Amiodarone and apparently unimproved survival from in-hospital cardiac arrest: Association, causation or a mix of both?

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In the present issue of *The Canadian Journal of Cardiology*, Pollak et al (pages 199 to 202) report the results of their study on the use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. Cardiac arrest research is notoriously difficult to carry out, and the authors deserve praise for their efforts to shed further light on the issue of antiarrhythmics in pulseless ventricular tachycardia and ventricular fibrillation. That said, no study is perfect, and the onus rests with readers to carefully consider the limitations of this study while interpreting the findings and determining what conclusions are warranted.

Pollak et al sought to answer the question ‘has the introduction of intravenous amiodarone to the in-hospital cardiac resuscitation algorithm improved basic survival outcomes for cardiac arrest at our institutions?’. They undertook a retrospective observational study of 95 cardiac arrest patients with ventricular arrhythmias at two institutions, and compared outcomes of those who received amiodarone with those who received other antiarrhythmics (predominately lidocaine) over a two-year period. The results indicated that both return of spontaneous circulation (ROSC) (66.7% versus 83.0%) and survival to hospital discharge (36.1% versus 55.9%) were lower for amiodarone than for other agents. The wide confidence intervals of the estimates for both outcomes overlapped and the differences were not statistically significant, possibly because of the small sample size. Nonetheless, this study suggests that the short- and long-term survival outcomes of cardiac arrest patients who received amiodarone at the institutions involved were no better, and may have been worse, than for those who received other agents. If this finding was not due to chance, then it remains unclear whether it represents association, causation or a mix of both.

The study conclusion states “...no evidence could be demonstrated that the introduction of intravenous amiodarone to the cardiac arrest carts was associated with an increased return of spontaneous circulation or survival to discharge”. Although arguably true, this statement is misleading in that its truth predominately arises not from the study results, but because of the weaknesses of the study design. In reality, the study as carried out was virtually incapable of isolating and quantifying the effect of amiodarone on return of spontaneous circulation or survival to discharge. This is a fixed limitation, independent of the findings. Thus, even if the outcomes in the amiodarone group had been dramatically superior to the comparison group, the appropriate interpretation would have been equally unclear. Moreover, the reported results do not eliminate the possibility that amiodarone actually benefitted the

subgroup of patients to whom it was administered. The two major reasons for this are acknowledged by the authors in their discussion: the nonrandomized nature of the administration of amiodarone arising from the observational design, and the limited patient-specific data available for analysis.

The differentiation between association and causation is difficult, and relies on the careful evaluation of numerous parameters. Various research designs have different abilities to support causal inferences, and even within the broad category of ‘retrospective studies’ there are distinctions. If, for example, Pollak et al had employed a retrospective case-control design, a before-after design, or a time series design, and the findings had been similar, then an argument for no benefit or a detriment from amiodarone would have been significantly strengthened. The strongest evidence for causality arises when researchers randomly allocate the intervention under investigation, thus increasing the likelihood that known and unknown factors influencing the outcome of interest are balanced between the comparison groups. Two recent randomized, controlled trials of amiodarone in out-of-hospital cardiac arrest provide evidence for a positive effect on short-term survival over placebo or lidocaine (1,2). Pollak et al undertook their study with these results in mind, based on the assumption that the survival advantage demonstrated in the out-of-hospital setting would also be seen in in-hospital cardiac arrest patients.

Perhaps the most interesting finding of the study by Pollak et al was the reported overall use of amiodarone at their institutions. In the first six months after the introduction of amiodarone to their formularies, it was used in 43% of cardiac arrests, while 18 months later, it was used in 37% of cardiac arrests. This led the authors to comment on the “surprisingly flat” uptake of amiodarone. However, the interpretation of this information depends on one’s opinion regarding what impact preliminary research and the grade 2B recommendation for amiodarone in the 2000 Emergency Cardiovascular Care (ECC) guidelines (in contrast to the indeterminate recommendation for lidocaine) (3) should have on clinical practice. Because there has been very little research on how guideline recommendations are translated to clinical practice, the findings in this regard are of particular interest.

One perspective is that given the low overall survival rate from cardiac arrest, the uptake into clinical practice of any potentially beneficial intervention that is not prohibitively complex or costly should be rapid. Such an argument was recently made in a controversial editorial in *The New England*

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Journal of Medicine, which accompanied a study on vasopressin in cardiac arrest (4). A counterargument is that previous cardiac arrest guidelines have been notorious for their endorsement of unproven interventions (some of which, like adrenaline, still remain 'standard therapy'), and that adopting new treatments prematurely is scientifically dishonest, precludes appropriate evaluation, and leads to resource misuse both for training and care delivery.

In the case of amiodarone, the randomized trials to date have only suggested an effect on short-term survival, and not on survival to hospital discharge. As a result, the 2000 ECC recommendations for amiodarone were controversial. At issue was not whether the evidence for amiodarone improving short-term survival exceeded that of lidocaine, but whether this warranted a grade 2B recommendation and what 'message' such a recommendation would send. In fact, the decision to use ROSC or short-term survival as a primary outcome in preliminary cardiac arrest studies, although common, is predicated on the assumption that there is a relationship between such outcomes (as 'predictors' of a clinically relevant treatment effect) and survival to hospital discharge (if a survival benefit actually exists). This assumption has never been proven, and it has been shown that different commonly reported ROSC and short-term survival definitions lead to strikingly different treatment effect estimates (5).

The context of the 2000 ECC guidelines is highly relevant when considering why fewer than one-half of the patients with an eligible rhythm in the study by Pollak et al received amiodarone. Although unstudied, it is conceivable that there may be institutional and individual variation in the enthusiasm with which the controversial grade 2B recommendation for amiodarone translates to clinical care. This, coupled with the 20-fold higher cost of amiodarone over lidocaine when the study occurred, makes it reasonable to speculate that patients who were administered amiodarone during the study period were likely fundamentally different from those who were not. As the authors note, their finding that arrests in the amiodarone group were 7 min longer in duration supports this speculation and the hypothesis that resuscitation leaders may have withheld amiodarone to use as a 'last resort' medication. Given the known reduction in survival for every minute a cardiac arrest patient is in ventricular fibrillation, this single factor could have accounted for the entire outcome difference between the study groups. Further information on the study population, regarding such factors as initial rhythm, 'down time' before arrival of the code team, timing of drug delivery and comorbidities would have facilitated a better understanding of who received amiodarone and when, and how this compared with the other group. Unfortunately, despite the authors' efforts, such information could not be obtained from the charts.

A difference between the results of the study by Pollak et al and the positive randomized trials could only be viewed as unexpected in the fortunate circumstance where all other factors that could influence survival were balanced between the two study groups (as they likely were in the randomized trials).

We cannot determine if this was the case, and what information exists plus scores of analogous observational studies suggest that such a balance is exceedingly unlikely. As a result, as the authors note, it remains conceivable that the patients who received amiodarone in the study had a more dire prognosis than those in the comparison group (in that they were further along in their arrest without responding), potentially undermining the ability to detect a positive treatment effect if one actually exists. Or perhaps the in-hospital cardiac arrest population is different in its response to amiodarone than the out-of-hospital population. Or perhaps amiodarone is actually not superior, or is even detrimental, compared with lidocaine. There are many possibilities for the findings.

In the end, the study by Pollak et al raises far more questions than it answers, and the authors rightfully suggest further research is warranted to understand not only the uptake of ECC guideline recommendations but also the effect on clinical outcomes from changes in treatment approaches. Their call for an in-hospital cardiac arrest registry is a laudable vision, and the need for such a registry has also been proposed recently in this journal for the out-of-hospital cardiac arrest population (6). Clinical trials are expensive, and are not necessarily the ideal means to answer all questions. Rigorously collected data from a cardiac arrest registry would allow secular trends, regional variations and the impact of system and therapy changes to be efficiently evaluated to help reduce the incidence of untimely sudden death.

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COMPETING INTERESTS: Riyadh B Abu-Laban is an ACLS instructor, and sits on two advisory committees for the Heart and Stroke Foundation. He has led two randomized, placebo-controlled cardiac arrest studies, and was an active participant in the literature evaluation and consensus meetings leading to the 2005 Emergency Cardiac Care guidelines.

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