Amiodarone Versus Propafenone for Conversion of Chronic Atrial Fibrillation: Results of a Randomized, Controlled Study
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OBJECTIVES
The purpose of this study was to investigate the efficacy and safety of amiodarone and propafenone in the conversion of chronic atrial fibrillation in a prospective, randomized, placebo-controlled study.

BACKGROUND
The effectiveness of amiodarone and propafenone in the treatment of patients with chronic atrial fibrillation has not been adequately studied.

METHODS
One hundred one patients (48 men, mean age 64 ± 9 years) with atrial fibrillation lasting >3 weeks participated in the study. Thirty-four patients received amiodarone (300 mg intravenously over 1 h, followed by 20 mg/kg over the next 24 h plus 600 mg orally, in three doses, for 1 week, then 400 mg/day orally, for three weeks), 32 received propafenone (2 mg/kg intravenously over 15 min, followed by 10 mg/kg over 24 h and then 450 mg/day orally, for one month) and the remaining 35 served as control subjects. All patients received digoxin and anticoagulant treatment as indicated (International Normalized Ratio 2 to 3).

RESULTS
Conversion to sinus rhythm was achieved in 16 (47.05%) patients who received amiodarone, in 13 (40.62%) who received propafenone and in none of the control subjects (p < 0.001 for both groups vs. control subjects). Those who converted had smaller atria than those who did not and atrial fibrillation of shorter duration in both the amiodarone and propafenone groups. Treatment was discontinued in one patient of the propafenone group because of significant QRS widening.

CONCLUSIONS
Amiodarone and propafenone appear to be safe and equally effective in the termination of chronic atrial fibrillation. Left atrial diameter and arrhythmia duration are independent predictors of conversion. (J Am Coll Cardiol 1999;33:966–71) © 1999 by the American College of Cardiology

Previous studies suggest that both amiodarone and propafenone are highly effective in restoring sinus rhythm in patients with recent onset atrial fibrillation (1–8). However, their effect on patients with long-lasting atrial fibrillation, a condition under which chemical agents exhibit their lowest conversion rate, has not been adequately studied. The purpose of the present randomized, comparative, placebo-controlled study was to assess the efficacy and safety of both amiodarone and propafenone in restoring sinus rhythm in patients with chronic atrial fibrillation (lasting >3 weeks).

METHODS

Patients. From a total of 115 consecutive patients with chronic atrial fibrillation who came to the emergency department or were treated in our clinic, 101 (48 men, 53 women, mean age 64 ± 9 years) were selected for inclusion in the study. Patients with recent myocardial infarction (one patient), heart surgery within the last six months (one patient), acute pericarditis (two patients), severe uncontrolled heart failure (ejection fraction <30%) or cardiogenic shock (four patients), significant chronic obstructive pulmonary disease (three patients) or thyroid disease (three patients) were excluded. Other exclusion criteria were unstable angina, acute myocarditis, pulmonary embolism, pneumonia, liver or kidney failure, electrolyte disturbances, pregnancy or lactation, age <18 years, sick sinus syndrome, a history of second- or third-degree atrioventricular block or the taking of any other antiarrhythmic drug apart from digoxin within a period less than five half-lives of the drug in question before the study.

Study protocol. The study was approved by the hospital’s Ethics Committee. After informed consent was obtained, patients were randomized to receive either amiodarone,
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propafenone or placebo. Patients randomized to amiodarone received 300 mg intravenously for 1 h and then 20 mg/kg over 24 h. At the same time, they were given 600 mg per day in three doses, orally, for one week. Thereafter they received 400 mg per day for 3 weeks. Patients randomized to propafenone began with 2 mg/kg intravenously over 15 min, followed by 10 mg/kg over 24 h and then 450 mg/day, orally, for one month. Patients in the placebo group received an identical amount of saline on the first day, and then oral placebo for one month. Digoxin (0.5 mg intravenously initially, followed by 0.25 mg at 2 h and 0.25 mg every 6 h thereafter) was administered for 24 h to all patients who had not previously received it. Subsequently, the digoxin dosage was adjusted to maintain therapeutic serum concentrations in all patients. To prevent thromboembolic episodes, all patients who were not already taking anticoagulant medication were given acenocoumarol (International Normalized Ratio 2 to 3) for >21 days before cardioversion was attempted. This treatment was continued for 21 days after successful cardioversion or indefinitely when cardioversion was not achieved.

**Monitoring and follow up.** During the first 24 h (during intravenous administration) all patients were kept in the coronary care unit under continuous monitoring of the electrocardiogram (ECG) and blood pressure. They were then kept under observation in the cardiology department for at least two days before being discharged. Patients were evaluated in the clinic after the completion of one week of treatment and then each week until one month. Before the patients’ entry into the study, a full history was taken and the following examinations were carried out: physical assessment, 12-lead ECG, 24-h ambulatory ECG, chest roentgenogram and test of liver function. At each weekly follow-up visit, physical examination, routine laboratory tests, 12-lead ECG and rhythm strip were repeated. Tests of thyroid function were performed before entry and at the one-month visit. An echocardiographic examination was performed in all patients within a period of 7 to 30 days after they were entered into the study.

**Definition of terms.** Atrial fibrillation was considered chronic when its duration was at least three weeks, with no instances of sinus rhythm. For the precise determination of the onset of atrial fibrillation we took into account the electrocardiographically proven time of onset (for patients treated in our clinic) or the clearly determined time of onset of symptoms such as palpitations, dyspnea and chest congestion (for those patients who came to the emergency department). Repeated 12-lead ECG and 24-h Holter recordings were used to document the chronic nature of the arrhythmia before cardioversion.

Treatment was considered successful if conversion to sinus rhythm was achieved within the study period. In patients who did not convert to sinus rhythm, conversion was attempted using other antiarrhythmic drugs or current cardioversion.

**Statistical analysis.** Summary descriptive statistics are expressed as mean ± SD. Patients in whom normal sinus rhythm was restored by the end of the 1-month observation period were censored. All patients had complete follow-up data. Continuous variables were compared using the unmatched t test and categorical data by the chi-square test or Fisher exact test as appropriate. To assess whether the two drugs differed significantly in their effect, time to normal sinus rhythm curves were constructed using the Kaplan–Meier product limit estimate method and compared using the log-rank test. Log-rank comparisons of Kaplan–Meier curves were also used for a univariate assessment of the prognostic value of potential risk factors, such as age, gender, left atrial diameter, left ventricular ejection fraction, baseline ventricular rate, underlying cardiac disease and atrial fibrillation duration, measured at study entry. For all comparisons a p value <0.05 was the criterion for significance.

**RESULTS**

Of the 101 patients who were enrolled, 34 were randomized to amiodarone, 32 to propafenone and 35 to placebo. There were no significant differences between the three groups regarding age, gender, duration of atrial fibrillation, underlying cardiac disease, baseline ventricular rate, left atrial size or left ventricular ejection fraction measured echocardiographically (Table 1). Twelve patients (4 on amiodarone, 3 on propafenone and 5 on placebo) had had previous

<table>
<thead>
<tr>
<th>Patients’ Characteristics</th>
<th>Amiodarone Group</th>
<th>Propafenone Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/18</td>
<td>16/16</td>
<td>16/19</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64 ± 9</td>
<td>64 ± 10</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Mean ventricular rate (beats/min)</td>
<td>93 ± 10</td>
<td>92 ± 15</td>
<td>94 ± 14</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 ± 16</td>
<td>135 ± 14</td>
<td>133 ± 13</td>
</tr>
<tr>
<td>Underlying cardiac disease (%)</td>
<td>14 (41.17)</td>
<td>13 (40.62)</td>
<td>15 (42.85)</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>162 ± 95</td>
<td>162 ± 100</td>
<td>163 ± 100</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>46.89 ± 8.15</td>
<td>47.63 ± 5.68</td>
<td>47.97 ± 5.90</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50 ± 8</td>
<td>51 ± 6</td>
<td>50 ± 8</td>
</tr>
</tbody>
</table>

No significant differences were found between the three groups.

AF = atrial fibrillation; LVEF = left ventricular ejection fraction.
successful cardioversion (seven electrical). Seven of these 12 were under medication for the maintenance of sinus rhythm (four on sotalol, two on disopyramide, one on quinidine). These medications were discontinued five half-lives before the time of the patients’ entry to the study.

Conversion to sinus rhythm. Three of the 32 (9.3%) patients receiving propafenone and none of those given amiodarone or placebo converted to sinus rhythm within the first 24 h.

At two weeks, another 10 patients in the propafenone group had converted, making 13 of the 32 in all (40.7%). Eleven of the 34 (32.4%) in the amiodarone group and none of the placebo group had converted. The first conversion in the amiodarone group was on day 9.

By the end of the study period five more of the patients receiving amiodarone had converted, making 16 in all (47.05%). No other patients receiving propafenone and none of those receiving placebo had converted to sinus rhythm (p < 0.001 for amiodarone or propafenone vs. placebo for the whole study period). In 17 patients (5 on amiodarone, 3 on propafenone, 9 on placebo) beta-adrenergic blocking agents were added to the treatment regime to achieve better control of the heart rate. Of these patients, 4 (3 on amiodarone, 1 on propafenone) converted.

The estimated mean time to conversion was 23 ± 1.4 days in the amiodarone group and 20 ± 2 days in the propafenone group (p = NS). Figure 1 shows the cumulative conversion progression to normal sinus rhythm in the two treatment groups.

Predictors of conversion. Since none of the patients receiving placebo converted, we restricted our attention to the other groups, to identify potential predictors of conversion.

As can be seen in Table 2, those who converted to sinus rhythm after treatment with either amiodarone or propafenone had atrial fibrillation of shorter duration and smaller atria than those who did not. Gender, age, left ventricular ejection fraction, underlying cardiac disease and the baseline heart rate did not appear to have any significant relationship with conversion in any group.

To examine the role of left atrial size and atrial fibrillation duration in more detail, we dichotomized these two predictors at the statistical median and computed the conversion rates for both drugs (Table 3). Patients with left atrial size ≤48 mm or atrial fibrillation duration <3 months had very high monthly conversion rates with either amiodarone or propafenone. In contrast, in patients with left atrial size

Table 2. Predictors of Conversion by Drug Treatment (Univariate Assessment)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Risk Factors</th>
<th>Conversion</th>
<th>No Conversion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Gender (male/female)</td>
<td>8/8</td>
<td>8/10</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>66 ± 8</td>
<td>63 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Mean ventricular rate (beats/min)</td>
<td>94 ± 11</td>
<td>92 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure (mm Hg)</td>
<td>135 ± 16</td>
<td>133 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Underlying cardiac disease (%)</td>
<td>6 (42.85)</td>
<td>8 (57.15)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>AF duration (days)</td>
<td>108 ± 44</td>
<td>210 ± 103</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Left atrial diameter (mm)</td>
<td>41.04 ± 6.67</td>
<td>52.08 ± 5.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>LVEF (%)</td>
<td>52.81 ± 7.06</td>
<td>47.77 ± 7.90</td>
<td>NS</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Gender (male/female)</td>
<td>6/7</td>
<td>10/9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>62 ± 13</td>
<td>65 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Mean ventricular rate (beats/min)</td>
<td>90 ± 20</td>
<td>92 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure (mm Hg)</td>
<td>137 ± 15</td>
<td>132 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Underlying cardiac disease (%)</td>
<td>6 (46.15)</td>
<td>7 (53.85)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>AF duration (days)</td>
<td>99 ± 54</td>
<td>206 ± 102</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Left atrial diameter (mm)</td>
<td>42.93 ± 4.73</td>
<td>50.84 ± 3.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>LVEF (%)</td>
<td>52 ± 6</td>
<td>50 ± 5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
>48 mm or atrial fibrillation duration >3 months the conversion rates for both agents were dramatically lower. Furthermore, as Figure 2 clearly shows, patients with left atrial size ≤48 mm or atrial fibrillation duration <3 months had a greater likelihood of converting sooner, rather than later.

A multivariate stepwise proportional hazards Cox regression model revealed that left atrial size and atrial fibrillation duration were the only independently significant factors affecting time to conversion, (χ-square = 28.9, β = −0.1 ± 0.02, p < 0.0001, and χ-square = 8.4, β = −0.008 ± 0.031, p < 0.003, respectively). More precisely, the model implies that a 5-mm increase in left atrial size results in a 42% reduction in the conversion rate; every month of atrial fibrillation duration reduces the conversion rate by 22%.

Adverse effects. Treatment was discontinued in only one patient (propafenone group) because of significant QRS widening (from 0.10 to 0.16 s). No other adverse effects necessitating drug discontinuation occurred.

There were no proarrhythmic effects, defined as the new onset of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes, either in patients who converted to sinus rhythm or in those who remained in atrial fibrillation.

No side effects were observed in the placebo group.

**DISCUSSION**

Propafenone and amiodarone are considered to be among the most promising antiarrhythmic agents (1–8). Propafenone markedly slows conduction in the atrial myocardium (class lc antiarrhythmic drug), whereas amiodarone mainly

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**Table 3. Conversion Rate (%) of Significant Predictors Dichotomized at the Statistical Median**

<table>
<thead>
<tr>
<th>Significant Risk Markers</th>
<th>Treatment</th>
<th>Amiodarone (%)</th>
<th>Propafenone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial diameter ≤48 mm</td>
<td>88.5</td>
<td>70.6</td>
<td></td>
</tr>
<tr>
<td>&gt;48 mm</td>
<td>11.11</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>AF duration ≤3 months</td>
<td>68.75</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>27.8</td>
<td>23.53</td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation.
prolongs the effective refractory period of atrial myocardial cells (class III drug) (6,9). On the basis of the leading theory of atrial reentry and atrial fibrillation, drugs that have these properties should be potent antifibrillatory agents (4,9).

Although the effectiveness of these two drugs in the cardioversion of recent onset atrial fibrillation has been well documented, their effectiveness in cases of chronic atrial fibrillation has not been studied adequately. Existing studies of amiodarone or propafenone are few and include small numbers of patients. Furthermore, most of them did not use a placebo control group, and so the real value of their findings is limited (1–4,6–8,10). For this reason, our study was structured in such a way as to enable us both to evaluate the real efficacy and safety of the two drugs tested for the conversion of chronic atrial fibrillation and to make a comparison between them.

**Efficacy of the drugs.** Our findings indicate that both amiodarone and propafenone could be used for the conversion of chronic atrial fibrillation to sinus rhythm. However, factors such as the duration of chronic atrial fibrillation and the size of the left atrium must be taken into account. Patients with a small left atrium and/or relatively short lasting atrial fibrillation show the highest conversion rates and therefore reap the most benefit from treatment with both drugs. The larger the left atrium and the longer the duration of the atrial fibrillation, the lower the efficacy of both drugs, with the result that patients with a very large left atrium or long-lasting atrial fibrillation have a low conversion rate. However, the fact that these patients, according to our results, do not convert spontaneously, shows that both agents could be of some benefit even in such cases.

According to our findings, both agents are equally effective in restoring sinus rhythm in patients with chronic atrial fibrillation, even though they have different mechanisms of action. However, if we examine the results more carefully we see that propafenone starts to convert earlier; none of our patients receiving this drug converted after more than 15 days. In contrast, amiodarone, while relatively slow in terms of its first successful conversion (>9 days), continued to cardiovert at a steady rate until the end of the observation period. It is therefore possible that the slight superiority of amiodarone observed at 1 month (47% vs. 41%) could become significant with more months of treatment, assuming of course that amiodarone would continue to cardiovert at the same rate. The fact that amiodarone is known to have a relatively slow onset of activity, with its full action as a class III agent appearing after at least 1 month, explains its delayed effectiveness in cardioversion and supports our suggestion (1–3,9–11).

**Time to conversion.** The size of the left atrium and the duration of chronic atrial fibrillation affect not only the likelihood of conversion to sinus rhythm but also when this will happen. The larger the left atrium and the longer the duration of atrial fibrillation, the later the conversion is likely to occur, under treatment with either amiodarone or propafenone. It is indicative that all of our patients who had a large left atrium (>48 mm) or long-lasting atrial fibrillation (>3 months) began to convert after more than 6 days, regardless of treatment (Fig. 2). This probably has to do with the fact that both agents, amiodarone especially, need a long time to achieve their full efficacy, which is clearly needed in difficult cases such as these. Potential mechanisms for this are, first, the slow accumulation of both agents in the myocardium, which has been observed in previous studies, and second, the fact that both propafenone and amiodarone metabolize into substances (5-hydroxypropafenone and des-ethylamiodarone, respectively) that are able to exert antiarrhythmic effects and the levels of which increase gradually during long periods of administration (5,6,10–14).

**Intravenous and oral administration.** Both drugs were administered in a combination of intravenous and oral doses. This approach was designed to assess the role of the long-term oral administration of the two agents in the conversion of chronic atrial fibrillation in cases resistant to the short-term treatment, and not to make a direct comparison of the two modes of treatment. There are already many studies, especially in the case of propafenone, which have compared intravenous with oral administration and have come to the conclusion that there are no significant differences as regards effectiveness (1–6).

**Previous studies.** Previous studies that investigated the effect of chemical cardioversion on chronic atrial fibrillation reported lower conversion rates, both with amiodarone or propafenone and with other drugs (1–4,6,7,10,15–21). Our good results probably have to do with the long time of administration of the two agents in our study. This hypothesis is reinforced by the findings of Kerin et al. (18), who observed for amiodarone that the longer the duration of treatment, the higher the conversion rate.

Regarding the roles of atrial fibrillation duration and left atrial size in the conversion of atrial fibrillation, our results are not surprising. Most controlled trials of antiarrhythmic agents agree that the size of the left atrium and the duration of the arrhythmia are significant factors affecting the likelihood of the conversion of atrial fibrillation to sinus rhythm (1–4,22). However, the observation that they also affect the time needed for conversion is new.

**Safety.** Our results show that both agents are quite safe in the restoration of sinus rhythm. Only in one patient receiving propafenone did the treatment have to be discontinued because of QRS widening. However, previous studies have reported significant side effects for both drugs. More specifically, amiodarone has been implicated in many cardiac and noncardiac side effects. It has been proved that the majority of the side effects of amiodarone are dose related; thus, the absence of side effects in our patients was probably due to the relatively short time of administration (1–4,23). As regards propafenone, previous studies have reported a significant proarrhythmic effect, especially in patients with...
underlying cardiac disease. The fact that such patients were excluded from our study could explain our findings with respect to the safety of propafenone (1–5).

**Study limitations.** In our study all patients received digoxin. Digoxin was used in the control group to reduce the high ventricular rate. We chose this drug because it did not seem to affect the likelihood of conversion. Falk et al. (24), in a small, randomized, controlled study, reported similar conversion rates in a placebo group and a digoxin-treated group. However, to exclude any potential benefit or harm from digoxin in the conversion to sinus rhythm we used it in all groups (amiodarone, propafenone and placebo).

**Study implications.** Although electrical cardioversion is considered to be the treatment of choice in patients with chronic atrial fibrillation, amiodarone and propafenone could be used in cases where direct current cardioversion is contraindicated, unavailable or refused. In particular, patients with a small left atrium and/or relatively short-duration chronic atrial fibrillation have a high probability of rapid conversion with both drugs; when the size of the left atrium and the duration of the atrial fibrillation increase, so the likelihood of conversion decreases.

The size of the left atrium and the duration of atrial fibrillation also determine how long treatment must be applied before conversion. The larger the left atrium and the longer the duration of the arrhythmia, the longer the period of treatment required for conversion. However, further studies are needed to determine whether therapy over periods longer than the one-month interval we studied could lead to a higher overall success rate, especially in the case of amiodarone.

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**REFERENCES**