AMIODARONE FOR RESUSCITATION AFTER OUT-OF-HOSPITAL CARDIAC ARREST DUE TO VENTRICULAR FIBRILLATION

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ABSTRACT

Background Whether antiarrhythmic drugs improve the rate of successful resuscitation after out-of-hospital cardiac arrest has not been determined in randomized clinical trials.

Methods We conducted a randomized, double-blind, placebo-controlled study of intravenous amiodarone in patients with out-of-hospital cardiac arrest. Patients who had cardiac arrest with ventricular fibrillation (or pulseless ventricular tachycardia) and who had not been resuscitated after receiving three or more precordial shocks were randomly assigned to receive 300 mg of intravenous amiodarone (246 patients) or placebo (258 patients).

Results The treatment groups had similar clinical profiles. There was no significant difference between the amiodarone and placebo groups in the mean (±SD) duration of the resuscitation attempt (42±16 and 43±16 minutes, respectively), the number of shocks delivered (4±3 and 6±5), or the proportion of patients who required additional antiarrhythmic drugs after the administration of the study drug (66 percent and 73 percent). More patients in the amiodarone group than in the placebo group had hypotension (59 percent vs. 48 percent, P=0.04) or bradycardia (41 percent vs. 25 percent, P=0.004) after receiving the study drug. Recipients of amiodarone were more likely to survive to be admitted to the hospital (44 percent, vs. 34 percent of the placebo group; P=0.03). The benefit of amiodarone was consistent among all subgroups and at all times of drug administration. The adjusted odds ratio for survival to admission to the hospital in the amiodarone group as compared with the placebo group was 1.6 (95 percent confidence interval, 1.1 to 2.4; P=0.02). The trial did not have sufficient statistical power to detect differences in survival to hospital discharge, which differed only slightly between the two groups.

Conclusions In patients with out-of-hospital cardiac arrest due to refractory ventricular arrhythmias, treatment with amiodarone resulted in a higher rate of survival to hospital admission. Whether this benefit extends to survival to discharge from the hospital merits further investigation. (N Engl J Med 1999; 341:871-8.)

SUDDEN death from cardiac causes, often due to ventricular fibrillation, claims at least 250,000 persons annually in the United States.[1,2] The American Heart Association guidelines for advanced cardiac life support state that antiarrhythmic medications are "acceptable, probably helpful" for the treatment of ventricular fibrillation or pulseless ventricular tachycardia that persists after three or more shocks from an external defibrillator (often called "shock-refractory" ventricular fibrillation or tachycardia).[3] This guarded recommendation reflects the limited evidence supporting the use of these agents, none of which have been convincingly demonstrated to improve the success of attempted resuscitation after cardiac arrest.[4-6] We conducted a randomized clinical trial to determine the efficacy of intravenous amiodarone in patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or tachycardia.

METHODS

The study was conducted in Seattle and suburban King County, Washington. This region has more than 1.5 million residents and is served by 21 paramedic base stations and 15 hospitals, all of which participated in the trial. Seattle and King County have similar multitiered prehospital emergency-response systems that follow treatment protocols written in accordance with American Heart Association guidelines for advanced cardiac life support.[7]

Protocol

Victims of cardiac arrest were initially treated by fire-department personnel (first responders), who initiated basic life-support measures, including the delivery of shocks by an automated external defibrillator. When paramedics arrived, they provided advanced life-support measures. Adults with nontraumatic out-of-hospital cardiac arrest were eligible for inclusion in the study if ventricular fibrillation or pulseless ventricular tachycardia (on initial presentation or any time in the course of the resuscitation attempt) was present after three or more precordial shocks had been given, if intravenous access had been established, and if paramedics were on the scene with the study drug or placebo. After tracheal intubation, eligible patients received 1 mg of epinephrine intravenously and were then randomly assigned to receive either 300 mg of amiodarone (Cordarone, Wyeth–Ayerst Laboratories, Philadelphia) or its diluent, polysorbate 80, as placebo.

Amiodarone and placebo were packaged identically in unlabeled,

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amber-colored, 6-ml glass vials, each bearing an identifying number code, in permutations of blocks of four. When a patient met the enrollment criteria, a vial was broken; the contents were drawn with a large-bore needle into a sterile syringe, where they were diluted with 5 percent dextrose in water to a volume of 20 ml[8]; and the contents of the syringe were injected rapidly into a peripheral vein that was simultaneously being rapidly infused with 5 percent dextrose in water, while cardiopulmonary resuscitation was being continued. Eligible patients had received three or more precordial shocks, were pulseless, and had ventricular fibrillation or tachycardia at the time of the administration of the drug. Only a single dose of amiodarone or placebo was administered.

There were no differences in the further treatment of patients assigned to amiodarone or placebo, including the use of additional antiarrhythmic agents. Resuscitated patients were admitted to any of 15 community hospitals, without disclosure of their treatment assignment or any directives for further management.

Data Recording

All data were collected and analyzed by investigators who had no knowledge of the patients' treatment assignments. Prehospitalization data included a narrative history and detailed sequence of events during resuscitation. Automated external defibrillators with real-time or elapsed-time clocks provided both tracings of the cardiac rhythm and audio recordings of the resuscitation in progress. Rhythms were identified from defibrillator recordings made with use of cutaneous defibrillator patches that approximated a lead II configuration. Ventricular fibrillation was defined as irregular, disorganized ventricular electrical activity of variable amplitude, and ventricular tachycardia as an organized rhythm with a wide QRS interval ($\geq$120 msec) without associated P waves, at a rate of more than 150 beats per minute. The amplitude of ventricular fibrillation was measured as previously described.[9] The time of dispatch was defined as the time when the emergency-response center ordered emergency personnel to go to the scene of the cardiac arrest. Hospital records were reviewed, and survivors or their family members were interviewed after discharge.

End Points

The primary end point was admission to the hospital with a spontaneously perfusing rhythm. This meant that the patient had a sufficiently stable, organized rhythm and blood pressure (with or without the use of pressor drugs) to be assigned to a hospital bed. Patients who died in the emergency department were not considered to have been admitted. To permit us to assess the primary end point, patients were stratified before receiving amiodarone or placebo according to their initial cardiac-arrest rhythm (ventricular fibrillation, asystole, or pulseless electrical activity) and according to whether there was a transient return of spontaneous circulation, as evidenced by a palpable pulse. The secondary end points were adverse effects, the number of precordial shocks required after the administration of amiodarone or placebo, the total duration of resuscitative efforts, and the need for additional antiarrhythmic drugs. Hypotension and bradycardia were assumed to be present if there was a need for the infusion of vasopressor agents or for chronotropic therapy after spontaneous circulation had been restored. Survival to discharge from the hospital and functional neurologic status at discharge were also evaluated, although the trial, by design, did not have sufficient statistical power to demonstrate differences in these outcomes.

Consent

This study was approved by the Human Subjects Review Committee at the University of Washington, with an exception from informed consent, in compliance with interpretation of the federal policy for the protection of human subjects in place at that time.[10] Data were reviewed on three scheduled occasions by an independent data safety and monitoring board, which supplied interim reports to the Food and Drug Administration and the Human Subjects Review Committee. All survivors or their families were later informed of their participation in this study, and consent was obtained for a review of their hospital records. Access to the records of patients who did not survive was provided under the terms of a confidentiality agreement between the investigators and the Human Subjects Review Committee.

Statistical Analysis

The rate of survival to hospital admission after out-of-hospital cardiac arrest due to ventricular fibrillation in Seattle and King County ranges from 50 percent to 65 percent, but it was expected to fall between 15 percent and 40 percent in subgroups of patients with shock-refractory arrhythmias.[11,12] We estimated that 500 patients would be needed for the study to have the power to detect a 30 percent improvement in the proportion of patients surviving to admission to the hospital after initial or subsequent ventricular fibrillation or tachycardia, with a two-sided alpha of 0.05 and a beta of 0.80.

Differences in continuous and dichotomous variables were analyzed with use of Student's t-test, the chi-square test, or the Mann–Whitney test. Clinical end points were also examined by logistic-regression analysis to account for base-line differences and adjust for the effects of confounding and interactions between the variables that characterized patients and their treatment before assignment to amiodarone or placebo. Selection of the appropriate multivariate model was confirmed by the goodness-of-fit chi-square (Hosmer–Lemeshow) test. Statistical significance was indicated by a P value $\leq$0.05.[13]

RESULTS

Between November 1994 and February 1997, 3954 consecutive patients were treated for out-of-hospital cardiac arrest from any cause in Seattle and King County and were considered for enrollment in the trial; 3260 of these did not meet the eligibility criteria and did not undergo randomization.

Deviations from the Protocol

Because of the rapidly changing circumstances of resuscitation, a patient's eligibility for the study could change after the inclusion criteria had originally been met. Of the 667 consecutive patients who initially met the study criteria, 160 were not treated with amiodarone or placebo because of spontaneous conversion of their arrhythmia, technical problems, or protocol violations. Moreover, an additional 27 recipients of amiodarone or placebo were discovered, in fact, to be ineligible for the study.

The clinical characteristics of the 27 ineligible patients who were treated and the 160 who were eligible but untreated were similar to those of the eligible, treated patients. As might be expected, the 27 ineligible patients, who had received amiodarone or placebo before their third shock or after a pulse had already been restored, had a higher rate of admission to the hospital (19 of 27, or 70 percent) than the eligible, treated patients (200 of 507, or 39 percent; P=0.003). Sixty-nine of the 160 eligible but untreated patients (43 percent) survived until admission to the hospital, a proportion that did not differ significantly from the proportion of treated, eligible patients who survived until admission to the hospital. The treatment assignment of 3 of the 507 treated, eligible patients was not known (the empty drug vials

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS AND THE COURSE
OF RESUSCITATION BEFORE THE ADMINISTRATION OF AMIODARONE OR PLACEBO.*

CHARACTERISTIC	AMIODARONE (N=246)	PLACEBO (N=258)
Male sex — no. (%)	187 (76)	203 (79)
Age — yr	66±14	65±14
History of cardiac disease — no. (%)†	137 (64)	135 (59)
History of other disorders — no. (%)‡	101 (47)	119 (52)
Witnessed arrest (before arrival of first responder) — no. (%)§	155 (70)	182 (77)
Bystander cardiopulmonary resuscitation (before arrival of first responder) — no. (%)¶	155 (68)	138 (59)
Amplitude of initial ventricular-fibrillation rhythm — mV	0.42±0.2	0.45±0.2
Cardiac arrest after arrival of first responder — no. (%)	15 (6)	18 (7)
Location of arrest — no. (%)		
Home	154 (63)	161 (62)
Nursing home	6 (2)	5 (2)
Other residence	15 (6)	21 (8)
Public place	71 (29)	71 (28)
Initial cardiac-arrest rhythm — no. (%)		
Ventricular fibrillation	205 (83)	215 (83)
Pulseless ventricular tachycardia	0	1 (0.4)
Asystole converting to ventricular fibrillation	11 (4)	13 (5)
Pulseless electrical activity converting to ventricular fibrillation	30 (12)	29 (11)
Rhythm at time of study-drug administration — no. (%)		
Ventricular fibrillation	217 (88)	227 (88)
Pulseless ventricular tachycardia	22 (9)	15 (6)
Other pulseless rhythm	7 (3)	16 (6)
Time from dispatch to response or procedure — min‖		
Arrival of first responder	4.3±2.0 (4.0)	4.4±2.3 (4.0)
Arrival of paramedics	8.4±4.1 (7.8)	8.8±4.9 (7.9)
Treatment**		
First defibrillation shock	8.9±5.4 (7.6)	9.5±7.5 (7.4)
Intravenous access	13.1±4.1 (12.7)	13.7±4.1 (13.2)
Tracheal intubation	14.3±5.8 (12.7)	13.8±4.6 (13.1)
Administration of study drug	21.4±8.3 (19.2)	20.5±7.0 (19.3)

*Plus–minus values are means ±SD; medians are given in parentheses.

†Data were available for 213 amiodarone recipients and 228 placebo recipients.

‡Data were available for 216 amiodarone recipients and 228 placebo recipients.

§Data were available for 223 amiodarone recipients and 236 placebo recipients.

¶Data were available for 229 amiodarone recipients and 233 placebo recipients.

‖The values in parentheses are medians.

**Synchronized recordings of the resuscitation provided the duration of treatment for approximately half of the patients in both treatment groups. In the remainder, time measurements were incomplete because of technical problems.

were lost after use). These three patients were excluded from the analysis; however, the statistical conclusions were the same whether all three were considered to have received amiodarone or all three were considered to have received placebo.

Study Patients

After the exclusions just described, 246 eligible, treated patients (49 percent) were assigned to amiodarone and 258 (51 percent) to placebo, for a total of 504 patients. The treatment groups had similar clinical profiles (Table 1). In 84 percent of patients, the first documented arrhythmia was ventricular fibrillation (including one case of pulseless ventricular tachycardia). In the remaining 16 percent, initial asystole or pulseless electrical activity evolved to ventricular fibrillation during resuscitation. At the actual time of study-drug administration, 88 percent of the patients had ventricular fibrillation and 7 percent had pulseless ventricular tachycardia. In 5 percent (23 patients), the pulseless rhythm was not documented, was ventricular tachycardia at a rate of 150 beats per minute or less, or could have been considered asystole or small-amplitude ventricular fibrillation (<0.1 mV). The clinical characteristics and outcomes of these 23 patients were similar to those of patients in whom

TABLE 2. CHARACTERISTICS OF RESUSCITATION AND TREATMENT BEFORE AND AFTER
ASSIGNMENT TO AMIODARONE OR PLACEBO.*

CHARACTERISTIC	AMIODARONE (N=246)	PLACEBO (N=258)	P VALUE
Before study drug			
Transient return of spontaneous circulation — no. (%)	55 (22)	52 (20)	0.61
No. of shocks	5±2 (4)	5±2 (4)	0.73
Treatment for bradycardia — no. (%)	32 (13)	51 (20)	0.04
Pressor treatment — no. (%)	19 (8)	22 (9)	0.74
Antiarrhythmic-drug treatment — no. (%)	65 (26)	91 (35)	0.04
Prophylactic	13 (5)	19 (7)	0.43
For ventricular fibrillation or ventricular tachycardia	52 (21)	72 (28)	0.10
After study drug			
Total duration of resuscitative efforts — min†	42±16 (37)	43±16 (40)	0.87
No. of shocks until return of spontaneous circulation‡	4±3 (3)	6±5 (4)	0.17
Treatment for bradycardia — no. (%)§	63 (41)	36 (25)	0.004
Pressor treatment — no. (%)§	91 (59)	69 (48)	0.04
Antiarrhythmic-drug treatment — no. (%)	197 (80)	211 (82)	0.70
Prophylactic	34 (14)	24 (9)	0.15
For ventricular fibrillation or ventricular tachycardia	163 (66)	187 (73)	0.13
Blood pressure — mm Hg¶			
Systolic	104±41	117±36	0.02
Diastolic	64±31	78±22	0.002
Heart rate — beats/min‖	90±26	101±25	0.004
Rhythm — no. (%)**			
Supraventricular	76 (70)	52 (63)	0.4
Wide complex rhythm, ≤150 beats/min	28 (26)	27 (33)	0.32
Wide complex rhythm, >150 beats/min	2 (2)	0	0.32
Paced rhythm	1 (1)	2 (2)	0.39
Heart block, >60 beats/min	2 (2)	1 (1)	0.61

*Plus–minus values are means ±SD, with the median in parentheses. The use of antiarrhythmic medications was defined as prophylactic if they were given with the intention of maintaining an established perfusing rhythm and therapeutic if they were given for ongoing or recurrent ventricular fibrillation or tachycardia. Prophylactic lidocaine was permitted, whereas treatment with antiarrhythmic medications for persistent ventricular fibrillation or tachycardia before randomization was considered a protocol violation.

†The total duration was the interval from placement of an automated external defibrillator to the time when successfully resuscitated patients were ready for transport to the hospital; the interval was measured in 98 patients assigned to amiodarone and 76 assigned to placebo.

‡Data are for 138 amiodarone recipients and 121 placebo recipients who were successfully resuscitated and transported to the hospital (including 62 patients who died before admission).

§Data are for 153 amiodarone recipients and 145 placebo recipients who had either a transient or a sustained return of spontaneous circulation.

¶Data are for patients who had pulses and a recorded blood pressure on arrival at the hospital (systolic, 105 amiodarone recipients and 81 placebo recipients; diastolic, 80 amiodarone recipients and 64 placebo recipients).

‖Data are for 107 amiodarone recipients and 82 placebo recipients who had pulses and a recorded heart rate on arrival at the hospital.

**Data are for 109 amiodarone recipients and 82 placebo recipients who had pulses and in whom a rhythm was characterized on arrival at the hospital.

ventricular fibrillation or tachycardia was more clearly documented at the time of study-drug administration.

Characteristics before Study-Drug Administration

An average of five shocks were delivered before the administration of amiodarone or placebo (Table 2). More patients in the placebo group had been treated previously for bradycardia or arrhythmias, but these patients were otherwise similar to amiodarone recipients (Table 2). There were no differences between the treatment groups in the time from dispatch until the arrival of the first responders or the paramedics or until the performance of various resuscitation procedures (Table 1). The time from dispatch to the administration of amiodarone or placebo was long (>20 minutes).

Intermediate Outcomes

Among the patients receiving amiodarone, as compared with those receiving placebo, there was a slight reduction in the duration of resuscitation, the number of shocks, and the number of patients needing additional antiarrhythmic drugs for persistent ventricular tachyarrhythmias before arrival at the hospi-
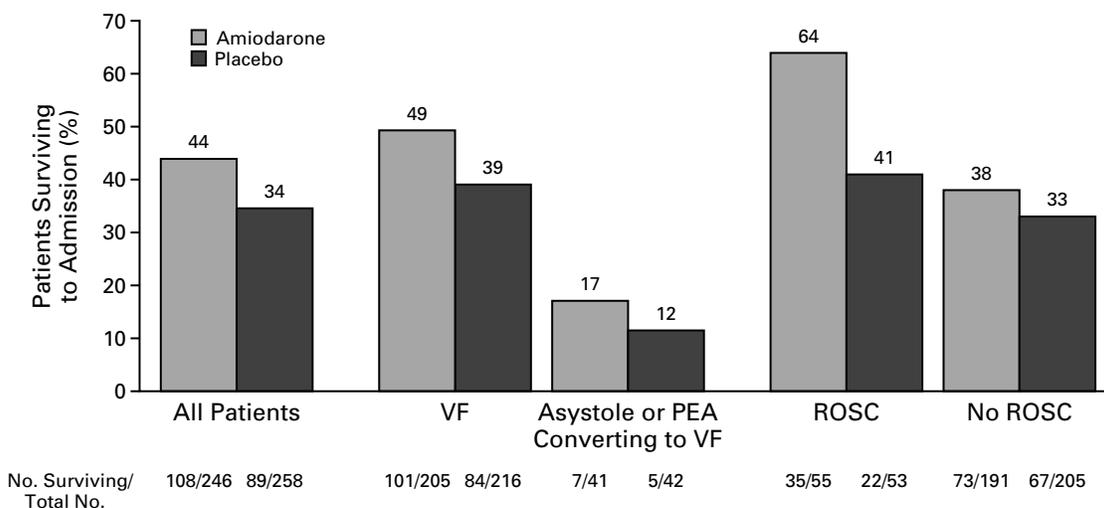
Figure 1. Effect of Treatment with Amiodarone or Placebo on the Rate of Survival to Hospital Admission in All Patients and Subgroups of Patients.

VF denotes ventricular fibrillation, PEA pulseless electrical activity, and ROSC return of spontaneous circulation before administration of the study drug. Values above the bars are the percentages of patients who survived to admission.

tal, but these differences were not significant (Table 2). Among the 298 patients who had a return of spontaneous circulation, recipients of amiodarone were more likely to require treatment for hypotension or bradycardia than recipients of placebo. Among the patients who had pulses on arrival at the hospital, the mean heart rate and blood pressure were lower in amiodarone recipients, but rhythms were similar in the two treatment groups (Table 2).

Survival until Admission to the Hospital

Of the 504 patients, 197 (39 percent) survived to be admitted to the hospital. Recipients of amiodarone were more likely to be resuscitated and admitted to the hospital than were recipients of placebo (44 percent and 34 percent, respectively; P=0.03), for a relative improvement of 29 percent (Fig. 1). After adjustment for other independent predictors of outcome (location of the cardiac arrest, presence or absence of bradycardia or hypotension before the administration of amiodarone or placebo, response time for paramedics, initial rhythm, presence or absence of transient return of spontaneous circulation during the resuscitation attempt, previous treatment with other antiarrhythmic drugs, and sex; P<0.001 to P=0.09), the odds ratio for survival to admission to the hospital in recipients of amiodarone, as compared with recipients of placebo, was 1.6 (95 percent confidence interval, 1.1 to 2.4; P=0.02), which was similar to the unadjusted odds ratio of 1.5 (95 percent confidence interval, 1.04 to 2.1; P=0.03).
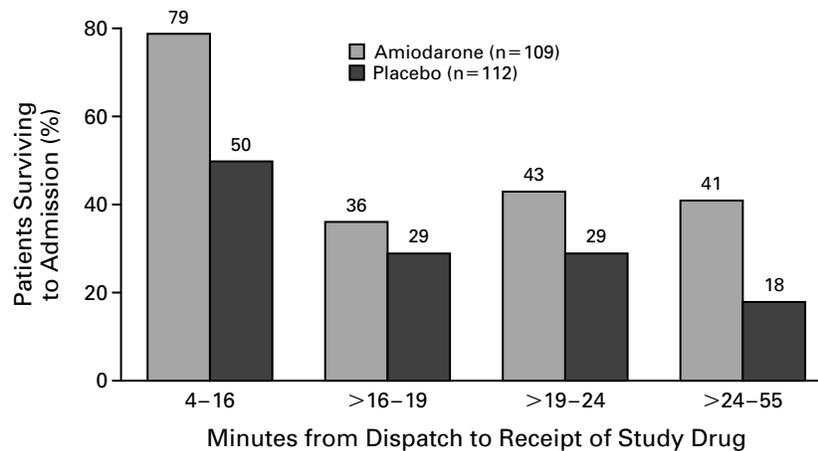
Among the 221 patients with witnessed cardiac arrests for whom the interval from dispatch to study-drug administration was known, there was no significant interaction between this interval and the effect of amiodarone on the rate of admission to the hospital. For all lengths of time to treatment, whether the interval was analyzed as a continuous variable or according to quartiles (as in Fig. 2), amiodarone recipients were more likely to survive to be admitted to the hospital than those who received placebo (P=0.008 by the Mantel–Haenszel chi-square test).

Subgroup Analyses

Patients whose cardiac arrest was due to ventricular fibrillation were more likely to survive to be admitted to the hospital than those whose initial rhythm was asystole or pulseless electrical activity (44 percent vs. 14 percent; adjusted odds ratio, 5.2; 95 percent confidence interval, 2.5 to 10.6; P<0.001). In addition, patients with a transient return of spontaneous circulation were more likely to survive to be admitted than those who remained pulseless before receiving amiodarone or placebo (53 percent vs. 30 percent; adjusted odds ratio, 2.7; 95 percent confidence interval, 1.7 to 4.5; P<0.001). A multivariate test of interaction showed no significant differences in the response to treatment with amiodarone with respect to either the initial cardiac-arrest rhythm or the presence or absence of a transient return of pulses before study-drug administration, suggesting that the benefit associated with amiodarone was essentially the same among these subgroups (Fig. 1).

Women tended to have better outcomes after cardiac arrest than men: 49 of 114 women (43 percent) and 148 of 390 men (38 percent) survived to be ad-

Figure 2. Effect of the Length of Time to the Administration of Amiodarone or Placebo on the Rate of Survival to Admission to the Hospital in Patients with Witnessed Cardiac Arrest, According to Quartile of Time from Dispatch.

As compared with the placebo group, the amiodarone group had a better outcome at all measured intervals, and the benefit was consistent whether the drug was administered early or late (P=0.008 by the Mantel–Haenszel chi-square test). Values above the bars are the percentages of patients who survived to admission.

mitted to the hospital (adjusted odds ratio, 1.6; 95 percent confidence interval, 0.97 to 2.6; P=0.06). The effect of amiodarone was also significantly modified by sex, independently of age or the other pretreatment variables listed in Tables 1 and 2. Women treated with amiodarone were more likely than women receiving placebo to survive to be admitted to the hospital (adjusted odds ratio, 4.3; 95 percent confidence interval, 1.03 to 17.8). Among men, the comparable adjusted odds ratio was 1.2 (95 percent confidence interval, 0.8 to 1.9). The interaction between treatment with amiodarone and sex was significant (P=0.008).

Patients who had received an antiarrhythmic medication to treat ventricular fibrillation or tachycardia before receiving the study drug were more likely than those who had not received such medication to survive to be admitted to the hospital (45 percent vs. 37 percent; adjusted odds ratio, 1.8; 95 percent confidence interval, 1.1 to 2.8; P=0.02). However, a multivariate test of interaction found no significant differences in the effect of amiodarone with respect to either previous or subsequent treatment with antiarrhythmic medications, suggesting an equivalent benefit of amiodarone regardless of the use of additional antiarrhythmic drugs.

Survival after Hospital Admission

Blinding was maintained throughout hospitalization, but the treatment of patients after their arrival at the hospital was not standardized. Of the 504 study patients, 67 (13 percent) were discharged alive from the hospital. Of the remaining 130 patients who were

admitted to the hospital, 13 patients awakened, and 117 (90 percent) never regained consciousness. In these patients, the identifiable contributing causes of death were cardiovascular in 35 percent, respiratory in 30 percent, and multifactorial or unspecified in the remainder, and the causes of death did not significantly differ between treatment groups.

The proportion of patients who survived until discharge from the hospital did not differ significantly in the amiodarone and placebo groups, regardless of whether the analysis included all treated patients (13.4 percent [33 of 246] and 13.2 percent [34 of 258], respectively), only patients whose presenting arrhythmia was ventricular fibrillation (16 percent and 15 percent), or only those who had a transient return of pulses before treatment (24 percent and 15 percent). More than half of the 67 patients discharged alive after treatment with amiodarone or placebo, all after lengthy resuscitation, resumed independent living activities or returned to their former employment (55 percent [18 of 33] in the amiodarone group and 50 percent [17 of 34] in the placebo group).

DISCUSSION

Although they are considered the standard of care in the United States, the benefit of antiarrhythmic agents has not been established in clinical trials or universally accepted as an essential component of treatment algorithms for cardiac arrest refractory to defibrillation.[4] Paradoxically, most antiarrhythmic medications increase the defibrillation threshold and, in theory, make defibrillation more difficult.[14-19] In a study involving historical controls, lidocaine appeared

to improve the success of resuscitation,[20] but it had no effect[21] or worsened the outcome[22,23] in other studies. Bretylium has been shown to be as effective as lidocaine,[24,25] but not necessarily better than placebo[26] for treating ventricular fibrillation. Use of procainamide for cardiac arrest is supported by observational data in only 20 recipients.[27] Two recent prospective trials showed no benefit of magnesium during resuscitation.[28,29]

As compared with placebo, amiodarone significantly and independently improved the rate of survival to admission to the hospital after shock-refractory cardiac arrest. A benefit was consistently observed in all major subgroups, regardless of the presenting cardiac-arrest rhythm or whether or not there was a transient return of pulse before treatment, and even when amiodarone was administered late in the course of resuscitation.

Women were more likely to be resuscitated than men, particularly when treated with amiodarone. The difference between men and women in the effectiveness of amiodarone could be due to a greater sensitivity to antiarrhythmic drugs in women[30] or to a higher dose of amiodarone in proportion to body weight in women, since a standard dose of 300 mg of amiodarone was given in this study. Earlier studies found that collapse in a public place, initial ventricular fibrillation, shorter intervals to the initiation of basic and advanced life-support measures, and female sex were independently associated with increased rates of survival to hospital admission after out-of-hospital cardiac arrest.[23,27,31,32] In this clinical trial, we have demonstrated the independent benefit of a specific pharmacologic intervention (amiodarone) in improving the rate of success of resuscitation.

Hypotension and bradycardia are expected adverse effects of intravenous amiodarone.[33] In animals, bradycardia has been attributed to the electrophysiologic effects of amiodarone itself and hypotension to its diluent, polysorbate 80.[34] Whether the hemodynamic effects of polysorbate 80 are as pronounced or as clinically significant in humans is controversial.[35-37] The hypotension and bradycardia associated with amiodarone were managed with fluids and inotropic or chronotropic drugs and did not offset the overall benefit of amiodarone.

In interpreting our findings, one should consider factors that may have affected the outcome. The diluent was used as a placebo in this study. Although hemodynamic derangements were less common after the administration of placebo than after amiodarone, it is possible that the diluent aggravated hypotension and bradycardia. The incidence and magnitude of these effects could also have been blunted by the previous administration of epinephrine.

The dose of amiodarone we selected was our best estimate of the maximal single dose with therapeutic efficacy and an acceptable level of adverse effects.[38]

Although previous studies found greater efficacy when higher doses of amiodarone were infused over longer periods,[33,39] the need to maintain the blinding with respect to treatment assignment throughout the trial precluded the use of additional doses or a continuous infusion of amiodarone. Amiodarone was administered peripherally during ongoing cardiopulmonary resuscitation, under conditions that could have compromised the concentration achieved in the central circulation and its therapeutic effect.[40,41] Amiodarone was administered relatively late in the course of the resuscitation attempt, when significant end-organ damage had probably already resulted from prolonged hypoperfusion. For these reasons, the potential benefit of treatment could have been underestimated. Finally, the treatment of patients after hospitalization was not standardized, nor did we evaluate the effect of care given in the hospital on survival.

The mechanisms by which amiodarone exerted its salutary effect were not addressed in this study. Pharmacologic defibrillation was not observed, implying that amiodarone acted primarily to prevent the recurrence of ventricular fibrillation, perhaps by stabilizing its electrophysiologic substrate.

The salient observation in this study is that adding amiodarone to advanced cardiac life-support measures resulted in a net benefit: 1 of every 10 patients treated survived to admission to the hospital. This result does not imply that amiodarone is superior to other antiarrhythmic agents or that pharmacologic therapy is a substitute for expeditious defibrillation.[42] Whether the benefits observed in this trial extend to survival to discharge from the hospital merits further investigation.

REFERENCES

1. National Center for Health Statistics. Report of final mortality statistics, 1995. Mon Vital Stat Rep 1997;45(11):Suppl 2.
2. Gillum RF. Sudden coronary death in the United States: 1980-1985. Circulation 1989;79:756-65.

3. Cummins RO, ed. Advanced cardiac life support. Dallas: American Heart Association, 1997:1-17.

4. Advanced Life Support Working Party of the European Resuscitation Council. Guidelines for advanced life support: a statement by the Advanced Life Support Working Party of the European Resuscitation Council, 1992. Resuscitation 1992;24:111-21.

5. Weaver WD. Resuscitation outside the hospital — what's lacking? N Engl J Med 1991;325:1437-9.

6. Jaffe AS. The use of antiarrhythmics in advanced cardiac life support. Ann Emerg Med 1993;22:307-16.

7. Cobb LA, Hallstrom AP. Community-based cardiopulmonary resuscitation: what have we learned? Ann N Y Acad Sci 1982;382:330-42.

8. Emerman CL, Pinchak AC, Hancock D, Hagen JF. The effect of bolus injection on circulation times during cardiac arrest. Am J Emerg Med 1990;8:190-3.

9. Weaver WD, Cobb LA, Dennis D, Ray R, Hallstrom AP, Copass MK. Amplitude of ventricular fibrillation waveform and outcome after cardiac arrest. Ann Intern Med 1985;102:53-5.

10. Federal policy for the protection of human subjects: notices and rules (45CFR46). Fed Regist 1991;56(117):28003-32.

11. Cobb LA, Weaver WD, Fahrenbruch CE, Hallstrom AP, Copass MK. Community-based interventions for sudden cardiac death: impact, limitations and changes. Circulation 1992;85:Suppl:I-98–I-102.

12. Cox SV, Woodhouse SP, Weber M, Boyd P, Case C. Rhythm changes during resuscitation from ventricular fibrillation. Resuscitation 1993;26:53-61.

13. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. Controlled Clin Trials 1984;5:348-61.

14. Babbs CF, Yim GKW, Whistler SJ, Tacker WA, Geddes LA. Elevation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs. Am Heart J 1979;98:345-50.

15. Yoon MS, Han J, Goel BG, Creamer P. Effect of procainamide on fibrillation threshold of normal and ischemic ventricles. Am J Cardiol 1974;33:238-42.

16. Echt DS, Black JN, Barbey JT, Coxe DR, Cato E. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs: sodium channel block and action potential prolongation. Circulation 1989;76:1106-17.

17. Kerber RE, Pandian NG, Jensen SR, et al. Effect of lidocaine and bretylium on energy requirements for transthoracic defibrillation: experimental studies. J Am Coll Cardiol 1986;7:397-405.

18. Dorian P, Fain ES, Davy JM, Winkle RA. Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. J Am Coll Cardiol 1986;8:327-32.

19. Tacker WA, Niebauer JM, Baggs CF, et al. The effect of new antiarrhythmic drugs on defibrillation threshold. Crit Care Med 1980;8:177-80.

20. Herlitz J, Ekstrom L, Wennerblom B, et al. Lidocaine in out-of-hospital ventricular fibrillation: does it improve survival? Resuscitation 1997;33:199-205.

21. Harrison EE. Lidocaine in prehospital countershock refractory ventricular fibrillation. Ann Emerg Med 1981;10:420-3.

22. Weaver WD, Fahrenbruch CE, Johnson DD, Hallstrom AP, Cobb LA, Copass MK. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. Circulation 1990;82:2027-34.

23. van Walraven C, Stiell IG, Wells GA, Hebert PC, Vandemheen K. Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest? Ann Emerg Med 1998;32:544-53.

24. Haynes RE, Chinn TL, Copass MK, Cobb LA. Comparison of bretylium tosylate and lidocaine in management of out of hospital ventricular fibrillation: a randomized clinical trial. Am J Cardiol 1981;48:353-6.

25. Olson DW, Thompson BM, Darin JC, Milbrath MH. A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. Ann Emerg Med 1984;13:807-10.

26. Nowak RM, Bodnar TJ, Dronen S, Gentzkow G, Tomlanovich MC. Bretylium tosylate as initial treatment for cardiopulmonary arrest: randomized comparison with placebo. Ann Emerg Med 1981;10:404-7.

27. Stiell IG, Wells GA, Hebert PC, Laupacis A, Weitzman BN. Association of drug therapy with survival in cardiac arrest: limited role of advanced cardiac life support drugs. Acad Emerg Med 1995;2:264-73.

28. Thel MC, Armstrong AL, McNulty SE, Califf RM, O'Connor CM. Randomised trial of magnesium in in-hospital cardiac arrest. Lancet 1997;350:1272-6.

29. Fatovich DM, Prentice DA, Dobb GJ. Magnesium in cardiac arrest: the magic trial. Resuscitation 1997;35:237-41.

30. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590-7.

31. Weaver WD, Cobb LA, Hallstrom AP, et al. Considerations for improving survival from out-of-hospital cardiac arrest. Ann Emerg Med 1986;15:1181-6.

32. Weston CFM, Wilson RJ, Jones SD. Predicting survival from out-of-hospital cardiac arrest: a multivariate analysis. Resuscitation 1997;36:27-34.

33. Scheinman MM, Levine JH, Cannom DS, et al. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. Circulation 1995;92:3264-72.

34. Platou ES, Refsum H. Acute electrophysiologic and blood pressure effects of amiodarone and its solvent in the dog. Acta Pharmacol Toxicol (Copenh) 1986;58:163-8.

35. Gough WB, Zeiler RH, Barreca P, El-Sherif N. Hypotensive action of commercial intravenous amiodarone and polysorbate 80 in dogs. J Cardiovasc Pharmacol 1982;4:375-80.

36. Sicart M, Besse P, Choussat A, Bricaud H. Action hemodynamique de l'amiodarone intra-veineuse chez l'homme. Arch Mal Coeur Vaiss 1977;70:219-27.

37. Munoz A, Karila P, Gallay P, et al. A randomized hemodynamic comparison of intravenous amiodarone with and without Tween 80. Eur Heart J 1988;9:142-8

38. Singh BN, Venkatesh N, Nademanee K, Josephson MA, Kannan R. The historical development, cellular electrophysiology and pharmacology of amiodarone. Prog Cardiovasc Dis 1989;31:249-80.

39. Kowey PR, Levine JH, Herre JM, et al. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation 1995;92:3255-63.

40. Emerman CL, Pinchak AC, Hancock D, Hagen JF. Effect of injection site on circulation times during cardiac arrest. Crit Care Med 1988;16:1138-41.

41. Kuhn GJ, White BC, Swetman RE, et al. Peripheral vs central circulation times during CPR: a pilot study. Ann Emerg Med 1981;10:417-9.

42. Martin TG, Hawkins NS, Weigel JA, Rider DE, Buckingham BD. Initial treatment of ventricular fibrillation: defibrillation or drug therapy. Am J Emerg Med 1988;6:113-9.1