Propafenone for Conversion of Recent-Onset Atrial Fibrillation*

A Controlled Comparison Between Oral Loading Dose and Intravenous Administration

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Study objective: To compare placebo vs two different regimens of propafenone administration—intravenous administration or short-term oral loading—in converting recent-onset atrial fibrillation to sinus rhythm. Design: Single-blind placebo-controlled study. Patients: Eighty-seven patients with atrial fibrillation of recent onset (≤7 days’ duration) admitted to the hospital without signs of organic heart disease (n=42) or with systemic hypertension without signs or symptoms of heart failure (n=45). The patients were assigned randomly to treatment with intravenous propafenone (29 patients), oral propafenone (29 patients), or placebo (29 patients). Interventions: Administration of propafenone intravenously (2-mg/kg bolus followed by 0.0078 mg/kg/min) or as short-term oral loading (600 mg orally single dose). Patients were submitted to Holter monitoring and conversion to sinus rhythm was evaluated at 1, 3, and 8 h.

Results: Conversion to sinus rhythm was obtained within 1 h in 28% with intravenous propafenone, in 3% with oral propafenone, and in 3% with placebo. At 3 h, the efficacy of intravenous propafenone (41%) and of oral propafenone (55%) were statistically superior to placebo (10% of conversions) and at 8 h either intravenous or oral propafenone were effective in almost two thirds of the patients with a statistical difference vs placebo, whose efficacy was 24%. No major side effects were observed.

Conclusions: Propafenone as an oral loading dose is an efficacious and fast way of treating atrial fibrillation of recent onset and due to its simplicity of administration and safety can be preferred to the intravenous route. (CHEST 1995; 108:355-58)

Key words: antiarrhythmic drugs; atrial fibrillation; propafenone

Paroxysmal atrial fibrillation (AF) is a very common arrhythmia whose pharmacologic conversion to sinus rhythm mainly depends on time of arrhythmia onset, atrial dimensions, and ventricular function. Margolis et al1 have already proposed the administration of an antiarrhythmic drug as oral loading dose and afterwards some reports addressed this topic.2,3 Propafenone is a class 1C antiarrhythmic drug whose efficacy, by intravenous administration, has been proved.4,5 Propafenone, however, has at least one active metabolite, 5-hydroxy-propafenone, that contributes to its antiarrhythmic efficacy.9,11 An oral loading dose of 450 to 600 mg may achieve significant plasma levels of both the compounds.12 The aim of this study was to compare efficacy and safety of intravenous vs oral propafenone administration in patients without organic heart disease or with systemic hypertension without signs or symptoms of heart failure. By considering the high spontaneous conversion rate of AF especially when it is short lasting, we consider also a group of patients treated with placebo as control.

Methods and Materials

Patient Selection

All the patients with recent-onset AF admitted to our institutions were considered for the study. Recent-onset AF was defined as an arrhythmia of 7 days’ duration or less. The main criteria to define the time of arrhythmia onset included either an electrocardiographic documentation during hospitalization or an abrupt, well-defined, onset of palpitations with subsequent electrocardiographic evidence of AF at the time of hospital admission.

The following exclusion criteria were considered: age older than 75 years, presence of underlying structural heart disease other than systemic hypertension, New York Heart Association functional class ≥2 or signs of heart failure at physical examination, a mean ventricular rate (calculated over 15 RR cycles) during AF <70/min, electrocardiographic evidence (present or past) of ventricular preexcitation or of complete bundle branch block, previous electrocardiographic evidence of II-III degree atrioventricular block or of bifascicular block, known sick sinus syndrome, hypokalemia (K <3.5 mEq/L), renal or hepatic insufficiency, severe hypoxia (P02 <55 mm Hg) or severe metabolic disturbances, and known thyroid dysfunctions. Patients were also excluded if they were currently taking

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digitalis, beta-blockers, electrophysiologically active calcium antagonists or antiarrhythmic agents, or had taken one of those drugs in the 8 h preceding the entry into the study. Patients with AF lasting more than 72 h were considered for the study only if they were receiving long-term anticoagulant treatment with warfarin (INR at least ≥2.5). An informed consent was requested from all the patients.

Study Protocol

As baseline evaluation, complete medical history, physical examination, routine biochemical laboratory testing, and a 12-lead electrocardiogram were performed. The patients who fulfilled the eligibility criteria had a 24-h Holter monitor placed. The patients were subsequently observed for 1 to 2 h to check the stability of AF and, after an electrocardiographic confirmation of arrhythmia persistence, were randomly allocated to one of the following treatments: intravenous propafenone (2 mg/kg as bolus in 5 min and then 0.0078 mg/kg/min infusion both diluted in 5% fructose [levulose] solution) or oral propafenone (two tablets of 300 mg as single oral dose) or oral placebo (three tablets as single oral dose). Moreover, intravenous saline solution was administered to the patients treated with oral propafenone or placebo. Drug administration was single blind. Patient’s rhythm was continuously monitored by telemetry since drug administration, cuff blood pressure was measured every 2 h, and a 12-lead electrocardiogram was recorded every hour in the first 4 h and then every 2 h until the end of the study. In every case, a 12-lead electrocardiogram was recorded as soon as conversion to sinus rhythm was observed on telemetry.

At the eighth hour following treatment administration, physicians were allowed to continue the treatment or to change the drug therapy: the present study relates to the results obtained within the first 8 h after initial treatment.

Holter monitor tapes were analyzed by computerized scanning systems (Marquette 8000) to precisely evaluate the time of conversion to sinus rhythm and to estimate other rhythm abnormalities (pauses >2 s, phases of atrial flutter, etc). Atrial flutter was defined as regularization of atrial waves with regular RR intervals. After conversion to sinus rhythm, a cross-sectional echocardiogram was performed in each patient and left atrial diameter was measured in the left parasternal long-axis view.

Analysis of Data

For data analysis, the rates of conversion to sinus rhythm were assessed at 1, 3, and 8 h. Statistical analyses were done using the χ² test for comparison of the number of patients who had conversion to sinus rhythm. The paired t test was applied for analysis of the electrocardiographic changes within each group and using analysis of variance and unpaired t test for comparison between groups in mean conversion times. A p value <0.05 was assumed as statistically significant.

Results

Eighty-seven patients were randomly allocated to one of the three treatments groups (29 to intravenous propafenone, 29 to oral propafenone, and 29 to placebo). As reported in Table 1, the three groups were comparable for age, gender, etiology, and New York Heart Association functional class. Also the length of AF before randomization, the percentage of patients with previous episodes of AF, and the left atrial size at the cross-sectional echocardiographic study were comparable (Table 1). Conversion rates to sinus rhythm at 1, 3, and 8 h respectively, are reported in Figure 1. Intravenous propafenone restored sinus rhythm within 1 h in 28% of the patients (8/29); meanwhile, only 1 patient of the placebo group and 1 of the patients treated with oral propafenone were converted to sinus rhythm (p<0.05 in both cases). The success rate at 3 h was 41% (12/29 cases) for intravenous propafenone and 55% (16/29 cases) for oral propafenone, and both were significantly more effective than placebo (p<0.02 and p<0.001, respectively), whose efficacy was 10% (3/29 cases). At the eighth hour, conversion to sinus rhythm was achieved in 66% (19/29 cases) of the patients treated with intravenous propafenone and 69% (20/29 cases) of the patients treated with oral propafenone, and both were significantly more effective than placebo (p<0.005), whose efficacy was 24% (7/29 cases).

Mean conversion times to sinus rhythm were 138±140 min for intravenous propafenone (range, 7 to 465 min), 163±114 min for oral propafenone (range, 60 to 480 min), and 240±144 min for placebo (range, 30 to 420 min) (NS).

Pauses ≥2 s were observed at the time of conversion to sinus rhythm in three patients treated with intrave-
ous propafenone (2.1, 4.5, and 4.8 s, respectively) and in one patient of each other group (2.6 s with oral propafenone and 2.4 s with placebo). Phases of atrial flutter before conversion to sinus rhythm were detected in one patient treated with intravenous propafenone, in two patients treated with oral propafenone, and in two patients treated with placebo. Atrioventricular conduction ratio was always \( \geq 2:1 \) with ventricular heart rate between 70 and 150/min.

No patient had symptoms of left ventricular insufficiency. Among the patients treated with intravenous propafenone, one subject had hypotension requiring study discontinuation and one had phlebitis in the site of drug infusion. In the group treated with oral propafenone, one patient had a significant QRS widening (from 0.11 to 0.16 s) with induction of a transient complete left bundle branch block and one developed transient hypotension with spontaneous recover. Not one side effect was observed in the placebo-treated patients.

On the electrocardiogram, QRS intervals measured immediately after conversion to sinus rhythm were shorter for placebo-treated patients (77 ± 12 ms) compared with either patients treated with intravenous propafenone (84 ± 12 ms, \( p < 0.05 \)) or oral propafenone (87 ± 12 ms, \( p < 0.01 \)); meanwhile, PR intervals (152 ± 27 ms after placebo) were longer in patients treated with oral propafenone (176 ± 32 ms; \( p < 0.01 \)) but not in patients treated with intravenous propafenone (164 ± 18 ms).

### Discussion

The results of this study confirm the high rate of efficacy of propafenone for converting recent-onset AF to sinus rhythm in patients without left ventricular dysfunction or heart failure.\(^4\)\(^8\) In previous articles, intravenous propafenone was considered and overall efficacy ranged from 43 to 81%.\(^4\)\(^8\) Moreover any prior direct comparison between intravenous and oral propafenone, controlled with placebo, is available in the literature.

By considering previous pharmacokinetic evaluations,\(^9\)\(^-\)\(^12\) oral loading with propafenone can be applied for treating AF of recent onset since significant plasma levels can be attained between 2 and 3 h after dosing.

As known, propafenone is submitted to extensive first-pass hepatic metabolism via hydroxylation and conjugation and among the metabolites the most relevant is 5-hydroxy-propafenone, which is able to exert antiarrhythmic effects.\(^13\)\(^-\)\(^15\) Oxidative metabolism is genetically determined and among white subjects 5 to 10% of the population has a genetically determined impairment in hydroxylation capacity,\(^16\)\(^-\)\(^18\) leading to high plasma levels of propafenone with low or no detectable levels of 5-hydroxy-propafenone.\(^18\)\(^19\) The results of the present article focus on the fact that the efficacy of propafenone, within 3 and 8 h after administration as oral loading dose, is not inferior to intravenous administration either considering conversion rates or mean conversion times. Intravenous administration of propafenone may achieve a 28% positive response within 1 h; however, its success rate increases significantly at 3 and 8 h. Two pharmacokinetic considerations may explain these findings; first a relevant role in antiarrhythmic efficacy may be played by 5-hydroxy-propafenone and some time is needed during intravenous administration before significant plasma levels can be reached,\(^12\) second, a relatively long myocardial uptake has been described for propafenone,\(^20\) thus suggesting either a prolonged time for achieving full efficacy or the need for prolonged intravenous infusions.\(^21\)

Individual assessment of hydroxylation capacity by a debrisoquin test\(^18\)\(^19\) is not a routine procedure;\(^2\) propafenone plasma concentrations are not routinely evaluated in clinical practice.\(^22\) Poor propafenone oxidizers would have higher concentrations of propafenone and low or undetectable levels of 5-hydroxy-propafenone, which is believed to be a more potent antiarrhythmic agent,\(^13\)\(^14\) thus conditioning antiarrhythmic efficacy following drug administration, at the time when 5-hydroxy-propafenone is produced in the liver.\(^9\)\(^12\)\(^13\)\(^19\) If the electrophysiologic effects of 5-hydroxy-propafenone played a significant role in AF conversion, its absence in poor metabolizers would negatively impair AF conversion rate in the hours following oral loading when 5-hydroxy-propafenone levels increase by hepatic metabolism,\(^9\)\(^12\) although this would be counterbalanced by higher propafenone levels.\(^12\)\(^19\) In clinical practice, an approach to propafenone treatment based on individual assessment of hydroxylation capacity seems not applicable, especially when short-term treatments are required, like in AF conversion. Therefore, even if we cannot exclude that

### Table 1—Patient Population

<table>
<thead>
<tr>
<th>Propafenone</th>
<th>Intravenous</th>
<th>Oral</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>M/F</td>
<td>17/12</td>
<td>18/11</td>
<td>17/12</td>
</tr>
<tr>
<td>Age, yr</td>
<td>55±15</td>
<td>57±13</td>
<td>57±15</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without organic heart disease</td>
<td>14</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Previous AF episodes</td>
<td>13</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>AF duration, h</td>
<td>8±7</td>
<td>9±10</td>
<td>7±8</td>
</tr>
<tr>
<td>Atrial diameter at echo, mm</td>
<td>37±7</td>
<td>36±7</td>
<td>38±7</td>
</tr>
<tr>
<td>Left atrial diameter &gt;45 mm</td>
<td>3</td>
<td>3</td>
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</tbody>
</table>

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some of the selected patients were poor propafenone metabolizers, this possibility does not seem to affect the main results of the present article, indicating that overall propafenone efficacy in the first 8 h does not differ between intravenous and oral administration.

In the present study, both oral and intravenous propafenone treatments were relatively safe with the patient lying in bed and under medical control. No one case of wide QRS complexes tachycardia was observed during the study period, although its potential occurrence suggests the need for electrocardiographic monitoring.

In conclusion, oral loading doses of propafenone are a safe, efficacious, and fast way of treating symptomatic episodes of recent-onset AF and due to the simplicity of administration can be preferred to the intravenous route.

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