Efficacy of Oral Mexiletine Therapy at a 12-h Dosage Interval

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The antiarrhythmic effectiveness and safety of 12-h oral administration of mexiletine were evaluated in adult outpatients with a baseline hourly rate of PVCs of 30 or higher who had initially shown at least a 50 percent reduction of this rate when treated with mexiletine at an 8-h dosage interval. Doses were titrated on the basis of 24-h Holter monitoring for both 8- and 12-h intervals. Seventeen of 26 patients showed PVC reductions after 8-h treatment. Fifty

Mexiletine, a class Ib antiarrhythmic agent, is an orally active lidocaine analog. Its electrophysiologic profile and its lack of cardiac depressant activity are characteristic of this class of antiarrhythmic drugs. A long terminal-phase half-life, ranging from about 9 h in normal volunteers to 10 to 15 h in patients with arrhythmias, allows mexiletine to be administered for maintenance therapy at 8-h intervals.

In controlled comparative studies with quinidine and procainamide as well as in several placebo-controlled trials, mexiletine administered orally every 8 h effectively suppressed ventricular extrasystoles. In pharmacokinetic studies, therapeutic plasma levels of mexiletine were maintained by oral administration of 200 to 300 mg every 6 to 8 h. Daily doses required for the control of ventricular arrhythmias have varied between 300 and 1,200 mg.

The present study was designed to determine whether the comparatively long elimination half-life of mexiletine would allow ventricular arrhythmias to be controlled as effectively and continually by 12-h as by 8-h administration in patients whose ventricular arrhythmias were first controlled with 8-h mexiletine therapy.

METHODS

This study was conducted at two clinical centers. The succeeding data presented cover all of the patients who participated in the study at both centers.

Patient Selection

Nineteen men, aged 65 to 75 years, and 12 women, from 58 to 70 years old, who had PVCs at an hourly rate of at least 30 were admitted. Eighteen of the 31 patients were diagnosed as having arteriosclerotic heart disease, while in eight patients the tachyarrhythmia was related to valvular heart disease, three had idiopathic ventricular arrhythmias, and two had cardiomyopathy. Six patients had a history of myocardial infarction, and eight had undergone coronary bypass surgery. In two thirds of the patients, PVCs occurred at hourly rates between 60 and 719.

Excluded from the study were patients who had had a myocardial infarction within the preceding two weeks, patients with sinus bradycardia, second- or third-degree AV block, patients with supraventricular arrhythmias, and patients using concomitantly other antiarrhythmic agents or any investigational drugs. Also excluded were pregnant women, hypertensive individuals and patients with epileptic disorders. At the time of study initiation, the patients had been suffering from their arrhythmias for periods ranging from about one month to 17 years.

The patients were screened by history and a physical examination including a 12-lead ECG. In addition, two 24-h Holter recordings were made—usually on consecutive days—to establish the baseline (untreated) rate of PVCs. Patients who had previously been receiving antiarrhythmic medication including mexiletine were to discontinue such treatment for at least two days before Holter electrocardiography was instituted. Patients previously treated with mexiletine were eligible for admission to the study only if they had a history of satisfactory response to administration of the drug at an 8-h dose interval. Admission laboratory tests, repeated at the end of the study, included a complete blood cell count, blood chemistry studies and a urinalysis.

All patients gave their written consent to participation in the study on a form approved by an institutional review board.

Drug Administration

Patients not previously treated with mexiletine were given a loading dose of 400 mg of mexiletine followed at 8-h intervals by doses of 200 mg. The capsules were always taken with food. To determine the response to this regimen, a Holter ECG recording was made during a 24-h period at any time between one and seven days after the first day of 8-h treatment.

If the average hourly PVC rate was not reduced by at least 50 percent of the average rate shown on the two baseline recordings, the dose given every 8 h was increased by 100 mg to 300 mg every 8 h, and another Holter recording was obtained within the same period as just mentioned. If the monitor tape again failed to show this degree of suppression of ectopic activity, the dose could be increased by the same amount to 400 mg every 8 h and the monitoring procedure repeated. If, on the other hand, arrhythmia
control was not satisfactory at the highest allowable dose of 400 mg
every 8 h, the patient was withdrawn from the study.

If within a week after Holter monitoring results had shown that
the patient's arrhythmia was reduced by at least 50 percent on the
8-h dosing schedule, another 24-h ambulatory ECG recording
was obtained to confirm adequate control. This required that the hourly
rate of extrasystoles did not exceed by more than 15 percent the
average rate recorded on the previous Holter monitoring. If the
previous measure of control was not being maintained and the
patient had not reached the maximum dose level, upward dose
titration was initiated as previously noted and the response was
monitored by new Holter recordings.

Patients who had previously been treated with mexiletine every
8 h interrupted therapy for two days and were then given a 400-mg
loading dose of the drug. Thereafter, they returned to the dose
level that had proved safe and effective prior to the study. If they
then failed to reach the goal reduction of the PVC rate, the
dose was raised and the response was monitored as described previously.

After Holter confirmation of continuing satisfactory arrhythmia
control with 8-h dosing, the 12-h regimen was substituted, using a
dose of 300 mg twice a day. If the Holter recording made after 48 h
on this dose showed that the number of PVCs was greater than that
seen on the 8-h schedule, the dose was titrated in daily increments
of 100 mg (daily doses of 700, 800 or 900 mg) until the number of
PVCs was equal to or below that during the 8-h regimen.

Once the target reduction of the hourly PVC rate was reached,
the patient continued to be treated with the same dose, and a week
later another 24-h Holter recording was made to confirm persistence
of this response. If on this last Holter recording the hourly rate of
PVCs did not exceed by more than 15 percent the final PVC rate
while the patient was receiving 8-h therapy, no further upward dose
titration was done. In the absence of this measure of control at the
maximum dose level, titration was continued and the response was
monitored as before.

In addition to PVCs, hourly rates of couplets and of episodes of
ventricular tachycardia (defined as runs of three or more consecutive
PVCs) were recorded at baseline and at the end of titration on the
8- and 12-h regimens.

Analysis of Holter Recordings

In all three observation periods (baseline and at every 8 and
12 h) the Holter PVC rates used to determine efficacy of the
treatment in each patient were the averages of two recordings.
Medians as well as means were used to characterize the central
tendency of the PVC rate since an extreme outlier was present on
12-h therapy. Means were used to summarize couplets and VT rates.

To determine whether the reductions in PVCs from baseline
observed during the treatment periods were in excess of reductions
that might be attributable to day-to-day variability in the PVC rate,
the Wilcoxon signed rank test was applied. The variation between
the two baseline PVC rates in each patient was used to characterize
the day-to-day variability. This study was not designed to take into
account the greater variability in PVC rates that may occur over
longer periods. Therefore, criteria reported from other studies
were used to distinguish a true drug effect from the effect of spontaneous variability over time. The Wilcoxon signed rank
test also served for comparison of the end-of-titration responses on
the 8-h regimen with those obtained on the 12-h schedule.

To track the time course of arrhythmia suppression during the
two different dosage intervals, the number of PVCs occurring every
hour after the morning dose were read off from the last two Holter
recordings made in each patient during 8-h and 12-h treatment;
these data were then grouped to arrive at the medians for each hour.

Mexiletine Measurement

Mexiletine steady-state plasma concentrations at the end of the
dose interval (trough) and 2 h after administration (approximate
peak) on the 8- and the 12-h regimens were evaluated. Blood was
sampled by venipuncture, centrifuged (2,000 rpm for 10 min) to
plasma and frozen until analysis. Mexiletine concentrations were
measured by a sensitive and specific HPLC method. They are
reported here as means with standard deviations.

RESULTS

Patient Response

Five of the 31 patients who were admitted and received
8-h treatment were dropped from the study because of protocol violations. Of the 26 remaining
patients, 17 responded to the 8-h regimen with the
desired degree of PVC suppression. Predictably, the
rate of response to the initial 8-h therapy was higher
in the group that had been effectively treated with
mexiletine before the study than in the group that was
receiving the drug for the first time.

Administration of mexiletine on the 12-h schedule
led to target reduction of ventricular arrhythmia in 15
(88 percent) of the 17 patients treated on this schedule. The
baseline hourly rate of PVCs in the 17 patients averaged 263. During treatment with mexiletine every
8 h this rate was reduced to a mean of 29 (a mean
reduction of 83 percent); treatment every 12 h reduced
the baseline rate to 59 PVCs per hour (a mean
reduction of 77 percent). Median reductions amounted
to 86 and 90 percent on the 8- and 12-h schedules,
respectively.

The mean hourly PVC rates after mexiletine given
either every 8 or 12 h were significantly (p<0.01)
lower than the baseline PVC rates. There was no
significant difference (p = 0.09) between the first and
second baseline PVC rates. Intervals between the two
baseline Holter recordings averaged 7.6 h. The periods
elapsing between the baseline Holter recordings and
the last Holter recording obtained during treatment
averaged eight days (range, 5 to 19 days) for the 8-h
regimen and 19.4 days (range, 9 to 42 days) for the
12-h.

There was no significant difference between the
responses to the two dosing regimens (p = 0.53 and
p = 0.60 for rates and percent reductions from base-
line, respectively).

The time course of the median PVC frequency at
baseline and on the two different dosing schedules
during a 24-h period is shown in Figure 1. At both
dosage intervals, the diurnal variations observed before
treatment were virtually absent after mexiletine
administration, and the curves of the median numbers
of PVCs recorded each hour nearly coincide on the
two dosage schedules.

Couplets were reduced from a mean hourly baseline
rate of 1.5 to a post-mexiletine rate of 0.1 on both the
8- and 12-h regimens. A mean baseline rate of 0.2
episodes of ventricular tachycardia per hour was

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reduced to a mean of 0.02 on the 8-h and of 0.01 on the 12-h schedule.

**Dosage**

For the 17 patients who were treated on both schedules, the mean daily dose was 600 mg every 8 h and 647 mg every 12 h. Individual changes in the daily dose from 8 to 12 h are shown in Figure 2. Although the protocol specified that 12-h dosage should begin with 600 mg daily, concerns about tolerability based on experience with the 8-h regimen caused two patients to receive only 200 mg every 12 h. Generally, the patients required the same or slightly higher daily doses on the 12-h than on the 8-h schedule. Table 1 gives each patient's daily dose together with hourly PVC rates and percent reductions from baseline on the two dosage schedules.

**Plasma Concentrations**

Blood level data were available from 12 of the 17 patients treated on both dose schedules. Their mean daily dose of mexiletine was 725 mg every 8 h and 657 mg every 12 h, while individual doses averaged 242 mg every 8 h and 328 mg every 12 h. The mean trough blood levels in these patients were 0.80 ± 0.55 μg/ml every 8 h and 0.73 ± 0.57 μg/ml every 12 h, while the peak levels of mexiletine averaged 1.2 ± 0.60 μg/ml every 8 h and 1.6 ± 0.64 μg/ml every 12 h.

Mean trough levels in patients receiving the same daily dose on both dosing regimens (200 mg three times a day or 300 mg twice a day) were 1.2 ± 0.5 and 1.4 ± 0.7 μg/ml, respectively. The difference between these values is not statistically significant.

**Side Effects**

All the 31 patients originally admitted were included in the safety evaluation.

Of the 17 patients treated on both regimens, 11 experienced side effects; these were tolerable and required no interruption of treatment. In the great majority of cases the symptom or symptoms were first noted within a day after administration of a given dose had begun. The most common symptoms were upper gastrointestinal distress (eight patients) and lightheadedness (five patients). Other reactions, occurring in

**Figure 1.** Median numbers of PVCs in each hour of a 24-h period before treatment and during 8- and 12-h mexiletine administration in the 17 patients who responded to the 8-h dosing regimen.

**Figure 2.** Changes in daily dose in milligrams from 8- to 12-h dosage (n = 17) (No. of lines = No. of patients).
Table 1—Daily Dose Levels, Hourly PVC Rates and Percentage Reductions from Baseline in Each of 17 Patients Treated Both Every 8 and 12 h

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<th>Patient No.</th>
<th>Baseline PVC/h</th>
<th>Daily Dose (mg)</th>
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<th>q8h</th>
<th>% PVC Reduction from Baseline</th>
<th>q12h</th>
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*The negative sign denotes an increase over baseline.

Discussion

The problem of differentiating a true drug effect from spontaneous changes in the frequency of ventricular ectopy has received increasing attention in the last ten years.15,16,18-26 It is now recognized that variability changes with time, namely, that PVC variability increases when ambulatory monitor recordings are separated by longer intervals of time.15,16 In the present study, the average length of time from the first baseline Holter recordings to the last Holter recording obtained during each treatment was 8.0 days for the 8-h and 19.4 days for the 12-h dosage regimen.

Anastasiou-Nana et al15 and Schmidt et al16 studied the reductions in total PVCs required to exceed the 95 percent confidence limits of spontaneous variability in patients with chronic ventricular arrhythmias. Anastasiou-Nana et al16 found that for elapsed times of one, two and three weeks between baseline and treatment observations, reductions in PVCs would have to be at least 85, 86 and 93 percent, respectively. Schmidt et al16 determined that for periods ranging up to six days, the minimum reduction in PVC frequency should be 63 percent, and for intervals of 7 to 89 days it should be 79 percent. The baseline characteristics of these investigators' study populations were comparable to those of our patients in terms of PVC frequency (>30/h), the proportion of patients with CAD (approximately 50 percent) and the presence of some patients with no detectable organic heart disease. On the other hand, LV function was considerably more depressed in patients of Schmidt et al.16 However, Pratt et al.,18 using multiple linear regression for analysis of variability of ventricular arrhythmias in patients with poor (LVEF<40 percent) vs preserved (LVEF>=40 percent) LV function, found no significant difference in variability between them. They did observe a significantly higher PVC variability in patients with CAD than in patients without CAD. It, therefore, appears legitimate to gauge our results by the efficacy criteria that
Anastasiou-Nana et al\textsuperscript{15} and Schmidt et al\textsuperscript{16} derived from their studies. Given the elapsed times between baseline and treatment Holter recordings in our study, the median PVC reductions we obtained are within the range of the standards established by these investigators.

In our patients, levels of PVC suppression were being steadily maintained during each hour of the 24-h period regardless of whether mexiletine was administered every 8 or every 12 h. Thus, extension of the dosage interval to 12 h is unlikely to alter either the degree or the hour-by-hour consistency of arrhythmia suppression in the majority of patients responding to oral mexiletine given three times a day.

Our results were obtained with doses within the range that is thought to be required to maintain therapeutic plasma levels of mexiletine.\textsuperscript{17,20} Mexiletine plasma levels reportedly have a "therapeutic window" with a lower threshold of 0.4 \mu g/ml.\textsuperscript{20} An upper limit of 2.0 \mu g/ml usually is imposed by CNS side effects.\textsuperscript{2}

In our patients, the mean peak and trough levels of mexiletine were within the therapeutic range on both dosing schedules. Our data confirm that a minimum trough concentration of 0.4 \mu g/ml is in fact generally needed to obtain suppression of ventricular ectopy.

Despite the higher mean individual doses and higher average peak plasma levels on the 12-h regimen the incidence rate of adverse experiences was unchanged as compared with the 8-h dosage.

Our study has demonstrated that patients with ventricular arrhythmias who respond to 300 to 900 mg of mexiletine daily at an 8-h dose interval can also be effectively maintained on a 12-h dosage schedule. The longer interval between doses should improve compliance, especially since it does not seem to be associated with a higher incidence of untoward drug effects.

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