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# Long-Term Efficacy of Hybrid Pharmacologic and Ablation Therapy in Patients with Pilsicainide-Induced Atrial Flutter

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## Summary

*Background:* Combination therapy with catheter ablation of the cavo-tricuspid isthmus and continued drug therapy, that is, "hybrid therapy," in patients with atrial fibrillation (AF) and drug-induced atrial flutter (AFL) is reported to be an alternative means of achieving and maintaining sinus rhythm. With respect to choosing this method among the rhythm control therapies, its long-term efficacy and the prevalence of AFL in patients with AF are very important and have not been fully elucidated.

*Hypothesis:* The purpose of this study was to investigate the long-term effectiveness of this hybrid therapy and the dose prevalence in Ic drug-induced AFL.

*Methods:* The subjects were 89 patients (aged 62.4 years, 72 men) with episodes of AF (paroxysmal type: 65, persistent type: 11, permanent type: 13). After 4 weeks of oral pilsicainide administration, the dose was increased in those with no documented AFL. The patients who experienced AFL with pilsicainide (Ic-AFL) underwent ablation.

*Results:* Pilsicainide administration resulted in the common type AFL in 17 patients (19.1%). The pilsicainide plasma concentration in the patients with Ic-AFL was significantly higher than in those without AFL ($0.79 \pm 0.41$ vs. $0.51 \pm 0.24$ μg/ml, respectively, $p < 0.01$). During a 10–54 (mean $37 \pm 14$) month follow-up period, sinus rhythm was maintained in 10 of 12 patients after successful ablation followed by continued antiarrhythmic drug administration.

*Conclusions:* Hybrid therapy with ablation and high doses of pilsicainide was useful in maintaining sinus rhythm in some selected patients with AF and drug-induced AFL.

**Key words:** atrial fibrillation, class Ic drug, atrial flutter, pilsicainide, catheter ablation, hybrid therapy

## Introduction

Antiarrhythmic drugs may occasionally provoke a new arrhythmia. It is known that atrial fibrillation (AF) in selected patients may convert into atrial flutter after treatment with antiarrhythmic drugs, especially strong Na-channel blockers (Vaughan-Williams class Ic drug).[1–4] Since class Ic-drugs prolong the cycle length of induced atrial flutter and have no suppressive effects on the atrioventricular (AV) conduction, episodes of atrial flutter with 1:1 AV conduction may occur and are regarded as high-risk proarrhythmias.[5–9]

On the other hand, in such patients with so-called class Ic-atrial flutter, a combination therapy with catheter ablation of the cavo-tricuspid isthmus and continued drug therapy, that is, "hybrid therapy," has been reported to be a promising means of rhythm control of AF.[10–16] The most important issue of this therapy is its long-term efficacy, which has not been fully investigated. Since this therapy cannot be applied to patients with AF in whom atrial flutter cannot be induced by antiarrhythmic drugs, the factors affecting the prevalence of drug-induced atrial flutter are also a matter of concern.

Pilsicainide hydrochloride is a newly synthesized drug with class Ic antiarrhythmic properties available in Japan.[17–19] Some studies have demonstrated that this drug is effective in restoring and maintaining sinus rhythm without major adverse effects in patients with AF.[20, 21] Pilsicainide has been widely used to treat AF in Japan, and we have selected that drug for this study.

The purpose of this study was to investigate prospectively the long-term effectiveness of hybrid therapy using pilsicainide and to elucidate the relationship between the prevalence of Ic atrial flutter and the pilsicainide dose.

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## Methods

### Study Population

This study included 89 consecutive patients (aged 62.4 ± 11.6 years, 72 men) who complained of symptomatic episodes of AF which they suffered for 33.9 ± 47.9 months; they were enrolled from four centers from July 1999 to March 2004. Exclusion criteria included a history of myocardial infarction within 4 weeks, severe dysfunction of the left ventricle (ejection fraction < 30%), sick sinus syndrome or an obvious conduction disturbance, severe renal or hepatic dysfunction, and pregnancy. All patients had 12-lead electrocardiograms (ECGs) or 24-h Holter recordings showing AF but no episodes of atrial flutter before the administration of pilsicainide. Eighty-nine patients had paroxysmal (n = 65) or persistent (n = 11) AF and 13 had permanent AF.

The underlying diseases in 89 patients consisted of hypertension (n = 22), ischemic heart disease (n = 4), and valvular heart disease (n = 13). Left ventricular ejection fraction was 42–84% (67.4 ± 8.3%) and the patients' body weight ranged from 40–97 kg (62.2 ± 10.0 kg). Beta blockers, calcium antagonists, and digitalis were administered in 35, 22, and 17 patients, respectively, as concomitant drugs. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, nitrates, and diuretics were also used to treat hypertension, angina pectoris, and heart failure in 7, 2, 4, and 6 patients, respectively.

### Study Protocol

Initially, oral pilsicainide with a standard daily dose (75–150 mg/day) was administered in all patients for 4 weeks. The arrhythmia status in each patient was evaluated using the 12-lead ECG and the patient's symptoms observed at the end of Week 4 after starting the pilsicainide, and the plasma concentration of the pilsicainide was also measured. If the ECG showed sinus rhythm, the patients continued to receive pilsicainide to maintain sinus rhythm. If the ECG showed AF after 4 weeks of pilsicainide administration, the dose was increased in those patients in whom doses up to 150–225 mg/day seemed appropriate, taking their age, body weight, and cardiac function into consideration. These subjects were reevaluated again 4 weeks later. In patients who developed Ic atrial flutter, an electrophysiologic study and catheter ablation therapy were offered.

Following informed consent, the electrophysiologic study was performed using a steerable 20-pole catheter (St. Jude Medical, Daig Div., Minnetonka, Minn., or Cordis Webster Inc., Baldwin Park, Calif., USA) and steerable quadripolar catheters placed in the high right atrium, coronary sinus, and His-bundle positions. Furthermore, if the Ic atrial flutter was electrophysiologically diagnosed to have a cavo-tricuspid isthmus-dependent reentrant circuit, the patients underwent radiofrequency catheter ablation. Ablation was performed to achieve a line of block in the cavo-tricuspid isthmus during atrial pacing. A continuous application of radiofrequency energy generated using a HAT200S generator (Dr. Osypka, GmbH, Medizintechnik, Grenzach-Whylen, Germany) during pullback of the ablation catheter from the tricuspid annulus toward the inferior vena cava or the Eustachian ridge was performed using an ablation catheter (7 French-size, 4 or 8 mm tip electrode) with a target temperature of 55–60°C. Successful ablation was defined when the achievement of bidirectional complete isthmus conduction block could be demonstrated and no further induction of isthmus-dependent atrial flutter could occur under burst atrial pacing.

### Post-Ablation Follow-Up

After catheter ablation, pilsicainide administration was continued and the patients were evaluated by their symptoms, physical findings, and a 12-lead ECG every 4 weeks at the outpatient clinic.

### Data Analysis

The quantitative data were expressed as the mean ± 1 standard deviation (SD) and compared using a two-tailed Student's test. Categorical data were compared using a two-tailed Fisher's exact test. Univariate analysis of factors associated with the late occurrence of persistent atrial flutter was performed using a Fisher's exact test. A p value $< 0.05$ was considered statistically significant.

## Results

### Effects of Pilsicainide on Atrial Fibrillation

Of 89 patients with AF, pilsicainide caused atrial flutter in 17 (19.1%). Of these (15 men), the type of AF before the administration of pilsicainide was paroxysmal in 15 and persistent in 2 patients. There was no significant difference in the concomitant drugs and underlying disease among the 17 patients with induced atrial flutter and among the remaining 72 patients.

Of the remaining 72 patients, AF converted into sinus rhythm in 39 patients, was still recorded in 29 patients, and 4 patients stopped taking the drug for probable side effects such as dizziness, skin eruptions, or nausea. Of the 29 patients with AF, rate control therapy was selected in 9 with the permanent type of AF, and pilsicainide was changed to another Na-channel blocker and/or K-channel blocker to convert AF to sinus rhythm in 20 patients with paroxysmal or persistent type of AF.

### Electrophysiologic Study and Catheter Ablation

Of the 17 patients with atrial flutter, an electrophysiologic study was performed in 14, and 3 patients preferred not to undergo the study. In all 14 patients undergoing the electrophysiologic study, activation and entrainment mapping revealed counterclockwise (n = 13) or clockwise (n = 1) isthmus-dependent atrial flutter. Isthmus-nondependent atrial flutter was also induced in one of those patients with isthmus-dependent atrial flutter. Those 14 patients underwent radiofrequency

TABLE I Outcome after catheter ablation in 14 patients with class Ic atrial flutter

| No. | Age | Sex | Type of AF | Outcome of ablation | Cardiac after ablation | Oral AA (duration of no AF) | Present cardiac rhythm | Duration of SR (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 60 | M | Paroxysmal | S | SR | PIL (54) | SR | 54 |
| 2 | 45 | M | Paroxysmal | S | SR | PIL (43) | SR | 43 |
| 3 | 54 | M | Paroxysmal | S | SR | PIL (25) | SR | 25 |
| 4 | 62 | M | Paroxysmal | S | SR | PIL (54) | SR | 54 |
| 5 | 62 | M | Paroxysmal | S | SR | PIL (42) | SR | 42 |
| 6 | 77 | F | Paroxysmal | S | SR | PIL (35) | SR | 35 |
| 7 | 76 | M | Paroxysmal | S | SR | PIL (18) | SR | 18 |
| 8 | 66 | M | Paroxysmal | S | SR | PIL (10) | SR | 10 |
| 9 | 70 | M | Paroxysmal | S | SR | PIL (3)/CIB (44) | SR | 47 |
| 10 | 67 | M | Persistent | S | SR | PIL (7)/CIB (35) | SR | 42 |
| 11 | 61 | F | Paroxysmal | S | SR | PIL (29) | AF | 29 |
| 12 | 56 | M | Persistent | S | SR | PIL (< 1) | AF | < 1 |
| 13 | 52 | M | Paroxysmal | F | SR | PIL (< 1) | AF | < 1 |
| 14 | 53 | M | Persistent | F | AF | PIL (< 1) | AF | < 1 |

*Abbreviations:* AF = atrial fibrillation, SR = sinus rhythm, AA = antiarrhythmic agent, PIL = pilsicainide, CIB = cibenzoline, S = successful, F = failed.

catheter ablation of the atrial flutter at the isthmus. Bidirectional conduction block at the isthmus was achieved in 12 patients and the ablation failed in 2 patients.

### Follow-Up

The clinical features and follow-up data in 14 patients after catheter ablation of atrial flutter are summarized in Table I. All 12 patients in whom bi-directional conduction block was achieved continued to receive pilsicainide after successful ablation of the atrial flutter. In two patients, sustained AF recurred within 1 week after ablation and rate control therapy was selected in them. The remaining 10 patients remained in sinus rhythm on successively recorded ECGs throughout a 10–54 (mean 37 ± 14) month follow-up; this did not mean perfect freedom from AF because some of these patients complained of palpitation paroxysms lasting for a few minutes, and no Holter ECG was recorded during the follow-up period. Eight of those 10 patients remained in sinus rhythm by continuing to receive oral pilsicainide without any complications. In two of these patients, in whom AF recurred 3 to 6 months after the ablation procedure in spite of receiving pilsicainide, sinus rhythm was resumed and maintained by changing pilsicainide to another class I drug (cibenzoline).

### Prevalence of Ic Atrial Flutter versus Pilsicainide Dose

The incidence of class Ic atrial flutter with pilsicainide was 8 of 84 (9.5%) in those patients maintained on the initial dose and 7 of 15 (47.1%) in those receiving an increased dose. As indicated in Figure 1, the dose received by the patients in whom Ic atrial flutter was induced after pilsicainide administration was significantly higher than that in those without Ic atrial flutter. Furthermore, a pilsicainide dose ≥ 2.5 mg/kg was

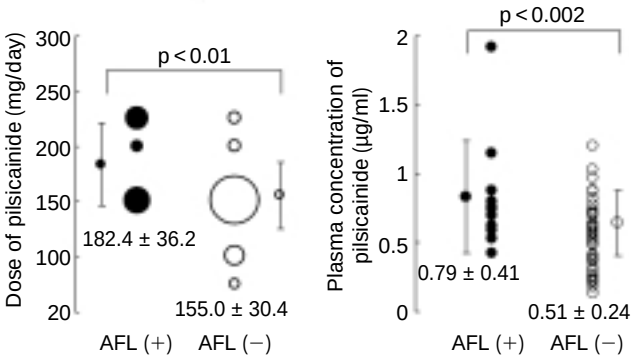


FIG. 1 Dose of pilsicainide and its plasma concentration versus the prevalence of Ic atrial flutter (AFL).

statistically significant in terms of inducing atrial flutter in patients with AF, as shown in Table II. Since the therapeutic range of pilsicainide is 0.3–0.9 μg/ml, the plasma concentration of pilsicainide in the patients with Ic atrial flutter was mostly within the therapeutic range as demonstrated in Figure 1. In two patients, the blood concentration level of pilsicainide was higher than the therapeutic upper limit of pilsicianide, but no complications including bradycardia or marked widening of the QRS complex were observed.

## Discussion

### Main Findings

1. In the 10 patients, who underwent successful catheter ablation of Ic atrial flutter and had no early recurrence of AF after catheter ablation, hybrid ablative and drug therapy was effective in maintaining sinus rhythm for 37 ± 14 months.

TABLE II Relationship between pilsicainide and the prevalence of Ic atrial flutter (AFL)

| Dose of pilsicainide | Ic-AFL (+) | Ic-AFL (−) |
|---|---|---|
| ≥ 2.50 mg/day/kg | 10 | 23 |
| < 2.50 mg/day/kg | 5 | 32 |
| Chi-square; $p < 0.01$ | | |

| Plasma concentration of pilsicainide | Ic-AFL (+) | Ic-AFL (−) |
|---|---|---|
| ≥ 0.53 μg/ml | 10 | 20 |
| < 0.53 μg/ml | 1 | 27 |
| Chi-square; $p < 0.0001$ | | |

2. Atrial fibrillation was converted to atrial flutter with pilsicainide in 17 of 89 patients (19.1%). The incidence of Ic atrial flutter increased significantly in the patients receiving a higher dose of pilsicainide as well as in those with a higher plasma concentration level of the drug.

### Long-Term Efficacy of Hybrid Therapy

Previous reports have proved the effectiveness of hybrid therapy, but the follow-up periods are 11–24 months.[10–16] In this study, we demonstrated that hybrid therapy was effective in maintaining sinus rhythm by administering pilsicainide or other class Ia drugs over long periods of up to 54 months in patients who underwent successful isthmus ablation and had no recurrence of AF within 1 month after catheter ablation.

It should be noted that no side effects, including ventricular proarrhythmic events or drug discontinuation due to heart failure, occurred in eight patients receiving pilsicainide for long periods. This may be related to the pilsicainide properties: it is a slow kinetic Na-channel blocker but has a less negative inotropic effect than disopyramide and possibly other class Ic drugs with significant negative inotropic effects.[17]

As described in Results, maintenance of sinus rhythm by hybrid therapy does not mean that all paroxysms of AF are totally suppressed all the time during the follow-up period; instead, sinus rhythm is maintained most of the time during the follow-up period and paroxysmal AF may occur but would not be sustained, and would most likely terminate within a few minutes.

### Prevalence of Ic Atrial Flutter and Pilsicainide Dose

When a hybrid therapy is chosen from among all the rhythm control therapies for AF, the prevalence of Ic drug-induced atrial flutter is a matter of concern because this therapy cannot be applied to patients with AF without Ic atrial flutter. Although there is a wide variation (3.5–20%) in the reported incidence of class Ic atrial flutter[11–16] using different kinds of Ic-drugs, the effects of different doses of an antiarrhythmic drug on the prevalence of Ic atrial flutter have not fully been investigated.

The overall incidence rate of Ic atrial flutter with pilsicainide was 19.1%, which appeared to be equivocal to that with other class Ic drugs. Clinically, pilsicainide is reported to be well tolerated and effective in maintaining sinus rhythm in patients with AF.[20, 21] It is noteworthy that the incidence of class Ic atrial flutter in the patients with an increased dose of pilsicainide was significantly higher than that in the patients maintained on the initial dose (47.1 vs. 8.3%). Therefore, the Ic atrial flutter induction rate with pilsicainide was variable and highly dependent on the administered dose of the drug, as shown in Table II, indicating that a dose > 2.5 mg/kg/day very frequently (approximately 30%) converted AF to atrial flutter.

### How to Use Drugs after Catheter Ablation of Class Ic Atrial Flutter

In two patients with paroxysms of AF recurring later than a month after catheter ablation, changing pilsicainide to another class I drug was useful in resuming and maintaining sinus rhythm. Thus, recurring AF in patients who had Ic atrial flutter and underwent catheter ablation appeared to be sensitive to class I drugs, as previously reported.[14]

## Possible Limitations

The incidence of class Ic atrial flutter with pilsicainide was possibly underestimated, because Ic atrial flutter observed after pilsicainide would have had to last long enough to be recorded on the ECG taken every 4 weeks. In addition, a higher dose of pilsicainide was not given to every patient whose ECG did not exhibit atrial flutter after the initial dose of pilsicainide. As a solution to these limitations, the intravenous administration of class Ic drugs may be an alternative method, since some investigators have reported that complete observation of the ECG during and after drug administration is feasible with that method.[22, 23]

## Conclusions

Higher doses of pilsicainide tended to convert AF into atrial flutter, and a hybrid therapy with ablation and continued pilsicainide was useful for maintaining sinus rhythm for a long period. This hybrid therapy might be one choice for rhythm control therapy in patients with AF and drug-induced atrial flutter.

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