHA functional class				
I/II	29 (45)	29 (42)	30 (46)	88 (44)
III	17 (27)	16 (23)	17 (26)	50 (25)
IV	18 (28)	24 (35)	18 (28)	60 (30)
Presenting arrhythmia				
VF	6 (7)	4 (4)	5 (5)	15 (5)
Incessant VT	22 (25)	32 (35)	27 (29)	81 (30)
HDVT	60 (68)	56 (61)	61 (66)	177 (65)
Cardiac substrate*				
Coronary disease	78 (89)	78 (85)	80 (86)	236 (86)
Cardiomyopathy	15 (20)	24 (27)	23 (25)	62 (23)
Valvular disease	25 (28)	26 (28)	31 (33)	82 (30)

*Some patients had more than one cardiac diagnosis. Data presented are mean value ± SD or number (%) of patients. HDVT = hemodynamically destabilizing ventricular tachycardia; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2. Double-Blind Dosage Regimen

Amiodarone Dose Group and Infusion Period	Infusion Rate
500 mg/24 h	
Initial rapid	75 mg over 10 min
Loading	0.50 mg/min (0–6 h)
Maintenance	0.25 mg/min (6–24 h)
1,000 mg/24 h	
Initial rapid	150 mg over 10 min
Loading	1.0 mg/min (0–6 h)
Maintenance	0.5 mg/min (6–24 h)
2,000 mg/24 h	
Initial rapid	300 mg over 10 min
Loading	2.0 mg/min (0–6 h)
Maintenance	1.0 mg/min (6–24 h)

symptoms of shock. The baseline and demographic characteristics of these patients are summarized in Table 1. There were no significant differences in any variable among dose groups at baseline. All patients had at least two episodes (mean 5.9) of hypotensive ventricular tachyarrhythmias in the 24 h before admission or were in incessant ventricular tachycardia, despite attempts at cardioversion. Cardioversion was required to terminate these events in >80% of the episodes; 15% required cardiopulmonary resuscitation; 51% resulted in loss of consciousness.

All patients included were refractory to (therapy failed, with breakthrough ventricular tachyarrhythmias) or intolerant of (limited by side effects) the standard doses of lidocaine (or oral mexiletine or tocainide), intravenous or oral procainamide and bretylium within the 72 h before blinded intravenous amiodarone administration was instituted. Patients were excluded if they were in cardiogenic shock (unrelated to their arrhythmia) or had significant hepatic dysfunction, chronic pulmonary disease, acute pulmonary edema or respiratory failure. Patients were also excluded if they had a history of torsade de pointes, congenital QT prolongation, sick sinus syndrome, sinus arrest, symptomatic bradycardia, sinoatrial block or second-degree or higher atrioventricular block (unless they had a pacemaker). All patients had systolic blood pressure >90 mm Hg (except during ventricular tachycardia or fibrillation), heart rate >50 beats/min, QT interval <0.55 s and arterial pH >7.25.

Institutional review board approval was obtained, and all patients gave written informed consent when possible; a waiver of informed consent was obtained before the study for patients who were unable to provide consent.

Study protocol. Patients were treated in areas with facilities for continuous monitoring and administration of advanced cardiac life support. Because a placebo treatment group was deemed by the investigators to be unethical, a dose-response study comparing three blinded dose regimens of intravenous amiodarone was instituted. Patients were randomly assigned to a dose regimen that delivered 525, 1,050 or 2,100 mg over 24 h. For convenience of expression, these dose regimens will be referred to subsequently as the 500-, 1,000- and 2,000-mg dose groups.

As shown in Table 2, each patient received an initial rapid infusion over 10 min, followed by a 6-h loading infusion and then a maintenance infusion from hours 6 to 24 of the study. Additional open-label supplemental infusions (150 mg over 10 min) of intravenous amiodarone were permitted for the treatment of breakthrough episodes of hypotensive ventricular tachycardia or fibrillation during the loading infusion (hours 0 to 6). *Breakthrough arrhythmia* was defined as an episode of hypotensive ventricular tachycardia or fibrillation requiring intervention. Therapy was considered a failure in patients with hypotensive ventricular tachycardia or fibrillation after hour 6. Blinded therapy was therefore discontinued.

During double-blind intravenous amiodarone therapy, the use of other antiarrhythmic medications for treatment of ventricular arrhythmias was not permitted; other concomitant drug therapies were allowed. After discontinuation of blinded therapy, open-label intravenous amiodarone therapy (including the additional 150-mg supplemental infusions) or other antiarrhythmic therapy could be instituted at the investigator's discretion.

Assessment of response to intravenous amiodarone. The primary end point was the proportion of patients who survived with a successful response defined as no further episodes of hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation and no adverse experiences requiring discontinuation of the drug during hours 6 to 24 of the double-blind period (Fig. 1). Secondary analyses of response during the 24-h double-blind phase included survival during the first 24 h, successful therapy as a function of left ventricular ejection fraction and as a function of underlying cardiac disease process

Figure 1. Study flowchart. Patients were randomly assigned to one of three doses of intravenous amiodarone. HDVT = hemodynamically destabilizing ventricular tachycardia; VF = ventricular fibrillation.
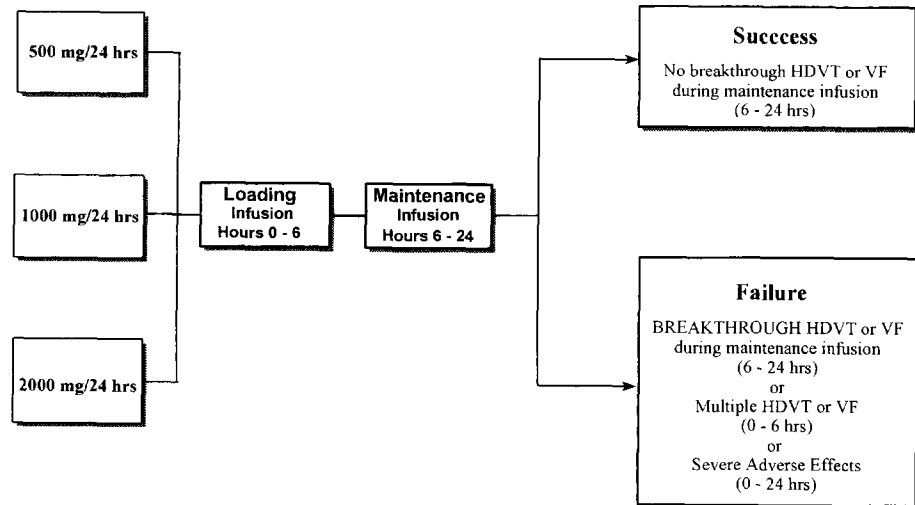
as well as the number of additional boluses of intravenous amiodarone given during the first 6 h. Other analyses, added post hoc after completion of enrollment, were time to first hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation event and cumulative dose (total, double-blind and supplemental doses). Other post hoc analyses included number of supplemental boluses given in the first 24 h, time to first event, proportion of patients requiring supplemental infusions and dose of supplemental infusions. Proarrhythmia, as defined by torsade de pointes or spontaneous new ventricular fibrillation, and breakthrough sustained hypotensive ventricular tachycardia/fibrillation were considered primary end points for failure of therapy. The primary and secondary end points were defined at the start of the study, whereas other analyses were added on an ad hoc basis after completion of the protocol patient entry phase.

Safety assessments. Cardiac examinations were performed daily for 10 days, at week 2 and at months 1, 2 and 3. Continuous electrocardiographic (ECG) telemetry was used during intravenous amiodarone therapy. Systolic blood pressure and heart rate measurements were obtained every 15 min to hour 6, every hour during hours 6 to 24 and then every 4 h during subsequent intravenous therapy. Adverse effects were recorded throughout the study. Because of the difficulty of determining whether recurrent intractable ventricular tachycardia or fibrillation represents a lack of response or proarrhythmia in these patients, many of whom were referred for enrollment under emergent circumstances, proarrhythmia was prospectively defined as episodes of torsade de pointes or spontaneous new-onset ventricular fibrillation (excluding ventricular tachycardia that degenerated into ventricular fibrillation). Clinical laboratory tests were evaluated at hour 24; on days 3, 5, 7 and 10; at week 2; and at months 1, 2 and 3. These tests included complete blood counts, serum chemical analyses with liver, renal, and thyroid profiles and electrolyte levels. A 12-lead ECG was recorded at hours 6, 12 and 24; on days 2, 3, 5, 7 and 10; at week 2; and at months 1, 2 and 3.

Statistical methods. Once assigned to a treatment group, patients were included in the intention-to-treat analysis. The double-blind period started at the first administration of amiodarone.

The overall response rate, the primary end point, was analyzed in patients who completed the loading infusion (hours 0 to 6). Only hypotensive ventricular tachycardia or fibrillation event data collected after the loading infusion were analyzed. Treatment was considered ineffective in patients with one or more episodes of hypotensive ventricular tachycardia or fibrillation during hours 6 to 24 or those not completing the full 24-h double-blind period. In the present analysis, treatment was not considered a failure in any patient who had recurrent arrhythmias, died or was withdrawn during the loading infusion; rather, these patients were considered ineligible for the response analysis. Treatment was also considered a failure in patients withdrawn from the trial before hour 6.

Although not protocol specified, the time to first hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation event was analyzed in all patients who completed the initial infusion, regardless of whether they completed the entire 24-h double-blind period. In most cases, this time was calculated from the end of the initial infusion (minute 10). Events that occurred before the initial infusion was completed were excluded from analysis unless the event overlapped the end of the infusion; in these cases, the time to first hypotensive tachyarrhythmic event was calculated from the end of that event.

Initially, either an overall test of differences among treatment groups or a linear trend test was performed for each variable. All tests were two-tailed and performed at the 0.05 level of significance. The results of the paired comparisons were considered descriptive statistics not requiring correction for multiplicity and were displayed only for tests resulting in a strong tendency (p < 0.10).

The proportion of patients with successful response was

Table 3. Response to Therapy by Dose Group

End Point	Amiodarone Dose Group				
	500 mg (n = 86)	1,000 mg (n = 92)	2,000 mg (n = 92)	Combined 1,000 and 2,000 mg (n = 184)	p Value (log-rank test)
No. of pts with successful response	78	80	79		
6–24 h [no. (%)]	32 (41%)	36 (45%)	42 (53%)		0.298
Median time to 1st event					
0–24 h	4.8	14.6	10.5	14.6	0.305,* 0.134†
0–12 h	4.8			>12	0.046

*500 mg versus 1,000 mg versus 2,000 mg. †500 mg versus 1,000 and 2,000 mg combined. pts = patients.

analyzed by the chi-square test to examine differences among dose groups. In addition, a test for trend (Mantel-Haenszel chi-square statistic) was done to determine whether there was a linear dose-response relation.

The Cochran-Mantel-Haenszel procedure was used to test for an association between the dose groups and the dose-response after adjusting for the influence of several prognostic variables. These variables included underlying cardiac disease, presenting arrhythmia and degree of left ventricular ejection fraction.

The log-rank test was used to test for trends across dose groups for the time to first hypotensive ventricular tachycardia or fibrillation event and for survival time. Hourly summaries of the product-limit (Kaplan-Meier) survival estimates were used to represent these data graphically. The log-rank test and product-limit survival estimates censored patients who withdrew before hour 24 or who completed 24 h without an event.

Analysis of variance was used to test for differences among dose groups in cumulative total dose, cumulative double-blind dose and cumulative supplemental intravenous boluses. Dose data were log(x + 1) transformed before analysis.

Results

One hundred ten (46%) of the 237 patients who completed the 6-h loading infusion survived the 6- to 24-h maintenance period without a recurrence of hypotensive ventricular tachycardia or fibrillation when intravenous amiodarone was used as a single agent. Another 29 patients (12%) responded to intravenous amiodarone in combination with another agent. A total of 36 patients (15%) were withdrawn from blinded intravenous amiodarone therapy during the first 6 h; 17 (7%) died; 14 (6%) were withdrawn due to adverse effects; and 5 (2%) were withdrawn because of intractable ventricular tachyarrhythmias. Of those patients whose arrhythmias were not controlled by intravenous amiodarone in the 6- to 24-h time frame, 14 (5%) died and 7 (3%) were withdrawn from therapy because of adverse effects.

Dose-response. There was a numerical trend observed in the primary end point response rate, with increased response at higher doses (41%, 45% and 53% for the low, medium and high dose groups, respectively). However, this numerical trend

did not reach statistical significance (p = 0.298). The results of this analysis are shown in Table 3.

As with the overall response rate, there was no dose-response in the time to first ventricular tachycardia or fibrillation event for the 24-h double-blind period. The analysis of time to first event showed that after hour 2, there was a separation between the 500-mg dose group and the two higher dose groups. This separation continued to increase and reached maximal separation by hour 12 (Fig. 2). The overall test for a dose-related trend among the three dose groups was not statistically significant (p = 0.305). However, there was a significant dose-response in time to first event during the first 12-h period but not at 24 h (post hoc analysis) between the 500-mg and the combined 1,000- and 2,000-mg dose group (median time 4.8 h vs. >12 h, respectively, p = 0.046). These data are shown in Figure 3 and summarized in Table 3.

A three-dimensional scatter plot of the time of next hypotensive ventricular tachycardia or fibrillation event as a function of time and cumulative dose of intravenous amiodarone (loading plus maintenance plus supplemental infusions) is shown in Figure 4. At earlier time periods and at lower cumulative doses (near the lower right portion of the plot) there was a shorter median time of next event. Longer times to recurrence were noted during the first 12 to 16 h with higher cumulative amiodarone doses and at higher infusion rates. After that, the time of next event is largely independent of cumulative intravenous amiodarone dose or time on therapy, irrespective of dosing regimen.

The assessment by an investigator of the overall condition of the patient vis-à-vis arrhythmia is a pertinent measure of overall response. That is, not every episode of ventricular tachycardia has the same clinical significance. The physician is subjectively able to synthesize a multitude of factors to determine the clinical significance of a breakthrough arrhythmia. The rate and frequency of the breakthrough tachycardia events and the patient's ability to tolerate the episode must be factored into the determination of clinical significance. A quantitative measure of this determination is the number of supplemental infusions given by the investigator (who had no knowledge of the patient's assigned dose regimen) to treat breakthrough episodes of ventricular tachycardia or fibrillation.
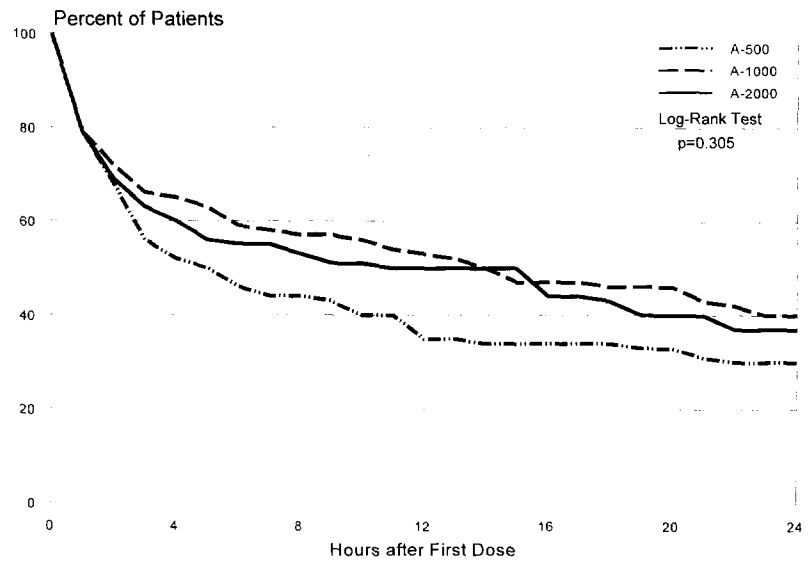
Figure 2. Hourly Kaplan-Meier estimates of the percent of patients remaining event free. A = amiodarone.

The number of supplemental infusions administered during the loading period (hours 0 to 6), when investigators were free to administer these supplemental infusions without considering treatment ineffective, was analyzed (Table 4). A significantly greater number of supplemental infusions of intravenous amiodarone (prespecified secondary end point) were administered during the loading period in the 500-mg dose group than in the 2,000-mg dose group ([mean ± SE] 1.09 ± 1.57 vs. 0.51 ± 0.97, p = 0.004), suggesting a dose-response relation. These results hold true even after correcting for varying lengths of time of therapy because of patient dropout by calculating the number of supplemental infusions administered per hour; again, the 500-mg dose group received a significantly greater number of boluses than the 2000-mg dose group (p = 0.011). Similarly, the total amiodarone dose

administered during the entire 24-h period as open-label supplemental infusions (post hoc analysis) was greater in the 500-mg dose group than in the 2,000-mg dose group (264.0 ± 553.0 vs. 168.1 ± 242.7 mg, p = 0.066). Finally, the proportion of patients requiring supplemental infusions during the loading period (post hoc analysis) was significantly greater in the 500-mg dose group than in the 2,000-mg group (47% vs. 29%, p = 0.013).

Relation of other factors to success of intravenous amiodarone therapy. The patient's response to intravenous amiodarone might have been related to the etiology of the heart disease and left ventricular dysfunction (predefined secondary end point). However, the presence or absence of underlying cardiac disease, including coronary artery disease, cardiomyopathy or valvular disease, was not predictive of outcome. The
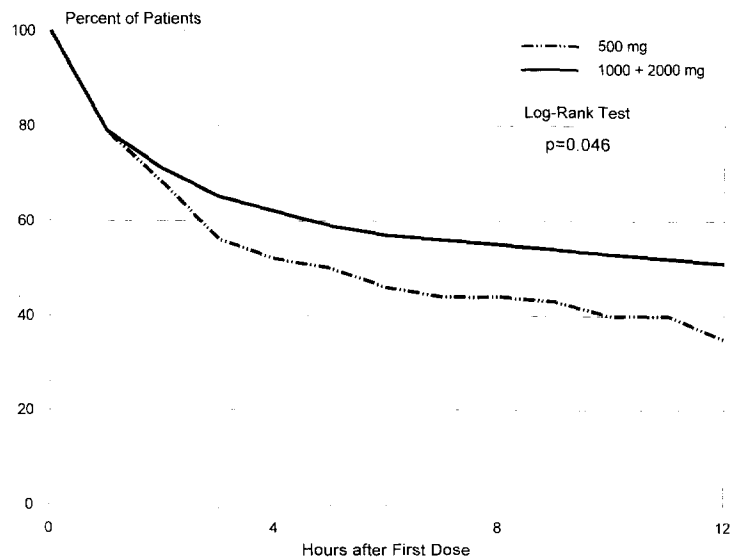

Figure 3. Hourly Kaplan-Meier estimates of cumulative percent of patients remaining event free during the first 12 h after initiation of intravenous amiodarone.
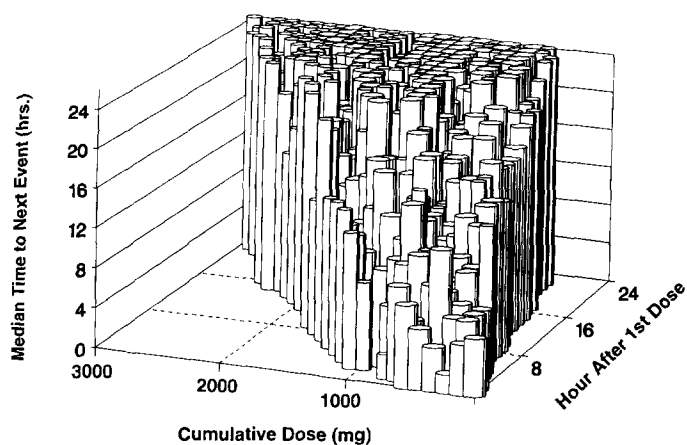
Figure 4. Three-dimensional scatterplot of median time to next ventricular tachycardia or ventricular fibrillation event (z axis) as a function of time (y axis) and cumulative dose of intravenous amiodarone (x axis). Note that **pillar** height is proportional to number of patients with data at each time period analyzed.

type of presenting arrhythmia (hypotensive ventricular tachycardia, ventricular fibrillation or incessant ventricular tachycardia) or the severity of left ventricular dysfunction had no significant influence on the results of the primary efficacy end point analysis.

Safety. Amiodarone-related adverse effects occurred in 105 patients (38%). The most commonly reported events are summarized in Table 5. The frequency of adverse effects was similar across dose groups. Hypotension, the most common adverse experience, required vasopressor therapy in 38 patients (14%) and led to death in 6 (2%). Bradycardia required temporary pacing in only two patients. The incidence of abnormal liver function tests did not increase with higher doses (2 of 88 patients at the 500-mg dose, 4 of 92 patients at the 1,000-mg dose, 3 of 93 patients at the 2,000-mg dose, p = 0.495).

Six patients (2%) developed proarrhythmia defined as new-onset ventricular fibrillation (two patients) or torsade de pointes (4 patients). Additional exacerbating factors were reported in all six patients, such as acute ischemia or electrolyte imbalances. Four of the six patients were assigned to the 500-mg dose group, one to the 1,000-mg dose group and one to the 2,000-mg dose group. Thirteen patients (5%) had a signif-

icant increase in corrected QT (QTc) intervals (>0.55 s), and 38 (14%) had QTc increases $\geq$25% from baseline. However, increases in QTc intervals were not dose related, and no patient with an increased QTc interval experienced proarrhythmia.

Overall, congestive heart failure was reported in 48 patients (18%): It was preexisting in 39 and new onset in 9. During intravenous amiodarone administration, severe, uncompensated congestive heart failure was observed in five patients: one in the 500-mg group and two each in the 1,000- and 2,000-mg dose groups. Seventeen patients (6%) died of congestive heart failure during the 90-day study, although in only three of these patients was the heart failure of new onset.

Mortality. The entry criteria for the present study required patients to have recurrent, sustained, hypotensive ventricular tachycardia or fibrillation refractory to standard intravenous antiarrhythmic agents. Additionally, many patients were in debilitated condition, and their ventricular tachyarrhythmias were manifestations of other life-threatening, sometimes terminal, cardiac and noncardiac disease. Therefore, the mortality rate in this trial was high; 52% of patients (n = 143) died during the overall 90-day study. Table 6 shows the number of deaths by dose group and time period. Within each time

Table 4. Mean ($\pm$SE) Cumulative Dose by Therapy Group

| End Point | Dose Group | | | p Value* | | | |
| | 500 mg (n = 87) | 1,000 mg (n = 92) | 2,000 mg (n = 92) | Overall† | Paired | | |
					L vs. M	L vs. H	M vs. H
Double-blind dose	477.6 ± 160.8	911.9 ± 283.0	1,753.1 ± 645.2	0.0001	0.0001	0.0001	0.0001
No. of supplemental infusions, 0 to 6 h	1.09 ± 1.57	0.88 ± 1.38	0.51 ± 0.97	0.0151	0.2829	0.0043	0.0689
Supplemental infusion dose							
0–6 h	156.6 ± 232.2	130.1 ± 203.3	76.6 ± 146.7	0.0366	0.3623	0.0114	0.0987
0–24 h	264.0 ± 353.0	263.3 ± 368.0	168.1 ± 242.7	0.1312	0.8146	0.0662	0.104
Supplemental infusions/h, 0–6 h	0.24 ± 0.43	0.18 ± 0.31	0.15 ± 0.52	0.0111	0.2604	0.0031	0.061
Total dose	741.9 ± 419.2	1,175.2 ± 483.7	1,921.2 ± 688.8	0.0001	0.0001	0.0001	0.0001
No. (%) of pts requiring supplemental infusions	41/87 (47%)	37/92 (40%)	27/93 (29%)	0.042	0.369	0.014	0.124

*Analysis of variance (rank transformed). †Chi-square statistic. H = high dose group (2,000 mg); L = low dose group (500 mg); M = medium dose group (1,000 mg); pts = patients.

Table 5. Emergent Drug-Related Adverse Events

| | Amiodarone Dose Group | | | |
Adverse Event	500 mg (n = 88)	1,000 mg (n = 92)	2,000 mg (n = 93)	Total (n = 273)
Cardiovascular				
Hypotension	15 (17)	9 (10)	16 (17)	40 (15)
Bradycardia	5 (6)	3 (3)	6 (6)	14 (5)
EMD/asystole	5 (6)	3 (3)	4 (4)	12 (4)
Proarrhythmia	4 (5)	1 (1)	1 (1)	6 (2)
Congestive heart failure	1 (1)	2 (2)	2 (2)	5 (2)
Shock	1 (1)	1 (1)	1 (1)	3 (1)
Noncardiovascular				
Nausea	7 (8)	1 (1)	3 (3)	11 (4)
Abnormal liver function tests	2 (2)	4 (4)	3 (3)	9 (3)
Fever	1 (1)	2 (2)	4 (4)	7 (3)
Increased SGPT	0 (0)	0 (0)	6 (6)	6 (2)
Vomiting	2 (2)	2 (2)	2 (2)	6 (2)

EMD = electromechanical dissociation; SGPT = serum glutamic pyruvic transaminase. Data presented are number (%) of patients.

period, the death rate did not differ significantly among the groups. Table 7 shows the most commonly reported causes of death. There were no significant differences among the dose groups in either number of deaths at any time period or in the primary causes of death.

Discussion

Overall, intravenous amiodarone use was associated with apparent antiarrhythmic response in ~40% of patients meeting study entry requirements (primary end point). The present study failed to demonstrate a dose-response to intravenous amiodarone with respect to the proportion of patients who survived with a successful response, defined as no further episodes of ventricular tachycardia or fibrillation (primary end point) and no adverse drug effects during hours 6 to 24, or with respect to mortality. However, some of the objective and subjective quantitative measures of clinical response did demonstrate a statistically significant dose-response to intravenous amiodarone.

Table 6. Mortality by Dose Group and Time Period

| | No. (%) of Deaths/Dose Group | | | |
Time Period	500 mg (n = 88)	1,000 mg (n = 92)	2,000 mg (n = 93)	p Value (log-rank test)
Hour 24	16 (18)	17 (18)	14 (15)	0.894
Double blind	11 (13)	11 (12)	9 (10)	
Open label	5 (6)	6 (7)	7 (8)	
Hour 48	18 (20)	19 (21)	20 (22)	
Day 5	27 (31)	29 (32)	32 (34)	
Day 10	30 (34)	32 (35)	32 (34)	
Day 20	35 (40)	35 (38)	37 (40)	
Day 30	37 (42)	36 (39)	44 (47)	
Total (>day 90)	43 (49)	46 (50)	54 (58)	0.406

Table 7. Primary Causes of Death by Dose Group

| | Dose Groups | | | |
Primary Causes of Death	500 mg (n = 88)	1,000 mg (n = 92)	2,000 mg (n = 93)	Total (n = 273)
All deaths	43 (48)	46 (50)	54 (58)	143 (52)
Cardiovascular events				
Refractory HDVT/VF	17 (19)	20 (22)	22 (24)	59 (22)
Cardiogenic shock	2 (2)	9 (10)	6 (6)	17 (6)
Cardiac arrest	6 (7)	0 (0)	3 (3)	9 (3)
Asystole	2 (2)	1 (1)	4 (4)	7 (3)
Cardiac failure	1 (1)	4 (4)	1 (1)	6 (2)
Congestive heart failure	2 (2)	2 (2)	2 (2)	6 (2)
EMD	3 (3)	0 (0)	1 (1)	4 (1)
Complete heart block	1 (1)	0 (0)	1 (1)	2 (1)
Myocardial infarction	2 (2)	0 (0)	0 (0)	2 (1)
Sudden cardiac death	1 (1)	1 (1)	0 (0)	2 (1)
Noncardiovascular events				
Sepsis	3 (3)	3 (3)	5 (5)	11 (4)
Multiple organ failure	0 (0)	3 (3)	1 (1)	4 (1)
Respiratory failure	2 (1)	0 (0)	1 (1)	3 (1)

Data presented are number (%) of patients. Abbreviations as in Tables 1 and 5.

One hundred ten (46%) of 237 patients who completed the 6-h loading infusion responded to intravenous amiodarone after therapy with lidocaine, procainamide and bretylium failed. This result is consistent with reports of others (6–9,11) in which 50% to 100% of patients responded to intravenous amiodarone. Our results are therefore consistent with those of others in this regard. Furthermore, to our knowledge, our results represent the largest series of patients studied in a prospective manner.

Both subjective and objective measures of response were evaluated. The subjective finding by the investigators of a positive effect of intravenous amiodarone on suppression of hypotensive sustained ventricular tachyarrhythmias was quantified by recording the number of supplemental boluses of intravenous amiodarone that a patient received (prespecified secondary end point). Patients were only to receive additional intravenous amiodarone if they had a breakthrough event; yet these boluses were not required for every breakthrough event. Rather, the boluses were given at the discretion of the investigator who had no knowledge of infusion rate and dose group. The decision was a clinical one based on the characteristics and frequency of the recurrent events, as well as on the stability of the patient's condition. Those patients in the 1,000- and 2,000-mg dose groups received significantly fewer supplemental boluses than those in the 500-mg dose group, suggesting a positive effect of the higher doses on suppression of the most clinically significant hypotensive sustained ventricular tachyarrhythmia episodes (Table 4).

There was also a suggestion that the time to next event (post hoc analysis) was related to cumulative amiodarone dose. As shown in Figure 4, there was both a dose- and time-dependent relation suggested between intravenous amiodarone administration and time to next event. However, these

data could not be analyzed statistically because of varying sampling frequency among patients. Nonetheless, it appears that with increasing dose at any time or with increasing time at any dose (Fig. 4, lower right portion), there is an increased time to next ventricular tachycardia or fibrillation event, which was most apparent during the first 12 h.

There were trends among treatment groups in the dose-response tendencies in the time to first ventricular tachycardia or fibrillation events. In the scatterplot of Figure 4, relating time to next event to cumulative time and dose, most of the cumulative drug effect was observed in the first 12 h, and when the first 12 h of therapy were considered, patients receiving the 1,000- and 2,000-mg dose of intravenous amiodarone had a longer time to first event (p = 0.046) than those receiving the 500-mg dose (Fig. 3).

The mortality rate of the present group of patients was high, as was expected. There was no relation between mortality and dose regimen of intravenous amiodarone. Because of ethical reasons, no placebo control was used, and supplemental boluses were allowed. Because more patients in the low dose group received boluses than those in the high dose group, actual differences in delivered intravenous amiodarone were smaller. In addition, the lack of a dose-response may have been the result of the very ill but heterogeneous nature of the patients studied. That is, in some patients the ventricular arrhythmia was situational rather than the result of severe end-stage cardiac disease. In these patients, control of the ventricular arrhythmia led to survival; in others, however, the arrhythmia was the final common pathway of a failing heart, and death occurred even with arrhythmia control. The study was not designed to control for these or other factors with respect to mortality analysis.

In addition, we cannot exclude the possibility that some of the deaths were due to proarrhythmia. In some cases, refractory tachyarrhythmias could have resulted from the amiodarone, whereas in others, they could have been consistent with the natural history of the patient. Thus, proarrhythmia was defined as new polymorphic ventricular tachyarrhythmias (torsade de pointes or ventricular fibrillation), but it is acknowledged that the true proarrhythmia rate may have been underestimated. This underestimation may have also contributed to the lack of dose-response in the mortality data.

There were no significant differences among treatment groups in the overall time to death. However, we do believe that intravenous amiodarone may have had a favorable effect in these patients. The patients enrolled in the present study had immediately life-threatening ventricular tachyarrhythmias that were refractory to all available drug therapies. Without successful therapy, the death rate in patients as ill as these would most likely have been much higher than the 24-h incidence of 18% found in the present study.

Study limitations. The borderline significance of the dose-response in the time to first hypotensive ventricular tachycardia or fibrillation event for the 24-h double-blind period (p = 0.1339) may have been the result of the small sample size in the study. The sample size required to detect a statistically signif-

icant difference (p = 0.05) between the 500- and 2,000-mg dose groups can be estimated on the basis of the proportion of patients who at least completed the loading infusion and who had a successful response from the end of the loading infusion to the end of the double-blind period. Thirty-two (41%) of 78 patients in the 500-mg dose group, 36 (45%) of 80 in the 1,000-mg dose group and 42 (53%) of 79 in the 2,000-mg dose group met these criteria. Using these observations, a sample size of 367 patients would have been required to observe a difference between groups, assuming a power of 90%. Thus, our sample size of 273 patients was insufficient. If additional patients had been enrolled, the nearly significant dose-response relation noted may have reached statistical significance.

The lack of a systematic dose-response relation is also consistent with similar benefit or lack of benefit in all three groups. The trends as well as the significant findings in the secondary end points and post hoc analyses (e.g., number of boluses given and time to first event in the first 12 h) suggest that there is a dose-response to amiodarone but that the study was limited by sample size.

The present study has other limitations: 1) We were unable to perform subset analyses within different diagnostic groups (e.g., types of coronary artery disease and cardiomyopathy); and 2) the lack of a control group precludes the interpretation of findings in terms of the true efficacy or in quantification of a success rate. Nonetheless, the favorable response to the drug is strongly suggested by our data.

Summary. Intravenous amiodarone use in patients with recurrent, refractory, hypotensive ventricular tachyarrhythmias is relatively safe and may be associated with a decrease in expected mortality in these critically ill patients. Measures of drug response, as quantified by the number of supplemental intravenous amiodarone boluses given in blinded manner, did demonstrate a statistically significant dose-response relation. There was a significant dose-response relation between the 500-mg dose group and the combined 1,000- and 2,000-mg dose groups in the time to first event when the first 12 h were considered (p = 0.046). However, there was no significant dose-response relation in time to first event over 24 h or in overall mortality, perhaps because of the insufficient sample size of the study or the relative insensitivity of these end points in measuring drug effect in this critically ill cohort. Larger studies using lower doses of amiodarone will be required to further demonstrate the dose-response relation needed to prove drug efficacy.

Appendix

Amiodarone Intravenous Multicenter Trial Group: List of Principal Investigators

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