Clinical Evaluation of Oral Mexiletine Therapy in the Treatment of Ventricular Arrhythmias

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The effect of oral mexiletine therapy on ventricular arrhythmias was evaluated in 58 patients in whom conventional drugs had been unsuccessful. Mean daily dose of mexiletine was 652 mg (range 250 to 1,500) and mean duration of therapy was 14.4 months (range 0.1 to 34.4). Mexiletine was associated with a decrease of 52% in total premature ventricular complexes in 24 hours compared with control (6,841 ± 1,053 [SEM] versus 3,248 ± 734, \( p < 0.005 \)) and 19 patients (36.5%) had a greater than 83% decrease in ventricular ectopic rhythm. The drug was discontinued in 6 of these 19 patients because 5 of them (26%) experienced side effects after a mean period of 29.6 weeks (range 0.83 to 63.2) and sudden death occurred in 1 patient (5%); this indicates effective suppression of ventricular ectopic rhythm without significant side effects in 13 (25%) of 52 patients during long-term therapy. Adjustment of drug dosage to achieve therapeutic blood levels resulted in an efficacy on ventricular ectopic rhythm similar to that obtained with the maximal tolerated dose. There was no correlation between drug dose and therapeutic effectiveness.

Mexiletine was associated with a 48% decrease in episodes of ventricular tachycardia (345.5 versus 179.3/24 h) and 5 of 10 patients with a history of cardiac arrest remained free of symptomatic ventricular tachyarhythmias for 14.8 months (range 3.7 to 24.3). In 12 patients left ventricular ejection fraction, determined by radionuclide angiography before and during mexiletine therapy, demonstrated no significant change (32 versus 34%). Adverse effects requiring discontinuation of mexiletine occurred in 12 patients (21%) in the entire group and were primarily related to the central nervous system and gastrointestinal tract. Mexiletine was effective in a modest proportion of patients in whom conventional antiarrhythmic therapy had failed. Ventricular function appeared to be unaffected by the drug and the side effects, although relatively frequent, were not serious.

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Mexiletine is an investigational antiarrhythmic agent that has shown promise in initial clinical trials against ventricular arrhythmias in heart disease of diverse etiologies (1–3). Structurally and electrophysiologically mexiletine resembles lidocaine but it also possesses membrane-stabilizing properties characteristic of procaainamide and quinidine (4,5). The drug has a prolonged pharmacologic half-life and has been associated with few serious side effects (6,7). However, the long-term antiarrhythmic efficacy of mexiletine and its effects on cardiac function have not been fully clarified. Therefore, we analyzed the results of oral mexiletine therapy in a large group of patients with ventricular arrhythmias treated for an average interval of more than 1 year. In addition, the effects of the agent on ventricular function were assessed in a subgroup of these patients.

Methods

Patients. The study group consisted of 58 patients (45 men and 13 women) of average age 59.5 years (range 27 to 82). Cardiac diagnoses included: coronary heart disease, 36 patients (62%); cardiomyopathy, 11 patients (19%); valvular heart disease, 6 patients (10%) and other diagnoses, 5 patients (9%). During this evaluation 53 patients (91%) were taking one or more cardiac drugs, including 18 patients (31%) receiving conventional antiarrhythmic agents (Table 1). The indications for mexiletine therapy were 30 or more premature ventricular complexes per hour and complex ventricular ectopic rhythm (multifocal premature ventricular complexes, couplets or ventricular tachycardia, defined as three or more consecutive premature ventricular complexes documented by ambulatory electrocardiographic monitoring). Fifty-three (91%) of the 58 patients had been treated...
unsuccesfully with one or more conventional antiarrhythmic agents (average 2.6 drugs per patient) and 50 of the patients (83%) had been treated without success with two or more conventional drugs, all of which were discontinued because of adverse reactions or lack of efficacy. Ten patients had had one or more episodes of ventricular tachycardia or fibrillation necessitating cardiopulmonary resuscitation.

**Mexiletine administration.** Mexiletine was administered in the form of 100 or 200 mg tablets. The initial dose of 100 or 200 mg two or three times per day was progressively increased until the onset of side effects (maximal 500 mg three times per day), at which time the dose was gradually decreased until side effects resolved. Mexiletine blood levels were measured by high pressure gas chromatography (8) in 33 of the patients (57%) in whom the drug dose was adjusted to achieve a therapeutic plasma level (0.7 to 2.0 μg/ml). Administration of mexiletine was approved by the Human Studies Committee of the University of California, Davis, and all patients gave written informed consent before receiving the drug.

**Ambulatory electrocardiography.** The efficacy of mexiletine was assessed by ambulatory electrocardiographic monitoring before and during treatment with the drug. Twenty-four hour ambulatory electrocardiography was performed at least once before mexiletine administration in all patients and 27 patients (51%) were assessed by two or more pre-treatment ambulatory electrocardiographic studies. Twenty-four hour ambulatory electrocardiography was performed at least once in all patients during mexiletine therapy and 29 patients (55%) were assessed by two or more ambulatory electrocardiographic evaluations during mexiletine therapy. The ambulatory electrocardiograms were analyzed on the Avionics Dynamic Cardiograph scanner, model 660, before November 1982. Tracings were analyzed visually and premature ventricular complexes were hand counted. After November 1982, ventricular ectopic activity was identified and quantitated automatically by the Del Mar Avionics Arrhythmia Analyzer 9020 A. This system has a sensitivity of 99.1% and a positive predictive accuracy of 99.9% as assessed by the American Heart Association arrhythmia database (9). Ventricular ectopic activity was evaluated in terms of frequency of premature ventricular complexes and number of episodes of ventricular tachycardia. All electrocardiographic tracings were reviewed by a member of the Division of Cardiovascular Medicine.

Efficacy of mexiletine on ventricular ectopic rhythm was evaluated for the entire group of patients and separate analysis was performed in the subgroup in whom mexiletine blood levels were obtained. The criterion for antiarrhythmic efficacy was an 83% quantitative decrease in premature ventricular complexes demonstrated by ambulatory electrocardiography during mexiletine therapy compared with the value on pre-drug ambulatory electrocardiography (10,11).

**Clinical assessment.** All patients were evaluated by history and physical examination before beginning mexiletine therapy, 1 to 2 weeks after initiation of treatment and at least every 3 months thereafter. The evaluation included detailed assessment of drug side effects which were recorded and followed up longitudinally. When indicated by side effects, drug dosage was adjusted or the drug was discontinued. Twelve lead electrocardiograms were obtained at rest before treatment and at least every 3 months and continuous ambulatory electrocardiography was performed as indicated in addition to the minimum of one recording before and one during mexiletine treatment.

**Left ventricular function.** Radionuclide ventriculography by gated blood pool scintigraphy was performed in 12 randomly selected patients before mexiletine therapy and at the time of therapeutic blood levels of mexiletine (12). Right and left ventricular wall motion was analyzed and left ventricular ejection fraction was calculated.

**Statistical analysis.** Statistical analysis was performed by Student's t test for paired data to determine differences between means of independent observations and by chi-square test with Yates' correction to determine differences between proportions.

### Results

**Mexiletine dose and antiarrhythmic efficacy.** The average dose was 652 mg/day (range 250 to 1,500) administered as a divided dose two or three times daily. Of the 58 patients in whom mexiletine therapy was initiated, 52 patients had adequate 24 hour ambulatory electrocardiographic data for analysis. In this group of 52 patients, the maximal tolerated dose of mexiletine was associated with a group mean decrease of 52% in the total number of premature ventricular complexes per 24 hours before mexiletine therapy (6.841 ± 1.053 [SEM]) compared with the total number during therapy (3.248 ± 734, p < 0.005). For the entire group no clear relation existed between the daily dose of mexiletine and the decrease of premature ventricular complexes (Fig. 1). Nineteen patients (36.5%) had a greater than 83% decrease in premature ventricular complexes on this maximal tolerated dose.
In these 19 patients, the drug required discontinuation because of side effects in 5 patients (27%) after a mean period of 29.6 weeks (range 0.83 to 63.2) and sudden death occurred in one additional patient (5%). Therefore, effective antiarrhythmia therapy (>83% decrease in premature ventricular complexes) without significant side effects was achieved during long-term treatment with mexiletine in 13 (25%) of the 52 patients. These patients were treated for a mean of 17.8 months (range 3.7 to 34).

Blood levels and antiarrhythmic efficacy. For those patients whose mexiletine blood levels were measured, the mean concentration was 0.94 μg/dl (< 0.2 to 2.1). At doses greater than 300 mg/day there was little relation between dose and blood levels (Fig. 2). In the 33 patients in whom therapeutic mexiletine blood levels were measured, the mean decrease in premature ventricular complexes per 24 hours was 55% (5,732 ± 1,228 versus 2,576 ± 625, p < 0.025), and 13 (39%) of these patients had a greater than 83% decrease in premature ventricular complexes. In these 13 responsive patients, discontinuation of the drug was required because of side effects in 4 patients (35%) and 1 patient died suddenly (the same patient in whom sudden death occurred on the maximal tolerated dose of mexiletine noted previously). Thus, of 33 patients with therapeutic mexiletine blood levels, 9 (27%) demonstrated drug efficacy without significant side effects. These nine patients were treated for a mean of 14.8 months (range 3.7 to 34.4).

Effect of mexiletine on ventricular tachycardia. The effect of mexiletine on ventricular tachycardia, defined by three or more consecutive premature ventricular complexes, was quantified in the 11 patients who demonstrated one or more runs of ventricular tachycardia on ambulatory electrocardiography before mexiletine therapy. There was a decrease of 48% (range 345.5 to 179.3) in the total number of episodes of ventricular tachycardia per 24 hours in this group of 11 patients. In six of these the average number of episodes of ventricular tachycardia diminished by 100% during mexiletine therapy (37.8/24 h versus 0.05/24 h), whereas there was no change in this finding in the other five patients.

Patients with history of cardiac arrest. Of the 10 patients who had ventricular tachycardia or ventricular fibrillation necessitating cardiopulmonary resuscitation before mexiletine therapy, the mean decrease in the total number of premature ventricular complexes for the group was 58.3% after mexiletine treatment. In five patients (50%), there were no further episodes of symptomatic ventricular tachyarrhythmias on mexiletine therapy during an average interval of 14.8 months (range 3.7 to 24.3). In this latter subgroup there was an 88% decrease in total premature ventricular complexes during mexiletine therapy (334.9/24 h versus 39.5/24 h). Of the other five patients, mexiletine was discontinued in one because of side effects, one had no response to drug therapy, one died of congestive heart failure, one underwent left ventricular aneurysmectomy and one died suddenly (the same patient noted previously).

Left ventricular function. Radionuclide ventriculography in 12 patients before and at the time of therapeutic mexiletine blood levels (mean 1.2 μg/dl, range 0.8 to 2.0) demonstrated no significant change in left or right ventricular wall motion or left ventricular ejection fraction which was 32% (range 13 to 61) before mexiletine therapy and 34% (range 10 to 63) during therapy (Fig. 3).

Adverse drug effects. Side effects were noted in 25 patients (43%). In 13 (52%) of them, a moderate decrease in dose allowed continued use of mexiletine and in 12 (48%) the drug had to be discontinued because of adverse reactions that were severe or persisted even after the dose was decreased. For all patients with side effects, the mean dose of mexiletine was 688 mg/day (300 to 1,200) and the mean blood level was 0.88 μg/ml (< 0.2 to 1.3). For those patients in whom side effects caused termination of therapy, the mean dose was 800 mg/day (range 300 to 1,200) and the mean blood level was 0.95 μg/ml (range 0.8 to 1.2).
The most frequent adverse effects were related to the gastrointestinal tract and central nervous system (Table 2). In the single patient with urinary retention during mexiletine therapy, the problem resolved after discontinuation of the drug. One patient complained of hair loss while taking mexiletine, and hair growth was considered to have returned to normal after discontinuation of the drug. Five patients showed possible aggravation of ventricular arrhythmias while taking mexiletine. In four of these patients there was an increase in the total number of premature ventricular complexes per 24 hours (268.3 before versus 609.3 during therapy). In the fifth patient, runs of ventricular tachycardia increased from 82 to 125/24 h in association with mexiletine therapy. Mexiletine administration resulted in no significant changes in the electrocardiographic QRS axis and no alterations in the PR, QRS and QT intervals or in ST segment and T wave configurations.

Table 2. Side Effects of Mexiletine Causing Termination of Therapy in 12 Patients

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. of Patients</th>
<th>Percent of Entire Study Group (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>7</td>
<td>12.1</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Memory loss</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Hair loss</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Discussion

This study demonstrated long-term efficacy and absence of significant side effects with mexiletine in the treatment of ventricular arrhythmias in 25% of patients with cardiac disease of diverse etiologies, more than 90% of whom had been unsuccessfully treated with conventional antiarrhythmic drugs. Therapeutic efficacy obtained by the maximal tolerated dose of mexiletine was similar to that associated with dosage given according to blood levels. Furthermore, in the small subgroup of patients studied by radionuclide ventriculography, mexiletine produced no significant alteration of ventricular function.

Therapeutic effectiveness. The criterion selected as an indication of antiarrhythmic efficacy of mexiletine therapy was an 83% decrease in premature ventricular complexes, as described by Morganroth et al. (11), a value intended to confirm drug effect as opposed to spontaneous variability of ventricular ectopic rhythm (10). Although 36% of our patients had an 83% decrease in total premature ventricular complexes during mexiletine therapy, the average decrease in the entire group was 53%. No correlation existed between drug dose and therapeutic effectiveness. It is emphasized that this therapeutic result by mexiletine was effected in a patient group of which almost all subjects had been unsuccessfully treated with one or more conventional antiarrhythmic agents; the average number of drugs unsuccessfully used before mexiletine administration was 2.6 per patient.

Comparison with previous studies. Our results are comparable with those of Podrid and Lown (7), who demonstrated long-term efficacy of mexiletine in 34% of patients treated for chronic ventricular ectopic rhythms. Others have shown efficacy of mexiletine treatment in more than 50% of patients (1-3,13,14). Furthermore, mexiletine has shown results comparable with those of quinidine (15), procainamide (16) and disopyramide (17) in the treatment of ventricular arrhythmias in ambulatory patients.

The effect of mexiletine in patients with recurrent ventricular tachycardia has been variable. DiMarco et al. (18) reported suppression of episodic ventricular tachycardia in a majority of patients with this finding treated with mexiletine, but of the 15 patients studied by Heger et al. (19), only 4 responded to the drug. Our results in this subgroup of patients are intermediate to these previous studies, with 6 of 11 patients showing virtual abolition of episodes of ventricular tachycardia and 5 patients having no response. Five of our 11 patients who survived cardiac arrest due to ventricular tachyarrhythmias had no further symptomatic ventricular arrhythmias on mexiletine for an average interval of 14.8 months. More extensive studies, including a large multicenter trial (20,21) assessing the efficacy of mexiletine for prophylaxis against sudden death, have indicated suppression of premature ventricular complexes but no effect on sudden death. However, these data pertain exclusively to high risk postmyocardial infarction patients.
Discrepancies in the frequency of success with mexiletine among current studies can be attributed to a number of factors, including the type of arrhythmia (premature ventricular complexes or ventricular tachycardia), criteria of efficacy, dosage, severity of the underlying cardiac disease, method of selecting patients and duration of study. Our patients were resistant to prior therapy and, as indicated by radionuclide ventriculography in randomly selected patients, included those with significant impairment of left ventricular function. Furthermore, earlier studies have not generally employed the stringent criterion of 83% premature ventricular complex suppression as an indication of efficacy.

Hemodynamic studies. Limited previous hemodynamic evaluations of mexiletine have been inconsistent, as determined by invasive and noninvasive studies, which have demonstrated either no cardiac depressant effects (22,23) or a modest reduction of ventricular function of lesser degree than that produced by disopyramide but greater than that produced by lidocaine (24). Our findings provide the first data regarding the effects of mexiletine on ventricular function evaluated by radionuclide ventriculography. These results are of interest because no deleterious effects of the drug were evident in a group of patients with significant impairment of left ventricular function, as reflected by a group mean left ventricular ejection fraction of 32% in 12 patients, of whom 6 had an ejection fraction of less than 30% (range 13 to 23%). Ejection fraction decreased no more than 3% (absolute value) in any patient after mexiletine administration.

Adverse reactions. Major adverse reactions to mexiletine in our patients, as has been reported previously, were relatively frequent (21%), were largely related to the gastrointestinal tract and central nervous system and were not serious (3,6,7). As anticipated in a lidocaine-like agent, no significant alterations were evident in intrinsic cardiac pacemaker function or atrioventricular and intraventricular conduction, as reflected in the scalar electrocardiogram.

Conclusion. Mexiletine demonstrated potential as successful therapy against resistant ventricular ectopic rhythm in a modest proportion of patients with no serious adverse reactions over a prolonged interval. Of particular note was its lack of deleterious effects on cardiac performance in patients with serious impairment of left ventricular function. These findings indicate that mexiletine may be a useful therapeutic agent for the management of ventricular arrhythmias in selected patients.

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References