A Prospective Comparison of Class IA, B, and C Antiarrhythmic Agents in Combination With Amiodarone in Patients With Inducible, Sustained Ventricular Tachycardia

Lauri Toivonen, MD; Alan Kadish, MD; and Fred Morady, MD

Background. Clinical experience suggests that combinations of antiarrhythmic agents provide more effective control of ventricular tachyarrhythmias than does therapy with single agents.

Methods and Results. Antiarrhythmic and electrophysiological effects of three class I antiarrhythmic agents, one from each subclass A, B, and C, were assessed in single use and in combination with amiodarone in patients with inducible, sustained ventricular tachycardia that was not suppressed by monotherapy with these agents. Thirty-one patients underwent an electrophysiology test on four occasions: at baseline; after 2–4 days of treatment with quinidine, mexiletine, or encainide; after 2 weeks of treatment with 1,200 mg/day amiodarone; and last, after 2–4 days of treatment with both amiodarone and the previously tested class I agent. The combination of a class I agent and amiodarone prevented the induction of sustained ventricular tachycardia in only one of 31 (3%) patients. Ventricular tachycardia became hemodynamically stable in 11 of 31 (34%) patients because of a marked prolongation in the tachycardia cycle length. It increased from 323±39 to 423±84 msec (n=11, p<0.01) by adding encainide to amiodarone therapy, and it showed a tendency to lengthen when quinidine was added to amiodarone (from 373±77 to 425±58 msec; n=10, NS). Each class I agent increased amiodarone-induced depression in myocardial conduction, but the extent of the additional depression seemed to differ among the three subclasses. Ventricular refractoriness was increased by all class I agents when used in combination with amiodarone, although not by mexiletine or encainide when used alone.

Conclusions. Class I antiarrhythmic agents slow ventricular conduction and increase ventricular refractoriness when used in combination with amiodarone. When amiodarone and class I drugs by themselves do not suppress the induction of ventricular tachycardia, the combination of amiodarone and a class I agent seldom results in noninducibility; however, it often lengthens the ventricular tachycardia cycle length and may render the ventricular tachycardia hemodynamically stable. (Circulation 1991;84:101–108)

Clinical experience suggests that combinations of antiarrhythmic agents provide more effective control of ventricular tachyarrhythmias than does therapy with single agents.¹⁻³ For example, the combination of a class I agent with amiodarone has been shown to suppress the induction of sustained ventricular tachycardia when amiodarone alone is ineffective.⁴ The addition of a class I agent to amiodarone therapy has also been demonstrated to result in slowing of the rate of induced ventricular tachycardia.⁵⁻⁷ However, no prior studies have compared the electrophysiological effects of the various types of class I agents in combination with amiodarone.

The aim of this prospective study was to compare the effects of class I agents in combination with amiodarone to determine the regimen most likely to improve the therapeutic response when amiodarone by itself is ineffective. One agent from each subclass⁸⁻⁹ was used: quinidine from subclass A, mexiletine from subclass B, and encainide from subclass C. Their effects were assessed individually and in com-

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bination with amiodarone in patients with inducible, sustained ventricular tachycardia.

Methods

Characteristics of Subjects

The subjects of this study were selected from a pool of 72 consecutive patients who were referred for the evaluation and treatment of ventricular arrhythmias and who had inducible, sustained monomorphic ventricular tachycardia during a clinically indicated electrophysiology test. A class I agent was administered in all patients, and electrophysiological testing was performed in 67. Sustained ventricular tachycardia was not inducible in 12 patients. Among the remaining patients, 48 were then treated with amiodarone, and 46 of these underwent electrophysiological testing. Eleven patients had a favorable response, and a combination regimen was started in the remaining 35 patients. An electrophysiology test was then performed in 31 patients, and these patients make up the population of the present study.

There were 30 men and one woman, and their mean (± SD) age was 62±9 years. All patients had coronary artery disease and a history of remote myocardial infarction. The mean left ventricular ejection fraction, determined by contrast or radionuclide ventriculography, was 0.29±0.09 (range, 0.15–0.40). The presenting arrhythmia was sustained, monomorphic ventricular tachycardia in 14 patients; cardiac arrest with documented ventricular fibrillation in three patients; symptomatic, nonsustained monomorphic ventricular tachycardia in 10 patients; and unexplained syncpe in four patients.

Electropharmacological Testing Protocol

After sustained, monomorphic ventricular tachycardia was induced during a baseline electrophysiology test, oral therapy was started with quinidine, mexiletine, or encainide. The choice of the antiarrhythmic agent was random, except that agents that had caused adverse effects or that had failed on a clinical basis to control the patient's arrhythmia were not used. If sustained ventricular tachycardia was inducible despite treatment with the class I agent, therapy with amiodarone was initiated. If sustained and hemodynamically unstable ventricular tachycardia was still inducible, the previously used class I antiarrhythmic agent was used in combination with amiodarone.

In assessing the therapeutic response to an antiarrhythmic regimen, the noninducibility of ventricular tachycardia and the induction of nonsustained or hemodynamically stable sustained ventricular tachycardia were considered to be adequate therapeutic end points. Ventricular tachycardia with a cycle length of more than 400 msec and a mean arterial pressure of 80 mm Hg or more was considered hemodynamically stable.

The daily dosages of quinidine, mexiletine, and encainide were 1,460–1,940 mg (quinidine gluconate), 600–750 mg, and 105–150 mg, respectively, and were given orally in three divided daily doses at 8-hour intervals. The daily dosage of amiodarone was 1,200 mg during the loading period. The electrophysiology study was performed after at least 2 days of therapy with quinidine and mexiletine and after 4 days of treatment with encainide, either when used alone or in combination with amiodarone, and after 14 days of treatment with amiodarone. Electrophysiological testing was performed during the last hour of the dosing interval, and the blood samples for determination of the plasma drug concentrations were drawn at the end of the test.

Programmed Electrical Stimulation

The study protocol was approved by the Human Research Committee at the University of Michigan. Electrophysiology tests were performed in the fasting, unsedated state after informed consent was obtained. The baseline studies were performed at least five half-lives after discontinuation of treatment with all antiarrhythmic medications.

Two quadripolar electrode catheters were positioned in the right atrium and across the tricuspid valve to record the atrioventricular conduction intervals during sinus rhythm and atrial pacing, then were advanced to the right ventricle. A short 5F cannula that was inserted into a femoral artery was used to continuously record the arterial pressure. Leads I, III, and V1 and the intracardiac electrograms were recorded on a Mingograf 7 recorder (Siemens-Elema, Solna, Sweden) at a paper speed of 100–200 mm/sec. Stimulation was performed with a programmable stimulator (Bloom Associates, Reading, Pa.) with an impulse duration of 2 msec and a current intensity of twice the late diastolic threshold, which was always 1 mA or less.

The AH, HV, and QT intervals were measured during sinus rhythm and atrial pacing at a cycle length of 600 msec. The QT interval was corrected for heart rate with Bazett's method. The ventricular effective refractory period was determined with an eight-beat basic drive train at cycle lengths of 600 and 400 msec and with 5-msec decrements in the extra-stimulus coupling interval. The duration of the QRS complex during ventricular pacing was determined after 15 cycles of pacing from the right ventricular apex at cycle lengths of 600 and 350 msec.

Programmed stimulation to induce ventricular tachycardia was performed at the right ventricular apex and outflow tract with drive cycle lengths of 600 and 400 msec. One and two extrastimuli were delivered at both ventricular sites and drive cycle lengths, after which three extrastimuli were delivered. The coupling intervals of the extrastimuli were shortened in steps of 10 msec. Ventricular tachycardia lasting at least 30 seconds or requiring prompt termination was considered sustained.
TABLE 1. Patients With Combined Antiarrhythmic Treatment and Responses in the Electrophysiology Studies

<table>
<thead>
<tr>
<th>Antiarrhythmic combination</th>
<th>Sustained VT</th>
<th>Noninducible</th>
<th>Sustained VT stable†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started (n)</td>
<td>Tested* (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>13</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Encainide</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>All patients</td>
<td>35</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia.
*Not tested in four patients because of side effects: central nervous system side effects in three patients receiving mexiletine and worsening of heart failure in one patient receiving encainide.
†Sustained ventricular tachycardia with a cycle length of more than 400 msec and mean blood pressure 80 mm Hg or more.

Statistical Analysis

A two-way analysis of variance with repeated measures was used to compare differences in continuous variables during various treatment phases. A Wilcoxon’s signed-rank test was used to analyze changes in the number of extrastimuli required to induce ventricular tachycardia. Linear regression analysis was used to examine correlations between electrophysiological variables and ventricular tachycardia cycle length. Continuous variables are expressed as mean±SD. A p value less than 0.05 was considered to be statistically significant.

Results

Effects on Ventricular Tachycardia

Noninducibility of sustained ventricular tachycardia was achieved in one of 31 patients with a combination of a class I agent (mexiletine) and amiodarone. Ventricular tachycardia became hemodynamically stable in 11 patients during combination therapy (Table 1).

The number of extrastimuli required to induce sustained ventricular tachycardia decreased during combination therapy compared with treatment with a class I agent only, from an average of 2.4 to 1.9 (p<0.05).

Quinidine and mexiletine increased the tachycardia cycle length, whereas no significant change occurred with encainide (Table 2). The greatest increase occurred with amiodarone. Encainide increased the tachycardia cycle length when combined with amiodarone. Overall, quinidine and mexiletine had no significant additive effect on the tachycardia cycle length in combination with amiodarone. However, individual responses varied within treatment groups.

In 12 of 30 patients, the morphology of the induced ventricular tachycardia was identical in all four study phases (in 3, 4, and 5 patients in the quinidine, mexiletine, and encainide groups, respectively). In 18 patients, it was different during at least one of the phases. The cycle length of the induced ventricular tachycardia increased in patients with an identical tachycardia morphology from 270±44 at baseline to 310±47, 337±60, and 423±88 msec during treatment with a class I agent, amiodarone, and a combination, respectively. The cycle lengths increased from 268±48 to 306±52, 343±63, and 394±72 msec in the respective phases in patients with nonidentical tachycardia morphologies. The cycle lengths did not differ significantly between these two subgroups.

Effects on Ventricular Conduction and Refractoriness

The duration of the paced QRS complex was prolonged by each class I agent and amiodarone (Table 3). The degree of prolongation was similar, except with mexiletine, which had the least effect. The increase in the duration of the paced QRS complex during treatment with the class I agents was not rate dependent. In contrast, amiodarone had a greater effect at a cycle length of 350 than at 600 msec (p<0.001). When used with amiodarone, all class I agents increased further the duration of the paced QRS complex. The increase was greater with encainide than with quinidine and mexiletine. The additive effects of the class I agents on the QRS duration during combination therapy were not dependent on rate (Table 3).
Table 3. Duration of the Paced QRS Complex

<table>
<thead>
<tr>
<th>Test phase</th>
<th>Treatment groups (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quinidine (10)</td>
</tr>
<tr>
<td>Pacing cycle length, 600 msec</td>
<td></td>
</tr>
<tr>
<td>Control phase</td>
<td>168±22</td>
</tr>
<tr>
<td></td>
<td>+23%*</td>
</tr>
<tr>
<td>Class I agent</td>
<td>205±20</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>212±29</td>
</tr>
<tr>
<td></td>
<td>+7%†</td>
</tr>
<tr>
<td>Combination</td>
<td>226±30</td>
</tr>
<tr>
<td>Pacing cycle length, 350 msec</td>
<td></td>
</tr>
<tr>
<td>Control phase</td>
<td>168±16</td>
</tr>
<tr>
<td></td>
<td>+28%*</td>
</tr>
<tr>
<td>Class I agent</td>
<td>214±19</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>235±34</td>
</tr>
<tr>
<td></td>
<td>+7%</td>
</tr>
<tr>
<td>Combination</td>
<td>249±31</td>
</tr>
</tbody>
</table>

Duration of the QRS complex (mean±SD) is given in msec. Changes from the control phase and from the amiodarone phase are indicated in percentages.

Comparison is performed between the baseline and the class I agent phase and between the amiodarone and the combination phases in the three parallel treatment groups. In addition, the amiodarone phase is compared with the baseline in the whole group.

*p<0.001, †p<0.05, ‡p<0.01.

The ventricular effective refractory period was prolonged by quinidine and amiodarone (Table 4). The changes were similar with the 600- and 400-msec drive cycle lengths. Mexiletine and encainide by themselves did not increase refractoriness. In combination, encainide increased the amiodarone-induced prolongation in the ventricular effective refractory period determined at both drive cycle lengths. At the 400-msec drive cycle length, quinidine and mexiletine in combination with amiodarone also prolonged ventricular refractoriness (Table 4). Therefore, each of the class I agents increased the ventricular effective refractory period when used in combination with amiodarone and each tended to do so more at a drive cycle length of 400 than at 600 msec.

The cycle length of induced ventricular tachycardia correlated with the ventricular effective refractory period (basic drive cycle length, 400 msec) during treatment with amiodarone (r=0.51, n=31, p<0.001) but not with the class I agents. The duration of the paced QRS complex did not correlate with the tachycardia cycle length during any treatment regimen, even when the analysis was restricted to identical tachycardia morphologies.

Inclusion only of patients who had an ineffective response in the next study phase may have biased the assessment of the electrophysiological variables if the efficacy was related to the extent of the electrophysiological changes. In this respect, nine patients who responded to quinidine were compared with 15 nonresponders, and 11 patients who responded to amiodarone were compared with 35 nonresponders. The success rate with mexiletine and encainide was not sufficient for a similar analysis. There were no statistically significant differences between the responders and nonresponders in the duration of the paced QRS complex, ventricular effective refractory period, and the QT interval.

Electrocardiographic Variables, Atrioventricular Conduction, Blood Pressure, and Adverse Reactions

The sinus cycle length was increased by amiodarone from 780±40 to 880±170 msec (n=31, p<0.001). The class I agents had no significant influence on the sinus cycle length when used alone or in combination with amiodarone. The AH interval was not affected by the class I agents during monotherapy. It was increased by amiodarone from 108±39 to 192±72 msec (n=21, p<0.001) during atrial pacing. In combination, only encainide increased the AH interval, from 195±79 msec with amiodarone alone to 222±94 msec in combination (n=9, p<0.05). The HV interval was increased by encainide from 55±13 to 67±22 msec (n=9, p<0.05) and by amiodarone from 53±11 to 64±15 msec (n=21, p<0.001) during atrial pacing. During combination of encainide and amiodarone the HV interval was further increased, to 74±20 msec (n=9, p<0.05). No significant changes occurred in the HV interval during quinidine or mexiletine.

The QT interval during sinus rhythm was prolonged from 388±30 to 442±39 msec by quinidine (n=10, p<0.001) and to 471±40 msec by amiodarone (p<0.001), but their combination did not result in a
Plasma Drug Concentrations

The mean plasma amiodarone concentration was 1.7±0.5 mg/l after 14 days of therapy and was 1.7±0.6 mg/l during combination therapy. The respective plasma desethylamiodarone concentrations were 0.9±0.3 and 1.0±0.2 mg/l. The mean plasma quinidine concentration was 2.3±0.7 mg/l during monotherapy and was 2.7±0.7 mg/l during combination therapy. The mean plasma mexiletine concentration was 0.7±0.2 mg/l during monotherapy and was 0.7±0.3 mg/l during combination therapy. The mean plasma encainide concentration was 30±20 ng/l during monotherapy and 40±20 ng/l during combination therapy. The respective concentrations during monotherapy and combination therapy were 130±60 and 140±60 ng/l for O-desmethyl encainide and 130±70 and 130±70 ng/l for 3-methoxy-O-desmethyl encainide. Only the plasma quinidine concentration differed significantly (p<0.05) between monotherapy and combination therapy.

Discussion

Main Findings

In this prospective study, the electrophysiological and antiarrhythmic effects of quinidine, mexiletine, and encainide were assessed in combination with amiodarone in patients who had inducible, sustained ventricular tachycardia. The design of the study allowed a comparison of the individual effects of class IA, B, and C antiarrhythmic agents with their effects in combination with amiodarone in the same patients.

Amiodarone-induced slowing of myocardial conduction was accentuated by agents from all subclasses but most prominently by the class IC agent, encainide. This indicates that, when used in combination, the class I agents and amiodarone both contribute to depression of myocardial conduction, consistent with blockade of sodium channels. Agents from all subclasses also had an additive effect on ventricular refractoriness when combined with amiodarone. Both mexiletine and encainide potenti-
ated the effect of amiodarone on the ventricular effective refractory period; however, neither agent had an effect on refractoriness when used alone.

The combination of a class I agent with amiodarone rarely resulted in the noninducibility of ventricular tachycardia when the individual agents were ineffective in suppression of induction of ventricular tachycardia. However, quinidine and encainide in combination with amiodarone markedly decreased the rate of ventricular tachycardia and often resulted in unstable ventricular tachycardia becoming hemodynamically stable. This may be a clinically significant effect because prior studies demonstrated that hemodynamically stable ventricular tachycardia is an adequate therapeutic end point in patients treated with amiodarone.9,11,12

Effects on Conduction

Quinidine and encainide slowed myocardial conduction (as reflected in the paced QRS duration) more than mexiletine did. The depression in conduction was similar at slow and fast rates, although quinidine tended to have a greater effect during the faster rate. Class I agents should demonstrate use-dependent slowing of myocardial conduction during ventricular pacing,10,13 but the methods used in the present study may not have been accurate enough to detect small changes with statistical significance. Amiodarone prolonged the paced QRS complex to a greater extent at the faster rate, indicating a rate dependency that is consistent with the known use-dependent properties of amiodarone.14,15

The additional depression of myocardial conduction produced by combining mexiletine and encainide to amiodarone was equal to the individual effect of these drugs. In contrast, the slowing of conduction produced by combining quinidine to amiodarone was less than quinidine’s individual effect.

Antiarrhythmic subclasses IA, B, and C differ in respect to their time constants of sodium channel blockade.8-10,16-18 The subclass B has the fastest, subclass A has an intermediate, and subclass C has the slowest kinetics. Amiodarone inhibits the sodium channel by binding to the receptors in the inactivated state, has rapid recovery kinetics, and also prolongs the duration of the action potential.14,15 It has been hypothesized that antiarrhythmic agents that have rapid recovery constants competitively inhibit the sodium channel blockade exerted by agents with slower kinetics.17,19-21 Amiodarone may, therefore, inhibit the depression of myocardial conduction by quinidine and encainide. This can explain why the slowing of conduction in the ventricular muscle during the combination of quinidine and amiodarone was less than the sum of their individual effects. However, similar attenuation of the combined effect was not seen with encainide, which also has slow kinetics.9,16,22-24 This difference may be caused by the state of the sodium channel on which the drugs exert their influence. Encainide affects sodium channels when they remain inactivated during the plateau of the action potential,9,22,23 whereas quinidine affects open channels.17,18 Therefore, amiodarone-induced prolongation in the duration of the action potential may enhance the effect of encainide. Amiodarone should not markedly change the effect of mexiletine because both have rapid kinetics.14,15,25,26 Accordingly, their combined effect on conduction was equal to the sum of their individual effects.

Effects on Refractoriness and Repolarization

Ventricular refractoriness was prolonged by agents from all three subclasses in combination with amiodarone. Of note is that encainide and mexiletine, when used by themselves, did not lengthen the ventricular effective refractory period either in the present or in previous studies.22,25,27 Therefore, the effects on ventricular refractoriness may represent complex pharmacodynamic interactions that are not equivalent to the sum of the effects of the individual drugs.

Combining quinidine with amiodarone did not further prolong the QT interval and did not result in proarrhythmia. Therefore, the combination of antiarrhythmic agents from classes IA and III may not markedly accentuate the risk of provoking ventricular arrhythmias associated with a long QT interval.28,29 In addition, neither of the other combinations resulted in adverse electrophysiological effects, although the HV conduction time was further prolonged by encainide.

Role of Drug Metabolites

The pharmacological influence of oral administration of encainide is exerted mainly by its metabolites O-desmethyl encainide and 3-methoxy-O-desmethyl encainide, which are electrophysiologically similar to encainide.23,24 The metabolites accumulate to produce steady plasma concentrations within 4 days. The main metabolite of amiodarone, desethylamiodarone, has electropharmacological properties similar to amiodarone, except it depresses the sodium channel to a greater extent.30,31 A stable ratio of this metabolite and the parent compound is achieved within 2 weeks.32

The metabolism of the class I agents can be influenced by amiodarone,33 which may distort the comparison of their individual and combined pharmacological effects. However, in the present study, only the quinidine plasma concentration was higher during combination therapy than during monotherapy and only by a mean of 0.4 mg/l.

Antiarrhythmic Efficacy

Suppression of the induction of sustained ventricular tachycardia during electropharmacological testing is predictive of long-term antiarrhythmic drug efficacy.11,34 A marked reduction in the tachycardia rate resulting in hemodynamic stability of the ventricular tachycardia suggests protection from arrhythmia-related mortality, although not necessarily from arrhythmia recurrence.11,12
Although only 3% of patients became noninducible, 34% of patients achieved hemodynamic stability of ventricular tachycardia during combination therapy. The results of this study indicate that the potential to slow the tachycardia rate may be greater with quinidine and encainide than with mexiletine.

**Limitations of the Study**

Evaluation of the effects of combination therapy may have been influenced by 2–4 additional days of therapy with amiodarone. However, given the known time course of the onset of the electropharmacological effects of amiodarone, the observed changes in cardiac effects between the amiodarone and the combination phases cannot be attributed to 2–4 days of additional therapy with amiodarone. The antiarrhythmic effect of amiodarone requires several weeks to reach its maximum.

The efficacy of combination therapy may have been underestimated because only agents that failed in monotherapy were evaluated in combination. Nevertheless, the present findings are relevant to clinical practice because antiarrhythmic combinations are generally used only when therapy with single agents is ineffective.

A limitation of this study is that the outcome of long-term combination therapy was not examined. A later deterioration in cardiac function by the negative inotropic effect of the drugs and a possible late incidence of proarrhythmia may counteract the initial beneficial effects of combination therapy. Therefore, the long-term outcome of the combination therapy needs further study.

**Clinical Implications**

This study demonstrates that the combination of class I antiarrhythmic agents with amiodarone can be helpful in the management of patients with inducible, sustained ventricular tachycardia. Noninducibility is rarely achieved, but the rate of the tachycardia often becomes markedly slower. An improvement in hemodynamic stability during ventricular tachycardia may be likely, especially when agents from subclasses IA and IC are added to amiodarone. The relatively small population size in this study does not exclude the possibility of adverse electropharmacological and proarrhythmic effects with combination therapy.

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KEY WORDS • amiodarone • quinidine • mexiletine • encainide • ventricular tachycardia
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