EMS MEDICAL DIRECTOR: James E. Pointer, MD, FACEP   DATE: May 16, 2000

LOCAL EMS AGENCY: Alameda County Emergency Medical Services

NAME OF PROPOSED PROCEDURE OR MEDICATION: Amiodarone HCl

1. DESCRIPTION OF THE PROCEDURE OR MEDICATION REQUESTED:

   Amiodarone HCl, Intravenous

2. DESCRIPTION OF THE MEDICAL CONDITIONS FOR WHICH THEY WILL BE UTILIZED:

   Pulseless ventricular fibrillation/ventricular tachycardia refractory to electrical defibrillation.
   May increase mortality in MI.

3. ALTERNATIVES (Please describe any alternate therapies considered for the same condition and any advantages and disadvantages):

	ADVANTAGES	DISADVANTAGES
Lidocaine	Long-time use; current drug of choice	No improvement in survival; Class II B
Bretylium	Long-time use	No improvement in survival; Not currently available
Procaineamide	Long-time use	No improvement in survival; Class II B; Also requires action by Scope Committee

4. PATIENT POPULATION THAT WOULD BENEFIT, INCLUDING AN ESTIMATE OF FREQUENCY OF UTILIZATION:

   V Fib/ V Tach cardiac arrests refractory to defibrillation: approximately 300 patients/year

5. OTHER FACTORS OR EXCEPTIONAL CIRCUMSTANCES:

   1 - Inclusion of amiodarone in 2000 ACLS ventricular fibrillation protocols is imminent.
   2 - At least ten other EMS agencies/providers have begun using amiodarone (attached).
   3 - Amiodarone is the only available agent to improve survival to hospital admission from ventricular fibrillation cardiac arrest.

6. ANY SUPPORTING DATA, INCLUDING RELEVANT STUDIES AND MEDICAL LITERATURE.

   See attached.

7. RECOMMENDED POLICIES/PROCEDURES TO BE INSTITUTED REGARDING USE, MEDICAL CONTROL, TREATMENT PROTOCOLS, AND QUALITY ASSURANCE OF THE PROCEDURE OR MEDICATION.

   See attached.

8. DESCRIPTION OF THE TRAINING AND COMPETENCY TESTING REQUIRED TO IMPLEMENT THE PROCEDURE OR MEDICATION.

   See attached.

Supporting Data, Including Relevant Studies, and Medical Literature

RELEVANT STUDIES

EFFICACY TO CONVERT VENTRICULAR ARRHTHYMIAS

1. Bretylium's use may be limited by high incidence of hypotension (See Kowey, et al.)

2. Amiodarone is effective in treating life-threatening tachyarrhythmias (See Scheinman, et al.)

3. Amiodarone and bretylium have comparable efficacies in the treatment of malignant ventricular arrhythmias (See Kowey, et al.)

SURVIVAL/MORTALITY STUDIES

1. Lidocaine may adversely affect MI mortality rates (See Sadowski, et al.)

2. ACLS drugs do not improve resuscitation from in-hospital cardiac arrest (See van Walraven, et al.)

3. Lidocaine, when compared to ACLS without lidocaine, fails to increase survival in out-of-hospital patients with refractory ventricular fibrillation arrest (See Harrison)

4. Epinephrine and lidocaine did not improve outcome in patients in ventricular fibrillation cardiac arrest (See Weaver, et al.)

5. Lidocaine, compared to epinephrine, associated with higher incidence of post defibrillation asystole (See Weaver, et al.)

6. Amiodarone increases survival to ED in out-of-hospital patients with ventricular fibrillation arrest (See Kudenchuk, et al.)

Do Advanced Cardiac Life Support Drugs Increase Resuscitation Rates From In-Hospital Cardiac Arrest?

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For the OTAC Study Group

Study objective: The benefit of Advanced Cardiac Life Support (ACLS) medications during cardiac resuscitation is uncertain. The objective of this study was to determine whether the use of these medications increased resuscitation from in-hospital cardiac arrest.

Methods: A prospective cohort of patients undergoing cardiac arrest in 1 of 5 academic hospitals was studied. Patient and arrest factors related to resuscitation outcome were recorded. We determined the association of the administration of ACLS drugs (epinephrine, atropine, bicarbonate, calcium, lidocaine, and bretylium) with survival at 1 hour after resuscitation.

Results: Seven hundred seventy-three patients underwent cardiac resuscitation, with 269 (34.8%) surviving for 1 hour. Use of epinephrine, atropine, bicarbonate, calcium, and lidocaine was associated with a decreased chance of successful resuscitation ($P < .001$ for all except lidocaine, $P < .01$). While controlling for significant patient factors (age, gender, and previous cardiac or respiratory disease) and arrest factors (initial cardiac rhythm, and cause of arrest), multivariate logistic regression demonstrated a significant association between unsuccessful resuscitation and the use of epinephrine (odds ratio .08 [95% confidence interval .04–.14]), atropine (.24 [.17–.35]), bicarbonate (.31 [.21–.44]), calcium (.32 [.18–.55]), and lidocaine (.48 [.33–.71]). Drug effects did not improve when patients were grouped by their initial cardiac rhythm. Cox proportional hazards models that controlled for significant confounders demonstrated that survivors were significantly less likely to receive epinephrine ($P < .001$) or atropine ($P < .001$) throughout the arrest.

Conclusion: We found no association between standard ACLS medications and improved resuscitation from in-hospital cardiac arrest. Randomized clinical trials are needed to determine whether other therapies can improve resuscitation from cardiac arrest when compared with the presently used ACLS drugs.

[van Walraven C, Stiell IG, Wells GA, Hébert PC, Vandemheen K, for the OTAC Study Group: Do Advanced Cardiac Life Support

secondary to co-intervention. Second, the number of patients surviving to hospital discharge was small, thereby limiting any analysis. Finally, if no association between a medication and successful resuscitation at 1 hour exists, it is unlikely that survival to discharge would be changed by the medication.
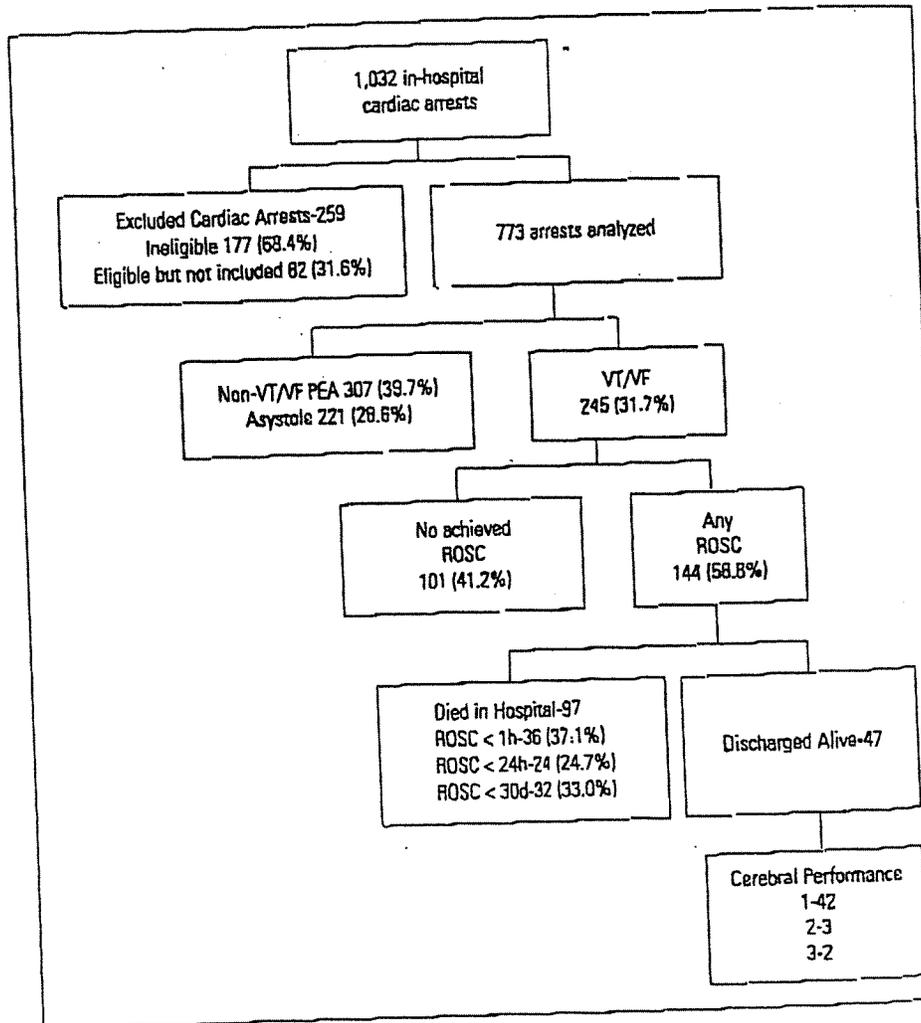
Data analysis

The association of each ACLS medication with survival to 1 hour was determined by describing drug administration as given or not (using the χ^2 test) and as the time to drug administration (using Student t test). To determine each drug's association with resuscitation outcome while controlling for potentially significant confounding variables, multivariate logistic regression using model-building strategies suggested by Kleinbaum et al[11] was used. Confounding variables were defined as those with a sig-

nificant ($P<.1$) univariate association with resuscitation outcome and were included in the logistic models. Logistic models did not show changes in the association of each drug with resuscitation outcome when either standard or ACD-CPR was used.[10] We did not model other specific interactions because we wanted to attain an overall estimate of each drug's effect adjusted for the confounders.[11] To identify subgroups that would benefit from the drugs, these models were repeated grouping patients by their initial cardiac rhythm.

Cox proportional hazards analysis was used to compare the proportion of survivors and nonsurvivors who received each medication by each minute of the resuscitation. For each drug, we modeled time to drug administration (dependent variable) while controlling for all significant confounders (independent variables) and grouping patients by survival status (stratifying variable). These

Figure 1.
Course of patients undergoing cardiac arrest during study. Eligibility criteria for study are listed in the Methods section. Cerebral performance refers to patients' cognitive function classification at hospital discharge. A rating of 1 indicates good function; 2 indicates moderate cerebral disability; and 3 indicates severe cerebral disability.[51] VT/VF, Ventricular tachycardia or fibrillation; ROSC, return of spontaneous circulation.

time from the start of CPR to defibrillation was significantly shorter in a successful resuscitation (4.9 minutes versus 8.0 minutes; $P<.001$). Survivors were more likely to have ventricular tachycardia or fibrillation (VT/VF) as their initial cardiac rhythm (40.6% versus 27.2%; $P<.001$) and were more likely to have a respiratory problem initiating their arrest (26.0% versus 11.6%; $P<.001$). Chronic ischemic heart disease was less prevalent in survivors (44.6% versus 51.0%; $P=.09$), but they were more likely to have a chronic respiratory disease (19.0% versus 13.7%; $P=.05$).

Table 2 displays the association of cardiac drug use and resuscitation outcome. Patients whose resuscitation was unsuccessful were significantly more likely to have received each of the ACLS medications except for bretylium. None of the drugs was significantly associated with an improved resuscitation outcome. Calcium was the only drug for which earlier administration was significantly associated with survival (survivors 8.47 minutes versus nonsurvivors 15.00 minutes; $P<.001$).

Using multivariate logistic regression, the association between each drug with resuscitation outcome was determined while controlling for confounding patient (age, gender, and previous cardiac or respiratory disease) and arrest (initial cardiac rhythm and cause) variables (Table 3). Odds ratios less than 0 indicate that drug administration was associated with a worse resuscitation outcome. The administration of almost all medications was significantly associated with a worse outcome. For each model, the likelihood ratio test was significant ($P<.001$) indicating that, overall, the model fit the data well. For all drugs, the models fit the data well as indicated by Hosmer-Lemeshow statistics that

Table 3.
Multivariate association between cardiac drugs and resuscitation outcome.

Drug	No. Patients Receiving Drug	Odds Ratio	95% Confidence Interval
Epinephrine	683	.08	.04, .14
Atropine	579	.24	.17, .35
Bicarbonate	257	.31	.21, .44
Calcium	105	.32	.18, .55
Lidocaine	214	.48	.33, .71
Bretylium	53	.55	.29, 1.07

The dependent variable is survival to 1 hour. An odds ratio less than 1.0 indicates the variable is associated with a decreased probability of survival at 1 hour. The effects of patient age and gender, initial cardiac rhythm, suspected cause of arrest, and chronic cardiac or respiratory disease were controlled for in all models

were greater than .2. Exceptions to this included calcium ($P=.08$) and bretylium ($P=.18$), whose models did not fit the data well. For each model, fewer than 10 observations (1.2%) had studentized residuals of more than 2.0.

To determine whether the association between cardiac drug use and resuscitation outcome varied with the initial cardiac rhythm, separate logistic regression models were performed for patients whose initial cardiac rhythm was VF/VT, pulseless electrical activity (PEA), or asystole (Table 4). Again, these models controlled for the effect of all significant confounding variables. Even when stratified by initial cardiac rhythm, none of the cardiac medications was associated with an improved outcome. Epinephrine, atropine, and bicarbonate were significantly associated with death in all 3 rhythm groups. The only medication whose association with resuscitation outcome varied significantly with initial cardiac rhythm was atropine, with slightly better outcomes when the initial rhythm was PEA. For patients whose initial cardiac rhythm was ventricular tachycardia or fibrillation, the inclusion of "time to defibrillation" in

Table 4.
Association between cardiac drugs and resuscitation outcome based on initial cardiac rhythm.

Variable	No. Receiving Drug	Odds Ratio	95% Confidence Interval
Initial rhythm ventricular tachycardia or fibrillation (n=245)			
Epinephrine	199	.06	.02, .15
Atropine	160	.16	.09, .29
Bicarbonate	75	.41	.23, .74
Calcium	32	.32	.13, .79
Lidocaine	42	.53	.31, .90
Bretylium	36	.56	.26, 1.23
Initial rhythm pulseless electrical activity (n=307)			
Epinephrine	267	.09	.04, .25
Atropine	221	.39	.21, .70
Bicarbonate	111	.25	.13, .48
Calcium	37	.24	.08, .76
Lidocaine	48	.31	.12, .78
Bretylium	10	.53	.09, 3.06
Initial rhythm asystole (n=221)			
Epinephrine	208	.11	.03, .43
Atropine	188	.23	.10, .51
Bicarbonate	67	.29	.14, .61
Calcium	35	.41	.16, 1.05
Lidocaine	43	.49	.22, 1.11
Bretylium	7	.39	.05, 3.43

The dependent variable is survival to 1 hour. An odds ratio less than 1.0 indicates the variable is associated with a decreased probability of survival at 1 hour. The effects of patient age and gender, initial cardiac rhythm, suspected cause of arrest, and chronic cardiac or respiratory disease were controlled for in all estimates.

trolling for resuscitation delay, endobronchial intubation, and whether the arrest was witnessed, epinephrine remained a predictor of unsuccessful resuscitation (odds ratio .5; 95% confidence interval .25–1.0).[25] Roberts et al[13] studied 310 consecutive in-hospital arrests and demonstrated a significant association between epinephrine and mortality (P=.0003). No improvement in survival was noted when higher doses of epinephrine were used during resuscitation.[26,27] In a randomized trial, patients who received epinephrine between countershocks had significantly lower resuscitation rates compared with those who received no drug.[7] Beurel et al[28] demonstrated that the administration of epinephrine was an independent predictor of death after in-hospital resuscitation. Increased amounts of epinephrine during resuscitation were significantly associated with acute renal failure after arrest, which is a significant predictor of death.[29]

Several physiologic explanations have been suggested to explain epinephrine's lack of benefit and possible harm.[30-32] However, the association of epinephrine and unsuccessful resuscitation is confounded by the increased probability of epinephrine utilization when patients are not revived. Although multivariate statistical methods attempt to adjust for this, the extremely heterogeneous and complex nature of patients undergoing cardiac arrest makes this a difficult feat.

This problem also applies to the rest of the ACLS drugs. We believe that randomized clinical trials are the best method of determining if new therapies, such as vasopressin,[33] improve outcomes when compared with standard ACLS drugs currently in use. With large randomized trials, treatment groups are balanced for both known and unknown confounders. Also, prospective trials permit the collection of the precise clinical parameters in which the drugs were administered. This information could be used in multivariate analyses to control for extraneous factors and possibly identify subgroups who might benefit from drugs given during resuscitation.

The effect of atropine and bicarbonate on resuscitation rates has also been questioned. Small case series have shown that atropine is beneficial during cardiac arrest.[34] Larger studies have produced conflicting results with some showing a significant benefit from atropine[4] and others showing none.[5] Animal models have shown no difference in recovery rates from PEA with atropine versus placebo.[35] In addition to epinephrine, the use of atropine has been associated with a significantly increased mortality for both in-hospital[36] and out-of-hospital[37] cardiac arrests. Laboratory[32] and clinical[38] studies evaluating the use of sodium bicarbonate also have produced conflicting results. The strongest evidence that raises doubt regarding bicarbonate's efficacy comes from a double-blind, randomized controlled trial of 245 patients where bicarbonate compared with placebo did not improve resuscitation outcome.[39]

Several studies of calcium during resuscitation have been performed. Small studies have shown a direct correlation between duration of resuscitation, low serum ionized calcium levels, and mortality. These observations have increased hope that calcium would improve resuscitation rates.[40] One randomized, blinded study with 90 patients showed a strong trend (P=.07) toward improved resuscitation rates for patients whose initial rhythm was PEA who were randomly assigned to the calcium arm.[41]

Figure 3.
Proportion of survivors and non-survivors receiving atropine. The figure shows the percentage of patients who received atropine by each minute of the resuscitation plotted for survivors (squares) and nonsurvivors (circles). These Cox proportional hazards models controlled for significant patient factors (including age, gender, and chronic history of cardiac or respiratory illness) and arrest factors (initial cardiac rhythm and cause of arrest). Ninety-five percent confidence intervals are provided.
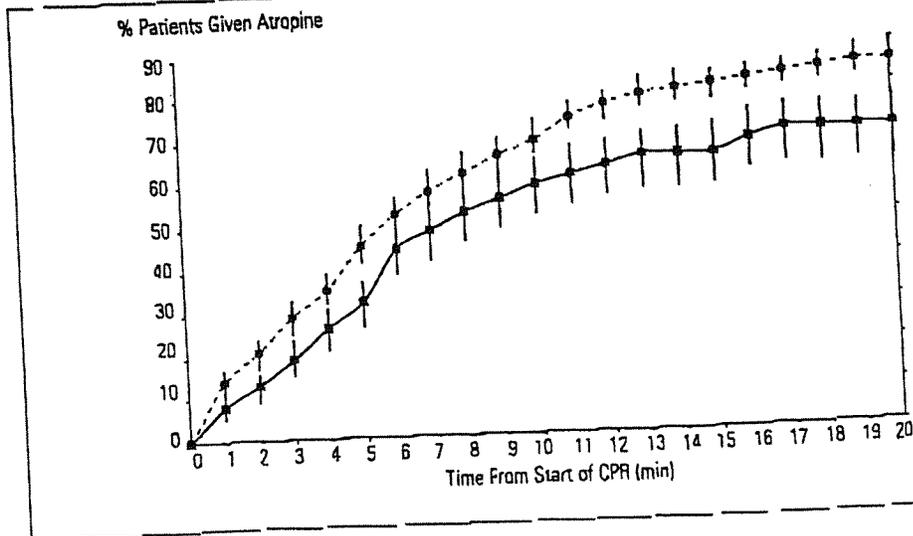
tation. For example, 160 patients whose initial rhythm was ventricular tachycardia or fibrillation received atropine during the resuscitation (Table 4), indicating that in these patients asystole, PEA, or a slow pulseless rhythm likely developed at some time during the resuscitation.

Second, we did not determine whether the medications were administered by central or peripheral line, or whether peripheral administrations were followed by saline solution bolus and limb elevation.[45] Third, although all supervisors of the cardiac arrests had ACLS certification, we are unable to determine how compliant these physicians were with ACLS recommendations. Compliance with ACLS protocols, however, has not been shown to correlate with resuscitation outcome.[16,47] Fourth, although the logistic and Cox regression models fit our data well, we did not validate the models and are unsure if they would appropriately describe a different sample of cardiac arrests. In addition, our models did not explore interactions between the various ACLS medications and resuscitation outcome.

Finally, and most importantly, patients having cardiac arrest are extremely variable and complex. It may be naive to expect a significant benefit from a single medication in such a heterogeneous patient group. Many physicians recall cases where ACLS medication use seemed to be the difference between life and death for a particular patient. Perhaps a more accurate assessment of patient prognosis at resuscitation initiation[48] or invasive monitoring to guide therapy[49] would give these medications a better chance of showing a benefit. Further studies in this area must try to collect these and other important intra-arrest data to more accurately identify which patients benefit from these drugs.

In summary, our exploratory analysis of prospectively collected data for 773 patients with in-hospital cardiac arrest associated the use of ACLS medications with increased mortality. We could not identify any subgroup of patients who may clearly benefit from any of these medications. Although further research into the treatment of patients not responding to defibrillation will be difficult,[50] it is necessary. We advocate the design and execution of large randomized clinical trials to determine whether other therapies improve resuscitation rates compared with the presently used ACLS drugs.

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Effect of Epinephrine and Lidocaine Therapy on Outcome After Cardiac Arrest Due to Ventricular Fibrillation

W. Douglas Weaver, MD, Carol E. Fahrenbruch, MSPH, Deborah D. Johnson, RN,

Alfred P. Hallstrom, PhD, Leonard A. Cobb, MD, and Michael K. Copass, MD

One hundred ninety-nine patients with out-of-hospital cardiac arrest persisted in ventricular fibrillation after the first defibrillation attempt and were then randomly assigned to receive either epinephrine or lidocaine before the next two shocks. The resulting electrocardiographic rhythms and outcomes for each group of patients were compared for each group and also compared with results during the prior 2 years, a period when similar patients primarily received sodium bicarbonate as initial adjunctive therapy. Asystole occurred after defibrillation with threefold frequency after repeated injection of lidocaine (15 of 59, 25%) compared with patients treated with epinephrine (four of 55, 7%) ($p<0.02$). There was no difference in the proportion of patients resuscitated after treatment with either lidocaine or epinephrine (51 of 106, 48% vs. 50 of 93, 54%) and in the proportion surviving (18, 19% vs. 21, 20%), respectively. Resuscitation (64% vs. 50%, $p<0.005$) but not survival rates (24% vs. 20%) were higher during the prior 2-year period in which initial adjunctive drug treatment for persistent ventricular fibrillation primarily consisted of a continuous infusion of sodium bicarbonate. The negative effect of lidocaine or epinephrine treatment was explained in part by their influence on delaying subsequent defibrillation attempts. Survival rates were highest (30%) in a subset of patients who received no drug therapy between shocks. We conclude that currently recommended doses of epinephrine and lidocaine are not useful for improving outcome in patients who persist in ventricular fibrillation. Lidocaine administration is commonly associated with asystole, and any possible attribute of initial adjunctive drug therapy is outweighed by its detrimental effect on delaying successive shocks for persistent ventricular fibrillation. (*Circulation* 1990;82:2027–2034)

The rationale for specific drugs administered during cardiac arrest is primarily based on observations made during experimental animal studies or from patients with ventricular arrhythmias complicating acute myocardial infarction. The American Heart Association Guidelines for Advanced Cardiac Life Support emphasize the use of both epinephrine and lidocaine for patients who persist in ventricular fibrillation after initial attempts at defibrillation.[1] During experimental cardiac arrest, epinephrine administration results in higher rates of resuscitation, seemingly by augmenting myocardial blood flow during chest compression.[2–8]. Lidocaine is also often used to treat persistent ventricular fibrillation because the drug has been shown in some studies to prevent the emergence of ventricular fibrillation during the early hours of acute myocardial infarction.[9–11] Other studies, however, have shown that lidocaine increases defibrillation energy level requirements and is relatively ineffective in terminating ventricular tachyarrhythmias after they have been established.[12–17]

Ventricular fibrillation persists after initial defibrillation attempts in 25–40% of patients discovered in cardiac arrest and may present a condition quite different from either acute myocardial infarction or experimental resuscitation, and thus may have different drug requirements.[18,19] The purpose of this trial was to determine prospectively whether the initial administration of either epinephrine or lidocaine improved resuscitation results in patients discovered in ventricular fibrillation that was refractory to an initial defibrillation attempt.