Efficacy and safety of moricizine in patients with ventricular tachycardia: results of a placebo-controlled prospective long-term clinical trial

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ABSTRACT This was a prospective, placebo-controlled, single-blind trial of moricizine (ethmozine) in a dose averaging 10 mg/kg/day in 50 patients, the single entrance criterion being the presence of 10 or more runs of nonsustained ventricular tachycardia (VT) on a screening 24 hr ambulatory electrocardiographic (ECG) recording. Electrophysiologic study was not included as part of this trial design. The placebo frequency of VT (average 3 days of recording) was 1036 ± 479 runs of VT per day. Most patients (31/50) had coronary artery disease. The study population had a mean left ventricular ejection fraction (LVEF) of 36 ± 16%; 20 patients also had a history of sustained VT. Protocol failure was defined as failure to achieve a 75% or greater reduction in runs of VT (as judged by ambulatory ECG recording) and/or recurrence of sustained VT while on moricizine. Among the 48 patients treated with moricizine, the drug was initially efficacious in 35 (73%), with two-thirds having total abolition of nonsustained VT. Although it was effective in reducing runs of nonsustained VT, moricizine was ineffective in preventing the recurrence of sustained VT (63% failure rate). Side effects were uncommon and the drug was well tolerated in most patients with LVEFs of 30% or less.

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IN SPECIFIC patient populations, especially patients with recent myocardial infarction, the presence of frequent and complex ventricular arrhythmias detected by ambulatory electrocardiographic (ECG) recording identifies a subgroup at increased risk for sudden cardiac death.1–3 Additionally, patient populations characterized by complex ventricular arrhythmia, especially nonsustained ventricular tachycardia (VT), and left ventricular dysfunction are at increased risk for sudden death.4–7 In contrast, relatively healthy subjects with frequent and complex ventricular arrhythmia appear to be at minimal risk for sudden cardiac death.8 The rhythm disturbance responsible for sudden death appears to be VT and ventricular fibrillation in the majority of patients.9,10

Although β-blockers reduce sudden death mortality after myocardial infarction, their usefulness is limited in patients with severely depressed left ventricular function.11–14 Despite the widespread use of type I antiarrhythmics, none have been shown to reduce the incidence of sudden death in any high-risk population.15 There are multiple shortcomings of the currently available antiarrhythmic drugs. First, the presently available type I antiarrhythmics have limited efficacy in suppressing premature ventricular complexes (PVCs). They also possess frequent side effects and potentially serious toxicity and they may significantly depress left ventricular function.16–22 Antiarrhythmic drugs frequently worsen existing ventricular arrhythmia, even causing torsade de pointes VT,23–31 with reported frequencies of “arrhythmia aggravation” up to 16% in high-risk patients.32

In published studies by our group and others, moricizine (ethmozine) has a number of desirable characteristics meriting further investigation as a new antiarrhythmic agent.33–36 Moricizine is a phenothiazine
derivative that effectively suppresses PVCs and has minimal effect on the QT interval of the scalar electrocardiogram. Importantly, moricizine has a low incidence of minor side effects. Serious toxicity has not been reported. However, all previous studies, including our published experience, are limited by the selection of patients with relatively benign, non-life-threatening ventricular arrhythmia who have preserved ventricular function. The effectiveness of moricizine in a patient population with VT and left ventricular dysfunction has not been previously reported. The goal of this clinical trial was to select patients with frequent nonsustained VT and to characterize their response to the long-term administration of moricizine, with drug efficacy defined by reduction in runs of nonsustained VT quantified on ambulatory ECG recording.

Methods

Study design. This was a prospective, single-blind, placebo-controlled trial of 50 patients. The sole entrance criterion was the presence of 10 or more runs of nonsustained VT on a single 24 hr ambulatory ECG recording. All qualifying ambulatory ECG recordings were performed at least 5 days after discontinuation of antiarrhythmic drug therapy, and patients were excluded if they had undergone prior investigational antiarrhythmic therapy. A previous history of sudden cardiac death or demonstration of previous sustained VT was not an exclusion criteria for this trial.

The details of study design are illustrated in figure 1. This protocol was approved by the Baylor Institutional Review Board in November 1982, and enrollment of patients was begun in December 1982. After eligibility was established and informed consent obtained, all patients were hospitalized in the General Clinical Research Center, where placebo ambulatory ECG recording was performed over 3 days for baseline quantification of ventricular arrhythmia.

Ambulatory ECG recordings were used as the sole end point to judge the efficacy of moricizine. Electrophysiologic study was not part of the study protocol. Therapeutic success was defined as a 75% or greater reduction in the mean daily runs of VT as detected by serial ambulatory ECG recordings. Moricizine was begun at a dosage of 10 mg/kg/day in three daily doses and never exceeded 14.6 mg/kg/day. Failure to achieve a 75% or greater reduction of the mean runs of VT was considered a therapeutic failure, resulting in withdrawal of the patient. A second criterion for withdrawal was the occurrence of sustained VT (defined as VT ≥120 beats/min for >30 sec that required drug intervention or cardioversion for resumption of normal sinus rhythm). Aggravation of arrhythmia by moricizine was defined as a 400% or greater increase in runs of VT or an episode of sustained VT in any patient with no previous episode, criteria more strict than those of Velebit et al. No patients were lost to follow-up, and sudden cardiac deaths (defined as death in ≤1 hr from the onset of symptoms) were documented carefully.

Patients. This study reports results from 50 consecutive patients, mean age 57 ± 10 years, including 42 men and eight women. The mean follow-up was 6 months (range 1 to 24). Sixty percent of patients were taking digitalis, 6% β-blockers, and 6% calcium antagonists. Twenty patients (40%) had prior documentation of sustained VT. Of these, 19 had ECG documentation of sustained monomorphic VT and one had polymorphic VT and cardiac arrest. In all cases the episodes of sustained VT had required intervention (drug or cardioversion). The range of VT rates was between 140 and 210 beats/min. Patients had failed an average of two conventional antiarrhythmic drugs before enrollment in the study.

Thirty-one patients (62%) had a diagnosis of coronary artery disease. Of these, 27 (87%) had previous myocardial infarction (defined as having appropriate history and ECG changes with positive creatine kinase MB isoenzyme findings). The diagnosis of coronary artery disease was established in 77% (24/31) of these patients by cardiac catheterization, with angiographic demonstration of a 70% or greater luminal narrowing of one or more major coronary artery. The diagnosis of coronary artery disease in the remaining seven patients was established by ECG evidence of myocardial infarction as well as by the demonstration of a segmental wall motion defect on two-dimensional echocardiographic examination. Cardiac diagnosis in the remaining 19 patients was established by cardiac catheterization in 14 and by a combination of clinical and two-dimensional echocardiographic findings in the remaining five patients. Diagnoses included mitral valve prolapse (four patients), dilated cardiomyopathy (four patients), and hypertensive cardiomyopathy (three patients); eight patients had no demonstrable organic heart disease.

Ambulatory ECG recording. Ambulatory ECG recordings were performed on Avionics 440B tape recorders and analyzed on an Avionics Trendsetter (Irvine, CA). Each 24 hr ambulatory ECG recording was analyzed hourly for the prevalence of PVCs, couplets, and runs of VT. All ambulatory ECG tapes were edited by a cardiologist. Quality control in our laboratory using standard test tapes shows a reproducibility of 92% for

<table>
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<tr>
<th>Inpatient</th>
<th>Placebo</th>
<th>Moricizine</th>
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<td>Days</td>
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<td></td>
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<td>1</td>
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<td>Months</td>
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<td>9</td>
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<td>12</td>
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FIGURE 1. Protocol summary. AECG = ambulatory electrocardiogram; 2D Echo = two-dimensional echocardiogram; EXT = exercise treadmill; P.E. = physical examination.
PVCs, 95% for couplets and 98% for VT runs (intraobserver variability). Agreement in PVC counts between two research ambulatory electrocardiographic scanners is 95% (interobserver variability). External quality control from the core laboratory of a national arrhythmia trial has verified a 95% or greater agreement in the detection of runs of VT.

Two-dimensional echocardiographic assessment of left ventricular function. Left ventricular ejection fraction (LVEF) was assessed by two-dimensional echocardiography with an ATL Mark V sector scanner equipped with a slow-motion, frame-by-frame, bidirectional playback video recorder. LVEF was determined from the average of several diameters measured in multiple views with the method previously validated in our laboratory.37

Moricizine plasma levels. Plasma levels of moricizine were determined by the absorption spectrometric method after high-pressure liquid chromatographic separation as detailed in previous reports.35,36 Peak and trough plasma moricizine samples (1 hr after and 1 hr before dose, respectively) were obtained weekly for the first month of therapy and then every 3 months in patients remaining in the trial.

Statistical analysis. For comparison of paired data, a two-tailed t test was performed if normality could be assumed. If normality could not be assumed, Wilcoxon signed ranks tests were performed. Analysis was carried out with the natural log (ln + 1) of arrhythmia frequency to produce a more normal distribution.

Results

Arrhythmia data at baseline. During placebo monitoring initial mean arrhythmia frequencies of 48 patients treated with moricizine were as follows: PVCs, 899 ± 126/hr, couplets, 68 ± 16/hr; runs of VT, 1036 ± 479/day (all mean ± SE). Analysis was performed on an average of 70 hr of ambulatory ECG recording during placebo therapy. The frequency distribution of runs of VT during placebo therapy is illustrated in figure 2. Although all patients had a 24 hr qualifying ambulatory ECG recording with 10 or more runs of nonsustained VT, nine had an average of less than 10 runs of VT on the consecutive placebo ambulatory ECG recordings. The distribution of initial left ventricu-

![FIGURE 2. Distribution of daily mean runs of VT during placebo.](http://circ.ahajournals.org/)

![FIGURE 3. Placebo LVEF in study population. SVT = sustained VT; NSVT = nonsustained VT.](http://circ.ahajournals.org/)
dyspnea and subsequently died, with autopsy findings confirming massive pulmonary embolism.

The arrhythmia reductions on moricizine at 1 month follow-up are summarized in table 1. Compared with the frequency of arrhythmias during placebo monitoring, suppression was 76% for PVCs, 90% for couplets, and 98% for runs of VT (all p < .001).

As seen in figure 5, an additional eight patients were dropped from the trial between the first and third months. Six of these patients were withdrawn because of drug failure. One of these patients with a history of sustained VT died suddenly while on moricizine. Three patients had recurrent sustained VT. One patient had an increase in nonsustained VT on moricizine (from 4 to 328 runs of VT per day) and was dropped from the trial.

A total of 22 patients received moricizine for 3 months or longer (figure 5). One patient with a history of sustained VT was dropped from the trial during this period because of recurrent sustained VT. Repeat ambulatory ECG recordings after 3 months of therapy with moricizine (table 1) revealed an 87% reduction in PVCs, a 93% reduction in couplets, and a 99% or greater reduction in runs of nonsustained VT (all p < .001 vs placebo).

Long-term follow-up for patients on moricizine (>6 months). Of the 18 patients followed for 6 months or longer, one died overnight at home after 10 months due to metastatic adenocarcinoma of the colon. An additional patient died of severe congestive heart failure after recurrent myocardial infarction. Moricizine effectively suppressed the arrhythmias in the remaining 16 patients. Two patients were removed from the trial during this interval because of physician refusal despite continued ambulatory ECG evidence of efficacy. In one of these cases, a physician changed therapy to disopyramide (Norpace) despite previous efficacy and tolerance of moricizine. That patient died suddenly approximately 3 weeks after cessation of moricizine therapy. Moricizine was discontinued in the second patient because the patient lived out of town and follow-up was difficult. Nine patients have received the drug for 1 year or longer (maximum 24 months) and continue to demonstrate a 96% PVC reduction and 99% or greater reduction in both couplets and runs of VT.

In summary 20 of 48 patients begun on moricizine were dropped because of lack of efficacy, 12 patients because of recurrent episodes of sustained VT, six patients because of failure of moricizine to suppress 75% or more of the runs of VT, and two patients because of increasing frequency of nonsustained VT on moricizine. Two patients experienced increasing congestive heart failure while taking moricizine, and three patients, all of whom had a history of sustained VT, had sudden cardiac death during the trial.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>At hospital discharge (n = 33)</th>
<th>At 1 month (n = 30)</th>
<th>At 3 months (n = 22)</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Moricizine</td>
<td>Placebo</td>
</tr>
<tr>
<td>PVCs/hr</td>
<td>999 ± 17</td>
<td>191 ± 60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1054 ± 188</td>
</tr>
<tr>
<td>Couplet/hr</td>
<td>76 ± 23</td>
<td>7 ± 3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 ± 23</td>
</tr>
<tr>
<td>VT runs/day</td>
<td>1424 ± 718</td>
<td>8 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1557 ± 787</td>
</tr>
</tbody>
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<sup>a</sup>All p < .001 vs respective placebo.
Individual responses to moricizine. As seen in table 2, of the 33 patients discharged on moricizine, 21 (64%) had total abolition of nonsustained VT. Of those patients continued on the drug for 1 and 3 months, respectively, total suppression of nonsustained VT continued in 47% and 68%. Individual reductions in PVCs as well as couplets are also detailed in table 2.

Outcome of patients with a history of sustained VT. In addition to the entrance criterion of 10 or more runs of nonsustained VT, prior documentation of sustained VT was accepted for 20 patients, 19 of whom received moricizine. These patients did not differ in the initial frequency of arrhythmias during placebo monitoring or in variability of nonsustained VT when compared with the remaining 30 patients (1172 ± 1063 vs 945 ± 390 runs of VT per day; p = NS). There was no significant difference in the distribution of global left ventricular function between patients with a history of sustained VT and the remaining 30 patients with frequent runs of nonsustained VT (figure 3), although most of the patients (14/20) with sustained VT had LVEFs under 40%.

Only seven of 20 patients with a history of sustained VT had no recurrence (37% success rate). Since the success rate in this group was much lower than the 68% success rate achieved in the 30 patients remaining with frequent nonsustained VT, additional comparative analysis was performed. Patients with a documented history of sustained VT had coronary artery disease more frequently than patients solely with nonsustained VT (17/20 vs 13/30; p < .01). The mean dose of moricizine was not different in the 20 patients with sustained VT than in the remaining 30 patients (10.2 vs 10.4 mg/kg/day); likewise the resultant peak moricizine plasma concentration achieved (0.94 ± .6 vs 0.58 ± .4 ng/ml; p = NS) was similar in both groups.

Ambulatory ECG monitoring was a poor predictor of subsequent prevention of recurrent sustained VT. Five of the 12 patients with recurrent sustained VT while on moricizine had total abolition of nonsustained VT documented by ambulatory ECG recording preceding the clinical episode. This was not different from the observations in four of seven patients with abolition of nonsustained VT who had no recurrence of sustained VT. Patients with recurrent sustained VT during therapy with moricizine invariably had underlying coronary artery disease (12/12) as compared with

![Figure 5](https://circ.ahajournals.org/)

**FIGURE 5.** Outpatient trial: outcome of therapy with moricizine. Pul = pulmonary; SCD = sudden cardiac death; CHF = congestive heart failure; VT = sustained VT; NSVT = nonsustained VT.

**TABLE 2**

<table>
<thead>
<tr>
<th>Percent reduction achieved</th>
<th>At hospital discharge (n = 33)</th>
<th>At 1 month (n = 30)</th>
<th>At 3 months (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PVC</td>
<td>Couplet</td>
<td>VT</td>
</tr>
<tr>
<td>100</td>
<td>5/33</td>
<td>14/33</td>
<td>21/33</td>
</tr>
<tr>
<td>90</td>
<td>18/33</td>
<td>23/33</td>
<td>28/33</td>
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<tr>
<td>80</td>
<td>21/33</td>
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<td>29/33</td>
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<tr>
<td>70</td>
<td>22/33</td>
<td>24/33</td>
<td>32/33</td>
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those with historical sustained VT without recurrence (5/7). LVEF was similar in patients with sustained VT refractory to moricizine as compared with the seven moricizine responders (34 ± 11% vs 33 ± 8%; p = NS). The seven moricizine responders in this group have been on therapy an average of 17 months (range 3 to 23 months).

**Relationship of initial LVEF to outcome of therapy with moricizine.** No patient had a decrease in LVEF of 4% or greater on moricizine compared with placebo. The mean LVEF of the 50 patients was 36 ± 16% (mean ± SD). As shown in table 3, left ventricular function was an important determinant of the antiarrhythmic efficacy of moricizine. Throughout the trial, patients who withdrew had poorer LVEFs than moricizine responders. The difference in LVEF between moricizine responders and patients who dropped out was statistically significant at both the 1 and 3 month intervals (p < .01, p < .04, respectively; table 3). Of the 22 patients entering the trial with LVEFs of 30% or less, only five had antiarrhythmic efficacy (78% failure). Sixteen of the 17 withdrawals were attributed to failure to achieve antiarrhythmic efficacy, while the remaining patient was dropped because of worsening congestive heart failure (LVEF 18%). Many of the 17 dropouts with LVEFs of 30% or less had a history of sustained VT as compared with the remaining moricizine responders (9/17 vs 0/5; p < .05).

**Relationship of plasma moricizine levels and antiarrhythmic efficacy.** Moricizine plasma levels were available in 40 patients. At a mean dose of 10.2 mg/kg/day, the trough (7 hr after dose) moricizine plasma concentration was 0.11 ± 0.15 μg/ml and the peak (1 hr after dose) moricizine plasma concentration was 0.71 ± 0.7 μg/ml (both mean ± SD). There was no significant difference in the plasma concentrations of responders as compared with dropouts, either in the entire study population or the subgroup of 20 patients with a history of documented sustained VT.

**Ventricular arrhythmias during treadmill exercise: response to moricizine.** All patients performed the standard Bruce exercise test during the placebo phase of the trial. Results of repeat exercise testing were available at the 1 month follow-up visit in 28 of the 30 patients on moricizine. On placebo, 95% of patients had PVCs and 57% had runs of nonsustained VT during treadmill exercise. Repeat treadmill exercise testing at 1 month of therapy with moricizine resulted in a reduction of exercise-induced PVCs to 50% of the patients, while only 21% had runs of nonsustained VT during exercise. Treadmill exercise time was unchanged on moricizine compared with placebo (6.0 vs 5.4 min; p = NS).

**Side effects and toxicity of moricizine.** Patients were questioned about any new symptoms at each clinic visit. Compared with placebo there was an increase of mild nausea during therapy with moricizine (6/48 on placebo vs 17/48 on moricizine; p < .01). However, this comparison is between 3 days of placebo and an average of 6 months of moricizine. This side effect was transient and never resulted in discontinuation of therapy. Importantly, no other side effect was increased significantly during therapy with moricizine. No patient was withdrawn from the trial because of drug intolerance. Transient elevations of LDH enzyme occurred early in three patients on moricizine but these resolved. No other hepatic, renal, or hematopoetic variables changed with moricizine. Congestive heart failure worsened significantly in two patients during initiation of moricizine as previously described. In both cases clinically significant deterioration of left ventricular function was not reflected by dramatic changes in two-dimensional echocardiographic assessment of LVEF, which changed 0% and 2%, respectively, with moricizine and placebo. These two patients demonstrate the lack of sensitivity of global LVEF in detecting clinically important hemodynamic alterations that might be caused by antiarrhythmic therapy. There were no statistically significant changes in PR and QRS intervals on the resting electrocardiogram (0.18 ± 0.02 and 0.10 ± 0.01 sec, respectively). Likewise, QT intervals were unchanged (0.36 sec on placebo and moricizine). No patient had an increase in QT interval of 0.03 sec or more. Worsening of arrhythmia occurred during therapy with moricizine in five patients. Two had dramatic increases in frequency of runs of

**TABLE 3**

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<th>Patient outcome in moricizine VT trial: relationship to LVEF at entry (mean ± SD)</th>
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<tr>
<td>LVEF at selected intervals in trial (%)</td>
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<tr>
<td>At discharge</td>
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<td>Successful therapy</td>
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<tr>
<td>Dropouts</td>
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<sup>a</sup>p < .01 vs successful group; <sup>b</sup>p = < .04 vs successful therapy.
nonsustained VT (fourfold or greater increase of VT). Three patients, all with a history of sustained VT, had sudden death while on moricizine. If all five are categorized as “arrhythmia aggravation,” the incidence is 10.4%.

Discussion

Studies reporting the efficacy and side effects of new investigational antiarrhythmic agents are difficult to compare. The patient populations must be adequately defined, not only with reference to the severity of the underlying ventricular rhythm disturbance but also to the clinical diagnosis and measurement of left ventricular function before treatment. Since the frequency of antiarrhythmic drug toxicity, the potential for suppression of left ventricular function, and the frequency of “arrhythmia aggravation” are all dependent on the patient populations selected, these variables must be specified.

Selected aspects of study design. The protocol was designed to enroll patients who were at increased risk for sudden cardiac death. In their study of patients with nonsustained VT, Follansbee et al. noted that patients with nonischemic cardiomyopathy were at increased risk for sudden cardiac death. The association of nonsustained VT to sudden death in patients with cardiomyopathy has been confirmed by others. Although the present study population (all with nonsustained VT) was heterogeneous, evidence of their increased risk for sudden death included a documented history of sustained VT in 40%, coronary artery disease in 62%, all but four of whom had previous myocardial infarction, and impaired ventricular function (LVEF < 40%) in 60%.

There was no previous use of investigational antiarrhythmic drugs. The protocol used ambulatory ECG recordings as the sole criterion for enrollment as well as assessment of drug effect. Electrophysiologic study was not part of this protocol. The 75% reduction in runs of VT required for documenting efficacy was based on our previous experience in estimating the variability of runs of VT in 63 patients with 10 or more runs of VT per day. We showed that the percent reduction in runs of nonsustained VT necessary to establish “drug effect” was 67% if ambulatory ECG recordings were performed over 3 days, a reduction substantially higher than that reported in a previous study that suggested a 45% reduction of runs of nonsustained VT for comparable monitoring periods. Thus we believe that a 75% VT reduction level is a conservative estimate with which to establish “drug effect.”

Efficacy of moricizine in nonsustained VT. Therapy with moricizine initially resulted in total abolition of nonsustained VT in approximately two-thirds of the patients. The majority of patients initially responding to moricizine in this fashion continued to have excellent suppression of nonsustained VT. Abolition of nonsustained VT and couplets by antiarrhythmic drugs may be prognostically important according to published data by Graboys et al. Preliminary results of therapy with moricizine in patients with VT were reported by Podrid et al. that differed from those of the present study in that their patients had previously received an average of six antiarrhythmic drugs, many of which were investigational. Moricizine was reported to be “effective” (VT abolition) in 56% of their 62 patients. Other than this preliminary trial, there are no other trials that report results of therapy with moricizine in a comparable patient population.

Efficacy of moricizine in patients with sustained VT. Although moricizine was effective in suppressing nonsustained VT in the majority of patients, it was ineffective in preventing the recurrence of sustained VT. The majority of these patients (12/19) had recurrence of sustained VT either before hospital discharge or within the first month of therapy. An interesting observation in this group was that the extent of suppression of nonsustained VT on ambulatory ECG monitoring during therapy with moricizine was not predictive of prevention of sustained VT or subsequent sudden death. In fact, total abolition of runs of nonsustained VT on moricizine was seen as frequently in patients who subsequently had recurrent sustained VT as it was in patients free of recurrence for an average of 6 months.

Tolerance of moricizine in patients with left ventricular dysfunction. Despite the depressed left ventricular function in this study group (mean LVEF 36%), hemodynamic deterioration on moricizine occurred in only two patients. These two patients (with LVEFs, of 18% and 30%) were the exception to the rule, since an additional 21 patients had LVEFs of 30% or less and tolerated moricizine well without clinical deterioration. Thus, in the majority of patients, moricizine in dosages up to 14 mg/kg/day did not appear to alter the clinical or echocardiographic assessment of left ventricular function.

Antiarrhythmic response relative to initial left ventricular function. An important observation from this trial is that patients’ antiarrhythmic responses to moricizine were related to the initial LVEF. Patients who were dropped from the trial because of failed arrhythmia suppression tended to be those with LVEFs of 30% or less despite an apparent lack of adverse effect on ventricular function, whereas patients responding to moricizine were those whose LVEFs were 40% or greater.
These differences were statistically significant at both the 1 and 3 month intervals during the trial (table 3). Regardless of risk category (sustained vs nonsustained VT, coronary artery disease vs other cardiac diagnosis), antiarrhythmic response to moricizine was more effective in patients with relatively preserved left ventricular function. This interdependence of eventual antiarrhythmic response and baseline left ventricular function emphasizes the necessity of initial assessment of LVEF when evaluating and comparing the efficacy of investigational antiarrhythmic drugs.

Side effects and “arrhythmia aggravation” due to moricizine. This study extends observations made in our previously published investigations of moricizine in patients with stable non-life-threatening arrhythmias.35,36 Moricizine is well tolerated with a low incidence of minor side effects. It can be safely used in the majority of patients with left ventricular dysfunction. Although some patients report mild gastrointestinal disturbances, these complaints are not of a serious nature to require discontinuation of therapy. The only serious toxicity we observed in our study was the development of clinical congestive heart failure in two patients. Therefore, as with most clinically available antiarrhythmic drugs, administration of moricizine in patients with LVEFs of 30% or less should be done under close observation, but the drug will usually be well tolerated. “Arrhythmia aggravation” has recently been defined by Velebit et al.32 to include: (1) fourfold increase in PVCs, (2) a 10-fold increase in couplets or nonsustained VT, or (3) first occurrence of sustained VT not present during control studies. By our more strict criteria, “arrhythmia aggravation” occurred in two of 48 (4%). However, three patients with prior sustained VT had sudden cardiac death during therapy with moricizine. Whether this represented drug inefficacy or whether moricizine actually worsened the arrhythmia is speculative; but if these patients are considered to have had “arrhythmia aggravation” this results in a 10.4% incidence, comparable with other antiarrhythmic drugs reported by Velebit et al.32

In summary, moricizine is effective in suppressing runs of nonsustained VT in approximately two-thirds of patients presenting with frequent nonsustained VT. Moricizine is less effective in patients with sustained VT and in fact prevented recurrence of sustained VT in only 37% of patients. However, it is a well-tolerated drug, even in patients with significant left ventricular dysfunction, with a low incidence of minor side effects and serious toxicity. Moricizine appears to be a safe and effective alternative drug in the treatment of non-sustained VT.

We appreciate the secretarial expertise of Mrs. Paula Johnson, the artistic assistance of Ms. Sharon Wells, as well as the contributions to trial design made by Sara A. Mahler, M.D. We extend special thanks for the technical echocardiographic expertise of Helen Koepien, R.N.

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