Dose-Response Effect of Flecainide in Patients With Symptomatic Paroxysmal Atrial Fibrillation and/or Flutter Monitored With Trans-Telephonic Electrocardiography

—— A Multicenter, Placebo-Controlled, Double-Blind Trial ——

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for the Flecainide Atrial Fibrillation Investigators

Background A double-blind, randomized, parallel-group, placebo-controlled trial was conducted in patients with paroxysmal atrial fibrillation or flutter (PAF/PAFL) experiencing 2 or more episodes of symptomatic PAF/PAFL during a 28-day observation period to determine the dose-response effect and safety of flecainide.

Methods and Results A total of 143 patients at 30 centers were randomized to receive 25, 50, or 100 mg of flecainide or placebo twice daily (BID). In 123 patients (per protocol set), those remaining free from PAF/PAFL after the treatment were 3.1% on placebo, 7.7% on 25 mg/BID, 9.4% on 50 mg/BID, and 39.4% on 100 mg/BID of flecainide. As a whole group, a significant linear dose-response (p<0.001) was observed and a significant difference between placebo and 100 mg/BID was observed (p<0.001). A similar dose-response between the present study and Caucasian study was demonstrated. Although there were 5 patients who needed cardioversion or ablation because of frequent episodes of PAF/PAFL (2 in 25 mg/BID, 1 in 50 mg/BID, and 2 in 100 mg/BID of flecainide), neither death nor ventricular proarrhythmic event was reported.

Conclusions This study indicated that flecainide exerted a significant dose-dependent effect on the prevention of symptomatic PAF/PAFL recurrence and showed that there was no inter-ethnic difference in the clinical effect of flecainide in patients with PAF/PAFL. (Circ J 2007; 71: 294–300)

Key Words: Double-blind trial; Flecainide; Paroxysmal atrial fibrillation or flutter; Trans-telephonic ECG monitoring

Flecainide, a potent Na channel blocker, has favorable electrophysiologic effects in the management of atrial fibrillation, and has been widely used in clinical practice. However, flecainide was approved in 1991 in Japan only for the treatment of ventricular tachyarrhythmias. This multicenter trial was conducted to investigate the usefulness of flecainide for the treatment of patients with atrial fibrillation or flutter and to establish the dose-response relationship in efficacy and safety in Japanese patients as compared with Caucasians in the USA.

Methods This study was a prospective, double-blinded, randomized, placebo-controlled clinical trial conducted in 30 centers in Japan from 4 December 2000 to 18 September 2003. The study protocol was approved by the Institutional Review Boards at each center, and all patients gave written informed consent. An independent Data and Safety Committee monitored the progress of the study. The protocol of this study used 4 parallel groups; placebo, 25, 50, and 100 mg twice daily (BID) flecainide to compare the preventive effect of flecainide on the recurrence of paroxysmal atrial fibrillation (PAF) or flutter (PAFL) via trans-telephonic electrocardiogram (ECG) monitoring.

Patients aged 20 years or older who had 2 or more symptomatic episodes of PAF/PAFL, which were documented with an ECG, including at least 1 episode transferred via trans-telephonic ECG during a 4-week observation period were included in the study. One of these subjective symptoms must have lasted longer than 1 min, and the sinus rhythm must have been confirmed immediately before starting the treatment period. The double-blinded 31-day treatment period consisted of the initial 3 days for attaining the steady-state plasma concentration of trial drugs, followed...
by a 4-week period for efficacy evaluation. To observe the
dose-response effect, we needed to avoid an early recur-
rence possibly at very low concentrations of flecainide.
After randomization, patients received either 25, 50, or
100 mg of flecainide (in a tablet form) or a placebo tablet
BID. The test drugs and matching placebo were provided
by Eisai Co, Ltd (Tokyo, Japan) and were indistinguishable
in size, weight, color and taste. Patients were excluded if
they met either of the following findings: arrhythmia related
cycle block, ventricular pacing rhythm, severe renal or
sinus bradycardia <40 beats/min, sick sinus syndrome with-
Heart Association Class III or IV congestive heart failure,
slow heart rate, syncpe, angina pectoris, transient ischemic attack, history
of cardiogenic stroke, myocardial infarction.

Clinical symptoms were assessed every 2 weeks during
observation and treatment periods. Laboratory evaluations
including 12-lead ECG were performed on the first day and
study-dose interaction. Demographics and baseline charac-
test (contrast [–7 –3 1 9]), and the comparisons of the flecainide groups
dose-response of the non-recurrence rate of symptomatic
PAF/PAFL, a linear dose-response was analyzed using Tarone

**Fig1. Study flow.** PPS, per-protocol set (primary efficacy analysis); FAS, full-analysis set.

**Statistical Analysis**

Data are expressed as mean ± SD. The efficacy analyses
were conducted in per-protocol sets (PPS). The sensitive
analyses were conducted in the full-analysis set (FAS). The
trend test was 1-tailed with a significance level of 0.025.
Other statistical tests were 2-tailed with a significance level
of 0.05 for the comparison of groups, and a significance
level of 0.15 for the uniformity in demographic data and
study-dose interaction. Demographics and baseline charac-
teristics of each group were summarized using descriptive
statistics. Continuous variables were analyzed using 1-way
analysis of variance (ANOVA) and classification variables
were analyzed using the Fisher’s exact or chi-square test.
The primary efficacy analyses were performed for a linear
dose-response of the non-recurrence rate of symptomatic
PAF/PAFL using the Cochran-Armitage trend test (contrast
[–7 –3 1 9]), and the comparisons of the flecainide groups
against the placebo group using Fisher’s exact test. In addi-
tion, the closed testing procedure was applied to avoid mul-
tiplicity of statistical tests, that is, the following order
(placebo-100 mg/BID, placebo-50 mg/BID, placebo-25 mg/
BID) tests were performed. Moreover, the similarity of
dose-responses in the non-recurrence rate in the present
study and the Caucasian data were investigated by using a
regression analysis and logistic regression analysis in a
model with ‘study’ as a classification variable, ‘dose’ as a
continuous variable, and ‘study-dose’ (df=1) as an interaction.

For the time to first recurrence of symptomatic PAF/
PAFL, a linear dose-response was analyzed using Tarone
test (contrast [–7 –3 1 9]) with log-rank score and inter-
group difference was analyzed using Log-rank test. For
changes in the frequency of symptomatic PAF/PAFL per
day from the observation period, a linear dose-response and
inter-group difference were analyzed using the Permutation

**Results**

A total of 218 patients were recruited at 30 centers and
143 of them were randomly assigned to receive flecainide
or placebo BID: 32 patients to receive 25 mg of flecainide,
36 to receive 50 mg, 37 to receive 100 mg, and 38 patients
to placebo. The remaining 75 patients were withdrawn from
the study during the observation period for the following
reasons: deviation from inclusion criteria (n=56), with-
drawal of study consent (n=6), aggravation of preexisting
arrhythmias (n=4), deviation from exclusion criteria (n=3),
difficulty to use trans-telephonic ECG recorder (n=2), and
other reasons (n=4). Of 143 patients, 123 were eligible for
the PPS and 136 for the FAS. Safety analysis was performed
Table 1 Baseline Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=32)</th>
<th>25 mg/BID (n=26)</th>
<th>50 mg/BID (n=32)</th>
<th>100 mg/BID (n=33)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Men</td>
<td>28 (87.5)</td>
<td>22 (84.6)</td>
<td>23 (71.9)</td>
<td>24 (72.7)</td>
<td>0.311</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.4±10.2</td>
<td>61.8±9.8</td>
<td>57.7±10.2</td>
<td>57.6±11.0</td>
<td>0.393</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.5±13.5</td>
<td>64.5±9.5</td>
<td>66.3±12.3</td>
<td>63.2±8.9</td>
<td>0.449</td>
</tr>
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<td>Arrhythmia</td>
<td></td>
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<tr>
<td>PAF</td>
<td>27 (84.4)</td>
<td>16 (61.5)</td>
<td>25 (78.1)</td>
<td>27 (81.8)</td>
<td>0.173</td>
</tr>
<tr>
<td>PAF and PAFL</td>
<td>5 (15.6)</td>
<td>10 (38.5)</td>
<td>7 (21.9)</td>
<td>6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>History of PAF/PAFL (years)</td>
<td>4.1±4.5</td>
<td>4.3±5.8</td>
<td>4.9±3.8</td>
<td>6.0±6.2</td>
<td>0.377</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>24 (75.0)</td>
<td>21 (80.8)</td>
<td>23 (71.9)</td>
<td>28 (84.8)</td>
<td>0.604</td>
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<tr>
<td>Valvular disease</td>
<td>3 (9.4)</td>
<td>3 (11.5)</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
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<td>Cardiomyopathy</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
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<td>Angina pectoris</td>
<td>0 (0.0)</td>
<td>1 (3.5)</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
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<tr>
<td>Hypertension</td>
<td>16 (50.0)</td>
<td>7 (26.9)</td>
<td>11 (34.4)</td>
<td>13 (39.4)</td>
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<tr>
<td>Pre-excitation syndrome</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Others</td>
<td>18 (56.3)</td>
<td>18 (69.2)</td>
<td>18 (56.3)</td>
<td>24 (72.7)</td>
<td></td>
</tr>
<tr>
<td>CTR (%)</td>
<td>45.8±4.6</td>
<td>46.6±3.7</td>
<td>48.6±5.8</td>
<td>47.6±4.5</td>
<td>0.119*</td>
</tr>
<tr>
<td>&lt;50</td>
<td>25 (80.6)</td>
<td>20 (76.9)</td>
<td>16 (51.6)</td>
<td>21 (63.6)</td>
<td></td>
</tr>
<tr>
<td>50±&lt;60</td>
<td>6 (19.4)</td>
<td>6 (23.1)</td>
<td>15 (48.4)</td>
<td>12 (36.4)</td>
<td>0.063*</td>
</tr>
<tr>
<td>No. of symptomatic PAF/PAFL per day during observation period</td>
<td>0.40±0.33</td>
<td>0.58±0.54</td>
<td>0.46±0.30</td>
<td>0.39±0.31</td>
<td>0.204</td>
</tr>
</tbody>
</table>

BID, twice daily; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; CTR, cardiothoracic ratio.
*p<0.15, 2-tailed.
Data are mean±SD or number (%) of patients.

Table 2 Non-Recurrence Rates of Symptomatic PAF/PAFL and Symptomatic/Asymptomatic PAF/PAFL

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=32)</th>
<th>25 mg/BID (n=26)</th>
<th>50 mg/BID (n=32)</th>
<th>100 mg/BID (n=33)</th>
<th>Dose-response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic PAF/PAFL</td>
<td>1 (3.1%)</td>
<td>2 (7.7%)</td>
<td>3 (9.4%)</td>
<td>13 (39.4%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>p=0.582*</td>
<td>p=0.613*</td>
<td>p&lt;0.001*</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Symptomatic and asymptomatic PAF/PAFL</td>
<td>0 (0.0%)</td>
<td>2 (7.7%)</td>
<td>3 (9.4%)</td>
<td>10 (30.3%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>p=0.197*</td>
<td>p=0.238*</td>
<td>p&lt;0.001*</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations see in Table 1.
* vs placebo.

in 143 patients (Fig 1). With reference to the Caucasian data, the main efficacy analysis was conducted in PPS. However, we performed the analyses using FAS for the primary endpoint as recommended in ICH-E9.

Patient Characteristics

There was no significant difference among the 4 treatment groups except for the cardiothoracic ratio (CTR) on chest radiography (Table 1). The effect of this disproportion of CTR among the 4 groups was thought to have no serious impact because the result remained the same after adjustment with CTR as the covariate. A total of 626 episodes of PAF/PAFL including 147 (23.5%) asymptomatic episodes were recorded in 123 patients by trans-telephonic ECG during the observation period, and 550 including 123 (22.4%) asymptomatic episodes were recorded in 112 patients during the treatment period including the initial 3 days. There was no significant difference in the frequency of asymptomatic PAF/PAFL episodes between the observation and the treatment period.

Recurrence of Symptomatic PAF/PAFL

Non-recurrence rates of PAF/PAFL were dose-dependently increased. In 136 FAS patients, at the end of the treatment period, non-recurrences of PAF/PAFL were observed in 1/35 patients (2.9%) on placebo, 5/31 patients (16.1%) on 25 mg/BID, 3/34 patients (8.8%) on 50 mg/BID,
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and 15/36 patients (41.7%) on 100 mg/BID. There was a significant linear dose-response across all groups (p<0.001; Cochran-Armitage trend test) and there was a significant difference between placebo and 100 mg/BID of flecainide treatment (p<0.001; Fisher’s exact test). This was also true for 123 PPS patients (Table 2). A similarity in a dose-response between the present study and the Caucasian study is demonstrated in Fig 2. A study-dose interaction in Japanese and Caucasian studies was not statistically significant (p=0.295; linear regression analysis, p=0.612; logistic regression analysis). Fig 3 shows the time to first recurrence of symptomatic PAF/PAFL in the 4 treatment groups. The median times to the first episode of symptomatic PAF/PAFL were dose-dependently increased. There was a significant dose-response relationship across all doses (p<0.001; Permutation test). To evaluate the durations of drug effects on symptomatic PAF/PAFL, subjective symptoms and ECG findings were assessed. Patients presenting a reduction of duration of symptomatic PAF/PAFL by 75% or more showed a significant linear dose-response (p<0.001; Cochran-Armitage trend test) (Fig 4). There was also a significant difference between the placebo and the 100 mg/BID of flecainide treatments (p<0.001; Fisher’s exact test).

Recurrence of Symptomatic and Asymptomatic PAF/PAFL

In the present study, many asymptomatic PAF/PAFL were recorded through daily trans-telephonic ECG. Therefore, we analyzed the percentages of patients without recurrence of PAF/PAFL, which included asymptomatic episodes. At the end of the treatment period, the non-recurrence rates were dose-dependently increased in the flecainide-treated groups. There was also a significant difference between the placebo and 100 mg/BID of flecainide treatments (p<0.001; Fisher’s exact test) (Table 2).

The median time to the first episode of recurrence was 3 days on placebo, and 2.5, 2 and 10 days on 25, 50 and 100 mg/BID on flecainide, respectively. A significant dose-response relationship across all doses (p<0.001; Tarone test) and a significant difference between placebo and 100 mg/BID treatments (p<0.001; Log-rank test) were observed.

Changes in frequency (mean number) of PAF/PAFL per
day from a 28-day observation period to a 28-day treatment period was −0.002 on placebo, −0.283 on 25 mg/BID, 0.047 on 50 mg/BID, and −0.377 on 100 mg/BID of flecainide. A significant linear dose-response across all doses (p=0.025; Permutation test) and a significant difference between the placebo and 100 mg/BID of flecainide treatments (p=0.006; Permutation test) were observed.

**Subjective Symptoms**
A total of 1,768 trans-telephonic ECG findings were accompanied subjective symptoms. The most frequent subjective symptom was palpitation (70.4%), and the second was chest discomfort (30.8%). The relationship between each subjective symptom and trans-telephonic ECG is summarized in Table 3. Chest pain and fatigue were less related with PAF/PAFL as compared with other symptoms.

The frequency of these subjective symptoms was reduced during the treatment period. Palpitations were reduced 14.5% on placebo, 22.4% on 25 mg/BID, 40.9% on 50 mg/BID, and 69.1% on 100 mg/BID of flecainide. A significant linear dose-response across all doses (p=0.010; ANOVA, contrast [7 3 −1 −9]) and a significant difference between the placebo and 100 mg/BID of flecainide treatments (p=0.025; Fisher’s least significant difference) were observed.

In the 50 mg/BID and 100 mg/BID flecainide treatment groups, there was a significantly positive correlation between improvement of subjective symptoms and ECG-confirmed PAF/PAFL (the correlation coefficient r=0.88; the percentage of reduction in the number of attacks, r=0.88; the percentage of reduction in cumulative durations) (Fig 5).

**Safety and Tolerability of Treatment**
The safety analysis was performed in all 143 patients who had taken at least 1 dose of the study drug (Table 4). No significant difference was observed in the frequency of adverse events among the 4 treatment groups. The most frequent adverse event in the flecainide treatment groups was headache. There were a total of 7 serious adverse events; 5 patients needed hospitalization and/or cardioversion or ablation because of PAF/PAFL. Two in 25 mg/BID, 1 in 50 mg/BID, and 2 in 100 mg/BID treatment groups) and 1 patient in the 100 mg/BID group had a sinus arrest. There were no reports of death or ventricular proarrhythmic events such as ventricular tachycardia.

When comparing 12-lead ECG in terms of sinus rhythm at the baseline observation period and on day 28 of the treatment period, flecainide prolonged the RR interval, PR interval, QRS width, QT interval, and QTc. At the maximum dose of flecainide (100 mg/BID), a prolonged RR interval from 0.867±0.148 to 0.894±0.169 s, PR interval from 0.165±0.032 to 0.185±0.035 s, QRS width from 0.091±0.017 to 0.102±0.024 s, QT interval from 0.382±0.032 to 0.400±0.041 s, and QTc from 0.414±0.024 to 0.426±0.040 s was observed.

**Discussion**
This clinical study was designed to confirm the efficacy of flecainide for PAF/PAFL, and to compare dose responsiveness with that in Caucasians. For this reason, we applied the trans-telephonic ECG monitoring system to evaluate the recurrence of PAF/PAFL. Therefore, the present study was considered to be valuable enough to investigate the recurrences of the arrhythmic events including asymptomatic arrhythmia episodes more accurately than previous reports. The study design of the current clinical study included using 4 parallel doses, and was conducted in double-blinded fashion. As the primary endpoint, no recurrence of symptomatic episodes was dose-dependently increased in the flecainide treatment groups. These data showed a significant linear dose-response across all groups, which were similar results found in the Caucasian data. Analysis including asymptomatic PAF/PAFL episodes found that there was also a significant liner dose-response across all groups.

In the management of supraventricular tachyarrhythmias, especially in patients with PAF/PAFL, flecainide has been used widely as a potent Na channel blocker to alleviate5,11 or prevent arrhythmic attacks.3,8,12–14 Approximately one-third (31%) of flecainide-treated patients (100–200 mg/BID) were free from PAF/PAFL recurrence during an
8-week observation period as compared with 8% of placebo-treated patients in a previous double-blind, cross-over study using trans-telephonic ECG monitoring.8 In a dose-response study conducted by Pritchett et al.,7 7% of patients had no episodes of PAF/PAFL while receiving placebo; the figure increased to 61% when receiving 150 mg/BID of flecainide. The overall free ratio was higher in their study than in the present study. In the present study, 3.1% of patients receiving placebo were free of recurrence at the end of the 4-week treatment period, but this was up to 7–8% in previous studies.8,9 Previous study patients seemed to have less frequent PAF/PAFL episodes than the patients in the present study.

The median time to the first episode of recurrence was also prolonged with flecainide, dose-dependently. In the Caucasian study data, the median time to the first recurrence was dose-dependent and was similar to the present study results, that is, 3 days on placebo, 5 days with 50 mg/BID, >25 days with 100 mg/BID and 14 days with 150 mg/BID. In the present study, we also analyzed the changes in frequency (mean number) of symptomatic and asymptomatic PAF/PAFL per day from a 28-day observation period to a 28-day treatment period. There was a significant linear dose-response across all doses, and there was a significant difference between the placebo and 100 mg/BID of flecainide treatment. Therefore, flecainide demonstrated not only obvious dose-response effects on the prevention of PAF/PAFL but also no racial difference when compared with the results found in the Caucasian study.8,9

Asymptomatic PAF/PAFL are not rare episodes in elderly patients and also in patients taking antiarrhythmic drugs10,11 or those who have digitalis.17 In the present study, asymptomatic PAF/PAFL was recorded in 23.5% of trans-telephonic ECGs during observation periods and this percentage did not change even in the treatment period. Changes in ECG parameters with flecainide treatment were all acceptable in terms of safely treating atrial tachyarrhythmias. Therefore, the dose-dependent effect of flecainide on arrhythmic events was confirmed in patients with and without asymptomatic PAF/PAFL in the present study.

Recently, assessment of the quality of life in these arrhythmic patients has become more important,18 however, this study did not include such an assessment.

The most frequent adverse event in flecainide treatment groups was headache, but this observed also in the placebo group. There was no significant difference in the frequency of adverse events among the 4 treatment groups. In the flecainide treatment groups, there were a total of 7 serious adverse events such as PAFL or transient sinus arrest, but there were no reports of death or ventricular proarrhythmic events. The frequency of these events did not differ from the earlier clinical studies conducted in Japan.19–21

**Conclusion**

Flecainide could prevent recurrences of PAF/PAFL in a dose-dependent manner as previously reported in Caucasian patients. No serious adverse effects including ventricular proarrhythmias were observed.

**Acknowledgment**

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**References**

18. Tsuneda T, Yamashita T, Fukunami M, Kamagai K, Niwano S,


**Appendix**

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