The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres

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BACKGROUND: Although amiodarone significantly increases survival to hospital admission when used in resuscitation of out-of-hospital pulseless ventricular tachycardia and fibrillation, there are limited data on its utility for in-hospital arrests.

OBJECTIVES: To determine whether the use of amiodarone, as recommended by the year 2000 American Heart Association Advanced Cardiac Life Support guidelines, improved survival following its introduction to the resuscitation algorithm at two tertiary care institutions.

METHODS: Charts of 374 cardiac resuscitations were retrospectively studied at the two institutions. Basic survival outcomes and demographic data were recorded for cardiac arrests with ventricular tachyarrhythmias qualifying for administration of antiarrhythmic agents.

RESULTS: Qualifying rhythms were present in 95 patients. Clinical uptake of amiodarone was limited. In the 36 patients who received amiodarone, survival of resuscitation was 67% versus 83% ($P=0.07$) in the 59 patients receiving only other antiarrhythmic agents (chiefly lidocaine [94%]), while survival to discharge was 36.1% and 55.9% ($P=0.06$) in these two groups, respectively.

CONCLUSIONS: Following two years' experience with the introduction of intravenous amiodarone for resuscitation in the institutions, use was less than 50% and no clinically observable survival benefit could be documented. Possible explanations for the difference between this experience and that found in out-of-hospital resuscitation trials include differing patient populations and operator bias during resuscitation. These results should provoke other institutions to question whether amiodarone has improved survival of cardiac arrest under the conditions prevailing in their hospitals. A patient registry or prospective, randomized trial will be required to assess what parameters affect the success of intravenous amiodarone for resuscitation in-hospital.

Key Words: *Advanced cardiac life support; Amiodarone; Antiarrhythmic drugs*

Intravenous amiodarone was shown to provide a clear short-term survival benefit in two recent trials, Amiodarone in the out-of-hospital Resuscitation of REfractory Sustained ventricular Tachyarrhythmias (ARREST) (1) and Amiodarone versus Lidocaine In prehospital Ventricular fibrillation Evaluation (ALIVE) (2). These studies involved resuscitation of pulseless ventricular tachycardia/fibrillation in an out-of-hospital setting. Based on the reasonable assumption that this survival advantage could be generalized to resuscitations performed in the in-hospital setting, intravenous amiodarone was added to the American Heart Association (AHA) guidelines for Cardiopulmonary

Le recours à l'amiodarone en cas d'arrêts cardiaques en milieu hospitalier dans deux centres de soins tertiaires

HISTORIQUE : Bien que l'amiodarone accroisse considérablement la survie en attendant l'hospitalisation lorsqu'elle est utilisée dans la réanimation de cas de tachycardie et de fibrillation ventriculaires non pulsatiles, les données sont limitées quant à son utilité en cas d'arrêts en milieu hospitalier.

OBJECTIFS : Déterminer si le recours à l'amiodarone, tel qu'il est recommandé dans les lignes directrices de 2000 sur la réanimation cardiorespiratoire spécialisée de l'American Heart Association, améliore la survie après son ajout à l'algorithme de réanimation dans deux établissements de soins tertiaires.

MÉTHODOLOGIE : Les dossiers de 374 réanimations cardiaques ont été étudiés rétrospectivement dans les deux établissements. Les principales issues de survie et données démographiques ont été consignées à l'égard des arrêts cardiaques accompagnés de tachyarythmie ventriculaire admissibles à l'administration d'antiarythmiques.

RÉSULTATS : 95 patients présentaient des rythmes admissibles. Le captage clinique de l'amiodarone était limité. Chez les 36 patients qui en ont reçu, la survie après la réanimation s'élevait à 67 %, par rapport à 83 % ($P = 0,07$) chez les 59 patients qui n'avaient reçu que d'autres antiarythmiques, principalement de la lidocaïne (94 %). La survie au congé était de 36,1 % et de 55,9 %, respectivement ($P = 0,06$) au sein de ces groupes.

CONCLUSIONS : D'après une expérience de deux ans après l'adoption de l'amiodarone intraveineuse pour la réanimation dans l'établissement, on l'utilisait dans moins de 50 % des cas, et aucun bienfait cliniquement observable sur la survie n'a pu être documenté. La disparité entre notre expérience et les résultats d'essais sur la réanimation extrahospitalière s'explique peut-être par des populations de patients différentes et par un biais de l'opérateur pendant la réanimation. Ces résultats devraient inciter d'autres établissements à se demander si l'amiodarone a amélioré la survie en cas d'arrêts cardiaques dans les conditions qui ont cours à leur hôpital. Un registre de patients ou un essai aléatoire prospectif s'imposerait pour évaluer quels paramètres influent sur le succès de l'amiodarone intraveineuse dans la réanimation en milieu hospitalier.

Resuscitation and Emergency Cardiovascular Care (AHA 2000 Adult Advanced Cardiac Life Support [ACLS] guidelines). In these guidelines, intravenous amiodarone received a class IIb recommendation (usefulness/efficacy is less well established by evidence or opinion) for the treatment of ventricular fibrillation and pulseless ventricular tachycardia in both out-of-hospital and in-hospital settings. In contrast, lidocaine had insufficient evidence for a strong endorsement (3,4). No trials comparing the efficacy of antiarrhythmic agents in the manner conducted in ARREST and ALIVE have been carried out to establish the survival benefit of intravenous amiodarone for in-hospital arrests.

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Following adoption of the AHA 2000 ACLS guidelines, the formulary policies at our two tertiary care institutions were updated to make intravenous amiodarone available on all resuscitation carts. A limited, retrospective, cohort study was then undertaken for quality of care purposes on behalf of our Drugs and Therapeutics Committees. The present study examined the clinical uptake of amiodarone and addressed the specific question 'has the introduction of intravenous amiodarone to the in-hospital cardiac resuscitation algorithm improved basic survival outcomes for cardiac arrest at our institutions?' and, if so, what is the magnitude of the benefit of this policy modification under real world clinical practice conditions? A retrospective design was employed to provide a rapid answer to the question.

METHODS

Specifically tutored medical trainees were used to extract the data at the two institutions. Permissions were obtained from the respective institutional Ethics and Health Records Committees for data extraction from charts of patients who had suffered in-hospital cardiac arrest within a period of two years. These included 374 patients in medical and surgical wards, and in the intensive care units. Emergency room resuscitations were excluded to maintain a more homogenous in-hospital study population. The resuscitations were performed by a 'code' team staffed by ACLS-certified resident physicians, except in the intensive care units, where the on-duty residents and intensive care unit health care staff (critical care nurses and respiratory therapists) carried out the resuscitations. The amiodarone available on the arrest carts was a generic intravenous form. Only records from patients with ventricular arrhythmias appropriate for administration of antiarrhythmic agents were abstracted – specifically, pulseless ventricular tachycardia and ventricular fibrillation. For patients who had suffered multiple arrests, only data from the first cardiac arrest were recorded. Both institutions from which data were collected are tertiary care, academic hospitals serving urban populations with many elderly patients. The Queen Elizabeth II Health Sciences Centre is a 650-bed institution in Halifax, Nova Scotia, and the London Health Sciences Centre is a 780-bed institution in London, Ontario. They differed only in being located 1900 km apart and functioning under disparate, publicly funded, provincial health care systems.

The dichotomous study end points, chosen to reduce the complexity of data extraction, were survival of resuscitation effort to return of spontaneous circulation, and survival to discharge. Patient cohorts were defined as those who had received intravenous amiodarone at any point during resuscitation or those who had received only other antiarrhythmic agents, predominantly lidocaine. Because of inconsistencies in the documentation of data in the arrest records, additional collection of data of sufficient quality to be useful was limited to the patients' age, sex and exposure to medications. Other demographic variables were not recorded in the charts with a consistency adequate for reliable analysis. Attempts to use such data did not improve the quality of the information provided by the analysis. Continuous variables were summarized as means and standard deviations and were compared using the Student's *t* test. Categorical outcomes were summarized as proportions and compared with χ^2 analysis. All *P* values reported are two-sided, with *P* < 0.05 considered significant.

RESULTS

After its introduction to the arrest carts, the clinical uptake of amiodarone use for cardiac arrest showed no detectable trend

toward increasing adoption. Over the two-year course of the study, amiodarone was used in 43% of arrests during the first six-month period after its introduction, and 18 months later during the last six-month period of the study, it was still used in only 37% of arrests. Of 374 patients identified as suffering a cardiac arrest, 95 (25%) suffered pulseless ventricular tachycardia/fibrillation amenable to acute therapy with antiarrhythmic agents. Intravenous amiodarone was administered to 36 patients, while 59 patients received only other antiarrhythmic agents during resuscitation. Of those 59 patients, lidocaine was administered to 94% and bretylium to 6%. Duration of cardiac resuscitation efforts was clearly recorded in 77 patients. For these patients, the mean $\pm$ SD duration for arrests involving amiodarone was 32.9 $\pm$ 28.1 min versus 25.82 $\pm$ 25.2 min (*P* = 0.25) for arrests using only other antiarrhythmic agents. There were also no statistically significant differences in age (63.9 $\pm$ 11.5 years versus 64.5 $\pm$ 15.7 years; *P* = 0.84) or sex (63% versus 56% men; *P* = 0.59) between the groups of patients receiving and not receiving amiodarone, respectively.

Among patients treated with amiodarone, short-term survival to return of spontaneous circulation was 66.7% (95% CI 50% to 80%), in comparison with 83.0% (95% CI 72% to 91%) in the patients treated with only other antiarrhythmic agents (OR = 2.45, 95% CI 0.94 to 6.38; *P* = 0.07). Survival to discharge was 36.1% for patients treated with amiodarone (95% CI 23% to 53%) and 55.9% for patients treated with only other antiarrhythmic agents (95% CI 43% to 68%) (OR = 2.25, 95% CI 0.96 to 5.23; *P* = 0.06). There was no evidence of heterogeneity in postresuscitation survival or survival to discharge between the two institutional sites.

To evaluate the chance that the experience with amiodarone in the two institutions had randomly failed to observe a true benefit from intravenous amiodarone after two years of use, a conditional power analysis was performed. The question asked was, 'given the pattern established in the first 95 patients, what would be the likelihood that given five years of use in the institutions, amiodarone would show a benefit in short-term survival equal in magnitude to that found in the ARREST trial?' This analysis predicted there would be only a 9% chance that such a benefit would be demonstrated given the proposed conditions.

DISCUSSION

The straightforward goal of this retrospective study was to determine if the introduction of intravenous amiodarone to the in-hospital resuscitation algorithm was associated with improved survival of cardiac arrests at the institutions. Although medication costs are not the primary motivator of therapeutic decisions, they were a motivator in conducting this study. At the time of the study, the generic intravenous amiodarone required for a typical cardiac arrest was 20 times the cost of the \$4 vial of lidocaine it replaced. Therefore, it was hoped that data supporting a survival benefit for amiodarone would be found to assure public payers of value for money spent.

The results were unexpected. Not only was the uptake of intravenous amiodarone use in cardiac arrest following the AHA 2000 ACLS guidelines surprisingly flat, but contrary to the a priori expectation that a survival benefit would be confirmed for the use of amiodarone, no statistical differences in outcomes were observed.

The study was of modest design, assessing a limited clinical question, and not gathering supplementary data of sufficient

quality to provide an explanation for the unexpected lack of benefit from amiodarone. However, such unexpected results from trial-proven therapy have been encountered in other retrospective studies. Westerhout et al (5) found that the clinical uptake of abciximab was not associated with the expected benefits demonstrated in clinical trials, and even their larger data set and more sophisticated observational design did not yield the exact reasons for this unexpected result. Even randomized prospective trials can fail to clearly explain why no overall benefit is demonstrated when a theoretically superior cardiac arrest management strategy is applied in a clinical setting, as occurred in the Australian Medical Early Response Intervention and Therapy (MERIT) study (6).

The expectation of improved outcomes in our study came from two trials that did show that amiodarone improved survival in cardiac resuscitation, but in an out-of-hospital setting. The first trial, ARREST, studied 504 patients who had undergone three defibrillatory shocks and been given 1 mg of adrenaline for ventricular fibrillation or for pulseless ventricular tachycardia outside of hospital (1). Patients were randomly assigned to receive either a single 300 mg bolus of intravenous amiodarone or a corresponding placebo followed by standard ACLS medications and procedures. Of the 246 patients who received amiodarone, 44% survived to hospital admission versus 34% of the 258 patients receiving placebo ($P=0.03$). Survival to hospital discharge did not differ between the amiodarone and placebo groups (13.4% versus 13.2%, respectively). The second trial, ALIVE, studied a similar out-of-hospital population of 347 patients experiencing ventricular fibrillation after three defibrillatory shocks and 1 mg of adrenaline (2). ALIVE differed from ARREST in its use of an active control and weight-adjustment of the intravenous antiarrhythmic agents. Patients were randomly assigned to receive amiodarone 5 mg/kg intravenously or lidocaine 1.5 mg/kg intravenously. If they still failed to recover, one-half the previous dose of amiodarone or a repeat full dose of lidocaine was administered with an additional shock. Of the 180 patients who received amiodarone, 23% survived to hospital admission, while only 12% of 167 patients receiving the lidocaine did so ($P=0.009$). There was no difference in survival to discharge.

Our inability to demonstrate a similar benefit associated with intravenous amiodarone used in an in-hospital setting was disconcerting. However, our results are consistent with personal communications received concerning an examination of the same question at two institutions in Cincinnati, Ohio. A retrospective review of 230 patients in those hospitals was similarly unable to demonstrate an advantage of intravenous amiodarone for in-hospital cardiac arrest (Reuter, personal communication, April 5, 2005). Because every arrest occurring during the study periods of both reviews was analyzed, the data fully represent the initial experiences with intravenous amiodarone at four disparate institutions, not an arbitrary sample from a single hospital.

It was quite clear that there was no pharmacological reason to expect amiodarone to be inferior to lidocaine in resuscitation (4). The use of lidocaine is largely based on its effectiveness in preventing ventricular arrhythmias following myocardial infarction (7,8) rather than on evidence of improved patient survival (9-11). In out-of-hospital resuscitations, lidocaine did not increase the rate of successful cardioversion (12) or survival to hospital discharge (13). Thus, it is tempting to disregard our negative results as observational

error and continue forward with no further examination of amiodarone resuscitation policies. However, it was thought that only publication of these findings would stimulate support for a definitive study as to whether intravenous amiodarone improves survival of resuscitation in an in-hospital setting.

In speculating on the reasons for the difference between our observations and those of the out-of-hospital arrest trials, we do acknowledge the limitations of a retrospective chart review. These include the following: incomplete documentation in the charts; retrospective collection of data; nonrandom assignment of drug intervention; and the inability to control for both bias in the application of the drug and other confounding factors. Variations in the quality of data recorded in the charts limited practical use of many parameters in interpreting the reasons underlying our results. As encountered in the Australian MERIT study (6), the survival rate from standard therapy was unexpectedly high. Just as the lack of events may have obscured any benefit of the medical emergency teams on the outcome of cardiac arrest, it may have played a role in our inability to detect a benefit from amiodarone. With a limited pool of arrests to examine, attempts at subanalysis using multivariate regression of patient-specific factors was unsuccessful. In contrast, a prospective study could have dictated drug dosage according to protocol and systematized collection of data on response times, underlying pathology, ventricular function, medications on admission, etc.

Nonetheless, several differences are apparent between the environment in which amiodarone was used in our hospitals and that existing for the ARREST and ALIVE trials.

First, regardless of what therapy patients received, the rate of return of spontaneous circulation was several-fold better than for patients in the out-of-hospital trials. In our institutions, spontaneous circulation returned in 83% of patients receiving lidocaine therapy compared with only 12% seen in the lidocaine arm of the ALIVE trial (2) and the 40% reported for all types of cardiac arrest recorded worldwide (14,15). These higher survival rates are likely explained by the fact that in-patient cardiac arrests benefit from shorter time to initiation of resuscitation, an important predictor of survival (16). Also, resuscitation of medically inappropriate patients with poor survival rates is more easily avoided in hospitals through the systematic application of advance directives and 'do not resuscitate' orders. Furthermore, by selecting and analyzing only the 25% of arrests potentially benefiting from antiarrhythmic therapy, the retrospective study avoids any dilution of success rates from patients having inappropriate rhythms for antiarrhythmic therapy. It should certainly be noted that the high rate of successful resuscitations for in-patient cardiac arrests diminishes any potential 'head room' for absolute improvement, even if a nearly perfect agent were introduced to resuscitation therapy.

Second, persons arresting out-of-hospital might be expected to have fewer concomitant health issues than in-hospital patients and, therefore, if resuscitated early enough, they would be more likely to derive a benefit from a pharmacologically effective therapy.

Third, bias in the application of amiodarone could not be controlled among the various classes of resuscitation providers found in our institutions. It would appear that, despite the new guidelines, providers applying ACLS remained unconvinced that amiodarone was the drug of choice in cardiac arrest. Less than 50% of the arrests in our institutions were treated with

amiodarone. In addition, if arrests involving amiodarone were truly 7 min longer in duration, then this suggests that many providers applied amiodarone as a drug of last resort. Reserving amiodarone for patients deemed less likely to survive would certainly bias against finding any association with improved outcomes. Unfortunately, data to confirm this were not consistently recorded, especially in the intensive care units where the arrest team was not called.

Thus, treatment populations and ACLS providers differed between out-of-hospital and in-hospital settings and this may in fact be the explanation for the differing observations. The weaknesses of the retrospective approach we took and our inability to collect data of sufficient quantity and consistent quality to prove this and adjust for differences in patient characteristics leaves the unexpected questions raised by our results unanswered. Randomization of patients in a clinical trial is the ideal way of eliminating bias in the answering of therapeutic questions, but retrospective studies, such as those identifying the association between smoking and lung cancer, have always served as a useful way to identify the clinical questions that need to be answered. They are often essential to justify funding of further research. While such studies seldom identify the etiology of the trends they observe, ignoring their results simply because they do not provide mechanistic answers would have left many important medical questions unconsidered.

CONCLUSIONS

Despite its limitations, the present retrospective study did provide an answer to the circumscribed question originally proposed. Not only was uptake of the use of intravenous amiodarone for cardiac arrest surprisingly flat, but after two years' experience with the new policy, no evidence could be found that the introduction of intravenous amiodarone to the cardiac arrest carts was associated with an increased return of spontaneous circulation or survival to discharge. Should the reason for this unexpected outcome prove to be as simple as

bias in application of the medication, this result itself would still warrant further consideration.

In light of these results, it would be prudent for any large hospital to ask the following questions: have the physicians conducting resuscitation adopted the use of amiodarone as recommended in the AHA 2000 ACLS guidelines?; when amiodarone is used, is it being reserved for the most desperate cases?; and, has the introduction of amiodarone altered outcomes for cardiac arrests in their institutions?

Clearly, the present retrospective study does not provide evidence for a change in clinical practice. Rather, it raises questions that should be considered at any institution using amiodarone for in-hospital cardiac arrests. Even if limited to nonrandomized outcome comparisons, further study at other institutions would have merit in determining how widespread these findings are. Certainly, the questions raised about the conditions under which amiodarone is applied during cardiac resuscitations would best be addressed through a prospective randomized, controlled trial comparing intravenous amiodarone with lidocaine in the in-hospital cardiac arrest setting. However, establishment of a registry of patient data from multiple institutions may prove to be a more practical solution to providing enough data to ascertain the reasons why amiodarone may not always be associated with improved cardiac arrest outcomes in the in-hospital setting.

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