Comparison of Intravenous *Flecainide*, *Propafenone*, and *Amiodarone* for Conversion of Acute Atrial Fibrillation to Sinus Rhythm

Francisco Javier Martínez-Marcos, MD, Jose Luis García-Garmendia, MD, PhD, Antonio Ortega-Carpio, MD, Juan Manuel Fernández-Gómez, MD, Jose María Santos, MD, and Crescencio Camacho, MD

In a prospective, single-blind trial, we randomized 150 consecutive symptomatic patients with acute (≤48 hours' duration) atrial fibrillation to receive intravenous flecainide, propafenone, or amiodarone. Flecainide and propafenone were administered as a bolus dose of 2 mg/kg in 20 minutes. A second bolus dose of 1 mg/kg in 20 minutes was administered if conversion to sinus rhythm was not achieved after 8 hours. Amiodarone was administered as a bolus of 5 mg/kg in 20 minutes followed by a continuous infusion of 50 mg/hour. By the end of a 12-hour observation period, conversion to sinus rhythm was achieved in 45 patients (90%) in the flecainide group, 36 (72%) in the propafenone group, and 32 (64%) in the amiodarone group ($p = 0.008$ for the overall comparison, $p = 0.002$ for flecainide vs amiodarone, $p = 0.022$ for flecainide vs propafenone, and $p = 0.39$ for propafenone vs amiodarone). When compared with amiodarone, this higher reversion rate with flecainide was present from the first hour of the study period. However, only after administering the second bolus was there a significant difference between flecainide and propafenone. Median time to conversion to sinus rhythm was different among groups ($p < 0.001$), and it was lower in the flecainide (25 minutes; range 4 to 660) and propafenone (30 minutes; range 10 to 660) groups than in the amiodarone group (333 minutes; range 15 to 710; $p < 0.001$ for both comparisons). Flecainide, at the doses administered in this study, is more effective than propafenone and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. Propafenone and amiodarone have similar conversion rates, although propafenone was faster in achieving the conversion to sinus rhythm.

(Am J Cardiol 2000;86:950–953)

The optimal approach for acute (≤48 hours duration) atrial fibrillation (AF) is still controversial.[1,2] In patients without significant symptoms, cardioversion using electric or pharmacologic methods may be unnecessary because a large number of patients will revert spontaneously to sinus rhythm within 8 to 18 hours.[3,4] In patients with more disabling symptoms, acute AF with rapid ventricular responses generally requires reduction of heart rate and conversion to sinus rhythm as soon as possible. When acute AF is associated with severe hemodynamic deterioration, electrical cardioversion is the treatment of choice. In a less urgent situation, there is room for a less aggressive strategy, and drug therapy can be considered.[5,6] The present study compares the efficacy of intravenously administered flecainide, propafenone, and amiodarone to revert acute AF within 12 hours in symptomatic patients.

From the Servicio de Cuidados Críticos-Urgencias and Servicio de Cardiología, Hospital Juan Ramón Jiménez, Huelva, Spain. Manuscript received March 3, 2000; revised manuscript received and accepted May 5, 2000.

Address for reprints: Francisco J. Martínez-Marcos, MD, Unidad de Cuidados Intensivos, Servicio de Cuidados Críticos-Urgencias, Hospital Juan Ramón Jiménez, Ronda Norte, s/n. 21005 Huelva, Spain. E-mail: cavaleri@viautil.com.

METHODS

Patients: This prospective, randomized, single-blind trial included all patients presenting at the emergency room with acute AF (≤48 hours duration). Patients were recruited during a period of 18 months. Criteria defining the onset of the arrhythmia included an abrupt, well-defined onset of symptoms, such as palpitations, chest discomfort, or dyspnea. AF was confirmed with a 12-lead electrocardiogram in all patients.

Patients were excluded for the following criteria: (1) uncertain or >48 hours duration of symptoms; (2) known left ventricular ejection fraction <35%, usual New York Heart Association functional class >II, current chest x-ray film with cardiothoracic ratio >0.6, or clinical or radiologic signs of congestive heart failure; (3) baseline systolic blood pressure <100 mm Hg; (4) baseline mean ventricular rate <110 beats/min; (5) unstable angina or myocardial infarction within the preceding month; (6) known sick sinus syndrome or high-degree atrioventricular block; (7) overt thyroid disease; (8) antiarrhythmic therapy with the trial drugs within the previous 3 months; (9) pulmonary fibrosis; (10) hepatic dysfunction; (11) renal insufficiency (creatinine >2.5 mg/dl); (12) pregnancy or lactation; (13) age <18

0002-9149/00/$–see front matter
PII S0002-9149(00)01128-0

TABLE 1 Clinical Characteristics of Patients in Each Study Group

	Amiodarone (n = 50)	Propafenone (n = 50)	Flecainide (n = 50)
Age (yrs)	62 ± 14	62 ± 11	57 ± 14
Men	24 (48%)	20 (40%)	26 (52%)
Weight (kg)	75 ± 12	78 ± 13	78 ± 11
Duration of atrial fibrillation (h)	5 (1–48)	6 (1–48)	7 (1–33)
Systemic hypertension	27 (54%)	30 (60%)	27 (54%)
Pulmonary disease	1 (2%)	3 (6%)	1 (2%)
Paroxysmal atrial fibrillation	22 (44%)	29 (58%)	24 (48%)
Previous cardiac therapy	8 (16%)	10 (20%)	14 (28%)
Digoxin	2 (4%)	2 (4%)	2 (4%)
Calcium antagonist	4 (8%)	4 (8%)	1 (2%)
β blocker	0 (0%)	2 (4%)	3 (6%)
Sotalol	2 (4%)	3 (6%)	8 (16%)
Ventricular rate (beats/min)	138 ± 29	138 ± 20	146 ± 22
Systolic pressure (mm Hg)	133 ± 26	141 ± 24	143 ± 23
Structural heart disease	6 (12%)	7 (14%)	5 (10%)
Left atrial size (mm)	40 ± 5	40 ± 3	39 ± 5
Left ventricular ejection fraction (%)	62 ± 7	64 ± 7	63 ± 7

No significant differences were found among groups regarding any of the clinical characteristics.

Data are presented as mean value ± SD, median (range), or number (%) of patients.

TABLE 2 Conversion to Sinus Rhythm in Each Study Group

	Amiodarone (n = 50)	Propafenone (n = 50)	Flecainide (n = 50)	p Value
Conversion rate after 1 h	7 (14%)	30 (60%)	29 (58%)	<0.001
Conversion rate after 8 h	21 (42%)	34 (68%)	41 (82%)	<0.001
Conversion rate after 12 h	32 (64%)	36 (72%)	45 (90%)	0.008

Data are presented as number (%) of patients. See text for pairwise comparisons.

years; and (14) unable or unwilling to give informed consent.

Study protocol: After informed consent was obtained, patients were randomly allocated to receive 1 of the 3 trial drugs according to a computer-generated randomization schedule. Drug administration was in single-blind fashion. Flecainide and propafenone were administered as an intravenous bolus of 2 mg/kg in 20 minutes. A second bolus of 1 mg/kg in 20 minutes was administered if conversion to sinus rhythm was not achieved within 8 hours after the first bolus. The second bolus was half of the first one to minimize any proarrhythmic risk. Amiodarone was administered as an intravenous bolus of 5 mg/kg in 20 minutes followed by a continuous infusion of 50 mg/hour. Patients were observed for a 12-hour period. Blood pressure was recorded every 20 minutes. Patients underwent continuous oscilloscopic monitoring during the observation period. A 12-lead electrocardiogram was obtained at baseline, as soon as conversion to sinus rhythm occurred, at the time of significant rhythm changes, and at the end of the observation period.

A Doppler echocardiographic recording was performed in all patients within a period of 30 days after entry into the study to determine ventricular function, atrial size, and underlying heart disease. All sonographic procedures were performed by the same operator, who was unaware of the patient's therapy group.

The primary end point was the conversion to stable sinus rhythm within 12 hours of starting medication. The study design was approved by the local ethical committee.

Statistics: The study was intended to detect a large, clinically relevant effect of 1 drug over the others. In this way, to detect a 50% increase in the rate of reversion to sinus rhythm with the most effective drug, assuming a rate of reversion of 60% with the other 2 drugs, with 80% power and a 2-tailed significance level of 0.05, the minimum sample size required was 144 patients (48 per group of therapy). Categorical variables were compared with the use of chi-square analysis or Fisher's exact test. Continuous variables were compared with the use of 1-way analysis of variance or Kruskal-Wallis test. The nominal 2-tailed p value set for the overall comparisons among the 3 drugs was 0.05. In accordance with Newman-Keuls multiple comparison procedure, the nominal 2-tailed p value set for the first of the 3 pairwise comparisons (flecainide vs amiodarone) was 0.017, increasing to 0.025 for the second one (flecainide vs propafenone), and to 0.05 for the third one (propafenone vs amiodarone). Relative risks of the primary end point were also calculated (with 95% confidence interval [CI]) for the pairwise comparisons. Mean values ± SD are given for continuous variables if normally distributed, and median values (with range) are given for data with an asymmetric distribution. Analyses were based on the intention-to-treat principle. SPSS software (version 9.0, SPSS, Chicago, Illinois) was used for statistical analyses of data.

RESULTS

Patient characteristics: Overall, 150 consecutive patients were enrolled in the trial. Gender was male in 70 cases (47%) and age was 60 ± 13 years. Median time from onset of symptoms to the start of therapy was 6 hours (range 1 to 48). Fifty patients were randomly assigned to each treatment group. Table 1 lists the clinical characteristics of patients in each study group.

Conversion rate: Table 2 lists conversion rates at 1, 8, and 12 hours. There was a significantly greater proportion of patients reverting to sinus rhythm in the flecainide than in amiodarone group ($p = 0.002$). Relative risk of conversion with flecainide compared with amiodarone was 1.41 (95% CI 1.12 to 1.77). There was also a significantly higher reversion rate in the flecainide than in the propafenone group ($p = 0.022$), with a relative risk of conversion with flecainide compared with propafenone of 1.25 (95% CI 1.03

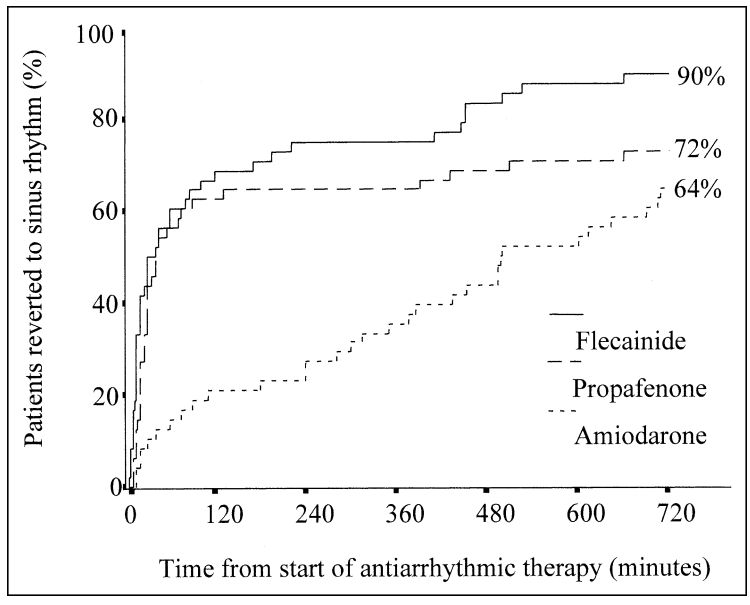

FIGURE 1. Cumulative conversion rates (%) of atrial fibrillation for flecainide, propafenone, and amiodarone based on time after start of antiarrhythmic therapy.

to 1.52). When compared with amiodarone, this higher reversion rate with flecainide was present from the first hour of the study period ($p < 0.001$). However, when compared with propafenone, no significant differences were found during the first 8 hours of the observation time ($p = 0.11$), and only after administering the second bolus was there a significant difference between flecainide and propafenone. Although for the first 8 hours of the observation period propafenone had a higher conversion rate than amiodarone ($p = 0.009$), no statistically significant differences were found between propafenone and amiodarone at the end of the observation time ($p = 0.39$)

Compared with amiodarone, 4 patients had to be treated with flecainide to achieve 1 more conversion to sinus rhythm (95% CI 3 to 10); when compared with propafenone, 6 patients had to be given flecainide to achieve 1 more conversion to sinus rhythm (95% CI 4 to 33).

An analysis of the subgroup of patients who required a second bolus of propafenone or flecainide showed that conversion to sinus rhythm was achieved in 2 of 16 patients (12.5%) in the propafenone group and in 4 of 9 patients (44.4%) in the flecainide group ($p = 0.07$).

The cumulative conversion rates for flecainide, propafenone, and amiodarone are shown in Figure 1.

Conversion time: Median time necessary to convert to sinus rhythm was significantly different among groups ($p < 0.001$), and it was lower in the flecainide (25 minutes, range 4 to 660) and propafenone (30 minutes, range 10 to 660) groups than in the amiodarone group (333 minutes, range 15 to 710; $p < 0.001$ for both comparisons).

Heart rate in nonconverters: Heart rate in nonconverters was controlled in 23 of 37 cases (62%). There were no significant differences among the 3 groups, with 13 of 18 patients (72%) with heart rate control in the amiodarone group, 6 of 14 (43%) in the propafenone group, and 4 of 5 (80%) in the flecainide group ($p = 0.16$). Time necessary for heart rate control in nonconverters was shorter in the amiodarone (287 ± 292 minutes) than in the propafenone (495 ± 308 minutes) and flecainide (615 ± 120 minutes) groups, but differences were not significant.

Adverse effects: During the study period, adverse effects occurred in 16 cases (11%). Most adverse effects were mild and self-limited (Table 3), with no patient requiring inotropic support or pacing. Three patients (1 from each group) did not terminate the study protocol. Causes were cerebral embolism (amiodarone group), heart failure (propafenone group), and atrial flutter with 1:1 atrioventricular conduction requiring electrical cardioversion (flecainide group). No ventricular arrhythmia was noted during the study period.

DISCUSSION

Major findings: The present study is the first to compare intravenous flecainide, propafenone, and amiodarone directly in patients with acute AF (onset within 48 hours). Our results show that flecainide is more effective than propafenone and amiodarone in converting acute AF to sinus rhythm after 12 hours of observation. This higher reversion rate with flecainide was present from the first hour of the study period when compared with amiodarone, and only after administering a second bolus when compared with propafenone. No differences in reversion rates were found between propafenone and amiodarone at the end of the observation time, although propafenone was faster in achieving the conversion to sinus rhythm.

Comparison with previous studies—flecainide versus propafenone: The efficacy of flecainide and propafenone to revert recent-onset AF has been compared in 2 studies. Capucci et al[7] compared single oral doses of flecainide, propafenone, or placebo (observation time 8 hours). Conversion rates with flecainide (78%) and propafenone (72%) were significantly more effective than those with placebo, but not statistically different from each other. Comparable reversion rates were found in our study at 8 hours, although after the addition of the second bolus, flecainide showed a significantly higher conversion rate than propafenone. Suttorp et al[8] compared intravenous flecainide and propafenone in 40 patients (observation time 1 hour). Conversion to sinus rhythm occurred significantly more often with flecainide (90%) than with propafenone (55%). Although in our study flecainide was superior to propafenone, at the end of the first hour there were no differences between them. This difference in results may

TABLE 3 Adverse Effects

	Amiodarone (n = 50)	Propafenone (n = 50)	Flecainide (n = 50)
Transient junctional rhythm	0 (0)	3 (6)	2 (4)
Transient atrial tachycardia	1 (1)	2 (4)	0 (1)
Atrial fluter with 1:1 atrioventricular conduction	0 (0)	0 (0)	1 (2)
Symptomatic hypotension	1 (2)	1 (2)	1 (2)
Paresthesia	0 (0)	0 (0)	2 (4)
Heart failure	0 (0)	1 (2)	0 (0)
Urticarial rash	1 (2)	0 (0)	0 (0)
Total*	3 (6)	7 (14)	6 (12)

*No significant differences were found among the 3 groups.
Data are presented as number (%) of patients.

be explained by the small number of patients enrolled in the study of Suttorp et al.[8]

In our study, a significant difference in reversion rates with flecainide and propafenone was found only after administering the second bolus; this may indicate that the second bolus of 1 mg/kg may have not been sufficient to achieve an optimal effect in the propafenone group. It has been suggested that propafenone and flecainide are not equipotent at the same dose, and either a higher dosage of propafenone or a faster rate of administration that leads to sufficiently high tissue levels is probably necessary for a greater efficacy of this drug.[8]

Comparison with previous studies—flecainide or propafenone versus amiodarone: Comparative studies have not demonstrated any clear superiority of either propafenone and flecainide over amiodarone in conversion rates of recent-onset AF to date, although flecainide[4,9] and propafenone[10,11] are faster in achieving the conversion to sinus rhythm. Comparable results were found in our study regarding the conversion to sinus rhythm with propafenone and amiodarone (propafenone was superior to amiodarone during the first 8 hours, but no significant differences were found at the end of the observation time). However, unlike previous reports,[4,9] the superiority of flecainide over amiodarone in our study was maintained until the end of the observation time. This disparity of results may be explained by the different doses and routes of administration of drugs, arrhythmia duration, and patients' baseline clinical characteristics in the previous reports.

Comparison with previous studies—flecainide versus other antiarrhythmic drugs: For acute termination of a recent-onset episode of AF, flecainide has been found to be more effective than placebo in 3 recent randomized studies,[7,9,12] equally effective as quinidine but acting more rapidly,[13] and more effective than verapamil,[14] digoxin,[15] procainamide,[16] and sotalol.[17] Ibutilide, a new class III agent, appears to be the most effective agent for the acute termination of atrial flutter.[18] It is also quite effective for converting AF of short duration, but has not been compared directly with class IC agents. Our conversion rate for flecainide in patients with AF of ≤48 hours duration compares favorably with that recently reported for ibutilide.[18]

Flecainide may be considered the drug of choice for conversion of acute AF to sinus rhythm in patients with uncompromised left ventricular function in which pharmacologic therapy is required. Although the drug is usually well tolerated with a low incidence of adverse effects, one should administer this drug only during close electrocardiographic monitoring, because of the possible adverse effects on cardiac conduction.

1. Ganz LI, Antman EM. Antiarrhythmic drug therapy in the management of atrial fibrillation. *J Cardiovasc Electrophysiol* 1997;8:1175–1189.
2. Hohnloser SH, Li YG. Drug treatment of atrial fibrillation: what have we learned? *Curr Opin Cardiol* 1997;12:24–32.
3. Falk RH, Knowlton AA, Bernard SA, Gotlieb NE, Battinelli NJ. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm. *Ann Intern Med* 1987; 106:503–506.
4. Donovan KD, Power BM, Hockings BE, Dobb GJ, Lee KY. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. *Am J Cardiol* 1995;75:693–697.
5. Ukani ZA, Ezekowitz MD. Contemporary management of atrial fibrillation. *Med Clin North Am* 1995;79:1135–1152.
6. Lie KI, Van Gelder IC. Therapy of recent onset atrial fibrillation and flutter in hemodynamically compromised patients: chemical conversion or control of the ventricular rate? *Eur Heart J* 1995;16:433–434.
7. Capucci A, Boriani G, Botto GL, Lenzi T, Rubino I, Falcone C, Trisolino G, Della Casa S, Binetti N, Cavazza M, Sanguinetti M, Magnani B. Conversion of recent-onset atrial fibrillation by a single oral dose of propafenone or flecainide. *Am J Cardiol* 1994;74:503–505.
8. Suttorp MJ, Kingma JH, Jessurun ER, Lie-A-Huen L, Van Hemel NM, Lie KI. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. *J Am Coll Cardiol* 1990;16:1722–1727.
9. Capucci A, Lenzi T, Boriani G, Trisolino G, Binetti N, Cavazza M, Fontana G, Magnani B. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol* 1992;70:69–72.
10. Treglia A, Alfano C, Rossini E. A comparison between propafenone and amiodarone in the conversion to sinus rhythm of atrial fibrillation of recent onset. *Minerva Cardioangiol* 1994;42:293–297.
11. Kochiadakis GE, Igoumenidis NE, Simantirakis EN, Marketou ME, Parthenakis FI, Mezilis NE, Vardas PE. Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset. *Pacing Clin Electrophysiol* 1998;21:2475–2479.
12. Donovan KD, Dobb GJ, Coombs LJ, Lee KY, Weekes JN, Murdock CJ, Clarke GM. Reversion of recent-onset atrial fibrillation to sinus rhythm by intravenous flecainide. *Am J Cardiol* 1991;67:137–141.
13. Borgeat A, Goy JJ, Maendly R, Kaufmann U, Grbic M, Sigwart U. Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. *Am J Cardiol* 1986;58:496–498.
14. Suttorp MJ, Kingma JH, Lie-A-Huen L, Mast EG. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. *Am J Cardiol* 1989;63:693–696.
15. Wafa SS, Ward DE, Parker DJ, Camm AJ. Efficacy of flecainide acetate for atrial arrhythmias following coronary artery bypass grafting. *Am J Cardiol* 1989;63:1058–1064.
16. Madrid AH, Moro C, Marín-Huerta E, Mestre JL, Novo L, Costa A. Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. *Eur Heart J* 1993;14:1127–1131.
17. Reisinger J, Gatterer E, Heinze G, Wiesinger K, Zeindlhofer E, Gattermeier M, Poelzl G, Kratzer H, Ebner A, Hohenwallner W, Lenz K, Slany J, Kuhn P. Prospective comparison of flecainide versus sotalol for immediate cardioversion of atrial fibrillation. *Am J Cardiol* 1998;81:1450–1454.
18. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, Vander Lugt JT. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;94:1613–1621.