

Intravenous Lidocaine Versus Intravenous Amiodarone (in a New Aqueous Formulation) for Incessant Ventricular Tachycardia

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The effectiveness of intravenous amiodarone for the treatment of incessant (shock resistant) ventricular tachycardia (VT) has not been established. This study evaluated the efficacy of a water-soluble amiodarone preparation or lidocaine for the treatment of shock-resistant VT. The trial was a double-blinded parallel design. Patients were randomized to receive up to 2 boluses of either 150 mg intravenous amiodarone or 2 boluses of 100 mg lidocaine followed by a 24-hour infusion. If the first assigned medication failed to terminate VT, the patient was crossed over to the alternative therapy. Twenty-nine patients were randomized to the study (18 received amiodarone and 11 received lidocaine). There were no significant differences between groups with

regard to baseline characteristics. Immediate VT termination was achieved in 14 patients (78%) with amiodarone versus 3 patients (27%) on lidocaine ($p < 0.05$). After 1 hour, 12 patients (67%) on amiodarone and 1 patient (9%) on lidocaine were alive and free of VT ($p < 0.01$). Amiodarone had a 33% drug failure rate, whereas there was a 91% drug failure rate for lidocaine. The 24-hour survival was 39% on amiodarone and 9% on lidocaine ($p < 0.01$). Drug-related hypotension with aqueous amiodarone was less frequent than with lidocaine. This study found that amiodarone is more effective than lidocaine in the treatment of shock-resistant VT. ©2002 by Excerpta Medica, Inc.

(Am J Cardiol 2002;90:853-859)

Amiodarone administered intravenously has been found to be effective in terminating ventricular tachycardia (VT) in a number of small, uncontrolled studies.¹⁻¹¹ However, concern remains due to hypotension found with the standard intravenous preparation (Cordarone IV, Wyeth, St. Davids, Pennsylvania), because when lidocaine is used first, it is reported to have a lower incidence of hypotension. Cordarone IV is amiodarone in a solution of 2 chemicals used to solubilize the material. These chemicals have deleterious cardiovascular effects. Tween 80 and benzyl alcohol are both known to exhibit negative inotropy and hypotension.¹²⁻¹⁶ The reason for using Tween 80 and benzyl alcohol is to solubilize the amiodarone and to keep it in solution, because amiodarone itself is not very water soluble. However, a new formulation of amiodarone has been devised, solubilizing amiodarone in an aqueous medium without the need for

detergents or other solubilizing agents. The new vehicle consists of an acetate buffer, 0.1 M, at a pH of 3.8. The new preparation, "Amio-Aqueous," was studied as a less toxic alternative to Cordarone IV in patients with incessant ventricular VT when rapid drug administration for early termination is required. It was believed that the high efficacy of Cordarone IV could be maintained with a reduced toxicity profile (hypotension) when the new preparation is administered by bolus.

Initial preclinical studies indicate that Amio-Aqueous lacks the cardiotoxic properties of amiodarone/Tween 80/benzyl alcohol, and therefore, is an ideal candidate to use in the clinical setting of incessant VT. As shown by IV injection in rats, Amio-Aqueous was significantly less toxic than Cordarone IV, the respective 50% lethal doses being 50 and 35 mg/kg.¹⁷ At the same milligram per kilogram of drug given for the 50% lethal dose of Cordarone IV, only 16% of the rats given Amio-Aqueous died. In addition, the degree of cardiac contractile depression produced by increasing doses of Amio-Aqueous (5 to 20 mg/kg) was significantly less than that of Cordarone IV. Finally, the amount of hypotension caused by Cordarone IV increased significantly over the dose range of 5 to 20 mg/kg, whereas Amio-Aqueous caused only a minimal nonsignificant decrease in blood pressure. These studies have been confirmed in a canine model directly contrasting the hemodynamic effects of the 2 preparations in conscious dogs.¹⁸

The present study examines whether the newly

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*A list of principal investigators appears in the Appendix.

Variable	Amiodarone (n = 18)	Lidocaine (n = 11)
Men/women	11/7	9/2
Age (yrs)	68 ± 13	64 ± 11
Weight (kg)	74 ± 17	85 ± 13
Baseline systolic BP (mm Hg)	92 ± 41	89 ± 43
Baseline diastolic BP (mm Hg)	54 ± 24	54 ± 25
Ejection fraction (%)	29 ± 16 (n = 10)	32 ± 16 (n = 8)
Congestive heart failure	10	5
Coronary artery disease	14	5
Myocardial infarction	8	4
Cardiomyopathy	5	4
Primary arrhythmia	2	3
Unstable angina pectoris	2	1
Systolic BP <90 mm Hg	9	5
Pulmonary edema	7	3
Energy of electroshock (J)	308 ± 85	303 ± 109
Hemodynamically unstable	10	5

BP = blood pressure.

perimental antiarrhythmic medication, (3) known life-threatening allergy to lidocaine or amiodarone, and (4) history of recent infusion of Ic antiarrhythmic agent, or suspicion of Ic antiarrhythmic drug toxicity. Eligible patients were assigned to receive amiodarone (Amio-Aqueous), or lidocaine based on a random number table generated for each study site. Amiodarone and lidocaine were packed identically in 10-ml clear vials, each bearing an identifying code. Either lidocaine or Amio-Aqueous were to be administered by the most available venous access site. Initially, the patient received a bolus of either 150 mg amiodarone or 100 mg lidocaine administered over 2 minutes. Both drugs were administered without dilution. If VT persisted, the patient received a second bolus. If VT did not terminate, the patient was electrically shocked. The number of shocks and the strength of the shock remained at the discretion of the investigators. If VT terminated, the patient continued with a 24-hour infusion. If the patient was randomized to Amio-Aqueous, they received 600 mg amiodarone in 1 liter of 5% dextrose in water that was administered over 24 hours. If the patient was randomized to lidocaine, 2 mg/min lidocaine was administered over 24 hours. If breakthrough VT occurred during the infusion, an additional bolus and then doubling the infusion rate was prescribed along with additional electroshocks.

If the patient failed to respond to the first assigned sequence, a crossover was allowed so the patient could receive the alternative sequence. If the patient was randomized to lidocaine and it failed, the patient might then receive amiodarone. If the patient received amiodarone first, and this therapy failed, the patient might then receive lidocaine. If a study drug afforded efficacy, then the patient was administered a 24-hour infusion of the drug that terminated the VT. If both drugs failed, the patient was discontinued from the study and received

therapy at the discretion of the treating physician.

Clinical measurements: Blood pressure was obtained before and then after a bolus and at the end of the 24-hour infusion, or at the time when the patient was withdrawn from the study. The reason for withdrawal was noted in the case report form. Medical history, physical examination, and 12-lead electrocardiogram were performed as soon as possible following patient stabilization and were recorded in the patient's medical record. Blood samples were obtained 30 to 60 minutes after bolus administration and at the end of the 24-hour infusion, or at the time the patient was withdrawn from the study. Blood samples were col-

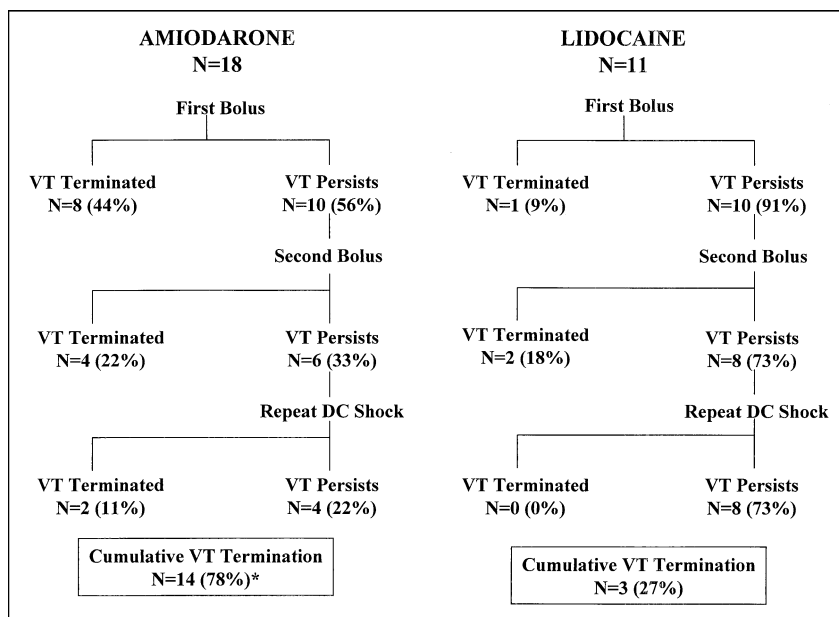


FIGURE 1. Effectiveness of amiodarone versus lidocaine in the termination of incessant VT. Amiodarone was more effective than lidocaine in the termination of shock-resistant VT with a cumulative initial VT termination rate of 78% compared with 27% with lidocaine ($p < 0.05$). * $p < 0.05$. DC = direct current.

formulated parental Amio-Aqueous resulted in more VT termination and a decrease in 1- and 24-hour mortality, in contrast to lidocaine.

METHODS

Protocol: The study was carried out as a double-blinded, parallel-designed trial with the lidocaine-treated group acting as controls. Patients with incessant VT were eligible for the study. Incessant VT was defined as sustained VT refractory to electroshock with a heart rate of >120 beats/min. The exclusion criteria were any of the following: (1) a "do not resuscitate" order, (2) concomitant use of another ex-

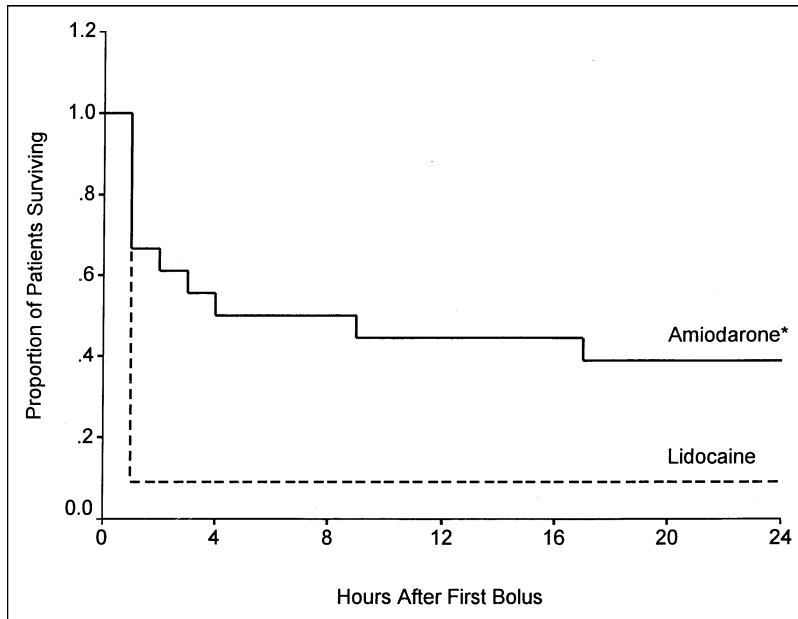


FIGURE 2. Time to treatment failure in patients with incessant VT. Kaplan-Meier analysis of the proportion of patients surviving for 24 hours. Amiodarone was superior to lidocaine during the 24-hour study period ($p < 0.01$). Treatment failure was defined as death or crossover to the alternative treatment due to the failure of the drug to terminate or suppress VT. * $p < 0.01$.

lected in 10-ml vacutainer tubes, and samples were separated by centrifugation for 30 minutes and then frozen and stored below -4°C . The blood samples were shipped frozen to Academic Pharmaceuticals (Lake Bluff, Illinois) and analyzed for amiodarone and desethylamiodarone levels using standard high-performance liquid chromatographic techniques.

End points: The following end points were measured to evaluate efficacy: (1) termination of the VT, (2) survival at 1 hour, (3) survival at 24 hours (primary end point), (4) number of sustained VT recurrences, and (5) recurrent VT/ventricular fibrillation (VF) requiring crossover to the alternative treatment group.

Patients who were crossed over to the alternative treatment group were considered a drug failure and counted as a failure in the initial randomization group. Additional end points measuring safety parameters included development or worsening congestive heart failure, conversion of the cardiac rhythm to a less stable rhythm, and development of hypotension or more severe hypotension.

Informed consent: All investigative sites obtained institutional review board authorization for the study and had approved informed consent and consenting procedures for those unable to give informed consent. The study was international and the consenting procedure was in accordance to Food and Drug Administration regulations, plus the laws and regulations of each country where the study was performed. Informed consent could be waived with institutional review board approval and the investigator and a physician not participating in the study certifying that all the requisites for a waiver of informed consent were present. These were: (1) that the VT was life threat-

ening; (2) that the informed consent could not be obtained because of the inability to communicate with the patient; (3) that there was insufficient time to obtain informed consent from the patient's legal representative; (4) that no alternative method of therapy was approved or generally well recognized that provided an equivalent or greater likelihood of saving the patient's life, and (5) that the procedures in the protocol offered minimal incremental risk above the risks the patient faced from the VT.

Statistical analysis: The study was powered based on the hypothesis that amiodarone would result in a 24-hour survival of 30% compared with lidocaine survival of 10%. It was estimated that 95 patients per group (total 190 patients) were needed to have 90% power to detect a difference using a 2-sided test with an α error of 0.05.

Differences in continuous and categorical variables were analyzed by independent sample t test and

Fisher's exact test. The primary end point was also assessed with Kaplan-Meier survival analysis. Differences were considered statistically significant at a $p < 0.05$.

RESULTS

This international study was performed in 63 centers from 3 countries (Canada, Hungary, and the United States) over a duration of 4 years. Principal investigators who succeeded with patient enrollment are listed in the Appendix. Due to problems in patient recruitment relating to entry criteria, only 29 patients were entered into the study. Of the 29 patients, 11 received lidocaine and 18 received amiodarone as first-line therapy following electroshock. Patient demographics are listed in Table 1. Both groups had similar baseline characteristics with no statistically significant differences.

The study was discontinued and analyzed due to a decision to present the safety data to the US Food and Drug Administration as part of an application. The efficacy data outcome was unknown to those who made the decision to stop the study and analyze the data. No interim analysis was performed before the decision to halt the study.

Initial ventricular tachycardia termination: Twenty-nine patients in sustained VT who did not respond to electroshock (external defibrillation) were studied. Amiodarone resulted in VT termination in 78% of the patients, whereas the success rate for lidocaine was 27% ($p < 0.05$) (Figure 1).

Eleven patients received lidocaine first, and 3 patients (27%) had their VT terminated. One of these patients whose VT was terminated developed brady-

TABLE 2 Efficacy of Intravenous Amiodarone Versus Lidocaine in the Treatment of Incessant Ventricular Tachycardia

	Lidocaine (n = 11)	Amio-Aqueous (n = 18)	p Value
VT termination	3 (27%)	14 (78%)	<0.05*
1-hour survival	1 (9%)	12 (67%)	<0.01*
24-hour survival	1 (9%)	7 (39%)	<0.01†
Crossed over	9 (82%)	7 (39%)	0.05*

*Fisher's exact test; †Kaplan-Meier test.

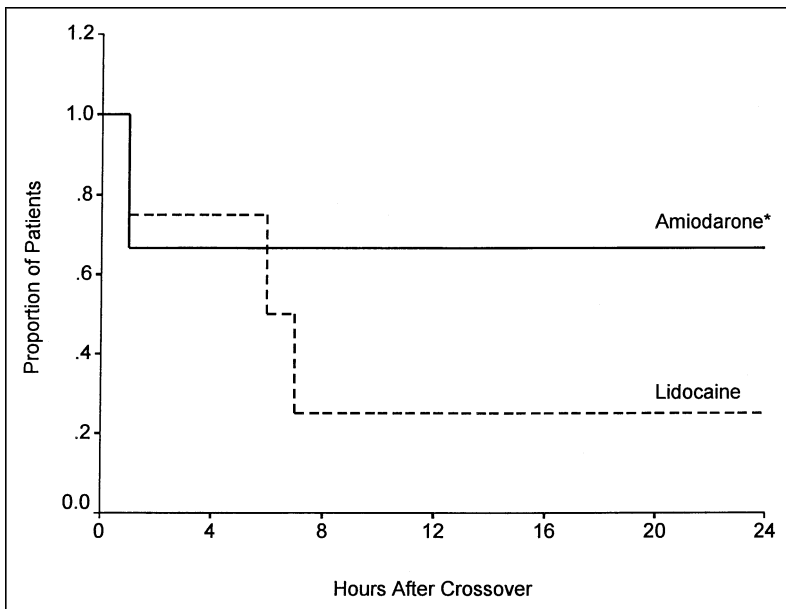


FIGURE 3. Time to treatment failure following crossover to the alternative treatment group. Kaplan-Meier analysis of patients without VT termination following initial bolus therapy who were crossed over to the alternative therapy. The proportions of patients who responded to the therapy after crossover are noted for each hour of study. The initial beneficial effect of amiodarone was seen to persist over the 24-hour study period, whereas the initial effectiveness of lidocaine progressively decreased over the 24 hours. Lidocaine was more effective following amiodarone pre-treatment than as the initial therapy. Treatment failure was defined as death or discontinuation of therapy. *p = NS.

cardia with electromechanical dissociation and died. Eight patients, whose VT did not terminate with 2 boluses of lidocaine followed by electric shock were crossed over and received amiodarone intravenously. Of these 8 patients, 5 responded to amiodarone and amiodarone therapy failed in the remaining 3.

Of the 18 patients who were randomized to amiodarone, 14 (78%) had their VT terminated. Two of them went into asystole after VT termination and died. Most of the initial VT terminations (86%) that occurred with intravenous amiodarone were pharmacologic; 2/3 of them were achieved with 1 bolus of 150 mg amiodarone. Four patients whose VT did not terminate with 2 boluses of amiodarone and electric shock were crossed over and received lidocaine. Three of them responded to lidocaine therapy.

One-hour survival: At 1 hour after the initial bolus, only 1 patient of the 11 who were randomized to

lidocaine was alive (9%), whereas 12 of the 18 patients (67%) who were randomized to amiodarone were alive (p <0.01).

Twenty-four-hour survival: Kaplan-Meier life-table analysis for the first 24 hours following the initial bolus is shown in Figure 2. At 24 hours, 1 patient was alive and free of VT on lidocaine and 7 patients on amiodarone were alive and free of VT, a success rate of 9% and 39%, respectively (p <0.01). The final outcome of the study is shown in Table 2. Four patients died on amiodarone (22%) and 7 were crossed over to lidocaine (39%) during the 24-hour study period. The drug failure rate on amiodarone was 61%. In the lidocaine group, 1 patient died and 9 were crossed over to amiodarone, indicating a 91% drug failure.

VT termination and survival after crossover to the alternative medication: Due to lack of initial VT termination, 8 patients (73%) were crossed over from lidocaine to amiodarone and 4 patients (22%) from amiodarone to lidocaine (p <0.05). The time course and their outcome are shown in Figure 3. Of the 8 patients who were crossed over from lidocaine to amiodarone, 5 had their VT terminated (63%) and all survived the 24-hour study period. Three patients did not respond to amiodarone and were discontinued from the study and received alternative therapies. Of the 4 patients who were crossed over from amiodarone to lidocaine, 3 had VT conversion on lidocaine (75%) and 1 of them survived 24 hours on lidocaine.

The time course of antiarrhythmic drug failure, resulting in crossover to the alternative treatment, is shown in Figure 4. Crossover from lidocaine to amiodarone happened early in the study in 9 patients, leaving a single survivor in the lidocaine arm of the study. Crossover from amiodarone to lidocaine shows a more gradual time course. Three patients who initially responded to amiodarone had breakthrough VT and were crossed over to lidocaine. All of them completed the 24-hour study.

Hemodynamic stability: Subgroup analysis was performed for hemodynamically stable and unstable patients. Hemodynamic stability was determined by the investigator. There was no significant difference in the proportion of hemodynamically unstable patients between amiodarone (56%) and lidocaine groups (45%) at baseline. In the amiodarone group, there were no statistically significant differences between hemodynamically stable and unstable patients in the rate of VT termination (stable 75%, unstable 80%), 1-hour survival (stable 75%, unstable 60%), and in 24-hour survival (stable 38%, unstable 40%). The only patient who completed the 24-hour study in the lidocaine

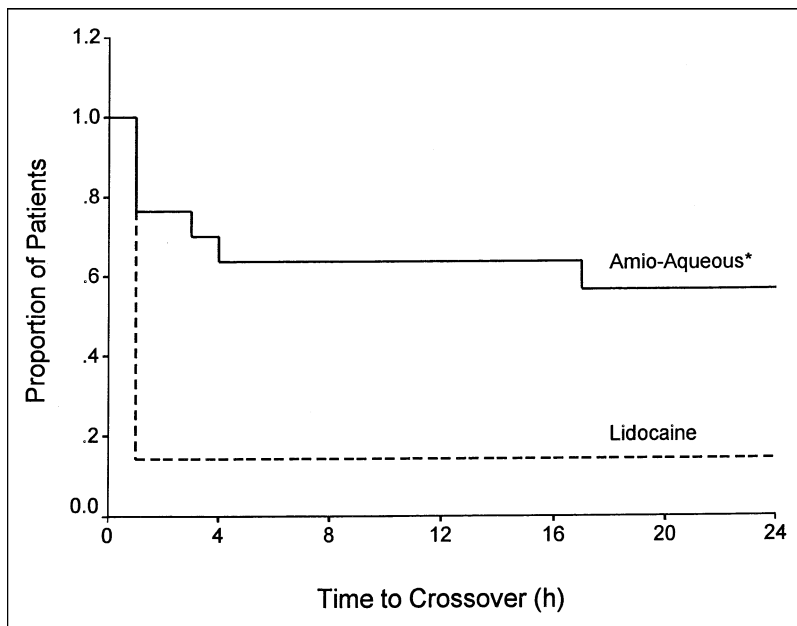


FIGURE 4. Time course of crossover to the alternative treatment. Crossovers from lidocaine to amiodarone were frequent and happened early in the study due to the lack of effectiveness of lidocaine. Crossovers from amiodarone to lidocaine were significantly less frequent ($p < 0.005$) with a more gradual time course. * $p < 0.005$.

	Amiodarone (n = 27)	Lidocaine (n = 18)
Cardiovascular		
Asystole	2 (7%)	1 (6%)
Bradycardia	1 (4%)	1 (6%)
Hypotension	2 (7%)	5 (28%)
Progressive heart failure	1 (4%)	1 (6%)
Central nervous system		
Seizure	0 (0%)	1 (6%)
Slurred speech, hallucination	0 (0%)	1 (6%)

group was hemodynamically stable before receiving lidocaine.

Amiodarone serum level: Amiodarone serum concentration was $0.876 \pm 0.212 \mu\text{g/ml}$ and desethyl amiodarone concentration was $0.017 \pm 0.002 \mu\text{g/ml}$ after bolus administration. At 24 hours, amiodarone concentration was $1.115 \pm 0.007 \mu\text{g/ml}$ and desethyl amiodarone was $0.016 \pm 0.002 \mu\text{g/ml}$.

Adverse events: Adverse events are noted in Table 3. Central nervous system-related side effects were associated with lidocaine, whereas the incidence of bradyarrhythmia and asystole was of equal frequency between amiodarone and lidocaine. Three patients who died in the amiodarone group had asystole or significant bradycardia (11%) as did 2 of the patients (11%) on lidocaine. One patient in each study group developed progressively worsening congestive heart failure. The incidence of hypotension was 7% for amiodarone (Amio-Aqueous) and 28% for lidocaine ($p = 0.06$) (Figure 5). Hypotension was defined as a

25% decrease in systolic blood pressure or the development of blood pressure of $<90 \text{ mm Hg}$. No patient from either treatment group developed phlebitis.

DISCUSSION

This is the first controlled clinical trial evaluating the effectiveness of amiodarone and lidocaine on shock-resistant VT. The results of this study show that Amio-Aqueous, a water-soluble intravenous amiodarone preparation, is more effective than lidocaine for the termination of shock-resistant VT and in terms of survival.

The Advanced Cardiac Life Support guidelines for the treatment of VT have recently undergone significant changes.¹⁹ Bretylium has been removed due to availability questions and its unfavorable side effect profile. Other traditional agents, lidocaine and procainamide, have received an "indeterminate" rating because of a lack of prospective, randomized trials confirming effectiveness.

Only amiodarone had received an acceptable effective classification (Ib) for VF or pulseless VT based on evidence provided by the Amiodarone in the out-of-hospital Resuscitation of Refractory Sustained ventricular arrhythmias Trial (ARREST).²⁰ Since then, the Amiodarone versus Lidocaine In prehospital Ventricular fibrillation Evaluation (ALIVE [VF]) trial has been completed and has shown that intravenous amiodarone is superior to lidocaine in the treatment of patients who are in cardiac arrest.²¹ However, the patient populations of both trials were different from those in this study. In the ARREST trial, 88% of the patients had VF and 7% had pulseless VT, whereas in the ALIVE trial $>90\%$ of the patients were in VF and only 1% had pulseless VT at the time of drug administration.^{20,21} In our study, half of the patients (48%) were in VT and hemodynamically stable and only 4 had pulseless VT. Thus, this prospective, controlled trial provides support to extend the use of amiodarone for the treatment of incessant VT.

Effectiveness of lidocaine in incessant ventricular tachycardia: Lidocaine was very ineffective in this study with a 91% drug failure by the end of the first hour following bolus administration. This finding is in accordance with the literature, which reported low success rates with lidocaine.²²⁻²⁶ In patients with hemodynamically stable sustained VT, conversion rates have been reported to be between 8% and 21%.²²⁻²⁵ The low effectiveness of lidocaine in resuscitation due to cardiac arrest has also been reported.^{21,26} Although in a retrospective study lidocaine increased the proportion of patients who survived until hospitalization after an out-of-hospital cardiac arrest,²⁷ lidocaine did not significantly increase short- and long-term survival.

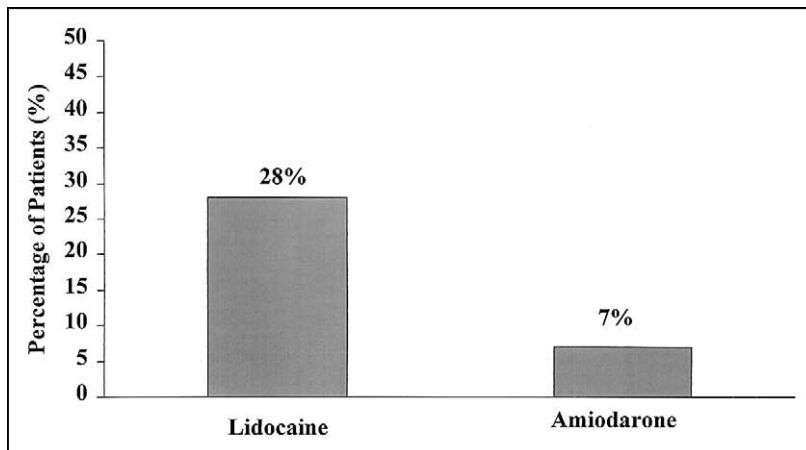


FIGURE 5. Development of hypotension following drug administration. Hypotension was defined as a decrease in systolic blood pressure to <80 mm Hg or a 25% decrease in systolic blood pressure to <90 mm Hg. Hypotension developed or existing hypotension worsened less frequently on aqueous amiodarone than on lidocaine ($p = 0.06$). Amiodarone was significantly more effective than lidocaine.

al.²⁶ The resuscitation rate (admission to an emergency department with pulse) was the same for lidocaine and bretylium (23%) with a “save rate” of 10% and 5%, respectively.²⁸

Effectiveness of amiodarone in incessant ventricular tachycardia: Intravenous amiodarone was highly effective in this study. Seventy-eight percent of the patients had VT termination in the amiodarone arm of the study and 67% were alive and free of VT at 1 hour after bolus administration, a significantly higher success rate compared with lidocaine. The rate of 24-hour survival was 4 times higher on amiodarone than on lidocaine (39% vs 9%).

Our result is in accordance with uncontrolled studies and case reports that found intravenous amiodarone effective when other measures failed to terminate or suppress life-threatening ventricular arrhythmias.¹⁻¹¹ The reported success rates in these studies ranged from 40% to 100%.

There have been 5 large controlled trials that evaluated intravenous amiodarone.^{20,21,29-31} The ARREST trial showed the effectiveness of amiodarone in patients with cardiac arrest who had shock-resistant VF or pulseless VT.²⁰ Forty-four percent of the patients who were randomized to amiodarone were admitted to a hospital alive, which was a significantly higher proportion compared with placebo (34%). In the ALIVE trial,²¹ amiodarone was significantly more effective than lidocaine in improving survival to hospital admission for out-of-hospital cardiac arrest characterized by VF (23% vs 11%).

Two controlled trials were dose-ranging studies attempting to show efficacy of intravenous amiodarone by determining a dose-response relation in patients with recurrent hypotensive VT, which was refractory to lidocaine, procainamide, and bretylium.^{29,30} Levine et al²⁹ reported a 40% overall survival at 24 hours. In the study of Scheinman et al,³⁰ 30% of the patients were in incessant VT at the start of blinded therapy. The primary end point was the

VT/VF event rate and the study was not powered for the assessment of VT termination. Analysis of the time to drug failure, defined as the time to the first hemodynamically destabilizing VT or VF, death, or discontinuation, had an approximately 40% success rate at 24 hours in the medium (500 mg amiodarone) and high (1,000 mg amiodarone) dose groups.

Kowey et al³¹ compared the efficacy of low- and high-dose amiodarone (125 and 1,000 mg) with bretylium in a patient population that was similar to the populations in the dose-ranging studies. They concluded that high-dose amiodarone was at least as effective as bretylium. Approximately 50% of the patients in the high-dose amiodarone group remained event free at

24 hours. This study was not designed to determine the effects of these agents on VT termination and only a small proportion of the patients were in incessant VT at the time of drug therapy. However, in this small group, the median time from initiation of therapy to the termination of VT was 4 hours. Combining these data with those of Scheinman et al³⁰ shows conversion in 3 hours for low-dose amiodarone and 1.4 hours for high-dose amiodarone.

The rate of 24-hour survival on amiodarone in our study was comparable to other controlled trials. However, these trials provide little or no information about the efficacy of amiodarone in VT termination and its potency compared with lidocaine. This study was designed to address these very important issues and found amiodarone effective and superior to lidocaine. In fact, the overwhelming majority of the VT terminations were pharmacologic. In the ARREST trial,²⁰ pharmacologic defibrillation was not observed, emphasizing the differences between the patient populations because most of these patients were in VF, a more recalcitrant rhythm to terminate pharmacologically.

In this study, pharmacologic VT terminations were observed within minutes following amiodarone bolus administration. This is remarkably different from the previously mentioned reports where the median time between the initiation of the therapy and VT termination was measured in hours.^{30,31} One possible explanation could be the rapid administration of amiodarone in our study. Amiodarone boluses were given over 2 to 5 minutes, which is at a faster rate compared with the other studies, a rate that may facilitate higher tissue uptake.

Safety of amiodarone: The aqueous preparation used in this study showed a reduced incidence of hypotension compared with that seen in previous studies.²⁹⁻³¹ Although successful termination of VT is an extremely important initial step and is the prerequisite of subsequent measures to save patients' lives,^{19,32} if

asystole develops, patients may not survive without emergency pacing although VT/VF has been terminated.

APPENDIX

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