Suppression of Ventricular Ectopic Depolarizations by Tocainide


SUMMARY In a previous clinical study we demonstrated that tocainide is effective in the suppression of ventricular ectopic depolarizations (VEDs) after single oral doses. This information provided the basis for evaluating this drug’s antiarrhythmic efficacy after multiple dose administration according to a loading-maintenance regimen. Twelve patients with stable VEDs were given loading doses of tocainide (400–600 mg) with maintenance doses every 12 hours. Every 48 hours the dose was increased until either arrhythmia suppression < 25% of VED frequency during placebo administration or side effects occurred. Computer analysis of 12-hr telemetric ECGs taken 24–36 hr after each dosage increment documented effective suppression (76–95%) in 8 of 12 patients. Those subjects demonstrating suppression were randomly assigned to a cross-over study of placebo or active drug at the dosage found effective in the dose-ranging phase. Dosages for the cross-over stage ranged from 400 to 1100 mg every 12 hours. Comparison of the two five-day periods documented suppression in these patients (mean ± SE = 83.3 ± 4%). No serious side effects or undue drug accumulation occurred during the study. The data indicate that tocainide can effectively suppress VEDs for 8–12 hours in many patients and that continuous suppression could be possible on an 8–12 hr dosage regimen.

ALTHOUGH AN EXCELLENT antiarrhythmic drug, lidocaine has pharmacokinetic characteristics (a high hepatic clearance and thus poor systemic bioavailability, and a short half-life) that preclude its effective oral use. Accordingly, lidocaine congeners with improved oral availability have been investigated for antiarrhythmic efficacy. Studies in animals demonstrated antiarrhythmic efficacy and high oral bioavailability for one such compound, tocainide hydrochloride. (Previous publications have referred to tocainide as W-36095 (Astra) or 2-amino-2',6'-propanoxyldiide hydrochloride.) Our previous evaluation of single oral doses of tocainide in patients with stable ventricular ectopic depolarizations (VEDs) found it to have prolonged antiarrhythmic efficacy, good oral bioavailability and a mean elimination half-life (t1/2) of 14.6 hours. The purpose of this study was to extend this initial information by assessment of the antiarrhythmic efficacy and pharmacokinetics of multiple-dose regimens designed for maintenance therapy.

Methods and Materials

Twelve consenting volunteer patients with stable VEDs were admitted to the Clinical Research Center (CRC) of Vanderbilt University Hospital. All patients were ambulatory while in the hospital and under constant electrocardiographic monitoring. A Hewlett-Packard Model 78100A telemetry system transmitted ECG signals to the hospital coronary care unit and also to an Ampex Model FR 1200 tape recorder. Twelve hour segments of ECG data were taped for computer analysis. All medications were discontinued on admission with the exception of cardiac glycosides or anticoagulants. Dietary sodium was controlled at 100 meq daily.

Subjects

The following criteria were used in excluding patients from this study: age less than 21 or greater than 75; premenopausal female patients without surgical sterilization; unstable concurrent illness; arrhythmia due to digitalis intoxication, electrolyte disturbance, correctable blood gas abnormality or acute myocardial infarction; arrhythmia requiring acute effective therapy; sick sinus syndrome; ventricular pre-excitation; atrial fibrillation or flutter; atrial tachycardia; bundle branch block; grade 2 or greater A-V block; myocardial infarction within the previous six weeks; unstable angina; pulmonary edema or greater than 2+ peripheral edema if attributed to heart failure; serum urea nitrogen > 30 mg%; and known allergy to lidocaine or local anesthetics.

Nine males and three females described in table 1 participated as volunteers in this study. Patients with complicating illnesses or NYHA cardiac status class IV were excluded. All patients had stable VEDs (> 500 per 12 hour period) and were able to have any established antiarrhythmic therapy discontinued for this study. Patients were accepted if their VED frequency was relatively constant throughout the 12 hours of observation. Patients with 15 consecutive minutes free of ectopic beats during control observations were excluded. All but three patients in this study had greater than 4 VEDs/min for every hour of observation during initial placebo therapy. Two of these three had a coefficient of variation for the hourly VED counts of 18 and 29% and more than 1 PVC/min for every hour analyzed. The only patient who had wide variation in hourly VED frequency was RM who had a constant daily pattern in which his VED frequency peaked at 12 noon and 6 p.m. with troughs at 9 a.m., 3 p.m., and 9 p.m. A minimum of 25 VEDs were counted in one hour and a maximum of 1235 in another hour; his hourly coefficient of variation was 103% for all pre-drug placebo data. Six of the twelve patients had known coronary vascular disease and had experienced a myocardial infarction two or more years prior to participation in this study. One patient had stable obstructive and restrictive lung disease but did not require bronchodilator therapy during the study. Three patients had mild essential hypertension; all became normotensive during the hospitalization while receiving a diet containing 100 meq...
sodium. Extensive medical evaluation including coronary arteriography was unable to discern an etiology for the arrhythmia in two other patients. Seven of the twelve patients had been found to be resistant to one or more antiarrhythmic drugs prior to being referred to this study. Ten of the patients had responded to quinidine prior to participating in this study but two had been unresponsive to quinidine, procainamide and propranolol.

Medication

Toacainide HCl as 50 mg and 200 mg tablets and an identical placebo were supplied by Astra Pharmaceutical Products and administered 30 minutes after a meal of varying composition.

Study Procedure

Patients were admitted to the CRC and allowed to stabilize without antiarrhythmic therapy for at least two days. Once the patient’s arrhythmias were stable, responsiveness to lidocaine was determined in the following manner. The number of VEDs were counted for six consecutive five-minute intervals and the mean five-minute incidence determined. A bolus of 50 mg of lidocaine was given intravenously followed by injections of 25 mg every ten minutes until either a total dose of 125 mg or 75% reduction in VEDs occurred. The response to lidocaine was evaluated by determining the percent reduction in the number of VEDs in each interval from the control mean. Lack of response was not a criterion for exclusion from the subsequent study.

The response to toacainide was determined in two stages (see fig. 1). Stage I was a placebo-controlled single-blind study in which patients were treated with increasing dosages of toacainide after an initial placebo period. Each patient was given an initial loading dose (400–600 mg) followed by a smaller maintenance dosage on a 12 hourly regimen. If antiarrhythmic efficacy was not seen after 48 hours, a fractional loading dose was administered in order to bring the amount of drug in the body toward the next steady-state level. The dosage was increased every 48 hours until efficacy or an adverse effect was seen up to a maximum daily dosage of 20 mg/kg. If 75% or greater arrhythmia suppression occurred in Stage I, the patient entered Stage II which consisted of placebo and toacainide treatment periods of five days each, the sequence of which was randomly assigned. The dosage of toacainide was that determined to be effective during Stage I. All treatment periods were separated by two day periods to allow drug washout and dissipation of any drug effects.

### Table 1. Description of Patients and Their Arrhythmias

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Sex</th>
<th>Diagnoses</th>
<th>V-T</th>
<th>VEDs</th>
<th>Concurrent medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO</td>
<td>53</td>
<td>75</td>
<td>F</td>
<td>HTN</td>
<td>+</td>
<td>MF</td>
<td>Dg</td>
</tr>
<tr>
<td>WC</td>
<td>57</td>
<td>78</td>
<td>M</td>
<td>ASCVD, stable angina</td>
<td>+</td>
<td>FC</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>60</td>
<td>55</td>
<td>F</td>
<td>IVA</td>
<td>-</td>
<td>FC</td>
<td>W, Dg</td>
</tr>
<tr>
<td>JJ</td>
<td>51</td>
<td>79</td>
<td>M</td>
<td>HTN</td>
<td>-</td>
<td>FC</td>
<td></td>
</tr>
<tr>
<td>EW</td>
<td>46</td>
<td>77</td>
<td>M</td>
<td>ASCVD</td>
<td>+</td>
<td>FC</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>33</td>
<td>122</td>
<td>M</td>
<td>COPD</td>
<td>-</td>
<td>FC</td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>51</td>
<td>87</td>
<td>M</td>
<td>HTN</td>
<td>-</td>
<td>FC</td>
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</tr>
<tr>
<td>RE</td>
<td>38</td>
<td>93</td>
<td>M</td>
<td>IVA</td>
<td>-</td>
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<tr>
<td>LL</td>
<td>54</td>
<td>71.3</td>
<td>F</td>
<td>ASCVD</td>
<td>-</td>
<td>PF</td>
<td></td>
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<tr>
<td>ES</td>
<td>58</td>
<td>70.3</td>
<td>M</td>
<td>ASCVD</td>
<td>-</td>
<td>FC</td>
<td></td>
</tr>
<tr>
<td>RO</td>
<td>54</td>
<td>68.2</td>
<td>M</td>
<td>ASCVD</td>
<td>-</td>
<td>Dg</td>
<td></td>
</tr>
<tr>
<td>WH</td>
<td>41</td>
<td>90.7</td>
<td>M</td>
<td>ASCVD</td>
<td>-</td>
<td>MF</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** HTN = hypertension; ASCVD = atherosclerotic coronary vascular disease; IVA = idiopathic ventricular arrhythmia; COPD = chronic obstructive pulmonary disease; V-T = previous history of ventricular tachycardia; FC = fixed coupled VEDs; MF = multifocal VEDs; PF = parasystolic focus; Dg = digoxin; Dt = digitoxin; Ds = diazepam; W = warfarin.

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**Figure 1.** Diagram of protocol for evaluation of multiple oral doses of toacainide in patients with stable ventricular arrhythmias.

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**STAGE I**

PLACEBO → STABILIZATION

PLACEBO → 400 mg BID → 600 mg BID

TOCAINIDE DOSE - RANGING

TOCAINIDE 300 mg BID

PLACEBO → 400 mg BID → 600 mg BID

**STAGE II**

PLACEBO → TOCAINIDE

TOCAINIDE 1.2.3.4.5

PLACEBO 1.2.3.4.5

RANDOMIZED CROSS-OVER
Arrhythmia Detection and Analysis

The patients were ambulatory and were encouraged to simulate normal activity as much as possible. Electrocardiograms were continuously monitored using a modified lead I and twelve hour segments of data were taped on the second of two placebo days and on the second day of each dosage regimen. If the patient entered Stage II, twelve hour segments were taped daily during the two five-day periods.

Computer programs for arrhythmia detection and quantification were developed in the Biomedical Engineering Division of Vanderbilt University. These programs were written for a Scientific Corporation SCC-650 computer and verified by comparison of VED counts made by the computer to visual counts made by trained observers. Prior validation found the two methods to agree within 10% (mean variance = 2.4%) when analyzing routine ambulatory data obtained from patients with unifocal or multifocal VEDs and over a frequency range from 0.5-30 VEDs/min. The agreement approached 100% when the data were free of motion artifact or noise.

The computerized arrhythmia analysis system required extensive man-machine interaction to assure accurate analysis by the computer. All ECG complexes that were classified as ectopic or unknown were stored in memory and recalled for verification by the trained operator at accelerated playback speed. Data with excessive noise preventing accurate analysis were not processed. Of the 192 hours of data analyzed during Stage II for determination of drug efficacy only five hours could not be analyzed. The operator was not informed of the drug regimen for any set of data and used the same criteria for exclusion of data, i.e., because of poor signal quality, for both drug and placebo periods.

Clinical Evaluation and Laboratory Tests

Blood pressure (supine and upright) and pulse were determined before and two hours after each dose of tocainide. Twelve lead ECGs were obtained before tocainide and two hours after each loading dose. A complete blood count (Coulter), differential, reticulocyte count, platelet count, serum electrolytes, serum urea nitrogen, glucose, serum glutamic-oxaloacetic transaminase, serum alkaline phosphatase, serum creatinine, serum bilirubin, serum albumin and total proteins, and urinalysis were obtained before tocainide administration, every 3-5 days during therapy and two weeks after discharge from the hospital. Twenty-four hour urine collections were obtained on the same days in order to determine creatinine clearance, tocainide excretion and sodium excretion. All stools were tested for occult blood. Pre-dose and two hours post-dose samples of blood were obtained for determination of the tocainide plasma concentration by gas chromatography as described previously. At the end of Stage I, plasma samples were collected at 0.5, 1, 2, 3, 4, 8, 12, 24 and 36 hours after the last dose. In order to determine the elimination half-life of tocainide, concentrations at 4, 8, 12, 24 and 36 hours were utilized.

Throughout the study a 15-second ECG rhythm strip was obtained every 15 minutes for measurement of the PR and QRS intervals and an estimate of VED frequency. The sinus rate (R-R interval), QRS duration and P-R interval were measured daily from these rhythm strips by one of the authors at 0, 1, 2, 3, 4 and 8 hours after each dose. The means of the values during the placebo periods were compared to those at each dosage tested in Stage I or II. The Student's t-test was used to determine significant changes in any parameter. A questionnaire was read to each patient daily by a member of the nursing staff in order to solicit possible adverse effects of tocainide. Positive responses were recorded and the severity quantified using a scale from 0 to 4 +.

Results

Twelve patients participated in the dose-ranging portion of the study (Stage I). Eight of the twelve demonstrated 75% or greater suppression of VEDs as summarized in table 2. Two patients developed side effects (see table 3) necessitating discontinuation of therapy or dosage reduction without experiencing arrhythmia suppression to less than 25% of control VED frequency. One patient (CR) experienced mild and tolerable side effects at a dosage which provided arrhythmia suppression and the drug was continued without worsening of symptoms. Two patients failed to respond at the maximum allowed dosage.

In the randomized cross-over comparison of tocainide with placebo, only the last three days of each period were compared to determine efficacy. The last three days of each five day period were compared for two reasons. First, because of tocainide's 12-20 hour elimination half-life, approximate steady-state conditions were not present during the first two days of the five-day drug period. Second, disappearance of drug effect persisted through the first two placebo days for two patients, whereas the VED frequency of the last

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage I</th>
<th>% VED suppression</th>
<th>Stage II</th>
<th>VED/min</th>
<th>Dosage (mg/12 hr)</th>
<th>Control</th>
<th>Tocainide</th>
<th>% suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO</td>
<td>87</td>
<td>400</td>
<td></td>
<td>9.58</td>
<td>2.1</td>
<td>78.1</td>
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<tr>
<td>WC</td>
<td>86</td>
<td>700</td>
<td></td>
<td>8.57</td>
<td>2.51</td>
<td>67.2</td>
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<td>500</td>
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<td>1.8</td>
<td>90.4</td>
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<tr>
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<td>95</td>
<td>600</td>
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<td>5.26</td>
<td>0.44</td>
<td>91.6</td>
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<td>EW</td>
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<td>1000</td>
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<td>36.4</td>
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<td>81†</td>
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</tr>
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<td>1100</td>
<td></td>
<td>11.5</td>
<td>1.24</td>
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<td></td>
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<tr>
<td>RM</td>
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<td>600</td>
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<td>4.94</td>
<td>1.30</td>
<td>69.7</td>
<td></td>
<td></td>
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<tr>
<td>RE</td>
<td>84</td>
<td>600</td>
<td></td>
<td>0.66</td>
<td>0.01</td>
<td>99</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SE</td>
<td>86 ± 2.5</td>
<td>688 ± 91</td>
<td>11.8 ± 4.3</td>
<td>2.08 ± 0.8</td>
<td>83.3 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean VED counts for first eight hours after tocainide or placebo on days 3, 4, and 5 of each cross-over period.
†Further dose-ranging after this study produced 100% suppression with a total daily dosage of 2200 mg in three doses.
three days of the placebo period was approximately equal to that of pre-drug placebo periods for all patients. The mean 12 hourly dosage during the cross-over period was 688 ± 91 mg (SE). Comparison of the first eight hours after drug or placebo administration on the last three days of each period demonstrated 83.3 ± 4% mean reduction in VED frequency. Figure 2 demonstrates the relationship between VED suppression and time after dosage. VED frequency began to increase eight hours after tocainide administration. Three patients maintained > 85% arrhythmia suppression (93, 89, and 86%) during the last four hours of each dosing interval. However, during this same period arrhythmia suppression fell to < 40% in five patients.

In the cross-over phase of the study, plasma tocainide concentrations between 3.5 and 12 μg/ml were associated with suppression of VEDs. The mean plasma concentration at the time VED frequency returned to >30% of control was 5.0 ± 1.0 μg/ml (range 3.5–7). The four nonresponders reached peak plasma levels from 10.7 to 14.6 μg/ml.

None of the patients demonstrated an increase in VED frequency above control levels during drug withdrawal. There were no significant changes seen in PR or QRS intervals or sinus rate. Three patients had a significant increase in blood pressure associated with suppression of VEDs (MAP increased from 106 to 127, 103 to 114, 127 to 136 mm Hg). There was no significant change in MAP in any of the patients who did not respond to tocainide. However, the accuracy of blood pressure measurements by sphygmomanometry is not always reliable in patients with frequent VEDs. There was no change in renal function in any patient as measured by creatinine clearance, serum urea nitrogen or sodium excretion. Body weight did not change significantly during the study. The clinical laboratory tests (see Methods) did not detect abnormalities during the study except for a decrease in hematocrit that could be attributed to the removal of blood for the multiple tests. When the laboratory screen was repeated two weeks after completion of the study, all values were normal including hematocrit.

The side effects occurring during tocainide treatment which did not occur during placebo therapy are listed in table 3. Two patients developed a transient tremor after administration of 800 mg and 900 mg at plasma tocainide levels of 10–12 μg/ml. One other patient developed dizziness and lightheadedness after 1100 mg with plasma levels of 15.6 μg/ml. All of the above symptoms were transient or resolved with either dosage reduction or discontinuation of therapy. Intravenous diazepam abolished the tremor in one patient within minutes of administration. An electroencephalogram taken 30 minutes after an episode of tremor in another patient was normal and unchanged from a previous study.

After the last dose of tocainide in the dose-ranging phase of this study, plasma samples were taken for 36 hours to determine the elimination half-life of the drug. The terminal half-life ranged from 11.5–22.8 hr with a mean value (± SD) of 16.1 ± 3.7 hr (N = 12). Peak plasma levels were reached from 0.5–4 hours after administration. Twenty-four hour urinary excretion of unchanged tocainide at steady-state ranged from 12–70% of the daily dosage (mean 35.6 ± 2.4%).

There was a positive correlation between responsiveness to lidocaine by the bolus infusion test and subsequent responsiveness to tocainide (r = 0.77) in that the four patients who did not respond to tocainide had the least response to lidocaine. Those who had the best response to tocainide were also very sensitive to lidocaine.

**Discussion**

It has been demonstrated clearly that patients with VEDs who have a history of prior myocardial infarction are at an increased risk of sudden cardiac death.\(^{5,6}\) Also many patients have VEDs so numerous as to substantially reduce cardiac output, causing symptoms that may include syncope. Many of these people have episodic ventricular tachycardia which may be potentially lethal. Antiarrhythmic therapy in these patients is necessary but frequently unsatisfactory because of the shortcomings of currently available drugs.

Intravenous lidocaine has proven to be rapidly effective for suppression of ventricular arrhythmias in patients with

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**FIGURE 2. Summary of responses of eight patients during Stage II. The mean number of VEDs for each hour after tocainide administration on the three drug days was compared to the mean number of VEDs for the same hour of the three placebo days.**

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**TABLE 3. Side Effects of Tocainide**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Wt (kg)</th>
<th>Side effect</th>
<th>Duration</th>
<th>Dosage (mg/hr)</th>
<th>Plasma level (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.H.*</td>
<td>90.7</td>
<td>Tremor, mild, intention tremor of hands</td>
<td>1 hr</td>
<td>800 mg</td>
<td>10.7</td>
</tr>
<tr>
<td>L.L.*</td>
<td>71.3</td>
<td>Tremor, gross, resting tremor of arms and hands</td>
<td>30 min†</td>
<td>900 mg</td>
<td>12.8</td>
</tr>
<tr>
<td>C.R.</td>
<td>122</td>
<td>Dizziness and lightheadedness</td>
<td>30 min</td>
<td>1100 mg</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*Arrhythmia not suppressed at this dosage.
†Responded to 5 mg diazepam intravenously in five minutes.
acute myocardial infarction. However, prolonged treatment requires that a drug be effective when administered orally and little of an orally administered dose of lidocaine reaches the systemic circulation because of its high hepatic extraction ratio (0.65). Accordingly, congeners of lidocaine have been sought that might have antiarrhythmic efficacy and lower hepatic clearance. One of these congeners, tocainide, has been effective in single oral doses for suppression of VEDs. It has a mean half-life of elimination of 14.6 hours which suggested that its dosing interval could be longer than that of currently available drugs. This investigation found tocainide effective for suppression of VEDs for eight to twelve hours after oral administration, as shown in figure 2.

Arrhythmia suppression > 70% was present for only eight hours in some patients. Continuous suppression was seen in two of the eight patients. Their dosages (500 and 600 mg every 12 hr) were not significantly higher than the other patients. Figure 2 compares the mean number of VEDs in each hour after dosing for the eight patients during the control and treatment periods. As can be seen, there is a significant increase in VED frequency after the eighth hour indicating more complete suppression might be feasible for some patients on an eight-hourly dosage regimen. Increased duration of effect might be possible by increasing the 12-hourly dosage, but peak blood levels would be excessive in many patients. Since the minimum effective range of plasma concentrations is between 3.5 and 7 μg/ml and CNS toxicity occurs at plasma levels between 10 and 15 μg/ml, it is difficult to maintain therapeutic plasma levels on a q 12 hr regimen without reaching excessive levels at the peak of drug absorption. Importantly though, these side effects are readily reversible and quite tolerable. They serve as reliable evidence that the drug concentration has exceeded those levels usually associated with antiarrhythmic efficacy and if efficacy has not been seen when they appear, further dosage increase would be unwarranted. Administration of tocainide on an eight-hourly regimen might allow less variation in plasma levels and maintain the level within the therapeutic window throughout the entire dosage interval.

Pharmacokinetic studies in normal volunteers found the elimination half-life to be 11 hours whereas our previous studies of patients with cardiac arrhythmias and our present study found the mean t1/2 to be 14.6 and 16.1 hours, respectively. These data suggest that drug elimination may be different in these patients compared to normal volunteers. No undue accumulation occurred during the five-day Stage II treatment period on a 12-hourly dosage regimen.

In agreement with our previous findings there is a positive correlation between the antiarrhythmic efficacy of tocainide and lidocaine. Comparison of the therapeutic range of plasma levels for the two drugs indicates that tocainide may have only half the potency of lidocaine since lidocaine appears to have efficacy in the range of plasma levels from 1.5–5 μg/ml and levels of 3.5–10 are required for tocainide. Plasma protein bindings of the two are very similar (about 50%).

Tocainide appears to be a comparatively safe and effective agent for chronic suppression of VEDs. Because troublesome but reversible CNS side effects occur during peak blood levels and antiarrhythmic effects last only eight hours in some patients, an 8-hourly regimen should be evaluated in future studies.

Acknowledgment

The authors wish to express appreciation to Dr. Thomas Harris, Dr. Stanley Higgins and Mr. Roy Woody of the Biomedical Engineering Division of Vanderbilt University for their assistance in computer program development and computerized arrhythmia analysis of electrocardiographic data.

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R L Woosley, D G McDevitt, A S Nies, R F Smith, G R Wilkinson and J A Oates

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