Flecainide Versus Quinidine for Treatment of Chronic Ventricular Arrhythmias
A Multicenter Clinical Trial

THE FLECAINIDE-QUINIDINE RESEARCH GROUP*

SUMMARY The antiarrhythmic efficacy and safety of oral flecainide acetate and quinidine sulfate were compared in a double-blind, 16-center parallel trial involving 280 patients with chronic premature ventricular complexes (PVCs). Eighty-five percent of the flecainide patients had at least 80% suppression of PVCs, vs 57% of the quinidine patients (p < 0.0001). Fifty-eight percent of the flecainide patients met the above criterion also and had complete suppression of couplets and beats of ventricular tachycardia, vs 33% of the quinidine patients (p < 0.0001). PR and QRS intervals were prolonged by flecainide without clinical consequence, but they were not substantially affected by quinidine (p < 0.0001). Quinidine prolonged JT (QT minus QRS) intervals significantly more than flecainide (p < 0.05). Nineteen of 141 flecainide patients and 21 of 139 quinidine patients discontinued therapy because of side effects (p > 0.50). Flecainide side effects included dizziness, blurred vision, headache and nausea. Quinidine side effects included diarrhea, nausea, headache and dizziness. Flecainide was more effective than quinidine in suppressing chronic ventricular arrhythmias (especially complex forms), and thus is an important new antiarrhythmic agent.

VENTRICULAR ARRHYTHMIAS occur in two important clinical settings. In the first, patients have hemodynamically significant, symptomatic ventricular arrhythmias, usually paroxysmal ventricular tachycardia or fibrillation, and require immediate suppressive therapy, usually in hospital. Invasive electrophysiological methods to determine antiarrhythmic drug efficacy are often used in these patients.

In the second setting, patients have chronic ventricular ectopy characterized by non-hemodynamically significant but frequent or complex premature ventricular complexes (PVCs). These patients are at high risk of sudden cardiac death, especially in the presence of underlying structural heart disease. Noninvasive techniques are often used to define antiarrhythmic drug efficacy in ambulatory patients with this type of arrhythmia. This study was conducted in this second group of patients.

Optimal therapy for chronic ventricular arrhythmias requires an antiarrhythmic agent that can effectively suppress these arrhythmias, has a wide therapeutic range with a low level of toxicity, and has a convenient dosing schedule to improve patient compliance during chronic outpatient management.

Flecainide acetate (Tambocor), a new antiarrhythmic agent, has been shown to have favorable pharmacokinetics and a high rate of antiarrhythmic efficacy in animals. Electrophysiologic studies indicate that flecainide has the properties of a class I antiarrhythmic agent similar to quinidine or procainamide. Atrial, nodal and ventricular conduction is slowed and refractoriness is prolonged. The average plasma elimination half-life of flecainide in young healthy men is about 14 hours, while in patients, an average half-life of 20 hours has been observed. Twice-daily dosing is effective and once-daily dosing may be possible in some patients. Oral doses of 100–300 mg twice a day have been used; 200 mg twice a day has been an effective dose in most patients. Recent placebo-controlled clinical trials of oral flecainide demonstrated a greater than 90% mean suppression of PVCs. A similar high response rate was also observed in patients with chronic ventricular arrhythmias resistant to other conventional agents.

This study reports the results of a large clinical trial. The purpose of the trial was to compare the efficacy and safety of oral flecainide with quinidine. The trial was multicenter and completely randomized, parallel and double blind.

Methods

Patient Selection

Sixteen centers were each to enroll approximately 20 consenting patients who were at least 21 years of age.

*U.S. adopted name.

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age and had a documented chronic ventricular arrhythmia that, in the opinion of the investigator, required treatment. Patients who were receiving prior antiarrhythmic therapy were allowed to participate if the therapy could be safely discontinued for at least 1 week. Patients with mild-to-moderate heart failure could be enrolled if they were in a compensated state and receiving digitalis or diuretics.

Patients were excluded if they had (1) an average of fewer than 30 PVCs per hour for 48 hours on Holter monitoring at baseline, (2) a known idiosyncratic reaction or serious toxicity to quinidine, (3) digitalis intoxication, (4) atrial flutter or fibrillation, (5) grade 2 or greater atrioventricular (AV) block, (6) bundle branch block with first-degree AV block, (7) a myocardial infarction within 6 weeks of study entrance, (8) unstable angina, (9) severe congestive heart failure (New York Heart Association class III or IV), (10) a cardiac pacemaker, or (11) physical or clinical laboratory findings indicating active noncardiac disease.

Protocol

This double-blind, parallel study included 2 weeks of active drug therapy, bounded before and after by placebo periods, each 7 days long. Patients were assigned consecutive numbers as they entered the study. A computer-generated randomization schedule, based on blocks of four, determined which patient numbers were assigned to which treatment groups. Two consecutive 24-hour Holter recordings were obtained during each week of the study. Other data collected on a weekly basis were vital signs, 12-lead ECGs, clinical laboratory tests and side effects.

The baseline for the study was the placebo stabilization period (week 1) during which patients took placebo every 6 hours. In weeks 2 and 3 patients were given active treatment under double-blind conditions. The dosing schedule for quinidine was every 6 hours, while that for flecainide was every 12 hours. To maintain the double-blind design, patients assigned to quinidine took active drug every 6 hours (6 a.m., noon, 6 p.m. and midnight). Patients in the flecainide group took active drug every 12 hours (6 a.m. and 6 p.m.), alternating with placebo every 12 hours (noon and midnight). All study medications were identical in appearance and were packaged on blister cards, one card per week, with each dose sequentially labeled by day and time. This assured good patient compliance, minimized dosing errors and preserved blinding.

During week 2, patients received the lower dose of assigned drug, either flecainide 200 mg every 12 hours or quinidine 300 mg every 6 hours. A unique feature of this study was the ability to determine each patient's response to week 2 treatment before dispensing week 3 medication. Placebo baseline PVC frequency data from two 24-hour Holter recordings were compared with data from one of the 24-hour recordings in week 2, which had been designated for rapid analysis as described below. Patients were "responders" if at least 80% of their baseline PVCs were suppressed. This level of suppression was chosen to rule out changes in PVC frequency due solely to spontaneous variability rather than antiarrhythmic drug effect. Patients who responded to week 2 treatment (lower dose) continued at the same dose in week 3. Nonresponders (<80% suppression) received the higher dose of active drug in week 3: either flecainide, 300 mg every 12 hours, or quinidine, 400 mg every 6 hours. The drug supplies for each patient included two blister cards for week 3 — one for the lower dose and one for the higher dose — which made it possible to treat patients appropriately without jeopardizing the blinded nature of the study. Week 4 was a washout period; all patients again took placebo every 6 hours. Quinidine and flecainide plasma levels were not obtained in this study.

Any patient who participated in the study was subsequently allowed to receive long-term flecainide or quinidine therapy in an open fashion. The long-term data are not reported here.

Data Analysis

Comparisons involving quantitative measurements of efficacy and safety were based on change from baseline at the end of week 2 and the end of week 3. The main basis for efficacy comparisons between flecainide and quinidine was the percent suppression of baseline PVCs. The percent suppressions of paired PVCs (couplets) and PVCs occurring in runs of three or more (ventricular tachycardia) were also compared. Median percent suppressions were used to summarize the results for the entire population. The median rather than the mean was chosen because extreme values have less effect on the former. Two-way analyses of variance on the ranks of percent suppression were used to determine drug differences and to test for center effect. Ranking also reduced the effect of extreme values.

A central research facility (Cardio Data Systems) analyzed all 24-hour Holter recordings for each of the 16 study centers. Analysts were blind to active treatments patients were receiving. As patients completed monitoring periods, the tapes were sent to Cardio Data for timely analysis and verbal report by telephone of the results to the center. Tapes that required rapid analysis in order to make dosage adjustments were sent via an overnight delivery service and analyzed on a priority basis with results reported by phone. In addition, Cardio Data provided complete computer-generated reports for each Holter tape analyzed. Quality control was ensured by randomly inserting hand-counted, 24-hour Holter tapes into the system to test accuracy; the same tapes were inserted at different times to test repeatability. The frequency of PVCs, couplets, and beats of ventricular tachycardia were precisely quantitated. The initial validation of the computer method for processing Holter tapes showed a sensitivity of 92% and a specificity of 99% for PVCs. Reproducibility and precision were 93%.19

Changes in ECG intervals and vital signs were analyzed by two-sample t tests to determine drug differences. QRS interval widening and PVC suppression for the flecainide group were compared using the Spearman rank correlation coefficient.

Chi-square tests were used to compare proportions.
Results

Patient Characteristics

The 16 centers screened a total of 342 consenting patients, of whom 280 qualified for the study. For the 62 patients who did not qualify, the main reasons were failure to achieve an average of 30 PVCs per hour at baseline (43 patients) and the presence of a positive antinuclear antibody titer at baseline (seven patients); miscellaneous reasons (12 patients) included placebo intolerance, intercurrent illness and logistical and technical problems. Table 1 shows the baseline characteristics of the 280 patients who qualified. There were no significant differences between the drug groups for any of the categories.

Of the 280 patients, 233 completed the study. Of the 47 noncompleting patients, 40 discontinued because of side effects (19 in the flecainide group and 21 in the quinidine group), one for increased PVC frequency (flecainide), two for noncompliance (one in each group), and four died (three in the quinidine group, one in the flecainide group). Patient data were analyzed whenever available up to the point of discontinuation. Therefore, the Holter monitoring data were analyzed on only 258 patients during week 2 and 228 patients during week 3. Two patients were included in the analyses who had Holter tapes obtained during week 3 but who did not complete the study. One was lost to follow-up and one discontinued due to side effects after the Holter monitoring. Seven completers were not included in the week 3 analyses: three patients were excluded because of technical failures during monitoring; one had no baseline Holter tape; one had no valid week 3 Holter tape; and two were involved in dosing errors.

Dosage Adjustments

Significantly more patients responded (≥ 80% suppression of PVCs) on the lower dose of flecainide than of quinidine. Forty-four percent (54 of 122) of the quinidine patients who entered week 3 required the higher dose, compared with 18% (23 of 127) of the flecainide patients (p < 0.0001).

Suppression of Ventricular Arrhythmias

Figure 1 shows the mean number of PVCs per hour for flecainide and quinidine groups over the course of the study. Median percent suppression of PVCs by flecainide was 99.4% at week 2 and 99.5% at week 3, vs 80.3% and 84.7% for quinidine at weeks 2 and 3.

Two-way analyses of variance on the ranks of percent suppression found that flecainide was significantly more effective than quinidine for both weeks 2 and 3 in suppressing PVCs (p < 0.0001), couplets (p < 0.001), and beats of ventricular tachycardia (p < 0.01). None of these analyses found significant differences between centers. In particular, the median percent suppression was greater for flecainide than for quinidine in all 16 centers.

Figure 2 shows the frequency distributions for percent suppression of PVCs at week 3. Seventy-five percent (88 of 118) of the flecainide patients had at least 95% suppression of PVCs, compared with 34% (37 of 110) of quinidine patients (p < 0.0001). Eighty-five percent (100 of 118) of flecainide patients had at least 80% suppression of PVCs, compared with 57% (63 of 110) of quinidine patients (p < 0.0001). (Although complete [100%] suppression of PVCs was unusual, it occurred significantly more often [p < 0.001] with flecainide than with quinidine, 16% vs 3%.)

Figure 3 shows the frequency distributions for percent suppression of couplets. Seventy percent (73 of 105) of flecainide patients had complete (100%) suppression of couplets, compared with 41% (41 of 99) of quinidine patients (p < 0.0001). Eighty-five percent (89 of 105) of the flecainide patients had at least 95% suppression of couplets, compared with 60% (59 of 99) of quinidine patients (p < 0.0001).

Figure 4 shows the frequency distributions for per-

Table 1. Baseline Characteristics of Patients in the Flecainide and Quinidine Groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Flecainide</th>
<th>Quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>141</td>
<td>139</td>
</tr>
<tr>
<td>Male</td>
<td>102</td>
<td>96</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 13*</td>
<td>58 ± 14</td>
</tr>
<tr>
<td>Diagnostic category†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Hypertensive cardiovascular disease</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Idiopathic ventricular ectopy</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Previous antiarrhythmic drugs</td>
<td>1.4 ± 1.3</td>
<td>1.6 ± 1.4</td>
</tr>
<tr>
<td>PVCs per hour</td>
<td>419 ± 448</td>
<td>429 ± 423</td>
</tr>
<tr>
<td>Couplets per hour</td>
<td>27 ± 65</td>
<td>20 ± 46</td>
</tr>
<tr>
<td>Beats of ventricular tachycardia per hour</td>
<td>7 ± 26</td>
<td>6 ± 19</td>
</tr>
</tbody>
</table>

*Mean ± sd.
†A patient may have more than one cardiac diagnosis.
Abbreviation: PVC = premature ventricular complexes.
percent suppression of beats of ventricular tachycardia. Seventy-nine percent (57 of 72) of flecainide patients had complete (100%) suppression, compared with 55% (37 of 67) of quinidine patients (p < 0.01).

Eighty-six percent (62 of 72) of the flecainide patients had at least 95% suppression, compared with 66% (44 of 67) of quinidine patients (p < 0.01).

In addition to determining percent suppressions for PVCs, couplets and beats of ventricular tachycardia, a further analysis for week 3 considered the number of patients in each drug group who had at least 80% suppression of PVCs plus complete (100%) suppression of both couplets and beats of ventricular tachycardia. In the flecainide group, 68% (80 of 118) of the patients met these criteria, compared with 33% (36 of 110) of the quinidine patients (p < 0.0001).

**Side Effects**

Nineteen of 141 flecainide patients (13%) and 21 of 139 quinidine patients (15%) discontinued the study before completion because of side effects (p > 0.50). Because prior quinidine intolerance was an exclusion criteria, the dropout rate for quinidine patients who had taken quinidine before was compared to the rate for those who had not; dropout rates were 10% (seven of 71) and 21% (14 of 68) (p = 0.078), respectively. Three of 23 flecainide patients (13%) receiving 300 mg every 12 hours were discontinued because of side effects, vs four of 54 quinidine patients (7%) receiving 400 mg every 6 hours.

The most frequently reported flecainide side effects were dizziness (30% of patients), blurred vision (28%), nausea (9%) and headache (9%). The most frequently reported quinidine side effects were diarrhea (40%), nausea (21%), headache (14%) and dizziness (11%). These side effects were also the main reasons for which patients discontinued from the study.

Two patients experienced increases in congestive heart failure symptoms while taking flecainide and were withdrawn from the study. Both had a history of myocardial infarction, congestive failure, and hypertension and were on digitalis. Their symptoms abated when flecainide was discontinued. One quinidine patient developed symptoms of congestive heart failure and was withdrawn from the study. This patient had no history of congestive failure, but had marked cardiomegaly and mitral insufficiency. Symptoms lessened after discontinuation of quinidine.

Overall, 84 flecainide patients (60%) and 89 quinidine patients (65%) reported at least one side effect (p > 0.05).

**ECG Intervals**

Both flecainide and quinidine affected ECG intervals during the course of therapy. Mean increases from baseline to the end of weeks 2 and 3 are shown in table 2.

Flecainide increased PR and QRS intervals signifi-
creases
However, most minus more significantly crease flecainide to one the compared and second atrioventricular gators. No ening val widened widening. taking flecainide; 141) of QRS cating rank 0.80) Prolongation the heart rate of laboratory interval Drug Flecainide 0.169 ± 0.032 0.042 ± 0.031* 0.039 ± 0.027* Quinidine 0.166 ± 0.027 (p > 0.40) 0.005 ± 0.021 0.004 ± 0.022 (p < 0.0001) (p < 0.0001) QRS Flecainide 0.084 ± 0.016 0.020 ± 0.019* 0.017 ± 0.020* Quinidine 0.088 ± 0.019 (p < 0.05) 0.004 ± 0.011 0.004 ± 0.011 (p < 0.0001) (p < 0.0001) QT Flecainide 0.382 ± 0.036 0.024 ± 0.035 0.028 ± 0.037 (p > 0.20) Quinidine 0.387 ± 0.037 0.027 ± 0.040 0.027 ± 0.042 (p > 0.50) (p > 0.50) JT Flecainide 0.298 ± 0.036 0.004 ± 0.034 0.011 ± 0.037 (p > 0.50) Quinidine 0.299 ± 0.036 0.023 ± 0.040 0.023 ± 0.042 (p < 0.0001) (p < 0.05) The p values compare flecainide and quinidine. *For PR and QRS, the means and standard deviations of increases are essentially constant for flecainide over the range of intervals in this study population.

The increase in QT intervals were similar for the two drugs. However, most of the increase in QT (about 60%) among flecainide patients was explained by the increase in QRS, while about 85% of the increase in QT among quinidine patients was explained by JT (QT minus QRS). Quinidine increased JT intervals significantly more than flecainide (p < 0.05).

Prolongation of the PR interval contributed to the discontinuation of flecainide in four patients, three from one center. The increases in PR interval (from 0.24 to 0.32 second, 0.18 to 0.23 second, 0.16 to 0.28 second and 0.21 to 0.26 second) were not unusual compared with other patients who successfully completed the trial, but were of concern to the two investigators. No patient in the study developed second- or third-degree atrioventricular block.

Within the flecainide group, 51% of the patients (72 of 141) had at least 25% widening of the QRS interval while taking flecainide; 21% (30 of 141) had 50% or more widening. In the quinidine group, the QRS interval widened by 25% or more in 13% of the patients (18 of 139); 50% or more widening was seen in 3% (four of 139) of the patients.

Duff et al.15 speculated that the extent of QRS widening correlated with the antiarrhythmic efficacy of flecainide and could be used as a marker of efficacy. When QRS widening was compared with percent PVC suppression during weeks 2 and 3 of this study, the Spearman rank correlation coefficients were 0.023 (p > 0.80) and 0.075 (p > 0.43), respectively, indicating that the degree of QRS widening did not allow accurate prediction of the degree of PVC suppression in a patient.

Vital Signs and Clinical Laboratories

No clinically significant changes in blood pressure, heart rate or respiratory rate were noted. A battery of laboratory tests was performed on each patient at base-

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**TABLE 2. Mean Changes in ECG Intervals (± s0) During the Study**

<table>
<thead>
<tr>
<th>ECG interval</th>
<th>Drug group</th>
<th>Baseline (seconds)</th>
<th>Increase from baseline (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 2</td>
<td>Week 3</td>
</tr>
<tr>
<td>PR</td>
<td>Flecainide</td>
<td>0.169 ± 0.032</td>
<td>0.042 ± 0.031*</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>0.166 ± 0.027</td>
<td>0.005 ± 0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &gt; 0.40)</td>
<td>(p &gt; 0.40)</td>
</tr>
<tr>
<td>QRS</td>
<td>Flecainide</td>
<td>0.084 ± 0.016</td>
<td>0.020 ± 0.019*</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>0.088 ± 0.019</td>
<td>0.004 ± 0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>QT</td>
<td>Flecainide</td>
<td>0.382 ± 0.036</td>
<td>0.024 ± 0.035</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>0.387 ± 0.037</td>
<td>0.027 ± 0.040</td>
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<tr>
<td></td>
<td></td>
<td>(p &gt; 0.20)</td>
<td>(p &gt; 0.20)</td>
</tr>
<tr>
<td>JT</td>
<td>Flecainide</td>
<td>0.298 ± 0.036</td>
<td>0.004 ± 0.034</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>0.299 ± 0.036</td>
<td>0.023 ± 0.040</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &gt; 0.50)</td>
<td>(p &gt; 0.50)</td>
</tr>
</tbody>
</table>

The p values compare flecainide and quinidine.

*For PR and QRS, the means and standard deviations of increases are essentially constant for flecainide over the range of intervals in this study population.

Deaths

Three quinidine patients and one flecainide patient died during the course of the study. All four had a history of severe coronary artery disease and myocardial infarction.

All three quinidine patients died within 3 days of starting active medication. One patient died in his sleep. At autopsy, a fresh thrombus was found in the right coronary artery. A second patient collapsed suddenly and was converted from ventricular fibrillation only after a prolonged resuscitation effort. During 2 days of hospitalization, an acute inferior myocardial infarction was documented. He never regained consciousness and died in the hospital. The third patient was found dead in a hotel room. Autopsy showed occlusion of the left anterior descending coronary artery.

One patient in the flecainide group died suddenly while taking placebo during week 4, 36 hours after the last dose of flecainide. A Holter monitor tape was recording until 1 hour before death. It showed high-frequency PVCs, couplets, ventricular tachycardia, aberrant conduction and ST-T changes consistent with acute ischemia.

Increases in PVC Frequency

Several patients experienced an increase in PVC frequency during week 2 — five of 132 patients (3.8%) in the flecainide group (range of increase, 34–248%) and 10 of 126 (7.9%) in the quinidine group (range 14–760%). By the end of week 3, one of 118 flecainide patients (0.8%) showed an increase (by 12%; this patient had a 124% increase in week 2). Twelve of 110 quinidine patients (10.9%) showed an increase (range 13–2160%). The flecainide patient
whose PVCs increased by 248% during week 2 was discontinued before week 3 Holter monitoring.

According to Velebit et al., a fourfold increase in the hourly frequency of PVCs over a control period is evidence of drug-induced aggravation of arrhythmia. By this criterion, two quinidine patients and no flecainide patients experienced a proarrhythmic effect in this study.

**Discussion**

In this multicenter, double-blind study, oral flecainide (200–300 mg every 12 hours) was compared with oral quinidine (300–400 mg every 6 hours) in the treatment of chronic ventricular arrhythmias. Quinidine was chosen as the comparative agent because it is the most commonly used antiarrhythmic agent available in the United States and the reference class I antiarrhythmic drug. Previous studies of quinidine in patients with chronic ventricular ectopy reported that the average quinidine efficacy is 25–62%. Comparative studies demonstrate that quinidine is at least as effective in the suppression of chronic ventricular arrhythmias when tested against tocainide, procarcinamide, and disopyramide. In this study, the median suppressions of PVCs were 99.5% for flecainide and 84.7% for quinidine (p < 0.0001). In 75% of the flecainide patients, at least 95% suppression of PVCs was achieved, compared with 34% of quinidine patients (p < 0.0001). Flecainide was also more effective than quinidine in the suppression of couplets (p < 0.001) and beats of ventricular tachycardia (p < 0.01), with total elimination by flecainide observed in 70% and 79% of patients, respectively. In addition, 68% of the flecainide patients experienced at least 80% suppression of PVCs plus complete elimination of couplets and ventricular tachycardia, compared with 33% of the quinidine patients (p < 0.0001).

These results and the results of other studies defining flecainide’s antiarrhythmic potency exceed the average suppression rate of other conventional or new antiarrhythmic agents. The average suppression of PVCs ranged from 50% to 90% and complete suppression was rare when using quinidine, procarcinamide, disopyramide, tocainide, and ethmozin. Degrees of suppression of ventricular ectopy comparable to those with flecainide, however, were demonstrated with encainide, which has properties similar to those of flecainide but requires four-times-daily dosing. Thirteen percent of the flecainide patients and 15% of the quinidine patients discontinued use of the drug because of side effects (p > 0.50). The most frequently reported side effects from flecainide were dizziness, blurred vision, headache and nausea at a rate similar to other studies. The most common side effects reported on quinidine were diarrhea, nausea, headache and dizziness at a similar percentage reported during other studies.

Flecainide increased PR and QRS intervals, consistent with the primary drug effects on His-Purkinje and ventricular conduction. Prolongation of the PR interval contributed to the discontinuation of flecainide in four patients, three from one center. Even though the increases in PR interval were not unusual compared to other patients who successfully completed the trial, two investigators were worried by these findings and chose to discontinue flecainide therapy in the patients. None of the patients in the study developed second- or third-degree AV block. Although widening of the QRS of at least 25% or even 50% or more was commonly seen in patients receiving flecainide, no patients experienced associated clinical problems such as complete AV block or syncope.

Duff et al. reported in a study of 11 patients that the extent of QRS widening correlates with antiarrhythmic efficacy of flecainide, thus possibly serving as a marker of efficacy. In the present study, the amount of prolongation of the QRS interval did not allow one to predict accurately the degree of PVC suppression.

No significant difference between flecainide and quinidine was found for QT interval change; both agents mildly prolonged the QT interval. Quinidine increased JT intervals significantly more than flecainide (p < 0.05). Thus, the prolongation of QT interval seen with flecainide therapy is explained largely by changes in QRS duration and does not appear to carry the same implications of potential induction of torsades de pointes ventricular tachycardia as with other class I antiarrhythmic agents such as quinidine. Antiarrhythmic drugs, even in the therapeutic blood range, may aggravate or induce ventricular arrhythmias in 6–16% of patients. At the end of week 3, one flecainide patient (0.8%) had experienced an increase in PVC frequency, compared with 12 quinidine patients (10.9%).

No significant changes in blood pressure, heart rate and respiratory rate were noted in patients receiving flecainide. Others have reported a favorable hemodynamic profile of flecainide, with unchanged exercise tolerance and no evidence of negative inotropic effects clinically or on echocardiography. In this study, two patients experienced a worsening of symptoms of preexisting mild congestive heart failure while receiving flecainide and one patient developed new congestive heart failure while receiving quinidine. Studies are being performed to determine the effects of flecainide on myocardial function during long-term therapy and in patients with more severe myocardial dysfunction. Until its effects are more fully defined, flecainide should be used cautiously in patients with underlying or overt left ventricular dysfunction. No changes of clinical significance were found in clinical laboratory testing during flecainide treatment.

**Acknowledgment**

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