A Comparative Study of the Efficacy and Safety of Procaainamide Versus Propafenone Versus Amiodarone for the Conversion of Recent-Onset Atrial Fibrillation

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The appropriate treatment for the restoration of sinus rhythm in patients with atrial fibrillation (AF) of recent onset is still the subject of controversy. In this prospective, randomized, single-blind, placebo-controlled clinical study, we investigated the effectiveness and safety of procaainamide, propafenone, and amiodarone, administered intravenously, for the conversion of recent-onset AF. We enrolled 362 consecutive patients (183 men; age 34 to 86 years; mean 65 ± 10) with AF duration of no >48 hours. Of these patients, 89 were given procaainamide, 91 propafenone, 92 amiodarone, and 90 placebo. Treatment was considered successful if conversion to sinus rhythm was achieved within the 24-hour study period. Baseline clinical characteristics were similar in the 4 groups. The treatment was successful in 61 of the 89 patients who received procaainamide (68.33%); median time 3 hours), 73 of the 91 patients who received propafenone (80.21%; median time 1 hour), 82 of the 92 patients who received amiodarone (89.13%; median time 9 hours), and 55 of the 90 patients who received placebo (61.11%; median time 17 hours; p < 0.05 for all medicated groups vs placebo; p < 0.05 for amiodarone and propafenone vs procaainamide). In conclusion, all 3 medications, when administered intravenously, are effective in the restoration of sinus rhythm in recent-onset AF. Amiodarone and propafenone are more effective whereas procaainamide and propafenone are faster. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1721–1725)

Several antiarrhythmic drugs with disparate electrophysiological effects on atrial tissue have been used for the restoration of sinus rhythm in patients with recent-onset atrial fibrillation (AF), but the appropriate treatment is still the subject of controversy.1–10 Although class Ic antiarrhythmic drugs have generally been found to have a higher success rate than drugs in classes Ia and III, there are minimal data from randomized clinical trials to confirm the superiority of any particular drug compared with the others.1–5,7,8 The aim of the present randomized, placebo-controlled study was to compare the efficacy and safety of intravenous procaainamide, propafenone, and amiodarone—drugs representative of classes Ia, Ic, and III, respectively—in the restoration of recent-onset AF to normal sinus rhythm. Preliminary results from pairwise comparisons based on a subset of the patients included in this study have already been reported.1

Methods

The study included 362 consecutive patients (183 men; mean age 65 ± 10 years) with AF of <48 hours duration. Patients with a recent myocardial infarction, heart surgery within the previous 6 months, unstable angina, acute myocarditis, acute pericarditis, baseline systolic blood pressure <100 mm Hg, hypertrophic obstructive cardiomyopathy, severe uncontrolled heart failure (left ventricular ejection fraction [LVEF] <30%), or cardiogenic shock were excluded, as were those with significant chronic obstructive pulmonary disease, pulmonary embolism, pneumonia, liver or kidney failure, thyroid disease, electrolyte disturbances, digoxin intoxication, pregnancy or lactation, or age <18 years. Also excluded were patients with sick sinus syndrome or a history of second- or third-degree atrioventricular block, as well as those who had taken any antiarrhythmic drug other than digoxin within <5 half-lives of the drug in question before the study.

After informed consent had been obtained, patients were randomized to receive procaainamide, propafenone, amiodarone, or placebo. Patients allotted to receive procaainamide began with 1 gram intravenously over 30 minutes, followed by 2 mg/min intravenously in the next 24 hours. Patients allotted to the propafenone group began with 2 mg/kg intravenously over 15 minutes, followed by 10 mg/kg intravenously in the next 24 hours. Patients allotted to the amiodarone group began with 300 mg intravenously over 1 hour, followed by 20 mg/kg intravenously in the next 24 hours. Patients in the placebo group received an identical amount of saline solution intravenously over 24 hours.

Digoxin (0.5-mg initial intravenous dose, followed by 0.25 mg after 2 hours and 0.25 mg/6 hours until completion of 24 hours) was administered to all patients who had not previously received it.

Treatment was considered successful if conversion to sinus rhythm was achieved within the 24-hour study period.

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In cases in which conversion to sinus rhythm was not achieved with a study drug, it was attempted using other antiarrhythmic drugs or direct-current cardioversion after the completion of 21 days of anticoagulation treatment withacenocoumarol (international normalized ratio of 2 to 3). In patients who were already receiving anticoagulant therapy, cardioversion was attempted directly.

In patients in whom there was a suspicion of heart failure, an echocardiographic examination was performed before the study. All patients underwent echocardiographic examination at the end of the study period. All echocardiographic recordings were reviewed by 2 experienced operators blinded to the results of the treatment.

During therapy all patients were kept in the coronary care unit under continuous monitoring of the electrocardiogram and blood pressure. They were then kept under observation in the cardiology department for ≥2 days before being discharged from the hospital.

Summary statistics are expressed as means ± SD or percentages as appropriate. Analysis of variance and chi-square tests were used for continuous and categorical variables, respectively, to compare the 4 patient groups at baseline with respect to potentially important predictors of conversion, such as gender, age, left atrial (LA) diameter, duration of AF, number of episodes, and heart rate.

We then followed a 2-stage approach. First, we assessed, at the univariate level, which factors were significantly associated with conversion. After the univariate analysis, we employed a multivariate stepwise logistic regression model to identify which of the significant univariate parameters contained independent prognostic information for conversion. The thresholds for entry into and removal from the model were 5% and 10%, respectively.

The progression rate to sinus rhythm was also assessed using Kaplan-Meier product-limit estimate curves that were compared across the groups with the log-rank test. A p value <0.05 was the criterion for significance throughout.

Results

Of the 362 patients who were enrolled, 89 were randomized to receive procainamide, 91 were randomized to receive propafenone, 92 were randomized to receive amiodarone, and 90 were randomized to receive placebo. There were no significant differences among the 4 groups regarding age, gender, number of episodes, baseline ventricular rate, underlying heart disease, systolic blood pressure, LA diameter, or LVEF (Table 1). One patient in the placebo group was censored at 10 hours because he refused to continue treatment.

In 69 patients, echocardiographic recordings were made in sinus rhythm and AF; in these patients, there were no significant differences in LA diameter (42 ± 6 vs 43 ± 7 mm; p = NS) or LVEF (49 ± 8% vs 48 ± 9%; p = NS) measured during the 2 studies.

Sixty-one of the patients who received procainamide (68.53%) showed conversion to sinus rhythm after an average of 9 hours, compared with 73 of those who received propafenone (80.21%) after an average of 8 hours, 82 of those who received amiodarone (89.13%) after an average of 12 hours, and 55 of those receiving placebo (61.11%) after an average of 17 hours. The likelihood of conversion differed very significantly among the 4 groups (p <0.001). Post-hoc Bonferroni-adjusted chi-square tests showed that all 3 drugs were superior to placebo and that amiodarone and propafenone were associated with better conversion rates than procainamide. Amiodarone and propafenone did not have significantly different rates.

Figure 1 shows the cumulative conversion progression to sinus rhythm in all treatment groups. The rate to progression was also different among the 4 groups (log-rank, p <0.001). Post hoc analysis showed that propafenone and procain-
amiodarone had an early, fast conversion rate (median times to conversion 1 and 3 hours, respectively) that reached a plateau after 3 hours, whereas amiodarone had a relatively steady conversion rate throughout the study period (median time 9 hours). All 3 drugs were superior to placebo.

As can be seen in Table 2, LA diameter, at the univariate level, was the parameter that consistently differentiated those in whom conversion to sinus rhythm was achieved from those in whom conversion was not achieved in all 4 groups. Other baseline clinical characteristics were not significant predictors of conversion.

To further examine the role of LA diameter in conversion, the LA diameter was divided into 3 tertiles and the conversion rate was calculated for each group (Table 3).

Among patients with LA diameters ≤40 mm, the conversion rate was high and comparable in all 4 groups. Among patients with LA diameters between 40 and 45 mm, the conversion rates of propafenone, procainamide, and placebo were lower, whereas the rate for amiodarone was significantly higher rate than the procainamide group, the only factor that influences the probability of cardioversion is high for all 3 drugs, the

Figure 2 shows Kaplan-Meier curves stratified by drug according to LA diameter as divided into 3 tertiles: small (≤40 mm), medium (40 to 45 mm), and large (>45 mm).

Treatment was discontinued in 1 patient receiving amiodarone because of an allergic reaction and in 4 patients receiving propafenone because of excessive QRS widening.

A significant decrease in systolic blood pressure (<90 mm Hg) was observed in 15 patients receiving amiodarone and in 6 patients receiving procainamide during the first hour of intravenous administration. All patients did well after administration of intravenous fluids, and no additional treatment was required.

Phlebitis over the site of amiodarone infusion was observed in 17 patients. In all these cases, the amiodarone administration was continued at a more central site.

There were no proarrhythmic effects, defined by the new onset of sustained ventricular tachycardia, ventricular fibrillation, or Torsades de pointes, in patients who experienced conversion to sinus rhythm or in those whose AF continued. No side effects were observed in the placebo group.

**Discussion**

In this study, we compared the efficacy and safety of intravenous amiodarone, propafenone, and procainamide in the restoration of recent-onset AF to sinus rhythm. All these drugs are known to be effective; they are representatives of antiarrhythmic classes III, Ic, and Ia, respectively, which are widely used in daily clinical practice for the restoration of recent-onset AF.1–10 However, there are only a few reports in the literature that have compared 1 of these drugs with another, and none of them compared all 3 drugs, as done in the present study.1–49

Our results confirm the findings of previous studies that all these drugs are effective and safe for the restoration of recent-onset AF.1–10 Moreover, they show that amiodarone and propafenone have the highest efficacy, whereas propafenone and procainamide act more quickly.

According to our results, the only factor that influences the effectiveness of all 3 medications is the size of the left atrium: the smaller the left atrium, the greater the likelihood of the restoration of sinus rhythm for all 3 drugs. However, it should be noted in the case of a small left atrium, although the probability of cardioversion is high for all 3 drugs, the
relative benefit of the treatment is small, because the spontaneous conversion rate is equally high (>90%) in such cases. In contrast, in a medium-sized left atrium, for all 3 drugs, and a large left atrium, for amiodarone and propafenone, although the conversion rate is lower, the relative benefit is greater because the probability of spontaneous conversion is much smaller.

Our study showed that amiodarone and propafenone are equally effective in restoring sinus rhythm within 24 hours in patients with recent-onset AF. However, if we examine the results more carefully, there are certain differences. More precisely, propafenone starts to convert earlier and reaches a plateau after 3 hours, whereas amiodarone had a relatively steady conversion rate throughout our study period.

It is therefore possible that the slight superiority of amiodarone observed at 24 hours (89% vs 80%) could become significant with more hours of treatment, assuming, of course, that amiodarone would continue to convert at the similar rate. It is worth noting at this point that, if this were true, the patients who would benefit most would be those with a medium or large left atrium, whose conversion to sinus rhythm is slow. Our findings indicate a small, albeit nonsignificant, advantage for amiodarone compared with propafenone in such atria, which tends to support this hypothesis.

The delayed action of amiodarone compared with propafenone could be explained in terms of the pharmacokinetics of amiodarone itself. It is well known that amiodarone has a complex pharmacokinetic profile with a multi-compartmental distribution and a long half-life, requiring more time for sufficient tissue impregnation. Furthermore, it has been shown that the antiarrhythmic effects of amiodarone, related to a prolonged refractory period, are
mainly because of its metabolite, desethylamiodarone; therefore, it is reasonable that such effects would take some time to appear.11,12

Our results indicated that all 3 drugs were generally safe and well tolerated in all our patients. However, previous studies have reported significant side effects for all.1–10,13 More specifically, amiodarone has been implicated in many cardiac and noncardiac side effects. It has been proven that most of the side effects of amiodarone are dose-related; thus, the absence of side effects in our patients was probably a result of the relatively short time of administration. With propafenone and procainamide, previous studies have reported a significant proarrhythmic effect, especially in patients with organic heart disease.1–10,13 The fact that such patients were excluded from our study could explain our findings with respect to the safety of these drugs.

In our study, all patients received digoxin, which was used in the control group to reduce the high ventricular rate. We chose this drug because it did not appear to affect the likelihood of conversion.14,15 However, to exclude any potential benefit or harm from digoxin in the conversion to sinus rhythm, we used it in all groups.