Suppression of Ventricular Ectopic Depolarizations by Flecainide Acetate, A New Antiarrhythmic Agent

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SUMMARY Flecainide acetate, a new antiarrhythmic agent, was given orally to 11 hospitalized patients with chronic high-frequency ventricular ectopic depolarizations. Drug effectiveness was evaluated with a dose-ranging single-blind protocol, which included placebo control and washout periods. Twice-daily dosing (average daily dose 436 mg) completely suppressed all ventricular ectopic activity in five of 11 patients; average suppression in the 11 patients was 96.3%. Complex ventricular arrhythmias, which were present in all 11 patients during the placebo control period, were completely suppressed in eight patients and markedly suppressed in the other three patients during flecainide therapy. Ejection fraction and velocity of circumferential fiber shortening measured by M-mode echocardiography did not change significantly during flecainide dosing. Ventricular arrhythmias returned in all patients during the placebo washout period. During subsequent outpatient therapy with flecainide, suppression was present after 1 and 2 weeks of treatment (94.4% and 93.3%, respectively). Drug elimination was slow (average plasma half-life 20 hours). Ninety-five percent suppression of ventricular ectopic depolarizations during dosing and 5% reappearance of arrhythmias during washout occurred with flecainide concentrations of 200–800 ng/ml. Side effects occurred in five of 11 patients, but did not require discontinuation of the drug. These results indicate that flecainide is a very effective antiarrhythmic agent that merits further clinical investigation.

EFFECTIVE antiarrhythmic agents that can gain patient acceptance and compliance are continually needed. Difficulties with currently available agents include short biologic activity (requiring frequent dosing and often resulting in poor patient compliance), troublesome or unacceptable side effects, and ineffectiveness. Flecainide acetate (2, 5-bis-(2, 2, 2-trifluoroethoxy)-N-(2-piperidylmethyl) benzamide acetate) (R-818) suppresses experimentally induced ventricular arrhythmias in dogs and mice.1–4 Preliminary studies indicate that flecainide has the properties of a class I antiarrhythmic agent, i.e., atrial, nodal and ventricular conduction is slowed and refractoriness increased.4 Studies in healthy young men indicate that the average plasma half-life of flecainide is about 14 hours with either oral or i.v. dosage, and that absorption after oral administration is essentially complete.8 We previously reported that a single i.v. dose of flecainide markedly suppressed ventricular ectopic depolarizations (VEDs) for 6 hours or more in patients with heart disease.6

In this study, we assessed the efficacy and safety of multiple oral administrations of flecainide in patients with frequent VEDs, using a protocol in which we increased the daily dose of flecainide until maximal control of ventricular arrhythmias was achieved. During a subsequent placebo washout period, we obtained pharmacokinetic data regarding the plasma half-life of flecainide.

Methods

Experimental Design

Eleven patients with chronic high-frequency, non-hemodynamically significant ventricular ectopic activity were studied (table 1). A 24-hour Holter ambulatory ECG was performed to verify the frequency of VEDs. The history of each patient was evaluated to determine that prolonged placebo therapy was safe. Although all patients had frequent VEDs, none had a history of syncope. Patients were hospitalized in a "step-down" cardiac care unit, where continuous telemetry monitoring of rhythm was possible. All antiarrhythmic medications were discontinued for at least six half-lives before hospitalization. During the first two full days of hospitalization, patients were given placebo capsules twice daily, during which time control ventricular ectopic activity was recorded (fig. 1). The study was single-blind (i.e., study personnel, but not patients, were aware of the content of medications given). The days of placebo were followed by three increasing oral doses of flecainide (100, 200 and 300 mg twice daily for 3 days at each dose level) until either 80% suppression of VEDs occurred or the 300- mg twice-daily dose was completed. Three patients (nos. 3, 7 and 11) who had greater than 80%, but less than 100%, suppression on the 100-mg twice-daily dose were given the 200-mg twice-daily dose in an attempt to achieve greater suppression. We did not go to the next higher dose in patients 1, 2 and 10 because the trendsciber data available to us suggested that suppression was nearly 100% at the final dose used. All medications were given at 0900 and 2100 hours. Throughout the study, patients were given either flecainide acetate or identical placebo capsules. After

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maximal dosage was reached, twice-daily placebo was resumed for 3 more days to observe the return of ventricular activity and to evaluate pharmacokinetics.

After completion of the inpatient protocol, each patient was given flecainide to take twice daily for 2 weeks as an outpatient. The dosage selected was that which was maximally effective during hospitalization. One and 2 weeks after discharge, patients returned for a repeat 24-hour Holter recording and plasma flecainide level measurements.

Rhythm Monitoring and Analysis

During the 8–14-day inpatient phase of the study (fig. 1), the ECG was continuously monitored by the nursing staff. We also recorded the ECG intermittently on a Lown trendscriber, a drum-like device that can record up to 30 minutes of ECG continuously or be programmed for intermittent automatic recording. We programmed the trendscriber to record 1 minute of ECG every 15 minutes; thus, rhythm samples from an entire day were recorded on three sheets of paper, which could be immediately analyzed for the presence, amount and severity of arrhythmias. Twenty-four-hour Holter ambulatory ECG recordings were performed on days 1, 2, 5, 8, 11, 12 and 14. Tapes were analyzed blindly and independently by the Cardio-Dynamics Laboratories, Inc., Los Angeles, California, using the Dyna-Gram III computer analysis system, which has a sensitivity of 99.7 ± 0.7% and a specificity of 99.7 ± 0.9%. The results were reported each hour, and included the total number of VEDs as well as the presence and amount of bigeminy, couplets and ventricular tachycardia (three or more VEDs in succession). The trendscriber records were analyzed by hand, and the total number of VEDs/min was recorded. The sum of VEDs from the four 1-minute recordings was multiplied by 15, giving an estimate of the total VEDs/hour. In this manner, we obtained estimates of the number VEDs/hour for the entire day.

For statistical analysis, we used the log (VED frequency + 1) rather than VED frequency because the latter had skewed distributions. For all VED data, this transformation reduced the variance and normalized the distribution, as evaluated by the Kolmogorov-Smirnov test. Others have also noted skewed distributions of VED activity. The number of VEDs on the Holter tape recordings (counted by computer) and on the trendscriber recordings (determined as described above) were compared for 60 days of recording between 0900 and 2100 hours. A strong correlation was found: \( r = 0.988; y = 0.975x + 0.114, \)

![Figure 1. Design of the protocol. Placebo capsules were given during the two control and three washout days.](image-url)
where \( y = \log (\text{VEDs} + 1) \) during 12 hours by Holter recording and \( x = \log (\text{VEDs} + 1) \) per 12 hours extrapolated from the trendscriber record. This regression line is not significantly different from a line of identity. This relationship was used to convert the trendscriber data to Holter data for days on which Holter recordings were not performed or for periods when tape recording was technically inadequate. The trendscriber data were also used to decide whether a patient should receive the next higher dose, as the Holter analysis was not returned for at least several days. The data reported in table 2 were obtained from the Holter recordings.

**Evaluation of Ventricular Function**

Ventricular function was evaluated by recording M-mode echocardiograms on two occasions: during one of the two placebo control days, and during the 2-week outpatient visit when the patient was receiving flecainide. The echocardiogram was recorded using standard techniques. The same external transducer location was used both times, with the echo beam directed to the midventricle just below the mitral valve. From the echocardiogram, the LV internal diameters (in cm) at end-systole (D\(_s\)) and end-diastole (D\(_d\)) were measured, and systolic and diastolic volumes and ejection fraction were calculated, using the method of Teichholz,\(^4\) which Kronik et al.\(^14\) showed to be the most accurate of several techniques available for volume calculations from M-mode echocardiograms. The mean rate of circumferential fiber shortening (Vcf, in \(\text{circ/sec}\)) was calculated using the formula

\[
\text{Vcf} = \frac{(D_d - D_s)/(\text{LVET} \times D_d)}{\text{circ/sec}},
\]

where LVET is the left ventricular ejection time (in seconds) measured from the recorded carotid pulse. Use of M-mode echocardiography to measure ejection fraction and Vcf has been validated previously with cineangiographic comparisons.\(^8\) Neither of the two patients with coronary artery disease had had a previous myocardial infarction by either clinical or ECG criteria. A two-dimensional echocardiogram in patient 8 revealed no regional wall motion abnormalities. Blood pressure and heart rate were recorded in each patient four times daily.

**Pharmacokinetic Analysis**

Blood was obtained on days 6 and 9, just before the next 0900 hours flecainide dose to evaluate trough plasma levels of flecainide at the end of each dosing period. These values were also used to construct plasma level-response curves. In addition, approximately 12, 18, 24, 36, 42 and 60 hours after the last maximally effective dose of flecainide, plasma specimens were obtained for analysis. Regression of the log of plasma flecainide concentration against time was used to determine the plasma half-life of flecainide.\(^16\) Five percent return of VED activity was determined by noting the hour during the placebo washout period when the total number of VEDs equaled or exceeded the average hourly VED activity during the two placebo control days.

**Determination of Flecainide Acetate in Plasma**

The concentration of unchanged flecainide acetate in plasma was measured with a sensitive and specific gas-liquid chromatographic method. Before chromatographic analysis, the drug and the added internal standard were separated from plasma by a sequence of solvent extractions and were derivatized; the derivatives were chromatographed and detected by electron capture using a Hewlett Packard model 5840 gas chromatograph. Relative area responses (flecainide/internal standard) from analytic reference samples were used for quantitation. The practical lower limit for quantitation of flecainide with 1 ml of plasma is about 10 ng/ml.

**Evaluation of Side Effects**

Each day at 1100 hours during hospitalization and at both outpatient visits, patients were asked about side effects using a standardized questionnaire that listed 29 symptoms. Patients were asked to grade the

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**Table 2. Results of Flecainide Treatment: Ventricular Ectopic Depolarizations per 24 Hours**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Control day 1</th>
<th>Control day 2</th>
<th>Flecainide treatment</th>
<th>Washout day 3</th>
<th>Outpatient week 1</th>
<th>Outpatient week 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 mg BID</td>
<td>200 mg BID</td>
<td>300 mg BID</td>
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<td>76,770</td>
<td>68,856</td>
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<td>†</td>
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*Recording technically unsatisfactory.
†No treatment given.
‡No data obtained.
severity of side effects using the following scale: 0 = absent, 1 = slight, 2 = uncomfortable, 3 = very uncomfortable and 4 = unbearable.

ECG Interval Analysis

One-minute rhythm strips were obtained each day at 0900, 1500 and 2100 hours from which the PR, QRS and QT intervals were obtained. The QT interval was corrected for heart rate (QTc) using the formula

\[ QTc = QT / (RR)^{0.5} \]

where RR is the interbeat time in seconds. Data from the placebo control days were averaged, and the resultant values compared with averaged values from the third day of maximal flecainide dosage.

Statistical Analysis

The t test for paired data was used for analysis of data obtained at different times from the same patient. Regression lines and correlation coefficients were obtained by the least-squares method. Normality of distribution was tested by the Kolmogorov-Smirnov test. A probability of less than 0.05 was required to reject the null hypothesis. Data are given as the mean ± SD.

Results

Ten of the 11 patients completed the protocol. Patient 9 was considered to have had 79% suppression at the maximal dose, as judged by trendscirber data, and was not continued into the placebo washout period because 80% suppression was required. Subsequent analysis of the Holter tape revealed that suppression was actually 82.3% (table 2). Thus, for the latter part of the study, data are reported for 10 patients only. During the 2-day placebo control period, the 11 patients averaged 21,127 VEDs/24 hours (range 2241-72,813) (table 2). This corresponds to an average of 14.7 VEDs/min (range 1.6-50.6 VEDs/min). Complex arrhythmias — bigeminy, couplets (two VEDs in succession) or ventricular tachycardia (three or more VEDs in succession) — were present in all patients (table 3). VED frequencies for the two placebo control days correlated well: \( r = 0.982; y = 1.07x - 0.30 \), where \( y \) is log (VEDs + 1) for day 1, and \( x \) is log (VEDs + 1) for day 2. There was no significant difference in VED frequency between the two days, as evaluated by the paired t test.

Suppression of Ventricular Ectopic Depolarizations

Flecainide markedly suppressed ventricular ectopic activity in all patients (figs. 2 and 3, table 2). The maximally effective dose of flecainide was 100 mg twice daily in one patient, 200 mg twice daily in seven patients, and 300 mg twice daily in three patients. At the maximally effective dose, average VED suppression was 96.3% (range 82.3-100%). Five of the 11 patients had complete suppression of all ventricular ectopic activity on the maximally effective dose, and two other patients had nearly complete (99.89% and 99.99%, respectively) suppression. On the third washout day, ventricular ectopic activity averaged 12% of the mean value during the two control days (range 6.5-316%) (fig. 2). In addition to an absolute reduction in ventricular activity, there was marked suppression of complex ventricular arrhythmias during flecainide dosing in all 11 patients (table 3). Episodes of ventricular tachycardia, which occurred in six patients during the placebo control period, were completely suppressed during flecainide therapy. In addition, VED couplets, present in every patient during placebo control, were completely suppressed in eight patients and markedly reduced in the remaining three (table 3).

During outpatient treatment with flecainide, all patients showed marked reductions in ventricular ectopic activity from placebo control at both 1 and 2 weeks. Average reduction was 94.4% at 1 week (range 72.5-100%) and 93.3% (range 64-100%) at 2 weeks compared with the 2 days of placebo control (table 2).

### Table 3. Complex Ventricular Ectopic Activity Before, During and After Flecainide Therapy

<table>
<thead>
<tr>
<th>Pt</th>
<th>Placebo*</th>
<th>Maximal dose†</th>
<th>Washout‡</th>
<th>Placebo*</th>
<th>Maximal dose†</th>
<th>Washout‡</th>
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<td>17</td>
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<tr>
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<td>87</td>
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<tr>
<td>3</td>
<td>816</td>
<td>0</td>
<td>336</td>
<td>6</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<tr>
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<tr>
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<td>9</td>
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</table>

*Average activity per 24 hours on two placebo control days.
†Activity per 24 hours on third day of maximally effective dose.
‡Activity per 24 hours on third day of placebo washout.
ŠNo data obtained.
Abbreviation: VED = ventricular ectopic depolarization.
Effects on Left Ventricular Function

No statistically significant changes in blood pressure, heart rate, ejection fraction or Vcf were noted during flecainide dosing. The ejection fraction averaged 55.4 ± 12.0% during placebo therapy and 59.5 ± 9.3% during peak flecainide therapy (NS). Corresponding figures for Vcf were 0.95 ± 0.27 and 1.11 ± 0.21 (NS).

ECG Interval Changes

During the placebo control period, the PR, QRS and QTc intervals averaged 0.16 ± 0.02, 0.08 ± 0.01 and 0.43 ± 0.03 second, respectively. At maximal flecainide dosing, the PR interval increased to 0.20 ± 0.03 second (25%), the QRS interval to 0.10 ± 0.01 second (23%), and the QTc interval to 0.45 ± 0.02 second (5%) (all p < 0.01 by paired t test).

Side Effects

Nine of 11 patients reported side effects. However, in four patients, the reported symptoms had also been reported before this study and were considered to be due to a prior condition (e.g., dyspnea in a patient with chronic lung disease). Most side effects were reported as grade 1 or 2 and no patient reported grade 3 or 4 side effects. Reported side effects considered to be caused by flecainide included an occasional sense of unsteadiness (three patients), transient blurring of vision (two patients), and a sense of warmth (one patient). No side effect was serious enough to require discontinuation of therapy.

Pharmacokinetic Results

The correlation coefficients for the relationship between log of plasma flecainide concentration and time were very high (average 0.997, range 0.994–0.999) (fig. 4). The plasma half-life average for the group was 19.7 ± 4.6 hours (range 11.8–26.5 hours). The plasma flecainide level at which a 5% return of ventricular arrhythmia occurred was 163–793 ng/ml (average 401 ng/ml) (table 4).

Discussion

Oral flecainide given twice daily completely suppressed ventricular ectopic activity in five of the 11 patients in this study and markedly suppressed activity in the other six patients. In addition, complex ventricular arrhythmias were completely or markedly suppressed in all patients. It is unlikely that the striking reductions in VEDs were due to chance, as most patients had a significant return of VEDs during the 3-day washout period after flecainide treatment (fig. 2). The 3-day treatment and washout periods were selected on the basis of a plasma flecainide half-life of about 14 hours for healthy male subjects.6 Had we observed our patients for more than 3 days of placebo washout, we probably would have seen an even greater return of VED activity. This suggestion is supported.
by the observation that patients with shorter plasma half-lives (e.g., patients 5 and 6) had the greatest VED return, and patients with longer half-lives (e.g., patients 2, 3, and 10) had the smallest VED return (fig. 2, table 4).

The average elimination half-life of flecainide in our patients after multiple oral doses was 20 hours rather than the 12–14 hours found earlier in healthy young male volunteers. Although we cannot explain this difference, our patients were older than those in the earlier study, which may contribute to differences in drug metabolism. Differences in elimination half-lives between normal younger subjects and patients with cardiac disease have been described for other new antiarrhythmic agents. The longer half-life of flecainide suggests that once-daily dosage may be possible in some patients.

The pharmacokinetic data obtained in this study suggest that the range of minimally effective plasma concentrations of flecainide is 200–800 ng/ml. The plasma concentration-response curves in figure 3 indicate that 95% suppression of VEDs—a suppression level not often achieved with other antiarrhythmics—occurs between approximately 200 and 800 ng/ml. The washout curves shown in figure 4 indicate that 5% return of VEDs occurred between approximately 160 and 800 ng/ml. Thus, the separate estimates of the drug effectiveness–concentration relationship agree remarkably well.

Because the plasma half-life of flecainide in these 10 patients averaged 20 hours, many of the patients may not have reached steady-state conditions when the placebo washout period began. This likelihood is supported by comparing the plasma flecainide levels obtained 12 hours after the last dose in hospital with the levels obtained during the 1- and 2-week outpatient visits, which were also obtained 12 hours after the last dose. The washout trough levels averaged 663 ± 218 ng/ml, compared with 830 ± 311 ng/ml at 1 week (p < 0.05) and 893 ± 335 ng/ml at 2 weeks (p < 0.01). Because effective control of VED activity had been obtained in hospital at the lower plasma levels, the higher plasma levels during outpatient treatment were probably not necessary to maintain suppression. Indeed, we have subsequently reduced the dosage in five of these patients and marked suppression of ventricular arrhythmias has continued.

A positive finding of this study was the relative benignity of side effects. Although a majority of patients reported side effects, they were not serious in any patient, and most occurred during the 2-week outpatient therapy, when plasma flecainide levels were higher than during hospitalization. These higher levels are probably not necessary to maintain complete or effective suppression. Although the paucity of serious side effects is encouraging in this small group, more patients must be studied to document the actual incidence and severity of side effects.

Roden et al. demonstrated that encainide, another new antiarrhythmic, completely suppressed ventricular ectopic activity in 10 of 11 patients. In the present study, flecainide achieved a comparable degree of suppression of ventricular ectopic activity. These results are in contrast to the degrees of suppression with other agents studied in a similar manner, including quinidine, propranolol, tocainide, acebutolol, perhexiline, disopyramide and ethmozin. In these other studies, average suppression ranged from 50–90%, and complete suppression was rare. Moreover, the striking suppression of VEDs by flecainide was achieved with twice-daily dosing, nanogram plasma concentrations and mild side effects.

### Table 4. Flecainide Efficacy and Pharmacokinetic Data

<table>
<thead>
<tr>
<th>Pt</th>
<th>Percent suppression of VEDs*</th>
<th>Suppressing dose (mg b.i.d.)</th>
<th>Plasma t½ (hours)</th>
<th>Time (hours)</th>
<th>Plasma flecainide (ng/ml)</th>
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<td>95.7</td>
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*Data rounded to one decimal place.  
†Data not obtained.  
Abbreviations: VEDs = ventricular ectopic depolarizations; t½ = half-life.
results of the present study indicate that flecainide is an important new antiarrhythmic agent that merits further clinical investigation.

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