Mexiletine in the Treatment of Resistant Ventricular Arrhythmias: Enhancement of Efficacy and Reduction of Dose-related Side Effects by Combination with Quinidine

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SUMMARY Mexiletine, an orally active lidocaine congener, was used to treat 21 patients whose ventricular arrhythmias were not responsive to conventional antiarrhythmic therapy (or in whom therapy produced limiting side effects). Seventeen of the 21 patients had ischemic heart disease; five had episodes of ventricular fibrillation, six had recurrent, sustained ventricular tachycardia requiring cardioversion, and the remainder had episodic nonsustained ventricular tachycardia. As the dosage of mexiletine was gradually increased, only three patients' arrhythmias were controlled without limiting side effects. One patient continued to have episodic ventricular fibrillation during mexiletine therapy and was excluded from the remainder of the study. The other 17 patients had a partial antiarrhythmic response (the mean suppression of ventricular ectopic depolarizations [VEDs] was 62.5 ± 25%) and 10 continued to have ventricular tachycardia, but dose-related side effects limited therapy (at a mean dose of 950 ± 202 mg/day). These 17 patients had not responded to or did not tolerate quinidine (mean dose of 1042 ± 362 mg/day). With the maximum well-tolerated dosage of quinidine, the mean suppression of VEDs was 59 ± 16%. Eleven of 17 patients (64%) continued to have ventricular tachycardia with quinidine, and therapy was limited by side effects (diarrhea) in 11. In the group of 17 patients, the addition of a previously well-tolerated dosage of quinidine (824 ± 298 mg) to a well-tolerated but only partially effective dosage of mexiletine (800 ± 239 mg) produced a significantly greater antiarrhythmic response. The mean suppression of VEDs during combination therapy increased to 85.9 ± 26%. Only one patient continued to have ventricular tachycardia, and limiting side effects occurred in only 12% of the patients. Continuation of quinidine and withdrawal of mexiletine was associated with recurrence of complex ventricular arrhythmias and documented the need for combination treatment in nine patients. Electrocardiographic intervals were measured at baseline, during mexiletine therapy and during combination therapy. The coupling interval of the predominant ectopic beat prolonged (p < 0.05) during mexiletine treatment and further prolonged (p < 0.05) with the addition of quinidine. After withdrawal of mexiletine from the combination treatment in nine patients, the QTc interval significantly prolonged (p < 0.05). Thus, mexiletine limited the quinidine-induced increase in QTc interval. During 18 ± 5.2 months of follow-up, three patients have died, one with intractable congestive heart failure and two related to documented noncompliance to their medical regimen. The addition of quinidine, which prolongs repolarization of the action potential in vitro, enhanced the antiarrhythmic efficacy of mexiletine, which shortens the action potential duration in vitro. We conclude that combinations of drugs with different electrophysiologic properties may provide enhanced antiarrhythmic efficacy.

ANTIARRHYTHMIC drugs are widely prescribed to suppress ventricular arrhythmias. However, these agents often have very narrow therapeutic indexes and produce intolerable side effects at dosages required to abolish ventricular arrhythmias. This has been particularly problematic in patients whose arrhythmias are life-threatening.1 Dose-related side effects occur frequently, not only with conventional antiarrhythmic agents but also when investigational agents such as mexiletine (an orally active lidocaine congener2–5) are used to treat life-threatening ventricular arrhythmias.6–8 In the studies of Heger et al.7 and Chamberlain et al.,8 dose-related side effects occurred in 40% and 25% of the patients, respectively, and necessitated discontinuing mexiletine. Combination drug therapy has been used when single agents were either ineffective or not tolerated. Combination drug therapy has anecdotally been described as being more effective in some patients,1,9,10 but systematic data to confirm this are limited.

We therefore evaluated the antiarrhythmic efficacy of mexiletine and quinidine alone and in combination. Because these agents have opposing effects on the action potential duration of isolated tissues and because of the possibility of electrophysiologic antagonism,10 we assessed the relation of the antiarrhythmic response to changes in the QTc interval, the electrocardiographic correlate of action potential duration. We attempted to answer the following questions in a group of patients with drug-resistant ventricular tachycardia: Would additional antiarrhythmic efficacy be obtained by combining quinidine and mexiletine in patients whose ventricular arrhythmias were resistant to mexiletine and quinidine when given alone? What electrocardiograph-
ic changes occur during treatment with mexiletine and quinidine alone and in combination?

Methods

Twenty-one patients with frequent ventricular ectopic depolarizations (VEDs) and recurrent ventricular tachycardia unresponsive to conventional oral antiarrhythmic agents are included in this report. Conventional antiarrhythmic agents were considered ineffective if computerized analysis of 12-24 hours of ambulatory electrocardiographic data documented a lack of sustained arrhythmia suppression (less than 70% decrease) or persistence of symptomatic arrhythmias when plasma concentrations were in the range usually associated with efficacy; ventricular tachycardia, defined as three or more consecutive ventricular ectopic depolarizations (VEDs) at a cycle length of less than 600 msec, persisted during ambulatory monitoring; patients developed allergy or intolerable side effects that necessitated discontinuation of therapy; or therapy with a given agent was contraindicated. The patients had received antiarrhythmic therapy with quinidine, procainamide, propranolol, and disopyramide (unless such therapy was contraindicated) without satisfactory response. When the patients entered the study, all previous antiarrhythmic agents were discontinued; unless symptomatic arrhythmias occurred, baseline ambulatory ECG data were recorded after a 24-48-hour drug-free state (three to five half-lives after discontinuation of therapy).

Study Design

VEDs and ventricular tachycardia frequency were quantitated before and during therapy with gradually increasing dosages of mexiletine. After each dosage level of mexiletine had been continued for at least 36 hours, arrhythmia frequency was assessed for 12-24 hours and electrocardiographic intervals were measured. The dosage of mexiletine was gradually increased (from 100 mg orally every 8 hours to a maximum of 400 mg every 8 hours) until the arrhythmias were suppressed or side effects developed. Dose-related side effects were controlled, if possible, by use of shorter dosing intervals or by the administration of mexiletine with a meal or snack. Patients were defined as unresponsive to mexiletine if complex ventricular arrhythmias (ventricular tachycardia or numerous ventricular couplets) persisted at the maximal tolerated dosage. In patients who did not respond to or did not tolerate mexiletine, the dosage was reduced to the maximum well-tolerated level, and a dosage of quinidine that had been well tolerated was added. Arrhythmia frequency and electrocardiographic intervals were then determined during combination therapy under assumed steady-state conditions (2 or more days after the addition of quinidine). In nine patients, mexiletine was subsequently discontinued for 12-36 hours and arrhythmia frequency was again monitored to document recurrence of complex arrhythmias during treatment with quinidine alone. Upon recurrence of the arrhythmias, quinidine was again administered to redocument suppression of the arrhythmias with this combination. Mexiletine was temporarily discontinued only in nine patients because a recurrence of arrhythmias was judged to be potentially life-threatening in the others. Electrocardiographic intervals were also measured when complex ventricular arrhythmias occurred in the nine patients during mexiletine withdrawal. PR, QRS, QT and RR intervals were measured after at least seven consecutive sinus beats; rate-corrected QT (QTc) was calculated as QTc/RR.

Arrhythmia frequency was quantitated by a Hewlett Packard computerized arrhythmia analysis system (HP78220) located in the coronary care unit, or the electrocardiographic data were recorded on eight-track FM magnetic tape (Honeywell, model 95 FM recorder). Then, a trained computer operator blinded to the treatment analyzed the tapes, using a PDP 11/60 laboratory minicomputer and a previously described arrhythmia analysis system. This system counts the number of VEDs and episodes of ventricular tachycardia using a template matching algorithm. The mean coupling interval of each ectopic template to the preceding sinus beat was also measured.

Statistical Analysis

Arrhythmia frequency and electrocardiographic intervals for corresponding hours during periods of no treatment, mexiletine treatment, and combined mexiletine-quinidine treatment were compared using one way analysis of variance with Newman-Keuls test for multigroup comparison.

Results

Patient Population

Seventeen of the 21 patients had ischemic heart disease, five had episodes of ventricular fibrillation, six had recurrent sustained ventricular tachycardia requiring cardioversions (more than 100 ventricular beats in a row with a coupling interval of less than 600 msec), and the remainder had symptomatic, nonsustained ventricular tachycardia. Because nine of these patients were critically ill and were hemodynamically compromised during episodes of ventricular tachycardia, we could not obtain prolonged drug-free baseline data (3.2 ± 1.8 hours were recorded in this subset). At least 12 hours of baseline data were obtained in the remaining 12 patients.

Antiarrhythmic Efficacy

Treatment with Quinidine or Mexiletine Alone

All patients had either not tolerated or not responded to quinidine therapy before entry into this study. Side effects had occurred frequently (table 1). Similarly, as mexiletine dosages were gradually increased, 81% of patients developed dose-related side effects before arrhythmia suppression. These side effects — paresthesias, nervousness, tremor and nausea — were similar to those seen with lidocaine and tocainide. At the maximum tolerated dosage of mexiletine, 18 of 21 patients continued to have complex ventricular arrhythmias, and one had episodic ventricular fibrilla-
Table 1. Effects of Combined Therapy with Mexiletine and Quinidine in 17 Patients

<table>
<thead>
<tr>
<th></th>
<th>Quinidine</th>
<th>Quinidine and mexiletine</th>
<th>Mexiletine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum dosage (mg/day)</td>
<td>1042 ± 362</td>
<td>824 ± 298 (Quin) 800 ± 239 (Mex)</td>
<td>950 ± 202</td>
</tr>
<tr>
<td>Suppression of VEDs (%)</td>
<td>59 ± 16</td>
<td>85.9 ± 26</td>
<td>62.5 ± 25</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>11/17</td>
<td>1/17</td>
<td>10/17</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11/17</td>
<td>1/17</td>
<td>0/17</td>
</tr>
<tr>
<td>Nausea</td>
<td>0/17</td>
<td>1/17</td>
<td>7/17</td>
</tr>
<tr>
<td>Tremor</td>
<td>0/17</td>
<td>1/17</td>
<td>7/17</td>
</tr>
<tr>
<td>Other</td>
<td>3/17</td>
<td>0/17</td>
<td>0/17</td>
</tr>
</tbody>
</table>

Abbreviation: VEDs = ventricular ectopic depolarizations.

tion. The mean suppression of VEDs due to mexiletine was only 62.5 ± 25% (± sd). Thus, only three of 21 patients were discharged on mexiletine alone.

Mexiletine-Quinidine Combination Treatment

Combination therapy with mexiletine and quinidine was evaluated in 17 patients who continued to have complex ventricular arrhythmias while taking maximum tolerated dosages of mexiletine. Combination mexiletine-quinidine therapy was not evaluated in the patient who had ventricular fibrillation during mexiletine therapy. Table 1 lists the antiarrhythmic effects seen with mexiletine and quinidine alone and in combination. Ventricular tachycardia was abolished with combined quinidine-mexiletine therapy in all but one patient, who later responded to the combination of mexiletine and propranolol. The extent of suppression of VEDs increased from 62.5% during mexiletine therapy alone to 85.9% during combination therapy. Lower doses of the agents given in combination were more efficacious than larger doses of each agent when given alone. One patient was allergic to quinidine and procainamide was substituted, achieving a similar enhanced antiarrhythmic effect when combined with mexiletine. In nine patients, mexiletine therapy was withheld (while quinidine therapy was continued) to document the need for combination therapy. After a mean of 11 hours (range 8–21 hours), complex ventricular arrhythmias returned in all patients. Mexiletine was then reinstituted and arrhythmia suppression was again seen in all these patients.

During the administration of maximal dosages of either mexiletine or quinidine, side effects occurred commonly (table 1). The incidence of side effects was smaller during combination therapy. This may relate to the smaller dosages of mexiletine and quinidine required for efficacy when used in combination than when each agent was given alone. Diarrhea occurred in 66% of patients during quinidine therapy and in 6% of patients during combined mexiletine-quinidine therapy. During mexiletine therapy, 81% had limiting side effects of nausea or nervousness, whereas during combination therapy only 12% had the side effects. Of the 17 patients who received the combination therapy, three developed side effects (without evidence of hemodynamic compromise). None of the patients had sinus bradycardia, atrioventricular block or hypotension. One patient had nervousness and lethargy, one nausea and anorexia, and one diarrhea. These side effects were severe enough to warrant discontinuation of combination therapy in the first two of these patients.

Fourteen patients were discharged on mexiletine-quinidine therapy for control of their arrhythmias and were followed for an average of 18 ± 5.2 months (range 11–24 months). Maintenance of arrhythmia control was documented at regularly scheduled clinic visits (monthly for the first 6 months and then every 2 months). Three patients have died during follow-up. One patient was an alcoholic and refused to take his medication. The second patient had failed to come to the clinic to renew his medications and was not taking them at the time of his death. A third patient, who had ischemic heart disease and an ejection fraction of 22% before treatment, died with intractable congestive heart failure after 22 months of follow-up. During follow-up, one patient required discontinuation of the combination therapy because of nausea. Three patients required dosage adjustments of the medications, one for symptoms of congestive failure and two for episodes of ventricular tachycardia. Dosage adjustments were successful in these cases.

Electrocardiographic Interval Changes

During mexiletine therapy alone, neither the PR or QRS durations changed significantly. The coupling interval of the predominant ectopic beat was prolonged (p < 0.05) relative to baseline (fig. 1), and during quinidine-mexiletine treatment there was a further significant increase (p < 0.05) in this coupling interval (compared with mexiletine alone). The other change noted after the addition of quinidine to mexiletine therapy was prolongation of the QTc interval, which had been shortened slightly (2.5%) by mexiletine (fig. 2A). However, after withdrawal of mexiletine treatment in nine patients, while quinidine therapy continued unchanged, the QTc interval prolonged further (p < 0.05) (fig. 2B), indicating that mexiletine had limited the quinidine-induced increase in the QTc interval.

Discussion

Efficacy and Side Effects of Mexiletine Alone

Mexiletine has been reported to be effective in over half of patients with ventricular arrhythmias. However, Heger et al. reported that only six of 19 patients with drug-resistant ventricular tachycardia had a favorable antiarrhythmic response to mexiletine alone. Because of dose-related side effects, mexiletine alone did not suppress ventricular tachycardia in the majority of patients in the present study. Only three of 21 patients in this series were discharged on mexiletine alone. Also, the types of side effects seen with mexiletine in this study were similar to those reported by Heger et al. In the current study, dose-related nervousness, tremor, and nausea were seen in 81% of patients taking...
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mexiletine alone. The somewhat higher incidence of side effects in this study may have occurred because patients were given increasing dosages of mexiletine until either efficacy or side effects occurred.

Combination Antiarrhythmic Therapy

The principle of combination therapy has been used in other areas of medicine, such as the treatment of drug-resistant hypertension. It has been found that with combination therapy, greater efficacy can be achieved at lower dosages and with fewer side effects than with single-agent therapy.14,15 In this study, combination therapy with mexiletine and quinidine also markedly suppressed ventricular tachycardia at lower dosages and with fewer side effects than during therapy with either agent alone.

The mechanisms by which an agent can exert antiarrhythmic action in the treatment of ventricular arrhythmias include changes in membrane responsiveness, automaticity, refractoriness or conduction velocity within a reentrant circuit. Therefore, antiarrhythmic combinations that have additive or synergistic effects on these variables could exert additive or supra-additive antiarrhythmic effects. An example of synergistic changes in electrophysiologic effects seen with drug combinations has been reported by Hondeghem and Katzung.16 In their study, the combination of lidocaine and quinidine depressed the conduction velocity

FIGURE 1. Changes in the coupling interval of the predominant ectopic beat during mexiletine and mexiletine-quinidine therapy.

FIGURE 2. (A) QTc interval duration at baseline, during mexiletine and during mexiletine-quinidine therapy. (B) QTc interval changes in patients in whom mexiletine was temporarily withdrawn during combination therapy.
of extrasystoles to a greater extent than either drug alone, but did not depress conduction of the normal action potential. Additive or supra-additive reduction in conduction velocity within a reentrant loop could abolish the circus movement responsible for ventricular tachycardia in many patients. This might explain the enhanced antiarrhythmic activity seen with the combination of mexiletine and quinidine. Our findings that the combination of mexiletine and quinidine prolonged the coupling interval of the predominant ectopic focus to a greater extent than seen with each agent alone while not prolonging the QRS of the sinus beats are consistent with the findings of Hondeghem and Katzung.16

Another plausible electrophysiologic mechanism for the enhanced antiarrhythmic efficacy seen with this combination therapy may involve changes in the ratio of the ventricular effective refractory period to action potential duration (VERP/APD). Increases in this ratio correlate with the antiarrhythmic activity of many agents and may reflect changes in membrane responsiveness.17-19 Therapy designed to optimize the VERP/APD ratio would increase the ventricular effective refractory period (VERP) and shorten the action potential duration (APD). However, quinidine prolongs both APD and to a greater extent VERP, resulting in an overall increase in this ratio. If quinidine were combined with an agent that shortened APD or minimized the quinidine-induced increase in APD, the VERP/APD ratio would be optimized. In this study, the presence of mexiletine appeared to limit the extent of QTc prolongation (the electrocardiographic marker of APD) seen with quinidine therapy. Because mexiletine can independently increase VERP,20 this combination theoretically should increase the VERP/APD ratio (relative to that seen with quinidine alone). Although our electrocardiographic data are in keeping with this hypothesis, electrophysiologic studies are needed to further evaluate this possible mechanism.

Acknowledgment
We are indebted to Deborah Fisher and Barbara Vesper for their assistance in the preparation of this manuscript.

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Mexiletine in the treatment of resistant ventricular arrhythmias: enhancement of efficacy and reduction of dose-related side effects by combination with quinidine.
H J Duff, D Roden, R K Primm, J A Oates and R L Woosley

Circulation. 1983;67:1124-1128
doi: 10.1161/01.CIR.67.5.1124

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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