Comparative effect of disopyramide and ethmozine in suppressing complex ventricular arrhythmias by use of a double-blind, placebo-controlled, longitudinal crossover design

CRAIG M. PRATT, M.D., JAMES B. YOUNG, M.D., MARILYN J. FRANCIS, R.N., ADDISON A. TAYLOR, M.D., H. JAMES NORTON, M.S., LADEAN ENGLISH, R.N., DAVID E. MANN, M.D., HELEN KOPELEN, L.V.N., MIGUEL A. QUINONES, M.D., AND ROBERT ROBERTS, M.D.

ABSTRACT This placebo-controlled, double-blind, longitudinal crossover study compares the efficacy of disopyramide and ethmozine, a new investigational drug, in suppressing frequent (40 or more per hour) ventricular premature depolarizations (VPDs) in 27 patients completing a 37 day protocol. Although both drugs significantly reduced VPDs relative to placebo, ethmozine was a superior antiarrhythmic drug in achieving near-total abolition of VPDs (30% of patients), which was never observed during disopyramide dosing (p < .05). At the 80% VPD reduction level, ethmozine was effective in 56% of all patients compared with an effectiveness in only 22% of patients during disopyramide therapy (p < .05). The mean peak plasma level of ethmozine was 0.66 ± 0.8 µg/ml, which significantly fell to a trough level of 0.1 ± 0.08 µg/ml (p < .001). Mean peak and trough plasma levels of disopyramide exhibited less fluctuation (2.6 ± 0.9 µg/ml vs 2.2 ± 0.9 µg/ml). Ethmozine had no effect on the QTc interval, whereas disopyramide prolonged it significantly. Importantly, while disopyramide produced serious side effects in 30% of patients, ethmozine was well tolerated with no statistically significant side effects compared with placebo. Circulation 69, No. 2, 288–297, 1984.

EPIDEMIOLOGIC STUDIES in which 12-lead electrocardiograms have been used have documented an increased risk of sudden cardiac death in patients with coronary heart disease who have ventricular premature depolarizations (VPDs).1–3 Ambulatory electrocardiographic recording has allowed a more systematic and complete quantification of these ventricular arrhythmias that are predictive of sudden cardiac death, especially in patients surviving myocardial infarction.4–7

The currently available antiarrhythmic drugs include the β-blockers, some of which have well-defined efficacy for suppressing VPDs.8,9 A number of multicenter clinical trials using β-blockers for patients in the late-hospitalization phase of acute myocardial infarction have shown an overall reduction of sudden cardiac death.10–12 None of these multicenter trials were designed specifically to define the mechanism of this reduction in sudden cardiac death that presumably was a result of preventing sustained ventricular tachycardia and ventricular fibrillation.13,14 The classical type I antiarrhythmic drugs (procainamide, quinidine, and disopyramide) are widely used to suppress ventricular rhythm disturbances. While effective in reducing the frequency of VPDs in many patients, all of these drugs have serious side effects. In addition to these undesirable side effects, all three have been documented to cause torsades de pointe ventricular tachycardia.15–17 A recent report by Velebit et al.18 documents the frequency with which antiarrhythmic drugs aggravate ventricular rhythm disturbances, with the highest reported frequency caused by quinidine (15.8%).

Disopyramide (Norpace, Searle Pharmaceuticals, Inc.; Chicago) is a recent addition to the type I antiarrhythmic group. Its development as an effective antiar-
rhythmic drug to suppress VPDs was documented in a number of clinical trials in the 1970s. In addition to suppressing VPDs, it was reported to be effective in some cases of drug-resistant ventricular tachycardia. Along with reports of its potential efficacy, there quickly followed a number of reports of frequent side effects and serious toxicity including: atypical ventricular tachycardia and disopyramide-induced ventricular fibrillation; precipitation of left ventricular dysfunction and congestive heart failure; and cardiovascular collapse. Nevertheless, since its approval by the Food and Drug Administration in 1978, disopyramide has gained wide acceptance and is used frequently.

Ethmozine (E.I. DuPont de Nemours Company, Wilmington, DE), a phenothiazine derivative, was initially developed in the Soviet Union and was noted to reduce the frequency of ventricular arrhythmias. Results of investigations in the United States indicate that ethmozine is an effective antiarrhythmic drug for suppressing VPDs with a low incidence of side effects.

Few clinical studies are available comparing the effectiveness and toxicity of ethmozine with the effectiveness and toxicity of currently available type I antiarrhythmic drugs. Since comparison of efficacy and toxicity are best done with the identical group of patients, this study reports the results of a double-blind longitudinal crossover trial comparing the relative efficacy of disopyramide and ethmozine in reducing VPDs.

Methods

Protocol. This randomized, placebo-controlled, double-blind, crossover study was performed in 33 patients. The occurrence of ≥40 VPD/hr on at least two consecutive 24 hr ambulatory electrocardiographic recordings (screening) made up the entry criteria. Of the 33 patients randomized, 27 patients (18 men and nine women, ranging in age from 36 to 72 years) completed the protocol and the data from these patients form the basis of this report. Six patients were dropped from the study. Three of these patients, although having the qualifying arrhythmia during screening (≥40 VPD/hr), failed to qualify on placebo monitoring. One patient had chronic heart failure that worsened during placebo and ethmozine dosing and was dropped from the study; invasive evaluation revealed a ventricular septal defect, for which she underwent surgical correction. One patient dropped out during disopyramide dosing due to urinary retention requiring hospitalization, and the sixth dropped out due to poor compliance documented by pill counts.

To qualify for enrollment and randomization, discontinuation of all antiarrhythmic drugs was necessary for 7 days. Previous use of any investigational antiarrhythmic drug was an exclusion criterion. β-Blockers (five patients) and digitalis (three patients) were not exclusion criteria, but doses were not changed throughout the protocol. Compliance with study medication was monitored by both pill counts and serum levels of the study medications. These 27 patients completed the 37 day protocol. Thirteen patients had ischemic heart disease, 10 with documented myocardial infarction and three with coronary artery disease documented at cardiac catheterization. Of the remaining 14 patients, three had hypertensive heart disease, five had mitral valve prolapse, and one was classified as having idiopathic cardiomyopathy. Five patients were presumably “normal” based on clinical evaluation, exercise testing, and echocardiographic assessment. Fourteen patients had previously received other antiarrhythmic drugs including β-blockers (six patients), procainamide (five patients), and quinidine (three patients).

Study design. A summary of the protocol design is shown in table 1. The study consisted of an initial 7 day period to receive placebos, followed by 10 day intervals on drug A, the second placebo, and drug B. After a patient demonstrated ≥40 VPD/hr on two 24 hr ambulatory electrocardiograms, the protocol was explained to the patient and informed consent was obtained. Important design features of this protocol are summarized in table 1 and include: (1) Three days of continuous ambulatory electrocardiographic recording at the end of each treatment period. This allowed 7 days for adequate drug washout and is far in excess of the minimum of five half-lives of the antiarrhythmic drugs being tested. (2) Serum levels of disopyramide and ethmozine were obtained four times on the final 2 days of dosing, with two trough (1 hr before dose) and two peak (1 hr after dose) levels being obtained. (3) Quantitation of VPD rates during the hours that plasma drug samples were obtained, allowing corre-

| TABLE 1  
Summary of protocol design |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Procedure</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>24 hr aECG</td>
</tr>
<tr>
<td>Echo/2D</td>
</tr>
<tr>
<td>Bruce ETT</td>
</tr>
<tr>
<td>12-lead electrocardiogram</td>
</tr>
<tr>
<td>Serum levels (peak and trough)</td>
</tr>
<tr>
<td>Routine lab</td>
</tr>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Symptom diary</td>
</tr>
<tr>
<td>Placebo 1</td>
</tr>
<tr>
<td>Days 1-4</td>
</tr>
<tr>
<td>Drug A</td>
</tr>
<tr>
<td>Placebo 2</td>
</tr>
<tr>
<td>Drug B</td>
</tr>
</tbody>
</table>

24 hr aECG = 24 hr ambulatory electrocardiographic recording; Echo/2D = two-dimensional echocardiogram; ETT = exercise treadmill testing.
loration of relative reduction of arrhythmias to peak and trough plasma levels. (4) Mode and two-dimensional echocardiograms for assessment of left ventricular function and Bruce exercise testing were performed in the last 2 days of each treatment sequence. The two drug sequences are summarized in table 2 with patients randomized to either sequence A or B. The 14 patients randomized to sequence A received ethmozine before disopyramide, and the 13 patients randomized to sequence B received disopyramide before ethmozine.

**Drug therapy.** Disopyramide was given at a dose of 600 mg daily (150 mg orally every 6 hr) on a dosage schedule of 6 A.M., noon, 6 P.M., and midnight. Ethmozine was given on a dosing schedule of every 8 hr (6 A.M., 2 P.M., and 10 P.M.) to achieve a total daily dose of 10 mg/kg, which averaged 800 mg/day. Ethmozine tablets were available in dosage forms of 50, 100, 200, and 250 mg. During ethmozine and disopyramide dosing, additional placebo tablets were provided so that all dosing sequences were identical to the placebo sequences (6 A.M., noon, 2 P.M., 6 P.M., 10 P.M., and midnight). The duration of drug dosing for both antiarrhythmic drugs was 10 days with an intervening 10 day period for placebos (table 1).

**Ambulatory electrocardiographic monitoring and exercise testing.** The ambulatory electrocardiographic recordings were performed on Avionics 445A two-channel recorders, were analyzed on an Avionics DCG Trendsetter, and were edited by a cardiologist. Ventricular arrhythmias were quantitated hourly for total VPDs, pairs, and ventricular tachycardia (defined as ≥3 consecutive beats at a rate of ≥120/min). Quality control in our laboratory by use of standard test tapes shows a reproducibility of 92% for total VPDs, 95% for paired forms, and 98% for ventricular tachycardia (intraobserver variability). Agreement in total VPD counts between the two research Holter scanners is 95% (interobserver variability). External quality control has been achieved by use of test tapes of the core laboratory of a national arrhythmia trial with 98% accuracy of VPD counts.

Maximal treadmill exercise testing was performed on a motor-driven treadmill (Quinton Instruments) with the standard Bruce protocol. The electrocardiogram was monitored continuously on a four-channel oscilloscope (Hewlitt-Packard) in patients at rest, during each stage of exercise, and 8 min into the recovery phase. Hard-copy confirmation of the 12-lead electrocardiogram, including quantitation of all VPDs, was obtained throughout the exercise and recovery phases.

**Ventricular function assessment.** M mode and two-dimensional echocardiography were performed on ATL Mark V equipment, with all studies recorded on videotape with the use of a Umatic Videocassette recorder (Panasonic VD-2600) interfaced to a back-scorer search module (Dynaciences EJ-104, Model 1). In addition to measurements of left ventricular systolic dimension, end-diastolic dimension, and left atrial dimension, the left ventricular ejection fraction was calculated from the two-dimensional echocardiogram by a determination previously described from our laboratory that compares favorably with gated blood pool imaging (r = .927).

Clinical evaluation, including recording of supine and up-right heart rate and blood pressure, was performed daily. A complete physical examination was performed at the end of each study sequence; ophthalmologic examination was performed during placebo and drug periods in the final 48 hr of each sequence. This included a slit-lamp evaluation and funduscopic examination by a board-certified ophthalmologist. Routine laboratory parameters were obtained in all patients during each dosing sequence. Standard 12-lead electrocardiograms were performed during the last 48 hr of each drug sequence.

**Plasma levels.** Disopyramide concentrations in the plasma were determined by the reverse-phase high-pressure liquid chromatographic method of Flood et al.2 There is a close correlation between the plasma concentration of disopyramide obtained by this method and those obtained by the Suya EMIP method. The therapeutic range of 2 to 5 μg/ml is the same for both methods. Serum levels of ethmozine were determined by the absorption spectrometric method after high-pressure liquid chromatographic separation. This procedure was described in detail in our previous article.39 Intra-assay and interassay coefficients of variation are 9.7% and 12.1%, respectively, for this method.

**Statistical analysis.** Statistical analysis was performed with Student's t test when measured variables were of a normal distribution. If normality could not be assumed, Wilcoxon rank-sum test was used. Categorical variables were compared with the chi-square test. To compare the significance of individual responses on each antiarrhythmic drug, McNemar's test was used.

To ensure complete washout of the active antiarrhythmic drug before the second placebo analysis, the comparability (paired t test) of total VPDs, pairs, and runs of ventricular tachycardia during the first and second placebo periods were compared and analyzed separately for each drug sequence. To test adequacy of randomization, the first placebo periods for sequences A and B were also analyzed for comparability (t test). Also, to eliminate the possibility that either drug sequence altered measured drug effect, the mean percent VPD reduction by each drug was compared in sequences A and B.

**Results**

**Baseline comparability of placebo periods.** The comparability of the two placebo dosing periods is demonstrated in table 3. In sequence A, ethmozine is given as the first active antiarrhythmic drug preceding the second placebo period. In this sequence there is no statistical difference between the first and second placebo periods for total VPDs, which were 465 ± 289 and 503 ± 484 VPD/hr, respectively (p > .3). There is similar comparability for ventricular pairs. Likewise, when disopyramide is the first active antiarrhythmic drug given, there is baseline comparability for total VPDs during the two placebo periods (570 ± 518 vs 590 ± 654 VPD/hr, p > .3) as well as for paired forms.

Randomization into sequences A and B successfully produced two groups of patients (table 2) with similar VPD frequency. The mean daily total VPDs during the first placebo periods for each sequence averaged 465 ± 289 VPD/hr in the 14 patients initially receiving ethmozine and was similar to that observed in the 13

### TABLE 2

**Protocol design: summary of drug sequencing**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>P₁-E</td>
<td>P₂-D</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>P₁-D</td>
<td>P₂-E</td>
<td>13</td>
</tr>
</tbody>
</table>

P₁ = first placebo period; P₂ = second placebo period; E = ethmozine; D = disopyramide.
patients initially receiving disopyramide (570 ± 518 VPD/hr, p > .3; table 3).

In the 14 patients in sequence A, there was a mean decrease in VPD frequency of 17 ± 12% during dosing with the second placebo, compared with dosing with the first placebo. Only one patient in sequence A had a change of ± 100% VPDs (138 ± 226 VPD/hr [first placebo]; 1330 ± 980 VPD/hr [second placebo]). In sequence B there was a mean decrease in VPD frequency of 15 ± 18% during dosing with the second placebo, compared with dosing with the first placebo. Again, only one patient in sequence B exhibited extreme (change of ≥ 100% VPD frequency) variability (64 ± 8 VPD/hr [first placebo]; 304 ± 267 VPD/hr [second placebo]). To further study individual patient variability, the daily VPD range for the 3 days of placebo recording during the first and second periods were compared for both drug sequences and were not significantly different (p > .3 for sequences A and B, paired t test). Also, there was no difference in the daily VPD ranges for the 14 patients in sequence A and 13 patients in sequence B when the respective first and second periods of placebo dosing were compared (p > .15, nonpaired t test). Randomization into sequences A and B also achieved similar individual patient variability in daily VPD counts. Analysis of the mean standard deviations of VPD counts in the 3 days of ambulatory electrocardiographic recordings from the first placebo periods of both sequences (A and B) revealed that they were similar (119 VPD/hr ± 106 and 134 VPD/hr ± 43, respectively, p = NS). Finally, we analyzed the mean percent VPD reduction achieved by each antiarrhythmic drug in sequences A and B to demonstrate comparable drug efficacy, regardless of drug sequencing. The mean reduction in VPDs by ethmozine averaged 78.4 ± 18.3% in sequence A and 81.8 ± 28.1% in sequence B (p > .3). Likewise, disopyramide was equally efficacious regardless of drug sequence, with mean VPD reductions of 62.5 ± 29.7% and 48.0 ± 31.6%, respectively (p > .25).

Despite the majority of patients having ventricular tachycardia during the placebo periods (19 of 27), a similar analysis of comparability was not undertaken since only 14 patients had ventricular tachycardia during both placebo periods.

**Group responses to ethmozine and disopyramide.** During ethmozine dosing, the mean frequency of VPDs was decreased from 524 VPD/hr to 151 VPD/hr, representing a 71.2% reduction (p < .001 vs placebo). Ethmozine reduced ventricular pairs by 78.6% (19/hr vs 4/hr, p < .01). In the 16 patients who had nonsustained ventricular tachycardia in the placebo period immediately preceding dosing with ethmozine, ethmozine reduced the total mean daily runs of ventricular tachycardia by 84.5% (203 ventricular tachycardia runs/24 hr to 31 ventricular tachycardia runs/24 hr, p < .01).

Disopyramide reduced the mean frequency of VPDs by 52.8% (535 VPD/hr to 253 VPD/hr, p < .01). Ventricular pairs were reduced 60.1%. Eighteen patients exhibited nonsustained ventricular tachycardia in the placebo interval immediately preceding disopyramide. In these patients, disopyramide reduced ventricular tachycardia runs 90.7% (147 ventricular tachycardia runs/24 hr to 14 ventricular tachycardia runs/24 hr, p < .01).

Although both antiarrhythmic drugs significantly reduced all grades of ventricular ectopy, reduction of the frequency of VPDs was significantly greater with ethmozine than with disopyramide (p < .01). Likewise, ethmozine was significantly more potent in reducing ventricular pairs than disopyramide therapy (p < .03). There was no significant difference of the two drugs in reducing the total runs of ventricular tachycardia.

**Individual response to ethmozine and disopyramide.** The efficacy of ethmozine and disopyramide in suppressing both single and repetitive VPDs can also be analyzed as a percentage reduction in individual patients (McNemar’s test). This is summarized in table 4, which shows that 56% of all patients achieved an 80%
TABLE 4
Comparative efficacy of ethmozine and disopyramide in suppressing single and repetitive forms of VPDs

<table>
<thead>
<tr>
<th>Suppression of VPDs relative to placebo (%)</th>
<th>No. of patients with total VPDs</th>
<th>No. of patients with pairs</th>
<th>No. of patients with VT runs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>100</td>
<td>5/27^</td>
<td>0/27</td>
<td>12/27^</td>
</tr>
<tr>
<td>≥99</td>
<td>8/27^</td>
<td>0/27</td>
<td>14/27</td>
</tr>
<tr>
<td>≥90</td>
<td>12/27^</td>
<td>0/27</td>
<td>17/27</td>
</tr>
<tr>
<td>≥80</td>
<td>15/27^</td>
<td>6/27</td>
<td>21/27</td>
</tr>
<tr>
<td>≥75</td>
<td>16/27^</td>
<td>8/27</td>
<td>21/27</td>
</tr>
<tr>
<td>≥70</td>
<td>17/27</td>
<td>11/27</td>
<td>22/27</td>
</tr>
<tr>
<td>≥60</td>
<td>22/27</td>
<td>12/27</td>
<td>22/27</td>
</tr>
<tr>
<td>≥50</td>
<td>22/27</td>
<td>15/27</td>
<td>22/27</td>
</tr>
<tr>
<td>≥0</td>
<td>25/27</td>
<td>25/27</td>
<td>24/27</td>
</tr>
</tbody>
</table>

VT = ventricular tachycardia; E = ethmozine; D = disopyramide.

^All p < .05, ethmozine > disopyramide; McNemar’s test.

or greater reduction of total VPDs during ethmozine therapy. In contrast, only 22% of patients on disopyramide achieved this reduction (p < .05). While ethmozine abolished more than 99% of total VPDs in 30% (eight of 27) of the patients, disopyramide failed to achieve this degree of reduction in any of the 27 patients (p < .05). While ethmozine achieved total abolition of ventricular pairs in 44% of patients, disopyramide suppressed all ventricular pairs in only 15% of patients (p < .05). There was no statistical difference in the ability of these antiarrhythmic drugs to suppress runs of nonsustained ventricular tachycardia. Equal efficacy of both drugs was noted in the 13 patients with documented coronary heart disease and in the remaining 14 patients.

Exacerbation of arrhythmias on ethmozine and disopyramide. Of the 14 patients in sequence A, two experienced an increase of VPDs during drug therapy. One patient was documented to have a 211% increase in total VPDs (265 VPD/hr to 825 VPD/hr) on ethmozine therapy. This patient also manifested one episode of 3 beat ventricular tachycardia that had not been present in the placebo period immediately preceding ethmozine dosing. A second patient was noted to have an 83% increase in total VPDs on disopyramide compared with the placebo period immediately preceding disopyramide (233 VPD/hr to 426 VPD/hr). Of the 13 patients in sequence B, two patients were noted to have exacerbation of arrhythmia. One patient demonstrated a 13% increase in total VPDs during disopyramide dosing (560 VPD/hr to 635 VPD/hr). A second patient was noted to have a 92% increase in total VPDs on ethmozine therapy (438 VPD/hr to 841 VPD/hr). This patient was also noted to have frequent runs of ventricular tachycardia during placebo dosing that increased during ethmozine dosing (38 ventricular tachycardia runs/24 hr increased to 372 ventricular tachycardia runs/24 hr).

Serum levels of ethmozine and disopyramide. The blood levels representing two serum samples obtained at both peak (1 hr after dose) and trough periods (1 hr before dose) during ethmozine and disopyramide dosing are shown in table 5. A mean peak plasma level of 0.66 ± 8.0 μg/ml was achieved during ethmozine dosing. One hour before ethmozine dosing, the mean trough serum level had decreased to 0.1 ± 0.08 μg/ml (p < .001 vs peak level). Serum levels of disopyramide were less variable with a mean peak serum concentration of 2.6 ± 0.9 μg/ml and a mean trough level of 2.2 ± 0.9 μg/ml (p > .3, peak vs trough).

Although plasma levels of ethmozine fluctuated significantly, there was no significant difference in the frequency of VPDs during the hours that peak and trough serum levels of ethmozine were obtained (160 ± 283 VPD/hr vs 132 ± 205 VPD/hr, p = NS). Quantitation of VPDs was also performed in all 27 patients during the 2 hr intervals that peak and trough serum levels of disopyramide were obtained. The mean frequency of VPDs was unchanged (300 ± 390 VPD/hr vs 389 ± 452 VPD/hr, p = NS). Correlation coefficients were determined for both samples of peak and trough serum levels of both drugs compared with the VPD rate for the hour the sample was drawn. There was no correlation of peak or trough level to rate of arrhythmia for either ethmozine or disopyramide (all r > .2; p > .5).

Exercise-related ventricular arrhythmias. Of the 27 patients completing the protocol, 16 completed Bruce exercise testing during all four dosing intervals. Of those, 15 patients had VPDs during exercise and/or the recovery phase in their respective placebo periods. During ethmozine dosing four of 15 patients had total abolition of VPDs, and during disopyramide dosing one of 15 had total abolition of VPDs. Of the seven patients with repetitive VPDs (pairs and ventricular tachycardia) during exercise or recovery, total abolition of these complex VPDs occurred in six of seven patients during ethmozine therapy and in five of seven during disopyramide therapy. Eight patients had only unifocal VPDs during exercise or recovery phase. Of these, five of eight developed paired VPDs during exercise or recovery phase while on disopyramide therapy, a development that was not observed with any patient during ethmozine therapy.

Laboratory, clinical, electrocardiographic, and echocardiographic findings. Routine physical examinations and
laboratory tests were performed in both placebo periods as well as during ethmozine and disopyramide dosing; no abnormalities were noted. Ethmozine significantly increased both PR and QRS duration (by 0.02 and 0.01 sec, respectively) without any effect on QTc interval. Disopyramide significantly increased the PR duration with a tendency to increase the QRS duration (p < .08). In contrast to ethmozine, disopyramide increased QTc duration an average of 0.03 sec (p < .001).

Echocardiographic measurements were made during placebo, ethmozine, and disopyramide dosing. Global left ventricular ejection fraction and left ventricular end-diastolic dimension as well as end-systolic dimension were unchanged during the two drug regimens compared with their respective placebo intervals. However, the subset of six patients with impaired left ventricular function (mean left ventricular ejection fraction of 37 ± 8%) had no change during ethmozine therapy (38 ± 6%), but demonstrated a trend of a decreasing left ventricular ejection fraction during disopyramide dosing (34 ± 9%, p = .08). There was no change in left atrial dimension on either drug regimen.

**Side effects and toxicity.** Side effects were classified as mild to moderate or severe. Mild-to-moderate side effects were defined as those of which the patient complained but that would not require discontinuation of the therapy due to unacceptable severity. Severe side effects were those that the patient felt would preclude continuation of the therapy after the 10 day protocol. As seen in table 6, there was no side effect during ethmozine therapy that was significantly greater than during placebo. In contrast, patients experienced a significant increase in both urinary complaints and dry mouths during disopyramide therapy. Eight of the 27 patients reported that side effects during the disopyramide dosing phase were unacceptable (dry mouth and urinary symptoms), and they would not continue that drug. Additionally, one patient was dropped from the study when he developed urinary retention during disopyramide therapy.

**Discussion**

**Study design.** A double-blind longitudinal crossover design has the advantage of comparing two antiarrhythmic drugs in the same patient population, rather than in two different patient populations as in a parallel-design protocol. The 10 day intervals between crossover of active antiarrhythmic drugs was far in excess of five drug half-lives of both ethmozine and disopyramide, both of which have half-lives less than 6 hr. We demonstrated “physiologic washout” of each antiarrhythmic drug by the return to baseline of the arrhythmia frequency during the second placebo period. Thus, we established the comparability of the first and second placebo periods in both drug sequences, that is, regardless of whether ethmozine or disopyramide was the first active antiarrhythmic drug given. We also confirmed that randomization of patients in drug sequences A and B produced comparable arrhythmia frequency and variability. Thus, based on this analysis, both successful randomization and the adequacy of drug washout during the second placebo period allowed meaningful comparison of these two antiarrhythmic drugs in this patient population defined by high frequency of VPDs.
The dosage range chosen for each of these antiarrhythmic drugs was in the moderate range. The majority of published studies reporting the antiarrhythmic efficacy of disopyramide have used an average dose of 150 mg four times daily,\textsuperscript{20, 23} although some have used lower doses of 100 mg four times daily.\textsuperscript{24} Although a higher dose of disopyramide could have been chosen for this study, the dose chosen led to unacceptable side effects in 30% of patients that may have increased further had a higher dose range been chosen.

The ethmozine dose of 10 mg/kg/day (divided three times a day) was selected on the basis of our own recent experience.\textsuperscript{39} Ethmozine is currently being administered in doses of up to 14 mg/kg/day in some clinical trials. Since the dose chosen for this protocol did not lead to significant side effects in any of the patients, it would be of interest to assess a higher dose. However, it was our experience that patients failing to respond to the 10 mg/kg/day dosage usually did not receive further benefit from higher doses.\textsuperscript{39}

Three days of 24 hr ambulatory electrocardiographic recordings were chosen to establish VPD frequency during placebo as well as VPD frequency during treatment in both treatment sequences; this was based on the well-documented variability of single and complex ventricular arrhythmias on sequential 24 hr ambulatory electrocardiographic recordings.\textsuperscript{43-45} Based on 3 days of ambulatory electrocardiographic quantitation of VPDs in patients on placebo and drugs, Morganroth et al.\textsuperscript{44} have established a 64.6% minimal VPD reduction rate to establish drug efficacy in individual patients. Using a mixed-model analysis of variance on 24 hr VPD frequencies, Sami et al.\textsuperscript{46} have concluded that the minimal percent reduction required to establish drug efficacy at a 95% one-tail confidence level may be somewhat lower than that reported by Morganroth et al. Regardless of which criteria are used for determining efficacy, the duration of ambulatory electrocardiographic recording in this study compares favorably with most drug trials and in fact exceeds that of most published data.\textsuperscript{47}

**Antiarrhythmic efficacy of disopyramide vs ethmozine.** Both disopyramide and ethmozine were effective in reducing the mean frequency of VPDs. For the entire group of 27 patients, a 52.8% reduction in total VPDs documented during disopyramide therapy is somewhat lower than that of other published studies, many using intravenous disopyramide with efficacy documented with only electrocardiographic rhythm strips\textsuperscript{19, 21} or short-term ambulatory electrocardiographic recordings combined with on-line telemetry in the coronary care unit setting.\textsuperscript{22} A report of Tramurco et al.,\textsuperscript{24} in which 100 mg disopyramide four times a day was used, documented 50% suppression of VPDs in 80% of patients. However, this study is not comparable with the present one because of minimal electrocardiographic recording (2 hr).\textsuperscript{24} Vismara et al.,\textsuperscript{20} evaluated disopyramide at an average dose of 600 mg daily in a 16 week outpatient study that was placebo-controlled and single-blind. In that study, seven of 10 patients with VPD frequencies of greater than 50 VPD/hr had a 50% reduction on disopyramide therapy. Vismara et al.\textsuperscript{23} also documented the efficacy of disopyramide in the abolition of "refractory ventricular tachycardia" with intravenous infusion of disopyramide and short periods (at least 4 hr) of ambulatory electrocardiographic monitoring in each patient.

The results of this study, in which 3 days of continuous ambulatory electrocardiographic recording was used in each dosing period, confirm that disopyramide can reduce total VPDs at a 50% reduction level in approximately one-half of patients. It is also interesting that total or near total abolition of VPDs was not observed in any of the 27 patients studied. Disopyramide was a more effective antiarrhythmic drug in suppressing repetitive forms of VPDs, with two-thirds of patients having total suppression of nonsustained ventricular tachycardia, confirming the previous report by Vismara et al.\textsuperscript{23} Ethmozine was superior to disopyramide in suppression of VPDs. Total or near-total abolition of ventricular arrhythmia was seen in 30% of patients. Ethmozine was superior to disopyramide in suppressing VPDs at all percent suppression levels above the 75th percentile. Likewise, ethmozine was statistically superior to disopyramide in the total abolition of ventricular pairs. Ethmozine and disopyramide were equally effective in suppression of nonsustained runs of ventricular tachycardia.

At the 80% VPD suppression level, ethmozine was effective in 15 of 27 (56%) patients, findings quite similar to our previous experience in a placebo-controlled, single-blind trial in which 23 of 39 (59%) patients with frequent VPDs responded with an 80% or greater suppression.\textsuperscript{39} By use of the criteria of Morganroth et al.\textsuperscript{24} for the minimum percent reduction in VPD frequency required to demonstrate individual antiarrhythmic effect, 66% of patients on ethmozine dosing compared with 44% of patients on disopyramide dosing had significant reductions (3 days of ambulatory electrocardiographic recordings for patients on placebo and drug).

This report on the efficacy of disopyramide, with information from 3 continuous days of ambulatory
electrocardiographic recording, merits comparison with the efficacy of other clinically available type I antarrhythmic drugs. In a recent report of a double-blind parallel study comparing quinidine to flecainide,48 quinidine sulfate in doses of 1200 to 1600 mg/day resulted in an average 84.7% suppression of VPDs and near total abolition of VPDs in 34% of patients. This is in contrast to the present study using disopyramide in which none of the 27 patients had total suppression of VPDs on doses of 600 mg/day. Panidis and Morganroth49 documented the efficacy of quinidine in 20 patients with 48 hr of continuous ambulatory electrocardiographic recording. At a dose of 1600 mg daily, which led to significant gastrointestinal side effects in 25% of all patients, only 14 of 20 patients had an equal or greater than 70% reduction in total VPDs. Winkle et al.30 reported on a placebo-controlled longitudinal study of patients with frequent VPDs. During this 5 week study, patients sequentially received placebo, propranolol (240 mg daily), procainamide (3 g daily), and quinidine (1.8 g daily) and then underwent a final control period. Sixty percent (six of 10) of patients who were able to tolerate the 1 week of procainamide therapy had a reduction in total VPDs exceeding 90%. However, at a dose of 3 g of procainamide daily, seven of 17 patients were unable to complete the week of treatment due to side effects. In this same protocol, eight of 13 patients (62%) had ≥90% reduction in total VPDs on quinidine therapy. Importantly, eight patients experienced side effects, three of which required termination of drug therapy. Thus, published reports of the antiarrhythmic efficacy of both quinidine and procainamide indicate that these drugs may have a greater ability to suppress total VPDs, but with a similar high frequency of side effects.

Assessment of arrhythmias in the 15 patients with VPDs during exercise or recovery is difficult to analyze. The only interesting finding was the development of paired VPDs during disopyramide dosing in five of seven patients with only unifocal VPDs recorded during the placebo period. This may be accounted for by variability of VPDs on repeated exercise testing.

Plasma concentrations of disopyramide and ethmozine. The mean peak plasma level of disopyramide achieved was 2.6 ± 0.9 ng/ml, which is within the reported therapeutic range of 2 to 5 ng/ml as reported by Flood et al.42 With the dosage regimen of 150 mg every 6 hr, eight of 27 patients reported unacceptable side effects during drug dosing. Therefore, although higher doses might have been preferable for increased efficacy, toxicity frequently precludes higher daily doses in many patients. Furthermore, severe cases of toxicity, including cardiovascular collapse, have been reported at plasma concentrations of disopyramide of 4.9 to 8.1 ng/ml.32 There was no significant change between peak and trough plasma levels of disopyramide in this study. Also, there was no demonstrable change in relative reduction of arrhythmia during monitoring periods of peak and trough levels (r < .2).

Plasma levels of ethmozine fluctuated significantly, reaching peak mean levels of 0.66 ± 0.8 ng/ml, a slightly higher mean plasma level of ethmozine than we previously reported in our 39 patients with an average dose of 10.1 mg/kg/day (0.42 ± 0.28 ng/ml).39 Despite low plasma trough levels (0.1 ± 0.08 ng/ml, p < .001), there was no significant change in the degree of VPD reduction. Drug effect did not appear to correlate with plasma level of ethmozine, a fact consistent with our previously reported data.39

Electrocardiographic, laboratory, and echocardiographic assessment. Disopyramide significantly increased PR duration and QTc duration, with a trend to increased QRS duration. These alterations of the standard 12-lead electrocardiogram are consistent with previously reported studies.19-24 While ethmozine significantly increased both PR and QRS duration, it had no effect on QTc duration. These findings were also consistent with previously reported electrocardiographic changes.37-39

There were no significant changes in routine laboratory parameters with either antiarrhythmic drug. Although there were no demonstrable changes in global left ventricular ejection fraction calculated from the two-dimensional echocardiogram,41 the trend to decreased left ventricular function on disopyramide therapy in patients with global left ventricular ejection fractions less than 40% is consistent with previously reported studies of reduced left ventricular function during disopyramide therapy.30-32 However, no patient developed overt congestive heart failure during disopyramide dosing. There were no changes in left ventricular function as measured by two-dimensional echocardiography during ethmozine dosing. However, one patient was dropped from the study when she developed congestive heart failure while on ethmozine therapy. This patient had a deteriorating clinical situation during the previous placebo period and was not responding to digitalization and diuretics; she was subsequently found to have a significant ventricular septal defect requiring surgery. It was not our opinion that this deterioration was due to ethmozine.

Assessment of side effects of drugs. The study design allowed assessment of side effects and toxicity of each antiarrhythmic drug compared with its respective pla-
cebo period. The previous reports of side effects with disopyramide\textsuperscript{20-24} were confirmed by this study. At moderate doses of disopyramide (150 mg every 6 hr) achieving a mean peak plasma concentration of 2.6 $\mu$g/ml, 30% of the patients reported intolerable side effects (either dry mouth and/or urinary symptoms) of sufficient magnitude that they would not consider continuing the medication on a long-term basis. Peak serum levels of disopyramide were not significantly different in patients who did or did not experience dry mouth ($2.27 \pm 0.98 \mu$g vs $2.79 \pm 0.83 \mu$g; $p = $ NS). Likewise, peak serum levels of disopyramide were not significantly different in patients with or without urinary symptoms ($2.65 \pm 0.62 \mu$g vs $2.55 \pm 0.93 \mu$g; $p = $ NS). The frequency of these side effects reached statistical significance compared with those of both placebo and ethmozine therapy. Patients on ethmozine were remarkably free of side effects, with none of the effects approaching statistical significance compared with those of patients on placebo. This is consistent with previous published data reporting this drug to have a low incidence of minor side effects with no serious toxicity.\textsuperscript{37-39}

Conclusion. Relative to placebo, both disopyramide and ethmozine significantly reduced total VPDs in this study. However, ethmozine was a superior antiarrhythmic drug, with near total VPD suppression in 30\% of all patients, which was not observed in any patient on disopyramide. Both drugs were effective in suppressing nonsustained ventricular tachycardia. Importantly, ethmozine does not prolong the QT interval. In contrast to disopyramide, ethmozine was not only a more effective antiarrhythmic drug but was also well tolerated with no significant side effects, meriting further consideration for long-term clinical studies to define its role relative to other new promising antiarrhythmic drugs.

We gratefully appreciate the technical assistance of Gregory Feldman, M.D. and the secretarial assistance of Candi Evans and Barbara Bond.

References

THERAPY AND PREVENTION—ARRHYTHMIA

Comparative effect of disopyramide and ethmozine in suppressing complex ventricular arrhythmias by use of a double-blind, placebo-controlled, longitudinal crossover design. C M Pratt, J B Young, M J Francis, A A Taylor, H J Norton, L English, D E Mann, H Kopelen, M A Quinones and R Roberts

_Circulation._ 1984;69:288-297
doi: 10.1161/01.CIR.69.2.288

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/69/2/288

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/