The Amiodarone–Class I Agent Combination Increases Refractoriness, Conduction, and the Number of Electrophysiologic Studies But Does It Increase Survival Rate?

Koonlawee Nademanee, MD

In the early 1960s, we used the few antiarrhythmic drugs available empirically, presuming that every premature ventricular contraction had to be suppressed. This presumption spurred ever greater effort, much of it going into antiarrhythmic drug development.1 Throughout the 1980s, one new drug was being developed about every six months,2 and the number of antiarrhythmic prescriptions rose exponentially.3 However, with this widespread use also came troubling reports of the drugs’ negative inotropic and proarrhythmic effects.4–5 Then CAST dealt a swift and decisive blow: Class IC agents, which had previously been highly regarded, were worse than placebo in treating patients with prior myocardial infarction who had premature ventricular contractions. This overturned conventional wisdom, and we had to revise our thinking: Spontaneously occurring premature ventricular contractions in patients with relatively normal ventricular function need not be treated; Holter monitoring may not be a good tool to guide antiarrhythmic therapy in patients with ventricular tachyarrhythmias.7

Our clinical response to antiarrhythmic drugs’ successes and failures (e.g., a drug could prevent ectopic beats yet fail to ward off sudden death) vacillated correspondingly. Even so, most experts still agreed that using the best antiarrhythmic agent selected by electrophysiological testing was the first approach to treat ventricular tachycardia and ventricular fibrillation.8 Yet use of many of these compounds—especially those with negative inotropic effects—was precluded by the fact that patients prone to sudden death generally had poor ventricular function.9 This left us with fewer safe agents. And of these, only 10–40% proved effective when tested electrophysiologically in this subset of patients.10 Today, with so many antiarrhythmic agents, it is a cruel irony that we are probably not much better off than we were three decades ago when we had only a few.

The scarcity of effective drugs naturally led us to combine them.11–14 But what are we combining? What is an antiarrhythmic agent? Philosophically, a drug which, quartered, hath but one part antiarrhythmic action and ever three parts undesirable effects? Electrophysiologically, Vaughan Williams2 classified them based on the four actions whereby a compound can affect cardiac tissue either by depressing depolarization (class I), inhibiting sympathetic output (class II), prolonging repolarization (class III), or blocking the calcium channel (class IV). He emphasized that his model was less a static categorization than a dynamic system of how electrophysiological drugs behave. And their behavior is complex, because many agents possess more than one of these four properties. Amiodarone, for example, has all four.15 Whether or not the inherent combined antiarrhythmic actions in amiodarone are the reason it is more effective than other agents is unclear, but it is an intriguing question for research.

With so many drugs, how do we combine them? Crucial because they can interact synergistically, antagonistically, or ineffectively.12 Adverse effects attributable to a single drug may combine additively in an adverse fashion, affecting, for example, the metabolism and pharmacokinetics of one or more of the drugs being combined.12 For ventricular arrhythmias, a logical choice for an effective combination regimen would be a drug that predominantly affects depolarization (class I) and one that predominantly affects repolarization (class III). In this issue of Circulation, Toivonen et al16 demonstrate that such a combination may exert salutary electrophysiological effects. Their data showed that when class I agents—regardless of the subclass—are combined with amiodarone, the refractoriness is further increased. Mexiletine (class IB) and encainide (class IC) on their own have little or no effect on the refractory period; however,
after being combined with amiodarone, the combination synergistically prolongs the ventricular refractory period. This observation suggests that after increasing the action potential duration, amiodarone lengthens the time in the inactivated state of the sodium channel, thus allowing more of these channels to be blocked. Consequently, the reactivation of sodium channels in response to repolarization is delayed, in turn further extending the time-dependent effective refractory period. Similar to the change in the effective refractory period, conduction is further increased by the combination of amiodarone and a class I agent. The finding that the increase in the conduction time was more considerable in the mexiletine–amiodarone and encainide–amiodarone groups than in the quinidine–amiodarone group fits nicely with quinidine’s pharmacology. Quinidine blocks the sodium channel more readily in the activated state, and so its effects would not be enhanced by an amiodarone-induced increase in the action potential duration.

The resultant increase in the refractory period and conduction should prolong the ventricular tachycardia cycle length, as indeed Toivonen’s data showed. A prolonged tachycardia cycle length will likely make the tachycardia more hemodynamically tolerable and less likely to degenerate into ventricular fibrillation — effects we consider desirable. But despite the substantial increase in the refractory period and conduction, this combination had, disappointingly, a negligible effect on the inducibility of tachycardia. Lacking long-term follow-up data prompts us to question the value of these electrophysiological changes. Do these findings mean that these patients will have a better chance of survival? At least one recent study of survivors of out-of-hospital cardiac arrest challenges this interpretation.

What do we really want from combination drug therapy? Improving inducibility of ventricular tachycardia, slowing tachycardia, both, or more? An ideal combination therapy should meet the following criteria in order to be judged effective. First, a combination of two or more drugs should be more effective than each individual drug in preventing clinical ventricular tachycardia, ventricular fibrillation, and sudden death. Second, a combination of drugs should not result in a higher incidence of proarrhythmic effects than each individual drug; the incidence of new life-threatening arrhythmias cannot be higher than that of the recurrent arrhythmias being treated. Third, we should be able to administer a lower dose of each drug to be combined to avoid toxicity while maintaining potency. The first two criteria must be met; the third is desirable but not crucial.

So far all the data on combination drug therapy (including the present study) have not unequivocally satisfied these criteria. Examining Toivonen’s data, only eleven of the thirty-one patients tested (36%) may have benefitted from that combination. The data clearly indicate that the mexiletine–amiodarone combination is unlikely to be a successful regimen and perhaps should never be included in the algorithm of drug testing. It is also troubling that we cannot predict which patient will likely have a tolerable tachycardia in a given regimen: apparently, we would have to keep testing. Must the patient undergo interminable electrophysiological testing of countless regimens before we say that we cannot find a viable combination? The matter is complicated by the fact that when treating patients whose ventricular function is poor, many cardiologists will be leery of using class IC agents for fear of proarrhythmic effects. Others will be wary of amiodarone toxicity, let alone combining it with a class IC agent. And then there are those who believe that patients who are treated with amiodarone would do well regardless of the outcome of drug testing. They will question whether combination drug therapy — any combination — will offer anything better than amiodarone alone.

If electrophysiological drug testing were our only recourse, we would probably be inclined to keep testing the patient, regardless of cost, time, hardship, and the possibility of not finding a viable regimen for some. But we do have an alternative: the automatic implantable cardioverter defibrillator (AICD). Although its opponents will argue that the AICD is not perfect, new data suggest that early AICD implantation is cost effective and yields a better prognosis than an effective antiarrhythmic agent based on electrophysiological testing.

Unfortunately, essential data to help us choose which way to go are still lacking. This lack of data should lead us to consider repeated electrophysiological drug testing as neither better nor worse than other modalities. We need large, randomized, double-blind prospective studies to compare the relative merits of protracted electrophysiological drug testing with antiarrhythmic combination regimens, amiodarone therapy, and the AICD.

If we elect to treat patients with antiarrhythmic drugs, Toivonen et al. have given us helpful pilot data: The finding that combining class IA agents with amiodarone may be an effective combination deserves further study. For the present, when electrophysiological drug testing fails to identify a single effective agent, the clinical path diverges. One path — certainly the popular one — is to go with the AICD. The path less travelled is to keep combining and testing agents. Only time and the data from large randomized studies will show us which is the best direction for reducing the incidence of sudden cardiac death.

Acknowledgments

The author wishes to thank Mary Kolb, BA, for editorial assistance.

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KEY WORDS: amiodarone • quinidine • mexiletine • encainde • ventricular tachycardia • Editorial Comments
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_Circulation_. 1991;84:429-431
doi: 10.1161/01.CIR.84.1.429

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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