Flecainide Acetate Prevents Recurrence of Symptomatic Paroxysmal Supraventricular Tachycardia

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Oral flecainide acetate was administered to 34 patients with documented symptomatic paroxysmal supraventricular tachycardia (PSVT) with a double-blind, placebo-controlled, 8-week crossover trial design. PSVT was defined as a regular tachycardia of at least 120 beats/min without evidence of atrioventricular dissociation. The study required considerable patient cooperation. Patients first entered a 4-week qualifying phase followed by a 3-week, open label, flecainide dose-ranging phase. They were then randomized in a blind fashion to receive either placebo or tolerated flecainide dose for an 8-week treatment period and then crossed over after four symptomatic documented episodes of PSVT or at the end of the treatment period. By all efficacy parameters analyzed, flecainide was superior to placebo. Flecainide was associated with an actuarial 79% freedom from symptomatic PSVT events compared with only 15% on placebo at 60 days (p<0.001). Of the 34 patients, 29 had recurrence of symptomatic PSVT at least once during the placebo phase; only eight patients had a recurrence during the flecainide phase (p<0.001). The median time to the first symptomatic PSVT event was 11 days in the placebo group and greater than 55 days in the flecainide group (p<0.001). Likewise, the interval between attacks was a median of 12 days on placebo compared with more than 55 days on flecainide (p<0.001). Finally, the flecainide slowed symptomatic PSVT heart rates to 143±12 beats/min from 178±12 on placebo (p<0.02) in the seven patients who had events in the placebo and flecainide treatment phases. In summary, flecainide significantly reduces the likelihood of symptomatic PSVT recurrences, and it, therefore, is an effective agent in patients who have symptomatic PSVT. (Circulation 1991;83:119-125)

Paroxysmal supraventricular tachycardia (PSVT) is a common clinical problem. Despite many advances in our knowledge of its mechanisms, proving that antiarrhythmic therapy reduces the incidence of spontaneous PSVT events has been difficult. With rare exceptions,1-3 most antiarrhythmic drug studies for PSVT have been uncontrolled. However, recent information regarding the natural history of PSVT4,5 and new clinical trial designs6 have fostered efforts to improve the clinical investigation of antiarrhythmic therapy in patients with PSVT.

Flecainide acetate, when evaluated by electrophysiological testing in patients with PSVT, has shown significant promise as an antiarrhythmic treatment.7-10 Flecainide is also known to suppress premature atrial and ventricular beats, the likely triggers of paroxysmal supraventricular arrhythmias. Based on this favorable preliminary information, a multicenter trial was organized in January 1985. The study was designed for patients with symptomatic, electrocardiographically documented PSVT to test the hypothesis that oral flecainide acetate was safe and superior to placebo for preventing recurrences of symptomatic PSVT.
**Methods**

This study used a randomized, double-blind, placebo-controlled, crossover design and required substantial patient cooperation. It was mandatory for entry that patients have two documented symptomatic episodes of PSVT while receiving no antiarrhythmic therapy during a 4-week qualifying phase. At least one of the qualifying PSVT episodes had to be verified by patient-actuated transtelephonic monitoring using a central monitoring service (Survival Technology, Bethesda, Md.). PSVT was diagnosed by the following electrocardiographic criteria: 1) mean ventricular rate greater than 120 beats/min, 2) less than a 0.02-second variation in successive RR intervals, 3) normal QRS complex morphology or functional bundle branch block, and 4) no evidence of atrioventricular dissociation.

All oral antiarrhythmic medications were discontinued (including β-blockers, calcium channel antagonists, digitals, and type 1 agents) during the qualifying phase and not administered throughout the study. Patients were excluded from the study if they had syncope, angina, or transient cerebral events during PSVT. Because flecainide suppresses atrioventricular conduction and has negative inotropic properties, patients were also excluded if they demonstrated second or third degree atrioventricular block or had New York Heart Association class III or IV congestive heart failure.

A PSVT recurrence for study purposes was defined as a symptomatic event during which the patient had electrocardiographic documentation of PSVT by either transtelephonic monitoring or electrocardiogram. To be defined as separate events, PSVT events had to be documented on 2 separate days with sinus rhythm documented in between.

The study had three phases, all outpatient (Figure 1). Phase 1, as described above, was the qualifying phase. The second phase involved a 3-week open label, flecainide dose-ranging trial. During week 1, 100 mg orally twice daily was administered; if not tolerated, 50 mg orally twice daily was administered. If tolerated, the dose was advanced during week 2 to 150 mg orally twice daily. During week 3, 200 mg orally twice daily was given. By protocol design, investigators assessed tolerance and safety, not efficacy of flecainide during dose ranging. Tolerance was assessed by weekly review of adverse experiences. Safety was assessed by weekly review of adverse experiences, weekly review of concomitant medications, and electrocardiographic analysis on the maximally tolerated flecainide dosage or 200 mg orally twice daily.

In the third phase, the efficacy phase, the patient was administered the previously identified (phase two) maximally tolerated flecainide dose (or at most flecainide 200 mg twice daily) during one of the two treatment periods (A or B) and placebo during the other. Flecainide was administered in a randomized, double-blind, placebo-controlled crossover trial. During weeks 1 through 8, the patients were administered treatment A, either flecainide or placebo, the identity of which was unknown to the patient and the investigators, until the end of the treatment period or until four separate symptomatic PSVT events were documented. Treatment B was then administered (the drug not given during treatment A in a double-blind fashion) for 8 weeks or until four separate symptomatic PSVT events were documented. As part of the initial study design, if symptomatic atrial fibrillation was documented during the efficacy phase, it was considered a PSVT event because PSVT is known to degenerate into atrial fibrillation. Paroxysmal atrial fibrillation occurred in only two patients in the randomized phase. In both of these patients, symptomatic paroxysmal atrial fibrillation and symptomatic PSVT events were documented. Also, of three others in whom paroxysmal atrial fibrillation events were recorded in the screening phase, only one continued in the randomized phase. Thus, our decision to handle symptomatic atrial fibrillation in this manner did not affect the results of the study. Symptomatic nonelectrocardiographically documented palpitations were not considered events.
To assure safety throughout the trial, prospective 12-lead electrocardiographic recordings and analyses were obtained (prestudy, end of dose ranging, crossover, and at the end of the study). Also, hematologic parameters, biochemical parameters, and urinalyses were examined (prestudy, at crossover, and at the end of the study).

An optional electrophysiological study could be performed before the dose-ranging phase to assess the mechanism of PSVT and the electrophysiological effects of intravenous flecainide. The results of the electrophysiological study involving intravenous flecainide were intended not to influence the patient’s entry into the dose-ranging or efficacy phases of the study.

Statistical Analysis

The effect of flecainide compared with placebo on the occurrence of symptomatic PSVT events was analyzed according to the following parameters: number of patients having no events, time to first event, interval between events, and ventricular rate during PSVT. Data from all centers were combined in the analyses. McNemar’s test for significant change was used to compare the number of patients with no symptomatic PSVT events for placebo and flecainide. When determining the time to first event and the interval between events, the first 3 days of each 8-week treatment period were excluded in deference to flecainide’s steady-state pharmacokinetics; day 4 of each period was defined as the first treatment day. Time to first attack was defined as the number of treatment days until the first attack. If a patient did not have any symptomatic events during the treatment, time to first event was defined as the number of treatment days plus one, and the measurement was censored at that time.

For patients with one to four events, the interval between events was defined as the number of days on treatment divided by the number of events. According to protocol, a treatment period ended after four events or 8 weeks, whichever came first. However, some patients had more than four events before crossing over to the next treatment. When determining the interval between attacks, only the first four events were used. If a patient did not have any events on treatment, the interval was defined to be the number of treatment days plus one and was considered a censored observation.

The data are presented in means, standard errors of the mean, and medians using the Kaplan–Meier product–limit estimates for censored data. Comparisons between placebo and flecainide were performed with the paired Prentice–Wilcoxon test for censored data. To compare ventricular rates during PSVT events for placebo and flecainide, only the patients with symptomatic events during both periods were included. The average ventricular rate during events was calculated separately for each patient for each treatment period. The analysis of variance model with sequence, patient within sequence, pe-

\[ \text{PATIENT FLOW} \]

\begin{align*}
\text{QUALIFIED:} & \quad N=51 \quad \rightarrow \quad N=3 \\
\text{DOSE RANGED:} & \quad N=48 \quad \rightarrow \quad N=11 \\
\text{TREATMENT A:} & \quad N=37 \quad \rightarrow \quad N=12 \\
\text{TREATMENT B:} & \quad N=35 \quad \rightarrow \quad N=11 \\
\text{ANALYZED:} & \quad N=34 \quad \rightarrow \quad N=17
\end{align*}

\[ \text{FIGURE 2. Flow chart for the 51 qualifying patients who had two paroxysmal supraventricular tachycardia events in the qualifying phase to the 34 patients who were analyzed. Patients who were discontinued during each phase are indicated to the right by arrows. A total of 34 patients were in the final analysis, and 17 patients were discontinued for various reasons (see text for details).} \]

riod effects, and treatment effects was used to test for differences between placebo and flecainide.

Results

Patients Studied

There were 51 patients who qualified with two documented PSVT events. Of these patients, 48 entered the dose-ranging phase, 37 entered treatment A of the efficacy phase, 35 entered treatment B, and 34 completed treatment A and treatment B (Figure 2) and were analyzed.

Of the 17 patients who did not complete the study, six withdrew for personal reasons, and three were discontinued after adverse cardiac events. Two of these three events occurred during electrophysiological testing: one patient had incessant PSVT after intravenous flecainide administration, and one patient had ventricular fibrillation induced during programmed ventricular stimulation after intravenous flecainide administration; neither of these patients received oral flecainide. The third patient had a documented myocardial infarction and was subsequently found angiographically to have normal coronary arteries. Three patients were discontinued from study because of noncardiac adverse experiences, two for protocol violations, one because the patient believed the drug was ineffective, and two because of noncompliance (lost to follow-up).

Characteristics of the analyzed patients and nonanalyzed patients are enumerated in Table 1. There were no differences in sex, age, race, alcohol or drug usage, smoking, height, weight, qualifying PSVT rates, or prior antiarrhythmic drug exposures. The study population, by design, had minimal or no structural heart disease and was in NYHA class I or II. However, two excluded patients, but no randomized patient, had prior myocardial infarction. Seven randomized and three excluded patients had hyper-
tension. Only two randomized and one excluded patient had premature ventricular beats (Table 1).

Of the 34 analyzed patients, the mean age was 50±15 years. There were 11 men and 23 women. Prior anti-arrhythmic drug exposure included a median of four medications with a range of 0–10. Thirty-one of the 34 analyzed patients (91%) previously received digoxin, a calcium channel antagonist, a β-blocker, or a combination. The median flecainide dose during treatment was 300 mg/day (100–400 mg).

The arrhythmia diagnoses for the 51 patients were classified according to an electrophysiological study in 23 patients (16 studies performed as part of the protocol and seven because of prior clinical indication); the remaining 28 patients were classified as having an unknown arrhythmia mechanism (see Table 2). As indicated in Table 2, of the 34 analyzed patients, seven had an atrioventricular reentry tachycardia with a retrograde accessory atrioventricular connection; two of these patients had manifest Wolff–Parkinson–White syndrome. Six patients had atrioventricular nodal reentry tachycardia, and three had atrial tachycardia. The other 18 patients did not undergo an electrophysiological study. The nonanalyzed patients had a similar distribution of arrhythmia diagnoses (Table 2).

**Comparison of Flecainide and Placebo Treatment Periods**

Figure 3 shows the time to first symptomatic PSVT event during the flecainide and the placebo randomized treatment periods for the 34 patients. During flecainide treatment, the cumulative proportion of patients remaining free of tachycardia for 8 weeks was 0.79 compared with 0.15 for placebo treatment (p<0.001) (Figure 3). In addition (Table 3), the number of patients with at least one PSVT event was 29 on placebo and only eight on flecainide therapy (p<0.001). Only one patient had an event during flecainide therapy without having one on placebo.

The median time to the first symptomatic PSVT event (Table 3) was 11 days on placebo and greater than 55 days on flecainide therapy. The median interval between attacks was significantly greater during flecainide treatment than during placebo (>55 days versus 12 days, p<0.001) (Table 3). The ventricular rates during PSVT in the seven patients with symptomatic PSVT events within both treatment periods were 178±12 beats/min for placebo and 143±12 beats/min for flecainide (p<0.02) (Table 3, Figure 4).

**Side Effects of Flecainide Therapy During Efficacy Phase**

Nuisance side effects during active treatment not requiring discontinuation or change in dosage were greater on flecainide therapy than placebo (Table 4). On flecainide therapy, 37% of the patients reported no side effects compared with 64% on placebo (p<0.05). Visual abnormality was the only side effect that was statistically greater with flecainide (29%) than with placebo (8%) (p<0.05) (see Table 4).

**Discussion**

We found flecainide clearly to be efficacious in our study population, markedly decreasing symptomatic PSVT events during the 8-week active treatment period (Figure 3 and Table 3). There were only eight events in the flecainide phase compared with 29 in the placebo phase. In addition, the median time to first PSVT event increased substantially (>55 days on flecainide compared with 11 days on placebo, p<0.001) as did the time between PSVT events (median number of days between attacks of 12 days on placebo and >55 days on flecainide, p<0.001).
Furthermore, there was an important decrease of the ventricular rate from 178±12 beats/min on placebo to 143±12 beats/min on flecainide in patients who had PSVT events during both placebo and flecainide treatments. By all efficacy criteria analyzed, flecainide showed significant benefit over placebo.

We designed this study to test the hypothesis that oral flecainide was more efficacious than placebo in preventing symptomatic PSVT and that it was safe to administer. Because of the sporadic occurrence and variable natural history of PSVT events, patients were required to have at least two symptomatic PSVT events while not receiving antiarrhythmic medication within a 1-month qualifying phase to participate in the study. Unlike many previous studies, our study did not accept symptomatic palpitations as evidence of arrhythmia; electrocardiographic documentation was required. Because palpitations are notoriously unreliable in diagnosing arrhythmias, electrocardiographic documentation of symptomatic events is an important feature of this study. On the other hand, in this study, we did not attempt to document asymptomatic PSVT events. We recognize that flecainide therapy could have slowed PSVT recurrences substantially, resulting in unrecognized, asymptomatic PSVT. However, based on the mechanism of action of flecainide on PSVT,8-10 we believe that if asymptomatic PSVT occurred, it did so rarely.

**Flecainide Dosing**

Because the study was designed to determine the efficacy of flecainide, we used the maximally tolerated dosage or at most 200 mg orally twice daily; the relative efficacy of different dosages was not addressed by this design. Despite the favorable results of this trial, we do not recommend that similar patients necessarily be treated with the maximally tolerated dose (200 mg orally twice daily) or with the median dose (150 mg orally twice daily) of flecainide used in this trial. Rather, we recommend individualized dosing based on the clinical situation. Clinicians should titrate to the lowest effective flecainide dose.

**Patient Population**

We recognize that the group of patients entering the randomized phase of the trial were "enriched" by the exclusion of patients intolerant of flecainide, noncompliant patients, and patients voluntarily withdrawing from the study. Because this study was designed to determine whether flecainide was efficacious in patients with high-frequency PSVT who could tolerate the drug,6 it was not possible to determine the overall response rate in a general population of patients with PSVT. However, the difference between the treatment and placebo treatment periods was so dramatic in our study that the results would likely not be substantially affected if, by design, "all" patients, a priori, had been intentionally included in the final analysis.

### TABLE 2. Baseline Arrhythmia Diagnoses

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analyzed (n=34)</td>
</tr>
<tr>
<td>Atioventricular reentry</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Atioventricular nodal reentry</td>
<td>6</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>3</td>
</tr>
<tr>
<td>Mechanism not known</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate patients with documented Wolff–Parkinson–White syndrome.

**FIGURE 3.** Plot of Kaplan–Meier product–limit estimate analysis for the proportion of patients during both treatment periods remaining paroxysmal supraventricular tachycardia (PSVT) event free from 0 to 60 days. Solid line indicates the proportion of PSVT event-free patients receiving flecainide, and dashed line indicates that for placebo. Proportion PSVT event-free patients during the 60 days for the flecainide (0.79) and placebo (0.15) treatment periods were statistically different (p<0.001).

**FIGURE 4.** Plot of the average ventricular rate in those patients who had paroxysmal supraventricular tachycardia (PSVT) events: placebo (n=29) on the left and flecainide (n=8) on the right. Each dot represents the mean rate of PSVT events for each patient during each treatment period. Solid lines connect average ventricular rates for seven patients who had PSVT events while receiving placebo and flecainide, and the dashed line indicates their mean change in ventricular rate. Note that in those patients who had PSVT events while receiving placebo and flecainide (n=7), the mean heart rate decreased from 178±12 to 143±12 beats/min.

**FIGUL**

**Figure 4**: Plot of the average ventricular rate in those patients who had paroxysmal supraventricular tachycardia (PSVT) events: placebo (n=29) on the left and flecainide (n=8) on the right. Each dot represents the mean rate of PSVT events for each patient during each treatment period. Solid lines connect average ventricular rates for seven patients who had PSVT events while receiving placebo and flecainide, and the dashed line indicates their mean change in ventricular rate. Note that in those patients who had PSVT events while receiving placebo and flecainide (n=7), the mean heart rate decreased from 178±12 to 143±12 beats/min.

- Atrioventricular nodal reentry
- Atrial tachycardia
- Mechanism not known
During oral administration of flecainide in this protocol, none of the patients had serious ventricular arrhythmias or sudden cardiac arrest. However, 48 patients is a relatively small number on which to estimate the true incidence of uncommon events. When flecainide was being studied for treatment of ventricular arrhythmias, it was thought to exacerbate ventricular arrhythmias in a small, but important, fraction of patients, particularly those with poor ventricular function.17 Also, flecainide was associated with an increased arrhythmic death and total cardiovascular mortality compared with placebo among patients with premature ventricular beats after myocardial infarction treated in the Cardiac Arrhythmia Suppression Trial.18 None of our analyzed patients (Table 1) had a prior myocardial infarction, presumably making them a low-risk group for ventricular arrhythmic events. When making a decision to initiate drug therapy for the generally benign arrhythmia of PSVT, the striking efficacy of flecainide demonstrated in this study must be considered in light of the unknown (though presumably low) risk of serious proarrhythmic events in patients such as ours, without prior myocardial infarction or other significant structural heart disease.

**Implications for Patient Therapy**

Based on our study results, in a patient population without substantial structural heart disease, yet with significant prior exposure to agents such as digoxin, calcium channel antagonists, and β-blockers, flecainide appears safe and clearly efficacious for the prevention of symptomatic electrocardiographically documented PSVT. Flecainide should be considered an important therapeutic alternative for patients having PSVT.

**Acknowledgments**

We appreciate the secretarial support of Monica D. Roby and Susan E. Lockshine in preparation of this manuscript.

**TABLE 3. Efficacy Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Flecainide</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with PSVT events (n)</td>
<td>29</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first attack (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>11</td>
<td>&gt;55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interval between attacks (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>12</td>
<td>&gt;55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular rate for patients with attacks in both periods (beats/min) (n=7)</td>
<td>178±12</td>
<td>143±12</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean±SEM†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>125–225</td>
<td>92–185</td>
<td></td>
</tr>
</tbody>
</table>

n=34 patients.

*Product-limit estimates for median data were analyzed using the paired Prentice–Wilcoxon test for censored paired data.

†Data were analyzed using the analysis of variance methods for a two-period crossover design.

Also, this study was not designed to stratify patients according to PSVT mechanism even though many patients did have antecedent electrophysiological studies (as a study option in some and on prior clinical grounds in others). Thus, patients having narrow QRS complex PSVT could reasonably receive oral flecainide without knowing the mechanism of their PSVT, if as in our study population, they did not have hemodynamically worrisome symptoms such as syncope. However, in the patient with Wolff–Parkinson–White syndrome, PSVT can degenerate into atrial fibrillation.15 Patients with Wolff–Parkinson–White syndrome who develop atrial fibrillation may be at risk for development of ventricular fibrillation15 and consequent sudden cardiac arrest. Thus, electrophysiological study should be considered for patients with Wolff–Parkinson–White syndrome16 before receiving empiric antiarrhythmic drug therapy, including therapy with flecainide. Also, patients having wide QRS complex tachycardia suspected to be PSVT should have the mechanism of their arrhythmia confirmed before undergoing empiric therapy, be it flecainide or any antiarrhythmic therapy. The implications are obvious. Empiric therapy of unrecognized ventricular tachycardia, erroneously presumed to be PSVT with aberrant ventricular conduction, is undesirable.

**Adverse Experiences and Proarrhythmia**

There were no significant adverse experiences in patients in the randomized phase. Two of three adverse cardiac experiences occurred after intravenous flecainide administration. One was possibly a nonspecific induction of ventricular fibrillation by ventricular stimulation, but we classified it as an adverse experience. One patient had incessant PSVT after intravenous flecainide administration that resolved after discontinuation of intravenous flecainide. One patient had a myocardial infarction with normal coronary arteries, probably unrelated to flecainide therapy. Other adverse experiences were characteristic of flecainide as previously recognized (Table 4).

**TABLE 4. Incidence of Side Effects**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients reporting side effect</th>
<th>Placebo (n=36)</th>
<th>Flecainide (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision abnormality</td>
<td>3</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Palpitation</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23</td>
<td>64</td>
<td>13</td>
</tr>
</tbody>
</table>

*Significant difference from placebo, p≤0.05 using McNemar’s test for a significant change.
Flecainide Supraventricular Tachycardia


KEY WORDS • paroxysmal supraventricular tachycardia • flecainide • antiarrhythmic therapy
Flecainide acetate prevents recurrence of symptomatic paroxysmal supraventricular tachycardia. The Flecainide Supraventricular Tachycardia Study Group.
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Circulation. 1991;83:119-125
doi: 10.1161/01.CIR.83.1.119

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