Ethmozin, A New Antiarrhythmic Drug for Suppressing Ventricular Premature Complexes

PHILIP J. PODRID, M.D., ANATOLI LYAKISHEV, M.D., BERNARD LOWN, M.D., AND NICHOLAI MAZUR, M.D.

SUMMARY Ethmozin, a phenothiazine derivative, is an antiarrhythmic drug synthesized in the USSR. Preliminary data suggest that it is effective against a diversity of ectopic arrhythmias. The present study, carried out in the USSR, was designed to assess efficacy and patient tolerance of this new drug. Thirty-seven patients with chronic, persistent, frequent and symptomatic ventricular premature complexes (VPCs) were studied. VPCs were exposed by means of 24-hour ambulatory monitoring and exercise stress testing. Two drug schedules were used. Group 1, consisting of 11 patients, received 225 mg/day of ethmozin, while group 2, consisting of 26 patients, received 600 mg/day. Acute drug testing with a single large dose of ethmozin was followed by multiple dosing for a minimum of 4 days. Placebo was given in a single-blind fashion only to responders.

Only two patients in group 1 had a significant reduction in VPCs as evaluated by both monitoring and exercise testing. Fourteen patients in group 2 (54%) showed striking suppression of VPCs. Mild and transient effects were encountered in only four of the 37 patients. We conclude that ethmozin appears to be a well-tolerated, relatively effective agent for controlling VPCs.

PATIENTS with ventricular arrhythmias are being detected in increasing numbers because of the widespread use of ambulatory monitoring and exercise stress testing. Currently available antiarrhythmic drugs, however, are not consistently effective, safe, or well tolerated. There is an urgent need for drugs that suppress ventricular arrhythmias, cause minimal adverse reactions and have a prolonged duration of action so as to gain patient acceptance and adherence.

In 1965, the Institute of Pharmacology of the USSR Academy of Medical Sciences synthesized a new antiarrhythmic drug, ethmozin, the hydrochloride of 10-(3-morpholinopropionyl)-phenothiazine-2-carboxylic acid, ethylester (fig. 1). Early reports in the USSR have shown that ethmozin effectively controls ventricular and supraventricular arrhythmias in experimental animals and in man. However, these studies were not completely persuasive, because the evaluation of drug efficacy was based exclusively on brief electrocardiographic records and the reports of patients. In the USA, Danilo et al. showed that ethmozin possesses lidocaine-like properties on isolated Purkinje fibers. Morganroth and coworkers in preliminary clinical investigations, have found the drug to be effective and induce few adverse reactions.

These promising results with ethmozin invited further clinical investigations using currently available technology. Using protocols for acute and chronic antiarrhythmic drug testing developed and used in the cardiovascular laboratories at the Harvard School of Public Health, a joint study of patients with frequent ventricular premature complexes (VPCs) was conducted in Moscow in 1977. Because the aim was to establish drug efficacy for suppressing ventricular arrhythmias and to assess patient tolerance, the group studied was recruited exclusively on the basis of VPC frequency and included subjects both with and without heart disease.

Material and Methods

Thirty-seven patients with frequent ventricular ectopic activity constituted the study population. There...
were 21 males and 16 females; the average age was 45 years (range 16–56 years). Ten patients had coronary heart disease and five had cardiomyopathies; 22 patients had no evidence of structural heart disease. All patients were in normal sinus rhythm and antiarrhythmic drugs were withheld for at least 48 hours before the study. No patient was receiving digitalis, diuretics, other cardiac medications or psychotropic agents. Each patient had a complete blood count, routine blood chemistry as well as serum electrolyte determinations. These investigations were conducted at the National Cardiology Research Center in Moscow, Academy of Medical Sciences, USSR.

Patients were recruited from among those referred to the Center because of documented chronic, frequent and symptomatic ventricular ectopic activity unresponsive to antiarrhythmic therapy, including quinidine, procainamide and propranolol. Symptoms were generally palpitations, the sensation of “skipping of the heart,” and dizziness. All patients had frequent ventricular arrhythmia documented by repeated ECGs obtained by referring physicians. Inclusion into the study was based on the findings derived from 24-hour ambulatory electrocardiographic monitoring with a tape recorder and maximal exercise stress testing on a bicycle ergometer. The hourly frequency of VPCs during a 24-hour monitoring session was determined. The presence of multiform ectopic activity, couplets and episodes of ventricular tachycardia was noted. The following criteria were adhered to in patient selection:

Exercise: demonstration during maximal exercise stress test of one of the following: 1) occurrence of at least 2 VPCs/min in a 3-minute period at peak or immediately after cessation of exercise when VPCs were absent in the 3-minute control period; 2) development of repetitive forms (couplets or ventricular tachycardia) or at least doubling of VPC frequency in any 3-minute period at peak or immediately upon termination of exercise stress when ectopic activity was present during the control period.

Ambulatory 24-hour monitoring: During a control monitoring session at least one of the following criteria had to be met: 1) frequent VPCs (≥30 VPCs/hour) during a majority of the patient’s waking hours and at least occasional VPCs during the remainder; 2) ≥10 VPCs/hour during a majority of sleeping hours; 3) ≥30 VPCs/hour in one-third of waking hours in conjunction with multiform ectopic activity or repetitive forms.

Twenty-eight patients had frequent VPCs during each hour of the entire 24-hour monitoring period. In each of these patients the hourly frequency was constant. Eight had frequent VPCs at a constant level during all waking hours and sporadic VPCs while sleeping. One patient with occasional VPCs during 24-hour monitoring had recurring couplets and bursts of ventricular tachycardia during exercise. These 36 patients had 64–1546 VPCs/hour (mean 529 ± 89 VPCs/hour) (table 1). Of the 36 patients meeting monitoring criteria for recruitment in this study, half exhibited more than 500 VPCs/hour. All patients had at least 3 VPCs/min during exercise or in the recovery period; 25 had ≥10 VPCs/min. Eight patients had couplets or ventricular tachycardia or both.

In the initial part of the study, 11 patients (group 1) received a total dose of ethmozin of 225 mg/day (range 2.7–3.9 mg/kg; mean ± SEM 3.2 ± 0.2 mg/kg). Permission was later granted by the Pharmacologic Commission of the Ministry of Health of the USSR to administer up to 600 mg/day. The 26 patients receiving this larger daily dose constitute group 2. The daily dosage was 7.3–11.5 mg/kg of body weight (mean ± SEM 9.6 ± 0.3 mg/kg).

There were three phases to this investigation: 1) acute ethmozin drug testing (phase 1); 2) chronic administration of ethmozin for 4 or more days (phase 2); 3) placebo phase in subjects who met the criteria for effective drug action during phase 2.

Phases — Acute Drug Testing

This technique has been described previously.11–14 The essential elements include: 1) administration of a single dose of the drug equal to half the total daily maintenance; 2) programmed “trendscription,” which permits on-line display of condensed electrocardiographic data with periodic printout of data depending upon the density of ectopic activity;15 and 3)

<table>
<thead>
<tr>
<th>Table 1. Frequency of Ventricular Premature Complexes per Hour Among 36 Patients* During the Control 24-hour Monitoring Session</th>
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<tbody>
<tr>
<td>VPCs/hr (mean)</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>&lt; 100</td>
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<tr>
<td>100–200</td>
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<td>300–400</td>
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<td>&gt; 1000</td>
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</table>

*One of the 37 patients studied had infrequent VPCs, but with exercise exhibited advanced grades.

Abbreviation: VPC = ventricular premature complex.
blood sampling for drug levels at the time of peak antiarhythmic effect, abatement of drug action or the emergence of adverse effects.

Antiarhythmic and other cardiac medication was withheld for 48 hours before testing. Breakfast was limited to tea and bread and the test was performed approximately 2 hours later. A 12-lead ECG was recorded before starting a control period of 30 minutes of trendscription. Once the prevalence of VPCs was determined, the trendscription programmer was switched from a continuous to a sampling mode of 1 minute during a 3-minute interval. This sampling rate permits prompt recognition of trends in arrhythmia prevalence without undue loss of data and facilitates visual determination of VPC frequency. After the control period, group 1 patients received 125 mg ethmozin orally, while group 2 patients were given a dose of 300 mg. Subjects were seated in a comfortable chair during the test. Reading material was provided and movement about the room was encouraged to relieve the boredom occasioned by the long procedure. Lead V5 or V4 was recorded hourly at a paper speed of 50 mm/sec to determine duration of the PR and QT intervals and the width of the QRS complex.

The objective of the test, which lasted 3 hours, was to record peak drug action and dissipation of its effect. A positive antiarrhythmic response during acute drug testing consisted of reduction in frequency of ectopic activity by 50% and elimination of repetitive or multiform ectopic activity if present during the control period. To be judged significant, such a change in arrhythmia had to occur at least 1 hour after ingestion of ethmozin and persist for at least 30 minutes.

Phase 2 Study

After acute drug testing, all patients began maintenance ethmozin therapy. Group 1 patients took 75 mg three times daily, and group 2 patients took 200 mg three times daily. The average duration of treatment was 5.6 days, range 4-9 days. At the end of the treatment period, patients were monitored for 24 hours and performed exercise stress tests.

Ambulatory Monitoring

A portable two-channel Holter monitor (Avionics model 425) was used with electrodes placed in the V2 and V4 positions. The 24-hour electrocardiographic tapes were read on the computerized Dynamic Electrocardioscanner (Avionics model 660) by one of the investigators. Identification of VPCs was based on criteria related to changes in QRS width, amplitude and prematurity. Each tape was analyzed at least twice, at least once for the hourly VPC frequency and once for the presence of multiform or repetitive ectopic activity. One-half of the tapes were analyzed twice for the hourly VPC frequency.

In order for ethmozin to be judged effective, three criteria had to be met during the 24-hour monitoring: 1) reduction of VPC frequency during each hour by at least 50% compared with the baseline monitoring ses-

sion; 2) reduction of the number of waking hours during which frequent VPCs (i.e., ≥30 VPCs/hour) were present by at least 50%; and 3) total abolition of multiform and repetitive ectopic activity. These criteria have evolved in our laboratory over a number of years. The objective was to reduce ectopic activity by use of antiarrhythmic drugs to a level that protects against ventricular fibrillation in patients with frequent recurrence of this arrhythmia.

Exercise Stress Testing

The technique for eliciting ventricular arrhythmias with exercise has been described. Exercise was performed on a bicycle ergometer. The initial load was 200 kg/m/min and was increased by 150 kg/m/min every 3 minutes. Electrocardiographic recording was performed on a minigraph (Siemens-Elema) and on the trendscriber. All patients had a 12-lead ECG before exercise. After a 3-minute control period of continuous trendscription, exercise commenced. Every 3 minutes during exercise and at peak exercise a 12-lead ECG was repeated. Blood pressure was determined at approximately the same intervals. The end points for exercise were disabling fatigue, intensifying angina or emergence of ventricular tachycardia, but not the development of multiform VPCs, couplets or ST-segment depression. After completion of exercise, trendscription monitoring was continued for an additional 10 minutes. Thus, the entire exercise was recorded as hard copy without loss of any arrhythmic events. During the recovery phase, a 12-lead ECG was obtained every minute and blood pressure every 3 minutes.

The exercise duration, reasons for stopping the test, ST-segment changes and any arrhythmias were noted. The number and type of VPCs in each minute of control, exercise and postexercise periods were recorded. Ethmozin was considered effective with respect to exercise if maximum VPC frequency per minute was reduced by more than 50% compared with baseline during a 3-minute period at peak exercise or during the immediate recovery period, including abolition of all multiform and repetitive ectopic activity through all stages of exercise. Thus, in these patients with chronic stable symptomatic arrhythmias, criteria of efficacy include both a quantitative and qualitative reduction of ventricular arrhythmia as evaluated by both exercise testing and ambulatory monitoring.

All patients in whom ethmozin was deemed effective, based on reduction of VPCs, consonant with the above criteria during both monitoring and exercise, were treated with placebo in a single-blind fashion. In each, the duration of treatment with placebo was the same as that with ethmozin. At the end of the placebo period, exercise testing and 24-hour ambulatory monitoring were repeated.

Blood Ethmozin Levels

The blood plasma ethmozin concentration was determined by means of high-pressure liquid chromatography according to the method of Wein-
stein and Gaylord. All determinations were performed on the Altex liquid chromatograph, model 322 (USA). During phase 1 study, blood samples were obtained 1, 2 and 3 hours after the ethmozin dose. During phase 2 study, blood samples were taken 2–4 hours after ethmozin ingestion after at least 3 days of drug therapy. In animal studies, this has been suggested as the time of peak drug level. The results were analyzed using t tests for independent or paired data. Differences of p < 0.05 were considered statistically significant. Results are expressed as mean ± SEM.

Results

Group 1

Acute drug testing in 11 patients with 125 mg of ethmozin after 3 hours of observation resulted in no antiarrhythmic effect. Blood levels could be obtained in only six of these patients (table 2). Peak levels were achieved within 1 hour after drug ingestion. Phase 2 study was completed in 10 of 11 patients. One patient experienced ventricular fibrillation 3 hours after a 75-mg maintenance dose and was not tested further after successful cardiopulmonary resuscitation. Only two of the remaining 10 exhibited antiarrhythmic effects. However, one of these patients continued to demonstrate suppression of ectopic activity on placebo. We conclude that a total dose of 225 mg/day of ethmozin was ineffective against ventricular arrhythmia in these patients.

Group 2

Phase 1 Study

Of the 26 patients who were tested acutely with 300 mg of ethmozin in a single oral dose, five showed VPC suppression. The onset of antiarrhythmic action ranged from 40–115 minutes (mean 75 minutes). In all five, this effect was maintained for at least 3 hours, when treatment ended. Five additional patients had a partial response. While VPCs were reduced by 50%, multiform or repetitive ectopic activity was not totally eliminated. In these patients, ethmozin’s effect on VPCs persisted for the duration of monitoring during the phase 1 study. The blood concentration data are presented in table 2.

Phase 2 Study

Fourteen of 26 patients (54%) had VPC suppression while on maintenance ethmozin therapy of 600 mg/day and showed an effective response during both 24-hour monitoring and exercise-stress testing. There was a remarkable reduction in VPC frequency during the monitoring session, from a control of 533 ± 106 VPCs/hour to 43 ± 12 VPCs/hour (p < 0.001) while on ethmozin maintenance therapy (table 3 and fig. 2). The mean reduction in each of the responders was at least 63%. In 11 patients, the reduction exceeded 80% and in four of these, all ectopic activity was abolished. No correlation between control VPC frequency and drug efficacy was found. Ventricular tachycardia was controlled in the two patients with this arrhythmia, couplets were eliminated in five of six, and multiform activity was abolished in three of six patients. In only three of the 12 patients in whom ethmozin was judged ineffective did the level of ectopic activity remain unaltered during the 24-hour monitoring session; in the other nine, the mean reduction in VPC frequency was 33%.

With exercise, the 14 responders changed from a control prevalence of 287 ± 77 ventricular ectopic beats to only 9 ± 7 VPCs during the entire test while on maintenance ethmozin therapy (p < 0.002) (fig. 2). Twelve patients (86%) had complete elimination of all arrhythmia, one patient had a decrease of 80% and in one, the reduction in VPCs during exercise was 67%. In addition to the 14 responders, five other patients showed control of VPCs with exercise but not with monitoring (table 3).

When the results of monitoring and exercise testing

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**Table 2. Blood Concentration of Ethmozin Among Six Group 1 Patients and 15 Group 2 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Loading dose (mg/kg)</th>
<th>Blood concentration (ng/ml)*</th>
<th>Dose mg/kg (2-4 hours after dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hour</td>
<td>2 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(n = 6)</td>
<td>1.8 ± 0.3</td>
<td>121.2 ± 20.1</td>
<td>60.5 ± 7.5</td>
</tr>
<tr>
<td></td>
<td>(1.5-2.2)</td>
<td>(62-325)</td>
<td>(16-103)</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 15)</td>
<td>4.5 ± 0.5</td>
<td>419.5 ± 25.7†</td>
<td>124.8 ± 17.8</td>
</tr>
<tr>
<td>Responders (n = 7)</td>
<td>(3.9-5.6)</td>
<td>(209-630)</td>
<td>(66-177)</td>
</tr>
<tr>
<td>Non-responders (n = 8)</td>
<td>4.5 ± 0.7 (3.7-5.8)</td>
<td>126.3 ± 18.6† (16-238)</td>
<td>116.2 ± 16.3 (12-238)</td>
</tr>
<tr>
<td></td>
<td>9.0 ± 1.4</td>
<td>45.8 ± 5.3†</td>
<td>9.0 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>(7.3-11.5)</td>
<td>(25-56)</td>
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*Mean ± SEM (range in parentheses).
†p < 0.003.
‡p < 0.01.
were analyzed on the basis of presence or absence of demonstrable heart disease, no difference in response was noted. Therefore, the effect of the drug seemed to be independent of the presence or type of heart disease.

In view of the disparity in results between acute drug testing and maintenance therapy in the initial period of this investigation, the last 10 patients were monitored immediately upon completion of phase 1 study. This permitted approximation of the onset of ethmozin's action. In only one patient was drug effect demonstrated during the initial 24 hours. In this patient, placebo also exerted a salutary effect.

Placebo Therapy

Of the 14 patients responding to ethmozin, an antiarrhythmic effect persisted in only two while receiving placebo (fig. 3). In 12, the arrhythmia while on placebo was not statistically different from that recorded during the 24-hour control monitoring or the exercise stress testing. A recurrence of arrhythmia during placebo is illustrated in figure 4. All patients reported a recurrence of symptomatic VPCs within 24 hours of placebo therapy. During monitoring, the mean number of VPCs dropped from 533 ± 106 to 382 ± 105 while on placebo (p > 0.06). With exercise, the prevalence of VPCs during control and placebo testing was nearly identical — 287 ± 77 and 231 ± 70, respectively (p = 0.1).

Side Effects

Ethmozin was well tolerated, with almost no adverse reactions. None of the side effects associated with phenothiazines occurred. No electrocardiographic or hemodynamic changes were observed either during acute drug testing or during maintenance therapy. The complete blood count and routine blood chemistries remained unaltered. Four patients had minor reactions, two complained of pruritus though no rash was noted, one experienced headache after 2 days on the drug and one noted twitching, which was not documented. Therapy was not interrupted in any of the 26 patients because of untoward effects. One patient with chronic first- and second-degree atrioventricular block experienced no increase in this conduction disturbance.

Table 3. Results in 26 Patients Receiving Ethmozin in a Dose of 600 mg/day. Comparison of Mean Ventricular Premature Complex Frequency in Responders and Nonresponders as Determined by Exercise Stress Testing and 24-hour Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>VPC frequency*</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Control</td>
</tr>
<tr>
<td>Exercise stress test</td>
<td>19</td>
<td>336 ± 64†</td>
</tr>
<tr>
<td>Monitor</td>
<td>14</td>
<td>533 ± 106‡</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
†Per exercise test.
‡Per hour.

Abbreviation: VPC = ventricular premature complex.

Figure 2. Results during phase 2 testing with 600 mg/day of ethmozin in the 14 patients who responded during both monitoring and exercise.

Figure 3. The effect of ethmozin on ventricular premature complexes (VPCs) as shown by 24-hour monitoring is compared with control and placebo treatments. Horizontal bars indicate mean number of VPCs during these three periods.
Blood Levels

In 15 patients, blood levels could be obtained hourly during acute drug testing and beyond the third day of maintenance therapy with 600 mg/day of ethmozin. Seven of these were drug responders and eight were nonresponders (table 2). The highest drug concentration was observed 1 hour after oral administration at a time when no antiarrhythmic effect was observed. Data from animal studies indicate that peak levels occur at 2–3 hours. During maintenance therapy the responders had a threefold greater concentration of ethmozin than the nonresponders ($p = 0.002$), even though the relative dosages were nearly identical (table 2). In the nonresponders, failure of antiarrhythmic drug action may result from inadequate drug administration.

Discussion

The present study is the first systematic clinical investigation of ethmozin in which acute drug testing, 24-hour ambulatory monitoring and exercise stress testing have been used in a systematic and formalized protocol to assess antiarrhythmic efficacy of this drug against ventricular ectopic activity. When evaluated by both monitoring and exercise testing, 14 of 26 patients (54%) had arrhythmia suppression, but only when the dose was $600 \text{ mg/day}$. At the lesser dose, which until our study had been the standard maintenance dose in the USSR, only one of 11 patients showed an effect. This contradicts the findings of a number of Soviet reports. However, there are considerable methodologic differences between their studies and ours. In the former, drugs were evaluated on the basis of episodic recording of electrocardiographic strips and reporting by patients. Such end points are known to be inaccurate. No information about frequency of arrhythmia is available. Furthermore, our population was selected on the basis of persistence of pronounced and symptomatic arrhythmia, with a mean of $529 \pm 89 \text{ VPCs/hour}$.

Morganroth and co-workers were the first to evaluate ethmozin in the USA. They studied 17 patients, 14 with VPCs and three with atrial ectopy, using a single-blind, in-hospital protocol, in which patients were given placebo for the first and last 3 days and ethmozin every 8 hours in a total dose of $300–750 \text{ mg/day}$ for the intervening 7 days. In this study, the patients were subjected to continuous ambulatory monitoring during the entire 13-day period and had a mean of $414 \text{ VPCs/hour}$, which approximates the frequency in our population. The findings of Morganroth et al. were similar to ours; thus, half their patients (seven of 14) had more than 60% reduction in mean hourly VPC frequency. Using a logarithmic transformation of data, 10 of 14 (71%) showed a response. However, patients were not selected on the basis of constancy of VPCs, exercise testing was not used as a methodologic tool and drug effect upon advanced grades was not considered in the analysis.

VPCs may vary greatly in frequency and form in successive monitoring sessions in the absence of therapeutic intervention. It is therefore legitimate to question whether the effect of ethmozin in the present study was due to the drug or to chance. Winkle used 5½ hours of ambulatory monitoring and showed wide variability during each 30-minute period. In our patients, ambulatory monitoring confirmed the hour-to-hour constancy of arrhythmia.

A placebo effect occurred in only two of 14 subjects. The fact that it required 24 hours for drug efficacy to be demonstrated argues additionally against a placebo effect, which in our experience has been prompt in onset. Equally important, no effect was noted at a lower dose of the drug. This would not be expected if either random variation or placebo effect played a major role in this study. It may be argued that the sequence of ethmozin followed by placebo treatment biased the results in favor of ethmozin, for the first treatment period might be more effective. However, when a subtherapeutic dose of ethmozin was administered in group 1, no suppression of arrhythmia was recorded. This argues against the likelihood that the initial use of ethmozin followed by placebo con-

Figure 4. A 1-minute sample of trendscirption recorded before exercise during control, day 4 on ethmozin and placebo. The frequency of high-grade ventricular ectopic activity is almost identical during control and placebo, but is totally eliminated during ethmozin treatment.
tributed to the effectiveness of the drug. The reduction of VPCs during exercise while patients were receiving ethmozin probably did not result from conditioning, because while on placebo, when the patient should have been further conditioned, VPC frequency was nearly identical to that recorded during control exercise testing.

Antiarrhythmic drugs in current use have many serious drawbacks, and a drug with few serious complications at therapeutic antiarrhythmic dosages is urgently needed. Ethmozin may be one such drug. In the present study neither a single oral dose of 300 mg nor a maintenance regimen of 600 mg/day provoked significant side effects. In none of the 26 patients was it necessary to reduce the dose or discontinue the medication during the 5-day course of testing. Morganroth et al., using up to 750 mg/day in three divided doses over a 7-day period, encountered no untoward reactions and no abnormalities in electrocardiographic, hematologic or blood chemistry determinations. Physicians using ethmozin in the USSR over the past 7 or 8 years have noted a low incidence of mild side effects such as dizziness, headache, nausea and epigastric distress. We observed minor side effects in only four patients (15%). However, experience with other antiarrhythmic drugs indicates that a brief period of drug usage does not provide a true measure of the actual magnitude of potential hazard. The studies with ethmozin in the USSR are therefore of some relevance. Using a dose not exceeding 225 mg/day, Lozinskiy encountered no drug reactions over a period of continuous use of 2-3 months.

The present study provides only preliminary information about the blood levels required for therapeutic effect, because the biochemical methods for determining the concentration of ethmozin are just being developed in the USSR. The acute drug effect appeared to be unrelated to serum ethmozin level at 3 hours: 77 ± 11.3 ng/ml for patients with control of VPCs compared with 90.8 ± 20 ng/ml for patients without any demonstrable effect. In the phase 2 study, however, seven of 14 patients in whom ethmozin affected VPCs had a significantly greater blood level on the third and fifth days than eight patients in whom the drug failed: 147.5 ± 11.1 ng/ml vs 45.8 ± 5.3 ng/ml (p < 0.003). Blood level alone may not be the critical determinant of drug action, because even though the highest concentration occurred at 1 hour (419.5 ± 25.7 ng/ml), the maximal drug action occurred after 24 hours of exposure to ethmozin. Morganroth et al. noted a weak trend relating ethmozin dose to plasma level and to antiarrhythmic drug efficacy. The blood levels we obtained on maintenance therapy were lower than those reported in the above study. The disparate results may be due to differences in blood sampling time, in analytic procedures and even in bioavailability of the Soviet and American drug preparations.

Morganroth et al. also noted a lack of antiarrhythmic drug activity during the first 24 hours of therapy. The reason for delay in drug effect may be related to the following factors: 1) slow accumulation of drug in the body; 2) antiarrhythmic activity due to a metabolite of ethmozin; and 3) delay in equilibrium between blood and effector site. If these factors are indeed operative, blood levels would presumably provide little clinical guidance as to drug efficacy during acute drug testing. During maintenance therapy, however, responders had a threefold greater concentration than either nonresponders or group 1 patients who received a subtherapeutic dose of ethmozin.

A pertinent question is whether ethmozin acts directly on the heart or indirectly through its phenothiazine sedative properties. Danilo and coworkers have shown direct electrophysiologic effects on Purkinje fibers that are similar in many respects to those of lidocaine. The most conspicuous action of ethmozin is on the voltage time course of repolarization. Phases 2 and 3 of repolarization are both speeded, which shortens the action potential duration as well as the effective refractory period. Ethmozin also caused a dose-dependent decrease in the maximum rate of depolarization during phase 0 and, at a higher dose, decreased conduction velocity. In the intact, open-chest dog, Ruffy et al. found that 4 mg/kg of ethmozin caused a rise in the left ventricular excitability threshold expressed as a change in stimulus duration. In voltage clamp experiments on frog atrial muscle, Rozenstraukh et al. observed that ethmozin depressed the rapid inward sodium current; they also noted changes in conduction velocity without altered rate of rise in action potential.

The antiarrhythmic action of ethmozin may derive as well from its phenothiazine-like configuration. Experimentally, phenothiazines produce changes at all levels of the nervous system. A key role for higher nervous activity has been proposed in the genesis of VPCs and in the precipitation of sudden cardiac death. Therefore, the neurophysiologic effects of a phenothiazine derivative like ethmozin may be of some significance in its antiarrhythmic effects. None of the usual side effects of phenothiazines were noted.

In summary, ethmozin is an effective and well-tolerated antiarrhythmic agent where onset of drug activity may require more than 24 hours. Acute drug testing, therefore, is not useful for predicting efficacy. The reason for the prolonged latency in onset of antiarrhythmic effect has not been determined. Studies of ethmozin in many more patients with diverse forms of heart disease are indicated to define its full spectrum of activity, safety and efficacy. Finally, ethmozin represents an antiarrhythmic drug with a unique chemical configuration that may serve as a model for investigation of other drugs with similar molecular structure.

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Circulation. 1980;61:450-457
doi: 10.1161/01.CIR.61.2.450

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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