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Editorial Comment

The Amiodarone Odyssey*

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A paradoxic agent. Amiodarone—that pharmacologic enigma—has been seeking its place as a cardiovascular therapeutic agent for >20 years. First developed by Labaz Laboratory in Belgium as an antianginal compound, it was later found to possess antiarrhythmic and electrophysiologic properties (1). It is a puzzling compound, whose pharmacodynamics and pharmacokinetics are poorly understood to this day (2,3). Not just a simple class III agent, amiodarone has many properties: sodium channel blocking, calcium channel blocking, nonspecific sympathetic blocking (3). The drug exerts effects on thyroid metabolism (4) and acts as a phospholipase enzyme inhibitor (5); the latter action may play a significant role in maintaining lipid cell membranes during ischemia. Amiodarone inhibits adenosine triphosphate-sensitive potassium channel activity (6), which may be a factor in modulating arrhythmogenesis during ischemia. In essence, amiodarone possesses anti-ischemic, antiarrhythmic and antifibrillatory properties. These actions have a delayed onset that, coupled with the drug's long elimination half-life (1,2,7), makes it difficult to titrate the optimal dose for individual patients and may also be the reason for its sustained effect. Given these multiple and complex pharmacologic behaviors, it is not surprising that there has been quite a disparity in the reports of the rates of efficacy and toxicity of amiodarone (7–11). The drug's poorly understood pharmacology and its reputed toxicity have made us reluctant to use it except as a last resort.

Nevertheless, most cardiologists believed that amiodarone was worth using in patients with refractory ventricular tachycardia and ventricular fibrillation (7–11). The belief that amiodarone helped those patients when all other standard therapy had failed was recognized by the Food and Drug Administration which, prompted by the reality that large numbers of physicians were prescribing the drug on a compassionate basis, took the unprecedented action of approving the drug even though it had bypassed the established governmental regulatory process of drug approval.

The present study. The study of amiodarone by Ceremuzynski et al. (12) in this issue of the Journal appears in the midst of our struggle with the paradox that the same drug can be at once so helpful and so toxic. These investigators compared amiodarone with placebo in postmyocardial infarction patients who did not necessarily have high density ventricular arrhythmias. Theirs is the first trial to convincingly show that an antiarrhythmic agent—amiodarone—reduces the incidence of cardiac death in postmyocardial infarction patients by reducing the incidence of sudden cardiac death. Like most secondary prevention trials (13,14) (trials of beta-blocking agents or angiotensin-converting enzyme inhibitors), it included all survivors of myocardial infarction except those who had contraindications to beta-blockers. Most deaths in this study were of cardiac origin (all 33 deaths in the placebo group and 19 of the 21 deaths in the amiodarone group). A significant number of these deaths were sudden (within 1 h of the onset of symptoms): 20 in placebo-treated and 10 in amiodarone-treated patients. However, in contrast to findings in the beta-blocker trials, amiodarone did not prevent reinfarction in this study: 14 and 10 patients, respectively, developed reinfarction in the amiodarone and placebo groups. It is thus likely that amiodarone reduces the incidence of sudden cardiac death by primary mechanisms such as antifibrillatory and antiarrhythmic properties rather than by lowering the incidence of ischemia-related ventricular fibrillation episodes because of the drug's favorable effect on the number of ischemic events.

Amiodarone caused remarkably few short-term side effects. At first glance, the incidence of side effects leading to discontinuation of treatment is quite modest. Fifty-five of the 305 amiodarone-treated patients were withdrawn from therapy when they developed "adverse" effects, as opposed to 19 of the 308 placebo-treated patients. But a closer reading of the data shows that most of the patients could have continued treatment with the drug because some of the side effects that led to drug discontinuation were inconsequential. The 11 patients who developed benign first-degree atrioventricular block and were withdrawn from treatment could have continued receiving amiodarone, as could have some of the 14 patients who developed bradycardia if the cutoff range had been altered from a heart rate of 50 beats/min to >45 beats/min, which is a safe threshold. Patients who developed right or left bundle branch block or QT interval prolongation also could have continued to receive amiodarone because these side effects were negligible. And many of those with abnormal thyroid function test results (which actually reflected expected changes in thyroid function induced by amiodarone) had no clinical signs and symptoms of hyperthyroidism or hypothyroidism; as the authors themselves point out, these patients could have continued to receive the drug. Thus, the number of serious side effects would decrease from 55 to approximately 25 in the total study group of 305 patients, a proportion much

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closer to that in the placebo group. Both results are an emphatic indication that amiodarone is very well tolerated in the short term.

The authors also cautiously interpret the findings on the effect of amiodarone on reducing the mortality rate. Of the 20 patients in the amiodarone-treated group who died, 10 died after they stopped taking the drug. Although the authors are justified in counting these as amiodarone-related deaths on the basis of the intention-to-treat principle, these circumstances may indicate that amiodarone is even more effective than is reported in this study.

These data show that amiodarone prevents cardiac death and sudden cardiac death in postmyocardial infarction patients. What makes this trial quite exceptional is that the investigators designed this to be a pilot study to be followed by a larger definitive trial. As it turned out, the present study yielded definitive findings. A critical examination of the preceding criteria for drug discontinuation and death rate yields an even more strongly positive evaluation of amiodarone. The results of the present study together with the results of Burkart et al. (15) and preliminary data from ongoing studies force us to ask the following questions.

Mechanism of amiodarone benefit. Why does amiodarone appear to benefit postmyocardial infarction patients when other class I drugs (phenytoin, mexiletine, aprindine, encainide, flecainide, moricizine) fail (16–18)? Although proponents of class III agents may infer from these data that amiodarone works by prolonging repolarization, the inference that all class III agents have the same effect as amiodarone is too simplistic because we still don't understand how amiodarone works. For example (bearing in mind that both amiodarone and sotalol have both class II and class III properties), the trial of sotalol reported by Julian et al. (19) did not show that sotalol reduced mortality, although there was a trend suggesting that possibility (the mortality rate was 18% lower in the sotalol than in the placebo group). Specifically, sotalol did not prevent sudden cardiac death, which had a rate of 2.9% in the sotalol group compared with 2.4% in the placebo group. Sotalol significantly reduced the incidence of myocardial infarction in the study of Julian et al. (19). This observation is interesting because if prolongation of the action potential duration is the principal mechanism of action in preventing sudden cardiac death in postmyocardial infarction patients, one would have expected sotalol to be as effective as amiodarone in the study of Julian et al. But it wasn't and, therefore, it cannot be solely the class III effect that accounts for the success of amiodarone. Having said this, one cannot rule out the possibility that the class III action plays a role in preventing sudden cardiac death. It may be that sotalol has more proarrhythmic effects that cause fatal arrhythmias, thus offsetting the drug's beneficial effects. Unlike sotalol, amiodarone has negligible proarrhythmic effects (3,7,8), perhaps because its calcium channel blocking properties may prevent early afterdepolarization induced by abnormal repolarization; this mechanism is believed to cause torsade de pointes and polymorphic ventricular tachycardia in patients with abnormal prolongation of repolarization (20). Thus, amiodarone may be effective because of, rather than despite, its pharmacologic complexity.

Ongoing and future research. Knowing what these data tell us about amiodarone, would it now be ethical to conduct additional large studies randomizing postmyocardial infarction patients to placebo and amiodarone to confirm the results of the present study as Ceremuzynski et al. suggest? Should we now treat all survivors of myocardial infarction with amiodarone because of our present knowledge that amiodarone saves lives? Before answering these questions, we should await the results of three ongoing major trials: the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), the European Myocardial Infarction Amiodarone Trial (EMIAT), and the Veterans Administration Cooperative Study Comparing Amiodarone vs. Placebo in Heart Failure Patients with Malignant Ventricular Arrhythmias. These studies will confirm or deny the results of the present study and should address the most serious concern about amiodarone: whether its benefits will continue over the long term and whether they will outweigh the risk of serious side effects that are likely to develop, the most worrisome of these being pulmonary fibrosis.

Other studies are needed to determine whether amiodarone would have greater benefit by itself or in combination with other therapy (angiotensin-converting enzyme inhibitors, aspirin, beta-blockers, for example). It is crucial as well that we test the drug in those patients who are at very high risk for sudden cardiac death (that is, patients who have a low ejection fraction and a high density premature ventricular complex rate) and randomize them to either amiodarone or beta-blockers. Throughout all of this ongoing research, we must bear in mind that the results of the present study apply only to short-term amiodarone therapy; when patients receive amiodarone for longer periods of time, they will develop side effects. Other clinical considerations will probably arise in studies of amiodarone administered over longer periods of time. For instance, long-term amiodarone therapy adversely affects lipid metabolism (21). In addition, it is not known whether amiodarone-induced high cholesterol levels will cause accelerated atherosclerosis in patients with coronary artery disease (similar to the present study patients).

Although new data clearly show that amiodarone is more effective and less toxic than had been thought, and although other clinical trials are needed, this research will not answer our questions about amiodarone's puzzling pharmacology. We still do not understand how amiodarone operates at the molecular and cellular level. Research on how this drug works will give insight into the mechanisms of sudden cardiac death and ways to prevent it: it is time for us to embark on that odyssey.

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