Short- and long-term therapy with tocainide for malignant ventricular tachyarrhythmias

Stefan H. Hohnloser, Helmut W. Lange, Ernst A. Raeder, Philip J. Podrid, and Bernard Lown

ABSTRACT Tocainide was administered to 228 patients referred for treatment of recurrent ventricular tachyarrhythmias that were refractory to therapy with conventional antiarrhythmic drugs. After baseline studies, 1200 to 2400 mg tocainide/day was given for 4 days. Tocainide was effective in 49% of 180 patients evaluated with monitoring and exercise testing and in 35% of 48 patients undergoing electrophysiologic testing. No clinical parameter predicted the response to tocainide, although there was a correlation with the effect of lidocaine. Tocainide was selected for long-term treatment in 73 patients who were followed for an average of 26.4 months (range 1 to 92 months). The incidence of sudden death was 4.3% per year and two patients had nonfatal recurrence of arrhythmia. It is concluded that tocainide is effective and well tolerated during long-term use if therapy is evaluated carefully and is individualized.

Circulation 73, No. 1, 143-149, 1986.

LIDOCAINE has long been in use for the short-term treatment of serious ventricular arrhythmia and is effective for preventing malignant ventricular tachyarrhythmias.1,2 An oral congener, tocainide, has recently been approved for treatment of ventricular arrhythmia. It has electrophysiologic properties identical to lidocaine3 and during short-term use has been an effective antiarrhythmic agent for suppressing ventricular premature beats (VPBs) in patients without a history of sustained tachyarrhythmias.3-9 However, there are few data about the effectiveness of the drug in suppressing arrhythmias in patients with a history of sustained ventricular tachycardia or fibrillation. Moreover, the usefulness of tocainide during long-term therapy is unknown. We have evaluated tocainide in a large group of patients referred for refractory ventricular tachyarrhythmia. Our short- and long-term experience with this drug forms the basis of this report.

Material and methods

The population of patients who underwent in-hospital evaluation of tocainide included 228 men and women referred for therapy for recurrent ventricular tachyarrhythmias. The underlying heart disease is summarized in table 1. In 70 patients, presenting arrhythmia was ventricular fibrillation, in 139 it was sustained ventricular tachycardia with hemodynamic compromise, and in 19 it was nonsustained ventricular tachycardia associated with dizziness. Each patient was intolerant to or had recurrent arrhythmia on quinidine, procainamide, disopyramide, and a β-blocking agent. Previous drug therapy was considered ineffective if arrhythmia had recurred at a time when blood levels were in the defined therapeutic range. In no case was the arrhythmia provoked by an acute reversible process such as myocardial infarction or hypokalemia. Selection of patients for long-term therapy with tocainide was based on drug testing adhering to the following protocol.

Drug evaluation

Control period. On admission of patients to the hospital all antiarrhythmic drugs were discontinued and patients were continuously monitored by telemetry. Digoxin, when administered for congestive heart failure, and β-blocking agents or calcium-channel blockers, when prescribed for angina pectoris, were continued if necessary. After four half-lives (24 to 36 hr) without antiarrhythmic drugs, each patient underwent 48 hr of continuous ambulatory monitoring10 and a symptom-limited exercise test by a Bruce protocol on a motorized treadmill.11,12 The Lown grading system13 for ventricular ectopic activity was used to categorize the type and frequency of arrhythmia as follows: grade 0, no VPBs; grade 1A, fewer than 30 VPBs/hr and less than 1/min; grade 1B, fewer than 30 VPBs/hr and occasionally more than 1/min; grade 2, more than 30 VPBs/hr; grade 3, multiform VPBs; grade 4A, repetitive VPBs (couplets); grade 4B, repetitive VPBs, runs of ventricular tachycardia (more than three successive cycles); and grade 5, early-cycle VPBs (R on T).
TABLE 1
Clinical characteristics of patients

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<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Men (n)</td>
<td>Women (n)</td>
</tr>
<tr>
<td>Cardiac diagnosis (n/%)</td>
<td>CAD 142/62</td>
<td>Cardiomyopathy 34/15</td>
<td>Valvular disease 16/7</td>
</tr>
<tr>
<td></td>
<td>CAD 142/62</td>
<td>Cardiomyopathy 34/15</td>
<td>Valvular disease 16/7</td>
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<tr>
<td></td>
<td>VF 70/31</td>
<td>VT 158/69</td>
<td>Sustained 139/61</td>
</tr>
<tr>
<td>Presenting arrhythmia (n/%)</td>
<td>Non sustained 19/8</td>
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</table>

CAD = coronary artery disease; VF = ventricular fibrillation; VT = ventricular tachycardia.

Drug efficacy was assessed noninvasively when arrhythmia was reproducible on ambulatory monitoring and exercise testing and when the following criteria for arrhythmia density were met: (1) grade 2 VPBs for more than 50% of the monitoring hours during each 24 hr period, (2) grade 4 VPBs for 3 hr or more during each 24 hr period, (3) at least 2 VPBs/min and the provocation of grade 4 VPBs during exercise.

Patients with a low density of VPBs or nonreproducible arrhythmias on both monitoring and exercise testing underwent invasive electrophysiologic testing for evaluation of drug efficacy. A hexapolar catheter was inserted under fluoroscopic guidance into the left subclavian vein and positioned at the right ventricular apex. Programmed premature stimulation was performed during both sinus rhythm and ventricular pacing at a cycle length of 500 msec. One to three extrastimuli (S1, S2, S3) were added sequentially at current strengths of twice and three times mid-diastolic threshold. The endpoints for the study were the reproducible induction of nonsustained ventricular tachycardia (more than three repetitive ventricular responses lasting up to 30 sec occurring after the last stimulated premature beat) or sustained ventricular tachycardia (>30 sec). In the latter patients, sustained ventricular tachycardia occurred without antecedent nonsustained ventricular tachycardia.

Short-term maintenance. During this phase the efficacy of tocainide and the patient's tolerance for the drug were evaluated during a short period of maintenance therapy. Tocainide therapy was initiated adhering to the following schedule: day 1, 400 mg three times daily; day 2, 600 mg three times daily; day 3, 800 mg three times daily. The dosage was titrated to the suppression of arrhythmia and was adjusted to the maximum tolerated. Drug efficacy was evaluated after 48 hr of therapy on a stable dose by repeated ambulatory monitoring and exercise testing or electrophysiologic study. Blood samples for determination of tocainide levels were obtained immediately after the exercise test or the electrophysiologic study, which was performed 2 hr after the dose of tocainide was given.

Long-term therapy. Long-term tocainide therapy was instituted if tocainide was the most effective and the best tolerated of a number of antiarrhythmic drugs evaluated and if it was preferred by the patient. Patients were followed in 3 to 6 month intervals at the Cardiovascular Laboratories of the Harvard School of Public Health. Routine laboratory tests, an electrocardiogram, exercise testing, and ambulatory monitoring were performed at these visits.

Outcomes during long-term therapy were categorized as follows:

(A) Alive — free of arrhythmia.
(B) Alive — recurrent arrhythmia.
(C) Drug discontinued because of side effects.
(D) Dead.

1. Noncardiac death.
2. Cardiac death.
   a. Sudden death.
   b. Nonsudden death.

(E) Drug discontinued for other reasons.

Criteria for drug efficacy. Criteria for drug efficacy during short- and long-term therapy by a noninvasive approach were (1) total elimination of ventricular tachycardia, (2) greater than 90% decrease in the frequency of couplets, and (3) greater than 50% reduction in the number of VPBs. For the drug to be considered effective, these requirements had to be met on both monitoring and exercise testing. During electrophysiologic testing, tocainide was deemed effective when no more than two repetitive responses could be elicited on completion of the stimulation protocol.

Tocainide blood levels. Venous blood samples were taken after 3 to 4 days of therapy when steady-state plasma concentrations had been achieved. Samples were analyzed by high-performance liquid chromatography.

Statistical analysis. Categorical data were analyzed by the chi-square test or by Fisher's exact test. Paired t test was used for comparisons of continuous data. The criterion of significance was a p value of less than .05. Probability of survival based on incidence of all cardiac deaths and of sudden cardiac death and the analysis for recurrence of arrhythmia was calculated by means of life table analysis.

Results

Control studies. Therapy was guided noninvasively with repeated ambulatory monitoring and symptom-limited exercise testing in 180 of the 228 patients (79%). In this group, ambulatory monitoring demonstrated grade 2 VPBs for 50% to 74% of the monitoring hours in 12 patients and for 75% to 99% of monitoring hours in 12, while 156 patients had grade 2 VPBs for 100% of monitored hours. Grade 4 arrhythmia was present in 168 patients. In 21 patients, grade 4A was the highest grade, while 147 patients had grade 4B. Grade 4B arrhythmia was present during 50% to 75% of the monitoring hours in 30 patients and during 75% to 100% of the monitoring hours in 31 patients, while 86 patients had grade 4B arrhythmia for less than 50% of the monitoring hours.

A control exercise test was performed in 155 patients. Twenty-two patients did not undergo exercise testing because of the presence of long runs of symptomatic ventricular tachycardia at rest. In three additional patients who had suffered a myocardial infarct 3 to 5 weeks before tocainide evaluation exercise testing...
was also not performed. The highest arrhythmia grade achieved on the treadmill was grade 2 in 19, grade 4A in 37, and grade 4B in 99 patients.

The antiarrhythmic effect of tocainide was assessed by means of electrophysiologic testing in 48 patients. During the control study, sustained ventricular tachycardia or fibrillation was elicited in 26 and nonsustained ventricular tachycardia was elicited in 22 patients. One extrastimulus was used in nine, two extrastimuli were used in 24, and three extrastimuli were used in 15 patients.

**Short-term maintenance.** Twenty-seven of the 180 patients undergoing noninvasive evaluation received only a single dose (800 mg) of tocainide as part of a short-term drug test and this dose was effective in 15 of these patients.

The remaining 153 patients received multiple doses of the drug. In five patients, the drug was discontinued before evaluation because of side effects that included aggravation of arrhythmia and congestive heart failure. Of the 148 patients completing the short-term therapy trial, tocainide was judged effective in 73 (49%) and ineffective in 75 (51%) (figure 1).

Of the 48 patients undergoing electrophysiologic testing, tocainide was effective in 17 patients (35%), while the arrhythmia continued to be inducible in 31 (65%). The efficacy of tocainide was unrelated to the endpoint achieved during the control study. When nonsustained ventricular tachycardia was used, nine of 22 patients responded to tocainide, while in eight of 26 sustained ventricular tachycardia was rendered noninducible (p = .73, Fisher’s exact test). The response rate was not significantly different for patients presenting with sustained ventricular tachycardia (eight of 24) or ventricular fibrillation (nine of 24). Overall, 90 of the 196 patients (46%) completing therapy responded to tocainide. There was no statistically significant difference between responders and nonresponders with respect to the daily dose of tocainide (1765 vs 1869 mg/day). The mean tocainide blood level in responders was 9.1 μg/ml (range 3.5 to 16.1 μg/ml) and that in nonresponders was 9.2 μg/ml (range 3.2 to 16.4 μg/ml).

**Relationship between drug efficacy and clinical parameters.** To examine whether any clinical parameter may predict effectiveness of tocainide therapy, the following variables were analyzed in relationship to tocainide response during short-term maintenance in the 196 patients completing this phase of therapy: age, underlying heart disease, presenting arrhythmia, hours of grade 4B arrhythmia on control ambulatory monitoring, and left ventricular ejection fraction assessed dur-

![FIGURE 1. Abolition of exercise-induced ventricular tachycardia (VT) in a patient on short-term tocainide therapy. As shown by the monitor equations on the bottom, VT (up to 7 beats at a maximal rate of 150/min) was recorded during 14 hr of control ambulatory monitoring and was completely suppressed by tocainide.](image-url)
ing catheterization or by radionuclide ventriculography. Statistical comparison of these variables demonstrated no significant difference between responders and nonresponders. There was no significant difference in response to tocainide for patients with a history of nonsustained ventricular tachycardia (59%), sustained tachycardia (48%), or ventricular fibrillation (44%) ($\chi^2 = 1.56, p > .5$). Grade 4B arrhythmias tended to be more frequent in the nonresponders (4.6 vs 3.6 hr). In addition, left ventricular ejection fraction was lower (36.8% vs 42.9%) in the nonresponders (NS).

**Tocainide-lidocaine comparison.** The effect of lidocaine was evaluated in 85 patients who received this drug before tocainide therapy was started. Concordant responses to the two drugs were observed in 60 patients (71%) (figure 2). In 83% of the patients in whom lidocaine was ineffective, tocainide failed to suppress the arrhythmia. Conversely, 54% of the patients with a positive response to lidocaine responded to tocainide therapy. Thus, the sensitivity of the response to the lidocaine was 71%, the specificity was 70%, and the predictive accuracy was 71%.

**TABLE 2**

<table>
<thead>
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<th>Characteristics of patients receiving long-term tocainide</th>
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<td>Men (n)</td>
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<tr>
<td>None</td>
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<tr>
<td>Presenting arrhythmia (n/%)</td>
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<tr>
<td>VF</td>
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<tr>
<td>VT</td>
</tr>
<tr>
<td>Sustained</td>
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<tr>
<td>Nonsustained</td>
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**Abbreviations are as in table 1.**

**Long-term outcome.** Tocainide therapy was continued after hospital discharge in 73 patients (32%), 65 of whom had undergone noninvasive and eight of whom underwent invasive evaluation of drug efficacy. The distribution of the underlying heart disease and presenting arrhythmias in these patients was similar to that in the entire population (table 2). After a mean follow-up period of 26.4 months (range 1 to 92 months) 36 patients (49.3%) continued on tocainide free of arrhythmias and side effects (table 3). Sudden cardiac death occurred in seven patients after 1 to 50 months. All had a history of out-of-hospital sudden death syndrome (ventricular fibrillation or sustained ventricular tachycardia with syncope). For all 73 patients, the sudden death mortality was 4.3% per year (figure 3). When the seven patients presenting with nonsustained ventricular tachycardia were excluded, the annual sudden death mortality was 4.8% among the remaining 66 patients with a history of sudden death. A nonfatal recurrence of sustained ventricular tachycardia was documented in two patients after 2 and 7 months of tocainide therapy. In eight of the patients experiencing

**FIGURE 2.** Correlation of effects of lidocaine and tocainide in 85 patients receiving both drugs. Overall concordance rate was 71%. Of the 48 patients who did not respond to lidocaine, 40 (83%) had no arrhythmia suppression with tocainide. By contrast, of the patients who responded to lidocaine, only 54% were successfully treated with tocainide.

**TABLE 3**

<table>
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<th>Outcome in 73 patients on long-term tocainide therapy</th>
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<tr>
<td>Outcome</td>
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</tr>
<tr>
<td>Alive</td>
</tr>
<tr>
<td>Sudden death</td>
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<tr>
<td>Nonfatal recurrence</td>
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<tr>
<td>Death — CHF</td>
</tr>
<tr>
<td>Death — noncardiac</td>
</tr>
<tr>
<td>D/C side effects</td>
</tr>
<tr>
<td>D/C other reasons</td>
</tr>
</tbody>
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CHF = congestive heart failure; D/C = discontinued.
recurrences (seven sudden cardiac deaths and one nonfatal event; 12%) effects of tocainide had been evaluated noninvasively, whereas in one patient with a nonfatal recurrence electrophysiologic testing had been performed (13%). Neither sudden death mortality nor the nonfatal recurrence rate were significantly different between patients evaluated noninvasively and those tested invasively (p = .43 and p = .21, respectively; Fisher’s exact test). Eight patients died after an average of 25 months (range 2 to 47 months) from slowly progressive congestive heart failure unrelated to tocainide therapy. Four other patients stopped taking tocainide on their own for unknown reasons.

**Side effects during tocainide treatment.** Adverse effects were reported by 101 of the 228 patients (44.3%) (table 4). The most frequent were those involving the central nervous system (28%). Among these, tremor, ataxia, dizziness, and lightheadedness were the most common complaints and often abated when the dosage was reduced. Other neurologic side effects such as nightmares, headaches, and thought disorders were not related to dosage and resolved upon discontinuation of drug therapy. Gastrointestinal side effects, primarily nausea and vomiting, were reported by only 11%. This incidence is lower than in other studies largely because the drug was administered with food. Aggravation of arrhythmia occurred in 14 patients (6.1%) during tocainide therapy. Exacerbation of congestive heart failure occurred in four patients during hospitalization and in two patients after 2 months of tocainide therapy. Other side effects developing during long-term treatment included central nervous toxicity (seven patients) and progressively more severe gastrointestinal complaints (two patients). Fever without leukocytosis or positive ANA titers occurred in two patients.

The daily tocainide dosage in patients with side effects was not significantly different from that in patients without side effects. The average blood level of the drug was 10.0 μg/ml (range 4.7 to 16.4 μg/ml) in the patients with side effects and did not differ from that in those without toxicity (NS).

**Discussion**

The present study demonstrates that tocainide is an effective drug for treatment of life-threatening ventricular arrhythmias. Overall, 46% of patients had suppression of spontaneous or induced arrhythmia during a short period of in-hospital drug evaluation; this is similar to our previous experience.4 As reported previously for other drugs,17,18 the response rate was higher when patients were assessed noninvasively than when they were evaluated by programmed stimulation (49% vs 35%). Other studies using ambulatory monitoring reported the drug to be effective in 50% to 70% of patients during short-term treatment;7-9 however, these investigations involved patients with frequent VPBs but no history of sustained tachyarrhythmias.

**FIGURE 3.** Sudden death mortality among 73 patients receiving long-term tocainide therapy. The annual cardiac mortality was 9.4%, while sudden cardiac death occurred in 4.3% per year. Solid line = patients discontinuing tocainide therapy because of recurrence of arrhythmia (sudden death and nonfatal recurrence); dashed line = all patients discontinuing tocainide therapy because of recurrent arrhythmia (sudden death and nonfatal recurrence), other cardiac deaths, noncardiac deaths, and side effects. N = number of patients continuing on tocainide at each interval of observation.
TABLE 4
Side effects

<table>
<thead>
<tr>
<th>Patients</th>
<th>101 (43%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>64 (28%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>22</td>
</tr>
<tr>
<td>Ataxia</td>
<td>13</td>
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<tr>
<td>Dizziness</td>
<td>8</td>
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<tr>
<td>Blurred speech</td>
<td>6</td>
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<tr>
<td>Visual disturbances</td>
<td>5</td>
</tr>
<tr>
<td>Thought disorder</td>
<td>5</td>
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<tr>
<td>Fatigue</td>
<td>5</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>4</td>
</tr>
<tr>
<td>Nightmares</td>
<td>4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
</tr>
<tr>
<td>Headaches</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25 (25%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>24</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Aggravation of arrhythmia</td>
<td>14</td>
</tr>
<tr>
<td>Increase in CHF</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
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</tbody>
</table>

CHF = congestive heart failure.

Furthermore, the criteria for therapeutic effectiveness in these studies were less stringent, being based only on a reduction in frequency of VBPs. We have reported a similar rate of efficacy with other investigational drugs such as mexiletine,20 ethmozine,21 encainide,22 and propafenone.21 Tocainide prevented the induction of sustained or nonsustained ventricular tachycardia in 35% of patients, which is similar to our results with other antiarrhythmic drugs.17, 18 Although there are no studies evaluating tocainide with electrophysiologic testing, the efficacy rate we observed is comparable to the experience of other investigators with different antiarrhythmic agents.22, 23 As with other agents, the response to tocainide did not correlate with the average daily dose used or the blood levels achieved.18, 21, 24

Side effects were noted in 44% of patients and were unrelated to the daily dose or the average blood level. The incidence and the type of adverse reactions were similar to what has been previously reported.4 The majority of these side effects were recognized in the hospital after a brief period of therapy and disappeared with dose adjustments. Nevertheless, drug toxicity necessitating discontinuation of therapy occurred in 13 patients (18%) on long-term therapy. Similar to our experience with other drugs,25 tocainide has the potential to aggravate arrhythmia. The incidence is less than previously reported in a smaller patient population. Its occurrence was not related to drug blood levels or changes in the electrocardiogram. In none of the 228 patients did the electrocardiogram disclose impairment of conduction. Therefore, tocainide can be safely administered in patients with preexisting conduction abnormalities. Exacerbation of congestive failure was observed in six patients (2.6%) and resolved on discontinuation of the drug. This incidence is similar to that observed with mexiletine.24 Thus, tocainide is safe in patients with significant left ventricular dysfunction and a history of congestive heart failure. The patients who developed central nervous system side effects after several months of tocainide therapy had not manifested any side effects during the in-hospital evaluation of the drug. Therefore, tocainide may cause neurologic toxicity after a prolonged period of therapy and continued observation is necessary.

The selection of an effective antiarrhythmic agent is empiric and there are no helpful guidelines. The large number of patients in this study provided an opportunity to determine if any clinical parameter would predict tocainide efficacy. We found that the nature of heart disease, presenting arrhythmia, left ventricular function, density of arrhythmia on control monitoring, and tocainide blood levels were not helpful in predicting tocainide effectiveness. Response to lidocaine provided some clue, but this was not absolute, with a predictive accuracy of 71%. Failure to respond to lidocaine predicted lack of response to tocainide in 83% of patients, whereas suppression of arrhythmia with lidocaine was less predictive of success of tocainide therapy. Therefore, even when two agents with similar electrophysiologic properties are compared, drug efficacy may be different. The correlation between effects of tocainide and lidocaine is similar to our previous results in 50 patients3 and that of Winkle et al.,6 who reported that 63% of patients successfully treated with lidocaine responded to tocainide, while in 83% of patients not responding to lidocaine, tocainide was also ineffective. We have also found that the response to mexiletine does not predict response to tocainide, although both drugs are lidocaine congeners.26 Therefore, determination of the effects of each drug requires a systematic evaluation in each individual patient.

This study confirms that the outcome of patients with life-threatening arrhythmias is improved during long-term tocainide therapy if short-term treatment has been effective and well tolerated. Thus, the annual sudden death rate of patients was 4.3%, which is similar to our results in 107 patients treated over the long term with mexiletine23 and to the rate in a group of 123
patients discharged on another antiarrhythmic agent.27
The expected yearly mortality in a comparable group of
patients receiving empiric therapy is unknown. In the
Seattle Heart Watch Program, recurrent sudden death was approximately 28% in the first year.28 The
patients in this study are not comparable to those of the
Seattle program since our patients had experienced multiple cardiac arrests and were refractory to conven-
tional drug therapy before referral. The recurrence rate in such a patient group might be expected to be even
higher than that reported in epidemiologic studies.
Survival was similar in patients undergoing invasive
and those undergoing noninvasive evaluation of drug
efficacy. Therefore, suppression of spontaneous ar-
hythmia or the prevention of arrhythmia induction by
tocainide predicts a favorable outcome.

In summary, tocainide is an effective antiarrhyth-
mic agent in a subgroup of patients with life-threatening
ventricular tachyarrhythmias. Whereas no clinical
features are helpful in predicting response to tocainide,
ilocaine appears to be useful. The drug was effective
in 46% of patients with refractory arrhythmias, but was
continued as long-term treatment in only 32% of the
patients. This was due to the high incidence of side
effects, the majority of which, however, were dose
related. When tocainide is selected for long-term ther-
apy based on efficacy and safety during a short trial,
the drug continues to be effective and reduces mortality
from sudden death.

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S H Hohnloser, H W Lange, E A Raeder, P J Podrid and B Lown

Circulation. 1986;73:143-149
doi: 10.1161/01.CIR.73.1.143
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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