Oral Propafenone To Convert Recent-Onset Atrial Fibrillation in Patients with and without Underlying Heart Disease

A Randomized, Controlled Trial

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Background: The effectiveness of oral propafenone in converting recent-onset atrial fibrillation to sinus rhythm has been established by controlled trials. However, it is not clear whether the effectiveness of propafenone is affected by the presence or absence of underlying heart disease.

Objectives: To investigate the safety and effectiveness of oral propafenone and the role of underlying heart disease.

Design: Randomized, single-blind, controlled study.

Setting: 3 teaching hospitals.

Patients: 240 hospitalized patients with recent-onset atrial fibrillation.

Intervention: Propafenone (one 600-mg oral dose) or placebo.

Measurements: Conversion rates at 3 and 8 hours.

Results: Propafenone was more effective than placebo for converting atrial fibrillation to sinus rhythm at 3 hours: Fifty-four of 119 patients (45%) receiving propafenone and 22 of 121 patients (18%) receiving placebo had conversion ($P < 0.001$). It was also more effective at 8 hours: Ninety-one of 119 patients (76%) receiving propafenone and 45 of 121 patients (37%) receiving placebo had conversion ($P < 0.001$). Subgroup analysis showed that among patients without heart disease, 78% of those receiving propafenone and 56% of those receiving placebo converted to sinus rhythm within 8 hours ($P = 0.02$). In those with hypertension, the rate was 70% for those receiving propafenone and 27% for those receiving placebo ($P < 0.001$); in patients with structural heart disease, the rate was 81% for those receiving propafenone and 17% for those receiving placebo ($P < 0.001$).

Conclusions: Oral loading of propafenone was more effective than placebo for conversion to sinus rhythm within 8 hours and had a favorable safety profile. The rate of spontaneous conversion to sinus rhythm was higher in patients without structural heart disease; this finding has important implications for the assessment of drug effectiveness in recent-onset atrial fibrillation.

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The optimal way to convert recent-onset atrial fibrillation to sinus rhythm is a subject of much debate. The effectiveness of intravenous propafenone has been shown (1–3), but the full antiarrhythmic effect of this regimen depends not only on the parent compound but on its 5-hydroxylated metabolite (4, 5). This dependence provides a strong rationale for the use of oral loading regimens (3). Results of previous controlled studies have shown that oral loading of propafenone is highly effective in converting recent-onset atrial fibrillation to sinus rhythm (6, 7).

Safety is a major concern with antiarrhythmic therapy. One of the primary proarrhythmic risks of propafenone and flecainide is the transformation of atrial fibrillation to flutter with 1:1 atrioventricular conduction and hemodynamic impairment (8–10).

We sought to determine whether the effectiveness and safety of propafenone differ in patients who have structural heart disease and patients who do not.

Methods

From June 1990 to June 1994, consecutive patients with recent-onset atrial fibrillation (≤7 days) who presented to one of three centers were considered for enrollment. Onset of arrhythmia was documented by electrocardiography or by an abrupt onset of palpitations with subsequent evidence of atrial fibrillation on electrocardiography.

Patients were excluded for any of the following reasons: age greater than 80 years, heart failure greater than NYHA (New York Heart Association) class II, mean ventricular rate during atrial fibrillation less than 70 beats/min, recent myocardial infarction (within <6 months), unstable angina pectoris, previous or current electrocardiographic evidence ventricular preexcitation or complete bundle-branch block, previous electrocardiographic evidence of second- or third-degree atrioventricular block or bifascicular block, the sick sinus syndrome, hypokalemia (potassium level <3.5 mEq/L), renal or hepatic failure with severe hypoxia ($PaO_2 < 55$ mm Hg), severe metabolic disturbances, or known thyroid dysfunction. Patients who were receiving long-term digoxin therapy or antiarrhythmic drugs or had received such treatments within 8 hours before study entry were also excluded. Patients who had atrial fibrillation that lasted 72 hours or longer were enrolled only if they were receiving long-term warfarin

therapy for anticoagulation. Patients provided informed consent.

Eligible patients had a 24-hour Holter monitor applied; after 1 to 2 hours of observation to assess the stability of atrial fibrillation, they were randomly assigned by center in a single-blind manner to receive propafenone (300 mg in two tablets as a single oral dose) or placebo. All patients received intravenous saline throughout the study period. The electrocardiogram was monitored by telemetry, blood pressure was measured every 2 hours, and 12-lead electrocardiography was done every hour for the first 4 hours and then every 2 hours for the next 4 hours. When patients converted to sinus rhythm, 12-lead electrocardiography was done immediately. Conversion was defined as a stable sinus rhythm that lasted for at least 1 hour.

Eight hours after the study drug was administered, physicians could continue treatment with the study drug or switch to a different therapeutic option.

Holter monitor tapes were analyzed by two blinded observers using computer scanning systems (Marquette 8000, Milwaukee, Wisconsin, and Del Mar Avionics, Irvine, California) to determine the time of conversion to sinus rhythm and whether an abnormal rhythm was present. Within 24 hours after enrollment, echocardiography was done for each patient and left atrial diameter was measured in the left parasternal long-axis view.

On the basis of clinical history and the results of physical examination, echocardiography, and chest radiography, patients were classified as having structural heart disease (defined as the presence of cardiac abnormalities other than atrial fibrillation), hypertension without structural heart disease (defined as previously recognized systemic hypertension according to the criteria of the World Health Organization), or neither.

Continuous outcomes and baseline characteristics of the patients were compared by using the chi-square statistic and *t*-test as appropriate. The rates of conversion to sinus rhythm were assessed at 3 and 8 hours. Odds ratios and corresponding CIs were calculated according to the methods of Gardner and Altman (11). We did logistic regression analysis to describe how the interaction of treatment with the presence or absence of heart disease and hypertension affected the probability of conversion to sinus rhythm. Analyses were done using SPSS software, version 6.1.3 (SPSS, Inc., Chicago, Illinois).

Table. Patient Characteristics

Characteristic	Propafenone Group (n = 119)	Placebo Group (n = 121)
Men/women, *n/n*	70/49	67/54
Mean age ± SD, *y*	59 ± 12	58 ± 13
Heart disease status, *n*		
No structural heart disease	50	54
Systemic hypertension	37	37
Structural heart disease	32	30
Coronary artery disease	11	9
Valvular heart disease	8	9
Cardiomyopathy	7	8
Congenital heart disease	6	4
New York Heart Association class I	93	95
New York Heart Association class II	27	26
Mean duration of atrial fibrillation ± SD, *h*	31 ± 38	30 ± 35
Mean diameter of left atrium ± SD, *mm*	42 ± 6	41 ± 7
Diameter of left atrium > 45 mm, *n*	24	23

Results

Patients

During the study period, 407 patients presented to the three centers and were screened for eligibility. Two hundred forty-three patients were eligible, and 240 gave consent. A total of 164 patients were excluded for one or more of the following reasons: age greater than 80 years ($n = 10$), heart failure greater than NYHA class II ($n = 33$), recent myocardial infarction ($n = 20$), bundle-branch block ($n = 24$), the sick sinus syndrome ($n = 6$), severe hypoxia ($n = 13$), thyroid dysfunction ($n = 12$), and previous antiarrhythmic treatment ($n = 63$). Two hundred forty patients were randomly assigned to receive propafenone ($n = 119$) or placebo ($n = 121$). The two groups were similar with regard to age, sex, cause of atrial fibrillation, NYHA class, left atrial dimension (measured by echocardiography), structural heart disease, and hypertension (**Table**). The duration of atrial fibrillation before randomization ranged from 2.5 to 120 hours and did not differ significantly between the treatment groups.

Conversion to Sinus Rhythm and Presence of Heart Disease

The probability of conversion to sinus rhythm was greater after propafenone than after placebo at 3 and 8 hours ($P < 0.001$) (**Figure**). Corresponding odds ratios were 3.8 (95% CI, 2.1 to 6.8) at 3 hours and 5.4 (CI, 3.0 to 9.4) at 8 hours.

At 8 hours, the probability of conversion to sinus rhythm was significantly higher in the propafenone group than in the placebo group for patients who had heart disease (odds ratio, 21.7 [CI, 5.9 to 80.1]; $P < 0.001$), patients who had hypertension (odds ratio, 6.4 [CI, 2.3 to 17.6]; $P < 0.001$), and patients who did not have structural heart disease (odds ratio, 2.8 [CI, 1.2 to 6.7]; $P = 0.02$).

Conversion rates at 8 hours for patients receiving propafenone were similar among the three heart disease subgroups, but conversion rates for patients receiving placebo differed significantly (56% for patients without structural heart disease, 27% for patients with hypertension, and 17% patients with

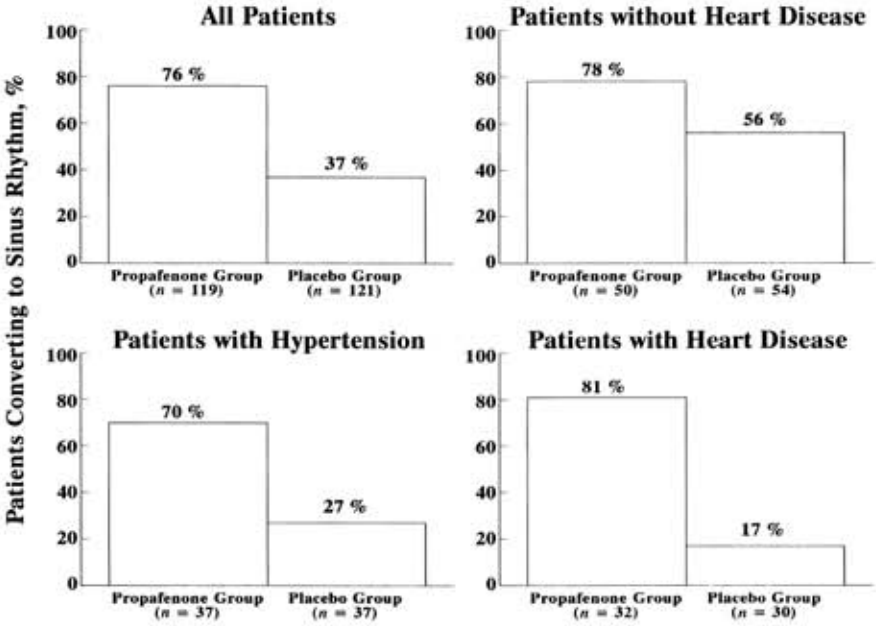

Figure. Conversion to sinus rhythm within 8 hours in patients receiving propafenone or placebo. Rates are shown for the whole population and for three subgroups: patients without heart disease, patients with hypertension, and patients with heart disease.

structural heart disease [$P = 0.009$ by logistic regression model]).

At 3 hours, the probability of conversion to sinus rhythm was higher in the propafenone group than in the placebo group for patients who did not have heart disease (48% for propafenone compared with 26% for placebo; odds ratio, 2.6 [CI, 1.2 to 6.0]; $P = 0.02$), patients who had hypertension (41% for propafenone compared with 16% for placebo; odds ratio, 3.5 [CI, 1.2 to 10.5]; $P = 0.02$), and patients who had structural heart disease (47% for propafenone compared with 7% for placebo; odds ratio, 12.3 [CI, 2.5 to 60.5]; $P < 0.001$). By logistic regression analysis, no significant correlation between heart disease and treatment was seen at 3 hours ($P = 0.2$).

Mean time ± SD for conversion to sinus rhythm within 8 hours was 181 ± 118 minutes for propafenone and 181 ± 112 minutes for placebo ($P > 0.2$).

Adverse Effects

Sustained atrial flutter or tachycardia (lasting ≥1 min) occurred in eight patients (7%) receiving propafenone and seven patients (6%) receiving placebo ($P > 0.2$), regardless of heart disease status. Among these patients, atrioventricular conduction was 2:1 in two patients receiving propafenone (heart rate, 115 to 140 beats/min) and three patients receiving placebo (heart rate, 120 to 150 beats/min), 3:1 in six patients receiving propafenone (heart rate, 60 to 95 beats/min) and three patients receiving placebo (heart rate, 60 to 100 beats/min), and 1:1 in one patient receiving placebo (heart rate, 240 beats/min). This patient developed atrial flutter and collapsed. Pauses in ventricular rate lasting longer than 2 seconds were seen in one patient (1%) receiving propafenone and three patients (2%) receiving placebo ($P > 0.2$).

Among patients receiving propafenone, nine (8%) had the following adverse effects: QRS complexes of the electrocardiogram greater than 120 ms ($n = 3$), hypotension ($n = 2$), slight hypotension and bradycardia at conversion ($n = 3$), and phases of junctional rhythm after conversion ($n = 1$). No ventricular proarrhythmic effects occurred.

Discussion

Oral loading of propafenone was effective for conversion to sinus rhythm in our study, as it has been in smaller studies (3, 6, 7, 12, 13). The recent findings of Wijffels and colleagues (14) in a model of chronic atrial fibrillation in animals indicate that electrophysiologic remodeling occurs within a few hours of persistent atrial fibrillation and results primarily from changes in atrial refractoriness that enhance the persistence of atrial fibrillation. This observation provides a strong rationale for prompt conversion to sinus rhythm. Therefore, oral loading of propafenone (which has an effectiveness similar to that of intravenous propafenone [3]) offers many advantages over such regimens as oral quinidine and intravenous amiodarone, which require titration of dose or a longer period of time to achieve an effect (6, 13, 15). In controlled trials, propafenone was shown to be more effective and to take effect more quickly than amiodarone (13) or digoxin plus

quinidine (6). Intravenous amiodarone was no more effective than placebo and was less effective than oral flecainide within the same evaluation period (12). No significant differences have been seen between oral loading of propafenone or flecainide (7).

We saw only minor adverse effects that were unrelated to underlying heart disease. Atrial fibrillation was transformed into atrial flutter with rapid ventricular response in one patient in the placebo group. It is known that such an effect occurs more often with class 1C drugs than with other drugs or spontaneously, may have the clinical appearance of tachycardia with wide QRS complexes on the electrocardiogram, may induce hemodynamic impairment (8–10), and is usually adrenergic dependent. Thus, it is advisable to keep patients at rest after oral loading of propafenone. It is unknown whether the slight β-blocking effect that is related to the administration of propafenone (16, 17) limits the occurrence of high ventricular rates. The occurrence of atrial tachycardia and flutter in the placebo group emphasizes that tachycardia with regular ventricular rhythm may spontaneously develop during atrial fibrillation even when patients are not receiving class 1C agents (18). Dynamic behavior of atrial fibrillation cycles was recently shown in patients who had lone paroxysmal atrial fibrillation (19).

Our study shows the importance of underlying heart disease in determining the probability of conversion to sinus rhythm: Spontaneous conversion was unlikely to occur in patients who had structural heart disease. This finding, which has not previously been emphasized in the literature, is important when the results of studies of drug effectiveness for conversion of recent-onset atrial fibrillation are considered. The inclusion of patients who do not have heart disease in such studies substantially changes the conversion rate for patients who receive placebo. Inclusion of these patients also increases the number of patients required to assess drug effectiveness. Effective treatment is necessary for patients who have heart disease; rates of spontaneous conversion to sinus rhythm after atrial fibrillation among such patients are extremely low. In patients with heart disease, the effectiveness of propafenone is unaltered. Patients who had hypertension had results that were between those of patients who had heart disease and those of patients who did not. Such results reflect the heterogeneity of the subgroup, which may include patients who have normal hearts and those who have mild-to-moderate left ventricular hypertrophy.

One limitation of our study is that we examined the effectiveness and safety of propafenone in selected patients who had atrial fibrillation treated in a hospital and did not have heart failure. The feasibility of propafenone in older, sicker patients or in outpatients requires further study.

In summary, spontaneous conversion to sinus rhythm occurred within a few hours of propafenone administration, mainly in patients who did not have structural heart disease. This observation is important when planning trials to assess drug effectiveness in recent-onset atrial fibrillation. Regardless of the presence of hypertension or structural heart disease, oral loading of propafenone has a relatively rapid effect (within 2 to 3 hours), a high rate of effectiveness, and a favorable safety profile in patients who do not have heart failure.

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