Original Article

Efficacy of Long-term Flecainide Therapy in Patients with Paroxysmal Atrial Fibrillation —Analysis Based on Time of Onset—

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This study sought to evaluate the efficacy of long-term flecainide therapy in maintaining sinus rhythms in patients with paroxysmal atrial fibrillation (AF) based on time of onset. Flecainide (150 mg/day) was administered as an antiarrhythmic drug to a total of 70 patients (54 men and 16 women: mean age 65 ± 10 years) after sinus rhythm was restored spontaneously or by electrical and/or pharmacological cardioversion. Paroxysmal AF was divided into three categories based on time of onset: diurnal type ($N = 11$), nocturnal type ($N = 13$), and mixed type ($N = 46$). The mean follow-up period was 37.7 ± 17.7 months. The duration of sinus rhythm maintenance in patients with diurnal and nocturnal paroxysmal AF was 32.4 ± 10.4 months and 20.8 ± 8.3 months, respectively; the duration of sinus rhythm maintenance in those with mixed paroxysmal AF was only 7.2 ± 2.1 months. Significant differences were observed in duration between diurnal and mixed cases (mean $\pm$ S.E., $P < 0.05$). Actuarial recurrence-free rates at 1, 3, 6, 9 and 12 months were 90.9%, 63.6%, 63.6%, 54.5%, and 54.5%, respectively, for diurnal cases; 84.6%, 76.9%, 53.8%, 38.5%, and 30.8%, respectively, for nocturnal cases; and 58.7%, 39.1%, 28.3%, 21.7%, and 15.2% respectively, for mixed cases. Significant differences in rates at 12 months were observed between diurnal and mixed cases ($P < 0.05$). These results suggest that flecainide is highly effective in preventing AF recurrence in patients with diurnal paroxysmal AF.
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Key words: Paroxysmal atrial fibrillation, Antiarrhythmic drug therapy, Flecainide, Circadian variation

Introduction

In previous studies, antiarrhythmic drugs for maintaining sinus rhythm in patients with paroxysmal atrial fibrillation (AF) were selected based on therapeutic efficacy as observed by the trial-and-

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error method or based on the personal experience of individual physicians. Japan's rapidly aging population (and hence AF morbidity) is expected to increase gradually but continuously, creating a need for a drug that prevents AF recurrence with high efficacy. According to Yamashita et al., paroxysmal AF, unlike other arrhythmic conditions in humans, tends to display specific circadian variations in patients,[1] allowing for an efficient therapeutic strategy based on the mechanism of initiation of paroxysmal AF employing a reasonable selection of antiarrhythmic drugs. Previously we discussed the efficacy of disopyramide,[2] cibenzoline,[3] and pilsicainide[4] in preventing AF recurrence based on time of onset of paroxysmal AF, demonstrating that the selection of antiarrhythmic drugs based on time of onset could enhance therapeutic efficacy in preventing AF recurrence. In the present study, we evaluated the long-term efficacy of flecainide based on time of onset of arrhythmia to maintain sinus rhythm in patients with paroxysmal AF, exploring whether the time of onset of arrhythmia could be used as a parameter in choosing flecainide treatment.

Subjects

Performed from June, 1997 to October, 2003, the study involved 70 patients with symptomatic paroxysmal AF (54 men and 16 women, aged from 32 to 84; mean age 65 ± 10 years) regarded as needing antiarrhythmic drug therapy (AAT) due to the severity of their symptoms. All patients underwent follow-up examinations once or twice a month at the Iwate Prefectural Iwai Hospital outpatient clinic. The examination at each visit assessed whether sinus rhythm was maintained without AF recurrence or whether AF had recurred, based on symptoms and ECG findings. Ambulatory 24-hour ECG recordings were repeated at 3-month intervals or when considered necessary by the physician. Pharmacological and/or electrical cardioversion was applied if AF recurred and did not terminate spontaneously. The mean duration of paroxysmal AF at hospital visits in the present study was 41.6 ± 110.5 hours, ranging from 2.3 hours to 7 days. The mean follow-up period was 37.7 ± 17.7 months, (mean $\pm$ one standard deviation; range 12 to 84) for all patients. All patients underwent chest X-ray examination, ECG recording, exercise ECG testing, echocardiography, and head CT scans before initiation of antiarrhythmic therapy. Eighteen patients had underlying heart diseases such as coronary artery disease (10 patients), valvular heart disease (3), hypertrophic cardiomyopathy (3), dilated cardiomyopathy (1), or cardiac syndrome X (1). Seven patients had pulmonary diseases such as healed tuberculosis (4 patients), bronchial asthma (2), and pulmonary emphysema (1). The study excluded patients taking beta-blockers or having congestive heart failure, left ventricular ejection fraction $<40\%$ as determined by echocardiography, bradycardias <40 beats/minute, duration of AF morbidity $\geqq 7$ days, severe intraventricular conduction disturbances, severe liver or renal dysfunctions, or other serious complications.

A total of 70 patients were divided into three subcategories, according to the time of onset of paroxysmal AF: diurnal type (11 patients), nocturnal type (13 patients), and mixed type (46 patients), and the efficacy of flecainide was compared among the three groups. The diurnal type was defined as AF occurring only during daytime between 7 a.m. and 5 p.m., whereas the nocturnal type was defined as AF occurring only during nighttime from 5 p.m. to 7 a.m. The mixed type was defined as AF occurring during both daytime and nighttime.[2–4]

Before antiarrhythmic drug therapy, ambulatory 24-hour ECG recordings were performed 1.4 ± 0.4 times in patients with diurnal type paroxysmal AF, 1.3 ± 0.3 times in those with nocturnal type paroxysmal AF, and 1.5 ± 0.3 times in those with mixed type paroxysmal AF. No significant differences in the frequency of examination recorded by ambulatory 24-hour ECG among the three groups were observed.

Protocols of Antiarrhythmic Drug Therapy

After restoration of sinus rhythms spontaneously or by cardioversion, one of three class-I drugs—disopyramide (300 mg/day), cibenzoline (300 mg/day), or aprindine (60 mg/day)—was selected by the envelope method and was administered orally as initial drug therapy. When AF recurred, sinus rhythm was restored, and one of three drugs—flecainide (150 mg/day), pilsicainide (150 mg/day), or bepridil (150 mg/day)—was selected by the envelope method. As to administration, a 50-mg tablet of flecainide was administered orally three times daily after each meal. The recurrence-free rates of patients treated with flecainide after AF recurrence refractory to initial drug therapy were then analyzed in this study.

Definition and Statistical Analysis

Paroxysmal AF was defined as AF terminating spontaneously within 7 days after occurrence. Duration of AF morbidity was defined as the period from the initial episode of paroxysmal AF to the initiation

Table 1 Comparison of clinical characteristics among patients with paroxysmal atrial fibrillation.

	Diurnal type	Nocturnal type	Mixed type	P-value
Number	11	13	46	
Age	65 ± 11	64 ± 14	66 ± 9	N.S.
Male:female	8:3	12:1	34:12	N.S.
Smoking	3(27%)	6(46%)	15(33%)	N.S.
Hypertension	5(46%)	2(15%)	19(41%)	N.S.
Diabetes mellitus	3(27%)	2(15%)	12(26%)	N.S.
Hyperlipidemia	2(18%)	2(15%)	6(13%)	N.S.
Hyperuricemia	0(0%)	1(8%)	2(4%)	N.S.
Alcohol	3(27%)	8(62%)	24(52%)	N.S.
Body weight (Kg)	57 ± 8	58 ± 9	59 ± 8	N.S.
ACE-I or ARB	3(27%)	2(15%)	10(22%)	N.S.
Follow-up period (months)	39 ± 22	37 ± 17	36 ± 15	N.S.
OHD	3(27%)	3(23%)	12(26%)	N.S.
OPD	2(18%)	2(15%)	3(7%)	N.S.
AF duration (hours)	33 ± 94	40 ± 109	52 ± 120	N.S.
AF morbidity (months)	29 ± 27	42 ± 75	35 ± 50	N.S.
LVDd (mm)	49 ± 3	46 ± 3	46 ± 7	N.S.
LAD (mm)	36 ± 6	32 ± 6	35 ± 7	N.S.
LVEF (%)	70 ± 12	72 ± 7	67 ± 14	N.S.
Mean heart rate (bpm)	112 ± 31	108 ± 28	111 ± 24	N.S.
Systolic blood pressure (mmHg)	129 ± 16	123 ± 14	126 ± 12	N.S.
Diastolic blood pressure (mmHg)	82 ± 12	80 ± 11	81 ± 10	N.S.
HANP during SR (pg/ml)	25 ± 12	28 ± 24	56 ± 51	$P < 0.05$*

$P < 0.05$*; Diurnal type, Nocturnal type vs Mixed type. ACE-I: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin-receptor blockers, OHD: Organic heart disease, OPD: Organic pulmonary disease, LVDd: Left ventricular end-diastolic dimension, LAD: Left atrial dimension, LVEF: Left ventricular ejection fraction, HANP: Human atrial naturiuretic peptide, AF: Atrial fibrillation, SR: Sinus rhythm

of AAT. Hypertension was defined as systolic and diastolic blood pressures greater than 160 mmHg and 90 mmHg, respectively.[5)]

Data were shown as mean plus or minus one standard deviation, while data for duration of sinus rhythms were shown as mean plus or minus one standard error. Clinical profiles of patients among the three groups were compared using one-way ANOVA for continuous variables and the Chi-square test for categorical variables. Survival curves were estimated by the Kaplan and Meier method and compared by the log-rank test. $P < 0.05$ was considered to indicate statistical significance.

Results

1. Comparisons of Clinical Characteristics

No significant differences were observed among the three groups with respect to age, gender, body weight, percentage of patients with coronary risk factors, and percentage of patients treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. No significant differences were observed among the three groups in AF duration and morbidity, distributions of underlying heart and pulmonary disease, end-diastolic left ventricular dimensions, left atrial dimensions, and left ventricular ejection fractions, as determined by echocardiography. Finally, no significant differences were observed among the three groups in mean heart rate or systolic and diastolic blood pressure during AF. Plasma concentrations of human atrial natriuretic polypeptides (HANP) during sinus rhythms in the mixed group were greater than those in the diurnal and nocturnal groups ($P < 0.05$, **Table 1**).

2. Comparison of AF Recurrence Prevention in Patients Treated with Flecainide

As shown in **Figure 1**, the actuarial recurrence-free rates of patients treated with flecainide therapy at 1, 3, 6, 9, and 12 months were, respectively, 90.9%, 63.6%, 63.6%, 54.5%, and 54.5% in the diurnal group; 84.6%, 76.9%, 53.8%, 38.5%, and 30.8% in the nocturnal group; and 58.7%, 39.1%, 28.3%,

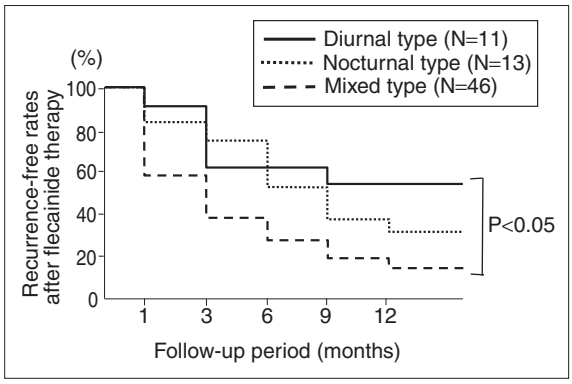

Figure 1 Actuarial recurrence-free rates among the three groups after flecainide therapy.

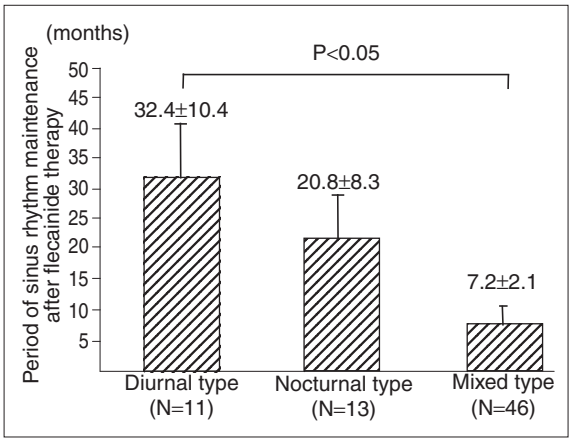

Figure 2 Periods of sinus-rhythm maintenance among the three groups after flecainide therapy.

21.7%, and 15.2% in the mixed group. At 12 months, recurrence-free rates for diurnal cases were significantly higher than these rates for mixed cases ($P < 0.05$). Periods of sinus rhythm maintenance when treated with flecainide therapy were 32.4 ± 10.4 months for diurnal cases, 20.8 ± 8.3 months for nocturnal cases, and 7.2 ± 2.1 months for mixed cases. The period for the diurnal group was significantly greater than that for the mixed group ($P < 0.05$) (**Figure 2**).

Discussion

According to the classification of antiarrhythmic drugs proposed under the so-called Sicilian Gambit,[6] the major pharmacological action of flecainide on single cardiac myocytes is regarded to be the blocking of sodium and potassium currents. With its sodium-channel inhibition properties, flecainide is classified as a slow kinetic drug due to differences in recovery relative to use-dependent blocks, and is expected to have inhibitory effects due to its relatively high accumulation. Flecainide has an affinity for the activated phase during depolarization and is not seriously affected by the duration of action potentials, as linkages between drug and receptors are formed in the emerging phase of the action potential; further, it is considered as acting in atrial muscle, which has a short action-potential plateau phase.[7] In Japan, slow kinetic sodium-current blockers such as flecainide are currently administered to patients with paroxysmal AF to maintain sinus rhythm.[8] As for the pharmacological actions of flecainide with respect to potassium currents, the blockade of voltage-dependent IKr and Ito, ligand-dependent IkATP, and IKACh currents have all been reported.[6,9] However, based on the Sicilian Gambit classification, the pharmacological actions of flecainide at the recommended doses are evaluated as less potent in inhibiting potassium currents than in inhibiting sodium currents.[6] Flecainide is considered to prolong the effective refractory period and intra-atrial conduction in the human atrial myocardium.[10]

Reports from Europe and the U.S. indicate varying efficacy in preventing AF recurrence among patients treated with flecainide. Previous reports put the recurrence-free rates for those treated with flecainide from 31% to 61% at several months, from 60% to 63% at 6 months, and from 62% to 72% at 12 months.[11–19] We have also examined the efficacy of flecainide in preventing AF recurrence among patients who demonstrated repeated AF recurrence despite class-Ia or -Ib antiarrhythmic drugs therapy, reporting actuarial recurrence-free rates of 33% and 30% at 12 months and 24 months,[20] respectively. Our data were considered to reflect values lower than those previously reported in Europe and the U.S. Such differences in recurrence-free rates may depend on patient clinical profiles; in our study, only half of the patients resistant to the first antiarrhythmic drug were free of AF recurrence after flecainide therapy. In Europe and the U.S., the efficacy of antiarrhythmic drugs was evaluated using doses higher by a factor of 1.5 to 2 times relative to doses used in Japan. Thus, the results obtained overseas are not perfectly comparable to those obtained in Japan. In previous studies, however, there has been little information on individualized selection of antiarrhythmic drugs to maintain sinus rhythms in patients with paroxysmal AF.

The present study classified paroxysmal AF cases as one of three types based on time of onset—diurnal, nocturnal, and mixed—and compared the efficacy of flecainide among patients assigned to one of the three categories. Also, a 50-mg tablet of

flecainide was administered orally three times daily after each meal to even out the serous concentration of flecainide over the course of the day. At 12 months after flecainide therapy, patients with diurnal AF showed a 54.5% recurrence-free rate, while patients with nocturnal or mixed AF showed recurrence-free rates of only 30.8% and 15.2%, respectively. This indicated that flecainide can serve as one of the first-line drugs for patients with diurnal paroxysmal AF when no contraindications are present.

Paroxysmal AF is believed to be caused by intraatrial random reentry induced by supraventricular extrasystole originating from the pulmonary vein, mostly due to triggered activity.[21] In fact, the prevalence of extrasystole that induces paroxysmal AF has not been fully elucidated. However, based on the assumption that the onset of diurnal-type atrial fibrillation is closely related to extrasystole induced by sympathetic hypertonia, a Na-channel blocker such as flecainide should suppress such extrasystole. Further, sympathetic hypertonia not only activates the Na channel via the β_1-receptor, but also induces intracellular Ca overload via the sarcoplasmic reticulum Ca-pump to induce arrhythmia by triggered activity.[22] In other words, a Na-channel blocker may also suppress arrhythmia induced by sympathetic hypertonia.

Since β_1 receptors activated by sympathetic hypertonia can enhance sodium currents when myocardial membrane potential is reduced,[23] blockading sodium currents may also inhibit supraventricular extrasystole in patients with diurnal AF. According to reports on the activity of the autonomic nervous system based on analysis of the heart-rate variability spectrum, flecainide was found to reduce activity in the low frequency band (LF), which is closely associated with sympathetic hypertonia.[24,25] Such data suggest that flecainide may be especially effective in preventing recurrence of paroxysmal AF in patients with diurnal AF in whom AF occurs predominantly during the daytime. In our previous study,[4] pilsicainide, a pure sodium-channel blocker, was shown to be effective in preventing recurrence of paroxysmal AF in patients with diurnal AF, based on analysis at the time of arrhythmic onset. Not only combination therapy with β-blockers, but also sodium-channel blocker monotherapy may be extremely useful for maintaining sinus rhythm in patients with diurnal AF.

The present study accounted for potential differences in patient characteristics among the three groups before comparisons of flecainide preventive efficacy, since age,[26] left atrial dimensions,[27] underlying heart disease,[28] and duration of AF morbidity[29] have all been found to affect the efficacy of AAT in preventing the recurrence of paroxysmal AF. This study found no significant differences in patient characteristics among the three groups, including those characteristics affecting AAT efficacy. However, the mean follow-up period was approximately 36 months in the present study, while the mean follow-up periods in most earlier studies reported in Europe and the U.S. have generally been shorter (ranging from one to nine months).[11–19] Given the serious complications arising in patients with paroxysmal AF, such as thromboembolism or heart failure, evaluating the efficacy of AAT for long-term follow-up periods appears appropriate.[18,19]

Limitation

In the present study, grouping of flecainide administration was random and prospective, whereas recurrence-free rates were analyzed retrospectively in patients with paroxysmal AF who were classified into three groups based on the time of onset. Diurnal type cases were defined as patients who had episodes of paroxysmal AF only during the daytime, nocturnal cases as those who had episodes of paroxysmal AF only during the nighttime, and mixed cases as those who had episodes of paroxysmal AF occurring irrespective of circadian variations. However, to confirm the validity of a system of classification based on the time of onset, we must clarify the close relationship between diurnal type AF and sympathetic hypertonia, and that between nocturnal type AF and parasympathetic hypertonia, through analysis of the heart-rate variation spectrum.[30,31] In addition, the frequency of examination recorded by ambulatory 24-hour ECG without antiarrhythmic drugs was only an average of 1.4, and therefore an event of AF recurrence in all patients was not examined fully in relation to the time of onset in the present study. Also, the number of cases in the present study was low, and further investigations involving the study of additional cases will be necessary. Page et al. have reported that in patients with paroxysmal AF, sustained asymptomatic AF occurs far more frequently than symptomatic AF.[32] In the present study, all patients were diagnosed as free of AF recurrence based on symptoms and ECG findings assessed once or twice a month at the outpatient clinic. However, the possibility of the occurrence of asymptomatic AF episodes in these patients cannot be ruled out, due to methodological limitations in identifying episodes of AF recurrence after AAT based on symptoms or ECG findings.

Furthermore, when selecting drugs to prevent recurrence of paroxysmal AF, in cases where onset is closely related to exertion or psychological tension, β-blockers are generally selected rather than class-I antiarrhythmic drugs such as flecainide.

Conclusion

We found that flecainide showed higher efficacy in the long-term prevention of AF recurrence in patients with diurnal type AF, in whom AF occurred only during the daytime.

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