Long-term Maintenance of Normal Sinus Rhythm in Patients With Current Symptomatic Atrial Fibrillation* Amiodarone vs Propafenone, Both in Low Doses

George E. Kochiadakis, MD; Nikos E. Igoumenidis, MD; Michail I. Hamilos, MD; Panos G. Tzerakis, MD; Nikos C. Klapsonos, MD; Evangelos A. Zacharis, MD; and Panos E. Vardas, MD, PhD

Study objectives: To compare the efficacy and safety of amiodarone and propafenone when used for the prevention of atrial fibrillation (AF) and maintenance of normal sinus rhythm in patients with refractory AF.

Design: Prospective, randomized, single-blind trial.

Setting: Tertiary cardiac referral center.

Patients: One hundred forty-six consecutive patients (72 men; mean age, 63 ± 10 years [± SD]) with recurrent symptomatic AF.

Interventions: We studied 146 patients after restoration of sinus rhythm; patients were randomized to amiodarone, 200 mg/d, or propafenone, 450 mg/d. Follow-up clinical evaluations were conducted at the first, second, fourth, and sixth months, and at 3-month intervals thereafter. The proportion of patients relapsing to AF and/or experiencing side effects was calculated for each group using the Kaplan-Meier method. End point of the study was recurrence of AF or occurrence of side effects necessitating discontinuation of medication.

Measurements and results: Of 146 patients, 72 received amiodarone and 74 received propafenone. The two groups were clinically similar. Of the 72 patients receiving amiodarone, AF developed in 25 patients, after an average of 9.8 months, compared to 33 of the 74 patients receiving propafenone after an average of 3.8 months. Twelve patients receiving amiodarone and 2 patients receiving propafenone had side effects necessitating withdrawal of medication while still in sinus rhythm.

Conclusions: Amiodarone tends to be more effective than propafenone in maintaining sinus rhythm in patients with AF, but this advantage is offset by a higher incidence of side effects. (CHEST 2004; 125:377–383)

Key words: amiodarone; atrial fibrillation; propafenone; sinus rhythm maintenance

Abbreviation: AF = atrial fibrillation

In recent years, a growing array of antiarrhythmic drugs has become available for use in patients with atrial fibrillation (AF), for the purpose of maintaining sinus rhythm after this has been achieved either spontaneously or by cardioversion.1–21 However, data for assessing the efficacy of any particular drug compared to the others are in short supply.

The objective of this randomized, single-blinded trial was to compare the efficacy and safety of two of the most promising agents for this purpose—amiodarone and propafenone—in the long-term maintenance of normal sinus rhythm in patients with recurrent symptomatic AF. For both agents, the objective was to administer the lowest dose that could maintain sinus rhythm without producing adverse side effects. A preliminary analysis comparing the effectiveness of these drugs was carried out at 1 year and has been already published.22

Materials and Methods

One hundred forty-six patients (72 men and 74 women; mean age, 63 ± 10 years [± SD]) who came to our emergency depart-
ment or were admitted to our clinic since 1998 with symptomatic persistent or paroxysmal AF were included in this study. These patients were selected from a consecutive series, based on the following entry criteria: age > 18 years; ECG documentation of AF; symptoms such as light-headedness, palpitation, chest pain, and dyspnea in association with AF; successful chemical or electrical cardioversion to sinus rhythm in the patients with persistent AF. The exclusion criteria were as follows: acute myocardial infarction < 7 days before entry to the trial; cardiogenic shock; transient AF related to an ongoing process, such as pneumonia, pulmonary embolism, recent cardiac surgery, or uncontrolled congestive heart failure; unstable hepatic or renal function; echocardiographic ejection fraction < 40%; hyperthyroidism; other major medical problems that would leave the patient with a life expectancy of < 1 year; or previous exposure to either amiodarone or propafenone. All patients gave their informed consent to inclusion in the study. The protocol was approved by the hospital Ethics Committee.

Definitions

Paroxysmal AF was defined as self-terminating episodes lasting < 48 h, alternating with periods of sinus rhythm. Persistent AF was defined as sustained AF that can be successfully cardioverted. AF was considered recurrent only if at least one prior episode of AF was documented that had either terminated spontaneously or had been successfully treated by drug or direct-current cardioversion.

Drug Treatment Schedule

Before the start of treatment, any other antiarrhythmic drugs were discontinued for five or more half-lives. Treatment of underlying heart disease was optimized and kept constant in all patients throughout the study. To prevent thromboembolic episodes in all patients who had AF lasting > 48 h or of unknown onset and who were not already receiving anticoagulant medication,acenocoumarol (international normalization ratio 2–3) was administered for > 21 days before cardioversion was attempted and was continued for 21 days after cardioversion. After restoration of sinus rhythm, eligible patients were randomly assigned in a single-blinded fashion to receive one of the drugs under investigation.

Patients randomized to amiodarone began with a dose of 15 mg/kg/d for 7 days, rounded up to the nearest 100 mg, followed by 10 mg/kg/d po for another 7 days, after which the drug dose was tapered to maintenance levels over 7 to 12 days. Thereafter, therapy was maintained at a dosage of 200 mg/d. Patients randomized to propafenone began with 150 to 300 mg po and were then administered a maintenance dose of 150 mg tid. The above dosages are the lowest used in previous studies for the maintenance of sinus rhythm and have been found to be effective, while causing relatively few side effects. Patients in the amiodarone group remained in the hospital during the initial loading phase (7 to 14 days). Patients receiving propafenone stayed in the hospital for 3 days.

Data Collection and Follow-up

Before patients were entered into the study, baseline demographic data were obtained, all relevant cardiac diagnoses and medical history were noted, and physical examination, 24-h ambulatory ECG, ophthalmologic examination, pulmonary function tests, chest radiographs, thyroid function tests, and laboratory tests (electrolytes, renal and liver function) were carried out. One- and two-dimensional echocardiographic examinations were used to determine left atrial size and left ventricular ejection fraction. All echocardiographic recordings were reviewed by two experienced observers.

Subsequently, patients were followed up in the first, second, fourth, and sixth months and at 3-month intervals thereafter. If symptoms suggesting arrhythmia recurrence were noted, and confirmed using a transtelephonic ECG transmitter system (Cardio-Pace, Medtronic, NY), or side effects were observed, additional examinations were performed.

At each scheduled or unscheduled follow-up visit, history, physical examination, routine laboratory tests, ECG, rhythm strip, or 24-h ambulatory monitoring (when clinically indicated) were repeated. In the amiodarone group, chest radiographs were performed every 6 months; pulmonary function tests and ophthalmologic examination were repeated every year.

Statistical Analysis

Patients eligible for the study were allocated to treatment using a computer-generated random number algorithm. Descriptive statistics are summarized as mean ± SD or percentage. Baseline continuous variables were compared across the two groups by analysis of variance, χ², or Fisher exact tests as appropriate. Adverse event-free Kaplan-Meier product limit estimate curves were constructed and compared across the two treatment groups using the log-rank test. The dependent variable in the primary analysis was time to adverse events, defined as either relapse to AF or intolerable side effects, whichever occurred first. A secondary analysis assessing the efficacy of the two drugs in keeping the patients AF free (regardless of side effects) was also carried out. In that analysis, patients who remained in sinus rhythm but who experienced side effects were censored from the analysis on the date the drug was discontinued. The time at risk commenced at the start of drug administration. We estimated that we needed approximately 80 patients per group, followed up for 3 years, for 70% power at the 5% level of significance in order to detect a 50% reduction in recurrence rate (assumed average monthly recurrence 4% for propafenone and 2% for amiodarone). Since we started administering propafenone in our clinic in 1998, when the amiodarone group had already started, for this report we included only those amiodarone patients who were enrolled in 1998 (contemporaneously with propafenone).

Kaplan-Meier curves were also constructed and compared by log-rank test to provide a univariate assessment of the prognostic value of selected clinical risk factors, echo-derived descriptors, etc. Continuous covariates (age, left atrial size, time from initial diagnosis of AF) were split at their statistical median or at appropriate prespecified cutoff points. In all analyses, the criterion for statistical significance was 5%.

Results

Of the 146 patients, 72 were assigned to amiodarone and 74 were assigned to propafenone. The two groups were comparable in terms of sex, age, left atrial size, left ventricular ejection fraction, time from initial diagnosis of AF, number of previous trials, percentage of patients with underlying heart disease, and pattern of AF (Table 1). The time between the restoration of sinus rhythm and the start of administration of amiodarone, or propafenone did not differ between the groups (13 ± 9 h, and 12 ± 7 h, respectively).
Twenty-five of the 72 patients receiving amiodarone relapsed to AF after an average of 9.8 months, compared to 33 of the 74 patients administered propafenone after an average of 3.8 months. Twelve patients receiving amiodarone and 2 patients receiving propafenone experienced significant side effects, and treatment was discontinued while they were still in normal sinus rhythm; another 5 patients receiving amiodarone and 2 patients receiving propafenone who relapsed also had side effects. The average time to the appearance of these side effects was 12.8 months for amiodarone and 3.7 months for propafenone.

The average follow-up time for the non-end point patients was 19 ± 6 months for the amiodarone group and 21 ± 7 months for the propafenone group. The primary analysis, counting adverse side effects as an end point, indicated that there were no significant differences between the two drugs for the suppression of recurrent symptomatic AF (p = 0.44). The average monthly progression rates to AF or side effects were 3.18% for amiodarone, and 3.96% for propafenone. Figure 1 shows the Kaplan-Meier product limit estimate curves from the primary analysis.

In patients receiving propafenone, the risk for AF relapse or side effects appeared to be highest during the first few months and greatly diminished afterwards. In patients receiving amiodarone, this risk appeared to remain constant throughout the period of observation, although after 18 months the patients appeared to progress to AF or side effects at a faster rate. As a result, the proportion of patients in sinus rhythm and free of side effects at 1 year was higher for amiodarone than for propafenone (72% vs 56%), while at 2 years the higher proportion was found in the propafenone group (51% vs 42%).

In the secondary analysis, when adverse effects were not counted as an end point, the difference between amiodarone and propafenone was just short of statistical significance (p = 0.058). More precisely, compared with the primary analysis the gap between amiodarone and propafenone became wider and persisted beyond 18 months, when patients receiving amiodarone had more frequent side effects. The 24-month AF-free percentage in patients receiving amiodarone jumped from 42 to 59%, while in patients receiving propafenone it remained practically the same, at 52%. All of the 14 patients (12 receiving amiodarone and 2 receiving propafenone) who were still in normal sinus rhythm, but were censored from the analysis because of side effects, progressed to AF on average 5 months (range, 1 to 9 months) after treatment was discontinued.

Table 1—Clinical Characteristics of the Subjects*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Amiodarone (n = 72)</th>
<th>Propafenone (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female gender, No.</td>
<td>37/35</td>
<td>35/39</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62 ± 9</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>Left atrium size, mm</td>
<td>44 ± 6</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>52 ± 12</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>Previous drug trials, No.</td>
<td>2.2 ± 0.8</td>
<td>2.2 ± 1</td>
</tr>
<tr>
<td>Months since AF diagnosis</td>
<td>7 ± 6</td>
<td>9 ± 8</td>
</tr>
<tr>
<td>Underlying heart disease, No. (%)</td>
<td>27 (37.5)</td>
<td>28 (37.5)</td>
</tr>
<tr>
<td>AF pattern, paroxysmal/persistent</td>
<td>43:29</td>
<td>49:25</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. No significant differences were found between the two groups.

Response to Therapy

The average monthly progression rates to AF or side effects were 3.18% for amiodarone, and 3.96% for propafenone. Figure 1 shows the Kaplan-Meier product limit estimate curves from the primary analysis.

In patients receiving propafenone, the risk for AF relapse or side effects appeared to be highest during the first few months and greatly diminished afterwards. In patients receiving amiodarone, this risk appeared to remain constant throughout the period of observation, although after 18 months the patients appeared to progress to AF or side effects at a faster rate. As a result, the proportion of patients in sinus rhythm and free of side effects at 1 year was higher for amiodarone than for propafenone (72% vs 56%), while at 2 years the higher proportion was found in the propafenone group (51% vs 42%).

In the secondary analysis, when adverse effects were not counted as an end point, the difference between amiodarone and propafenone was just short of statistical significance (p = 0.058). More precisely, compared with the primary analysis the gap between amiodarone and propafenone became wider and persisted beyond 18 months, when patients receiving amiodarone had more frequent side effects. The 24-month AF-free percentage in patients receiving amiodarone jumped from 42 to 59%, while in patients receiving propafenone it remained practically the same, at 52%. All of the 14 patients (12 receiving amiodarone and 2 receiving propafenone) who were still in normal sinus rhythm, but were censored from the analysis because of side effects, progressed to AF on average 5 months (range, 1 to 9 months) after treatment was discontinued.

![Figure 1. Kaplan-Meier curves for the primary analysis (left) and the secondary analysis (right). Amiodarone and propafenone are equally effective in maintaining sinus rhythm without side effects (SE). When adverse effects are overlooked, amiodarone tends to be superior to propafenone. There is no difference in the pattern of censoring between the two groups.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22005/ on 06/26/2017)
Effect of Risk Factors for Recurrence of AF

Univariate analysis showed that amiodarone is equally as effective as propafenone in maintaining sinus rhythm, without side effects, in patients with AF, regardless of sex, age, left atrial size, left ventricular ejection fraction, months since AF diagnosis, underlying heart disease, and pattern of AF (Table 2). However, when adverse side effects were overlooked, amiodarone appeared to be better than propafenone in women and in patients < 65 years old (Fig 2).

Adverse Effects

In the amiodarone group, significant adverse effects were observed in a total of 17 patients. Symptomatic bradycardia developed in two of them during the loading phase. These two patients were relatively bradycardic even before the administration of the drug, which made the condition worse. Eight other patients (of whom four had symptoms) had hypothyroidism (thyroid-stimulating hormone > 4 IU), six patients (of whom three had symptoms) had hyperthyroidism (thyroid-stimulating hormone < 0.4 IU), while ataxia developed in one patient. In all cases, amiodarone was discontinued and appropriate medication was administered. Minor side effects, predominantly GI discomfort, nausea, sun sensitivity, and ophthalmic problems, occurred in 9% of the patients. In all cases, these problems disappeared spontaneously or were eliminated by dose reduction, splitting of the dosage, or avoiding exposure to sunlight.

In the propafenone group, two patients had treatment discontinued while they were still in sinus rhythm, one because of unusual taste sensations and the other because of dizziness. In a further two patients who relapsed to AF during Holter monitoring, we observed a run of nonsustained broad QRS tachycardia up to a maximum of six complexes.

Discussion

This randomized comparative trial suggests that amiodarone tends to be more effective than propafenone in relatively low doses for the maintenance of long-term sinus rhythm in patients with recurrent symptomatic AF, but that this advantage is offset by a higher incidence of side effects. The maintenance of sinus rhythm in patients with paroxysmal AF, or in those with persistent AF that has been successfully cardioverted, is a fundamental aim of drug therapy. However, none of the currently available drugs has been found to be ideal for this purpose.

Findings from previous studies have suggested that the most effective drug is amiodarone, even when administered in low dosages. However, since this view is based mainly on noncontrolled, noncomparative studies, further confirmation is needed.

In the present study we compared the efficacy of low-dose amiodarone in maintaining sinus rhythm in patients with recurrent symptomatic AF with that of propafenone, another agent for which favorable clinical results have been reported, also in rela-

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Primary Analysis (AF/Side Effects)</th>
<th>Secondary Analysis (AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18/37</td>
<td>16/35</td>
</tr>
<tr>
<td>Female</td>
<td>19/35</td>
<td>19/39</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65</td>
<td>15/36</td>
<td>17/37</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>22/36</td>
<td>18/37</td>
</tr>
<tr>
<td>Left atrium size, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 45</td>
<td>15/32</td>
<td>15/37</td>
</tr>
<tr>
<td>&gt; 45</td>
<td>22/40</td>
<td>20/37</td>
</tr>
<tr>
<td>Time since AF diagnosis, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>18/38</td>
<td>13/35</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>19/34</td>
<td>20/39</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17/27</td>
<td>12/28</td>
</tr>
<tr>
<td>No</td>
<td>20/45</td>
<td>23/46</td>
</tr>
<tr>
<td>AF pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>25/43</td>
<td>26/49</td>
</tr>
<tr>
<td>Persistent</td>
<td>12/29</td>
<td>9/25</td>
</tr>
</tbody>
</table>

*Data are presented as No.
tively low doses. Furthermore, we compared the safety of the two therapies, another fundamental criterion that can affect the overall benefit of drug treatment, especially in the case of AF, which is a non–life-threatening arrhythmia.

In fact, our study showed that low-dose amiodarone tended to be more effective than propafenone in maintaining sinus rhythm, but that its effectiveness was limited by a number of side effects. In consequence, the overall benefit of the two drugs for the maintenance of sinus rhythm after 2 years of treatment did not differ significantly.

It is worth noting at this point that our findings indicate that low-dose amiodarone is superior to propafenone in maintaining sinus rhythm over the period studied here in two subgroups of patients: women and patients < 65 years old. However, the overall benefit again did not differ between the two drugs tested in these patients, because of the higher incidence of side effects under amiodarone. Perhaps in these subgroups, when maintenance of sinus rhythm is considered to be essential, it might be appropriate to administer amiodarone and to treat any side effects.

Safety

The proportion of patients who experienced adverse effects in the amiodarone group, in spite of the low doses administered, is not surprising. Many other clinical trials\(^2,7,8,21\) have reported similar findings. This may be related to the total dose administered over time, that is, to the amount of drug that has accumulated. The fact that most of the side effects of low-dose amiodarone in our study appeared late (mean, 12.8 months) reinforces this view. As regards propafenone, our study showed that it is relatively safe. However, the low doses of propafenone and the fact that patients with severe heart disease or low cardiac output were excluded must be taken into account, since it is well known that the side effects of propafenone are dose dependent and tend to be higher in patients with underlying structural heart disease.\(^2,5,12-21\)

Previous Studies

To our knowledge there is only one other study\(^21\) that has also compared these drugs; the authors claim that amiodarone is clearly superior to
propafenone in maintaining sinus rhythm. The discrepancy between their findings and ours is probably due to two basic factors: the first is a matter of methodology, since some of their patients who received propafenone were resistant to sotalol, and the second is the shorter duration of follow-up in their study. The latter factor is likely to be more significant, since our study shows that the risk of relapse to AF or side effects with amiodarone therapy rises after 18 months.

**Study Limitations**

Our study was designed to compare amiodarone and propafenone. Thus, little can be said about the absolute efficacy of the drug in maintaining sinus rhythm after cardioversion in patients with AF. However, the percentage in sinus rhythm was quite high for both drugs used in this study, which suggests that they are effective. Previous studies have reported that of patients who are converted to sinus rhythm, only 25% will remain so after 1 year without antiarrhythmic therapy.

We considered as an end point only the time to first relapse. Although the number and the severity of AF relapses is also fundamental for the evaluation of the efficacy of an agent, we did not consider these as end points in this study, since reliable pretrial relapse rates were not available for all our patients and are not applicable to those with chronic AF.

Because continuous monitoring of the rhythm was not feasible in this study, it is possible that transient asymptomatic recurrences of AF may have gone undetected. In theory, this would favor amiodarone, which slowed ventricular rate more and might thus be expected to have a higher percentage of undetected relapses. However, the fact that previous studies have shown that few patients (<10%) have asymptomatic recurrences of AF would suggest that the probable effect on our results would be relatively small. Furthermore, one should not forget that the transformation of arrhythmia recurrence from symptomatic to asymptomatic could itself be regarded as a beneficial therapeutic response.

Finally it should be noted that patients with ejection fraction <40% were excluded from our study. We were led to this decision by the high probability of such patients having side effects from propafenone. However, in consequence we do not know whether our results apply to patients with poor left ventricular function. An open-lades design was selected because it would have been technically difficult to maintain blinding in a study in which two drugs with different pharmacokinetics, pharmacodynamics, dosing regimen, and safety profile were used.

**References**

20 Rae AP. Placebo-controlled evaluations of propafenone for atrial tachyarrhythmias. Am J Cardiol 1998; 82:59N–65N

Enjoy the Convenience of CHEST on CD-ROM

Now search 2002 issues of CHEST and its supplements right on your computer. No more leafing through pages to find that article or topic you’re interested in. Just enter a key word, author, or other search field, and click your way to a wealth of valuable information.

This CD-ROM offers full-text and PDF files of all issues and supplements. View or print articles that look exactly like they did in the print journal.

Order your CHEST 2002 CD-ROM today!
800-343-2227 or 847-498-1400

ACCP member $60 • nonmember $75 • plus shipping