Intravenous versus oral initial load of propafenone for conversion of recent-onset atrial fibrillation in the emergency room: a randomized trial

Salvatore Madonia, Manlio De Simone, Giuseppina Brai, Daniela Gozzo, Anna Gristina, Liliana Luciano, Simonetta Maisano, Giuseppe Migliore, Riccardo Mineo*, Maria Patrizia Muzzo, Fortunata Nicchi, Antonino Randazzo, Giacinto Raspanti, Gaspare Rotolo, Antonio Russo, Filippa Sagona, Maurizio Schirosa, Mario Spinello, Rosa Stancampiano, Enrico Geraci*

*Department of Emergency, *Department of Cardiology, "V. Cervello" Hospital, Palermo, Italy*

Key words:
Propafenone; Atrial fibrillation.

Background. **Non-valvular paroxysmal atrial fibrillation is a common clinical condition associated with a high risk of thromboembolism and hemodynamic problems which increase with the duration of arrhythmia. Therefore, even if arrhythmia ceases spontaneously within 24 hours in about half of the patients, a higher early conversion rate is desirable. Propafenone either by intravenous or oral load has been shown effective in conversion to sinus rhythm.**

Methods. **We consecutively randomized all emergency patients with non-valvular atrial fibrillation lasting no more than 48 hours to either intravenous or oral initial load of propafenone. They all received further oral doses if still on atrial fibrillation after the initial load. Exclusion criteria were: mean ventricular rate < 65 b/min, age > 75 years, recent acute myocardial infarction, overt heart failure, conduction defects, ventricular preexcitation, thyroid dysfunction, renal or hepatic insufficiency, pregnancy, current treatment with propafenone or other antiarrhythmic drugs, and intolerance to propafenone. Primary and secondary end-points were the conversion to sinus rhythm within 12 and 48 hours of randomization respectively.**

Results. **Ninety-seven patients were randomized to intravenous (n = 49) or oral (n = 48) treatment. Overall, sinus rhythm restoration occurred in 83.3% of patients within 12 hours and in 98.9% at 24 hours. Recovery rate resulted significantly greater for intravenous treatment at 1 and 3 hours ($p < 0.001$ and $p = 0.001$, respectively). At 6, 12 and 24 hours no significant difference between the two groups was observed ($p = 0.77$, $p = 0.81$ and $p = 0.99$, respectively). No patient needed treatment suspension.**

Conclusions. **In patients with recent-onset non-valvular atrial fibrillation treated with propafenone within 48 hours, conversion to sinus rhythm occurred in more than 80% within 12 hours. Even if intravenous initial load appears to be slightly more rapid, the oral way is easier to administer and cheaper. The choice may depend on the specific organization of the single emergency room.**

(Ital Heart J 2000; 1 (7): 475-479)

Received March 13, 2000; revision received June 9, 2000; accepted June 20, 2000.

Address:

Dr. Salvatore Madonia

Reparto di Medicina Interna I Azienda Ospedaliera "V. Cervello" Via Trabucco, 180 90146 Palermo E-mail: madonia_cipolla@iol.it

Introduction

Non-valvular paroxysmal atrial fibrillation (PAF) is the arrhythmia most commonly encountered in the emergency room[1], but precise information about its incidence is lacking, at least in our country. PAF is associated with a high risk of thromboembolism, increasing with the duration of arrhythmia[2,3], is often accompanied by troublesome symptoms[4-6] and can cause hemodynamic problems[2,4,5,7]. Early conversion to sinus rhythm is therefore desirable. It occurs spontaneously in about 50% of patients within 24 hours[2,8].

Propafenone has been shown to be effective in arrhythmia cessation either by intravenous or by oral administration but studies comparing the two ways of administration of the initial load are scanty[9].

We carried out a randomized trial comparing intravenous and oral initial load of propafenone for conversion of recent-onset non-valvular atrial fibrillation in the emergency room.

Methods

Patient selection and study protocol. All patients with recent-onset non-valvular atrial fibrillation were eligible. The time of the

abrupt onset of palpitations, which brought about the visit to the emergency room, with evidence of atrial fibrillation at hospital arrival, was considered the time of arrhythmia onset. On admission to the emergency room a medical history, physical examination, 12-lead electrocardiogram (ECG), biochemical laboratory tests to evaluate liver and renal function and kaliemia were performed. Patients were excluded if matching one or more of the following criteria: atrial fibrillation lasting > 48 hours or not datable, mean ventricular rate < 65 b/min, age > 75 years, acute myocardial infarction < 3 months before, overt heart failure (NYHA functional class > II), complete bundle branch block, ventricular preexcitation, previous evidence of II-III degree atrioventricular block, sick sinus syndrome, history of thyroid dysfunction, renal or hepatic insufficiency, pregnancy, current treatment with antiarrhythmic drugs (including propafenone), known intolerance to propafenone.

Informed consent was requested from all patients. Randomization was performed by a computer-generated list. Treatment schedules adopted are shown in table I.

The primary end-point was the conversion to sinus rhythm within 12 hours of randomization. The secondary end-point was the conversion to sinus rhythm within 24 hours.

An ECG was repeated every hour for the first 12 hours and then every 3 hours until 24 hours from randomization. An extra ECG was performed when requested.

Patients randomized to initially intravenous propafenone were continuously monitored with ECG until the end of intravenous administration.

If arrhythmia duration exceeded 48 hours during the study period, subcutaneous heparin at the dose of 12 500 IU was started and repeated after 12 hours if necessary.

The following side effects of propafenone were looked for: headache, nausea, vomiting, hypotension (systolic blood pressure < 100 mmHg), bradycardia (mean ventricular rate during fibrillation < 65 b/min), conversion to atrial flutter.

Study setting. The emergency room of a reference hospital in a big city (about one million people) in southern Italy.

Statistical analysis. Patient characteristics at entry in the study and differences observed were described as proportions for discrete variables or means, medians and range for continuous variables. Differences observed on contingency tables were assessed by the χ^2 test and differences between means were assessed by the Student's t test.

Results

From October 1, 1997 to September 30, 1998, 234 patients who arrived at the emergency room for atrial fibrillation were registered (0.4% of total patients, 1% of those with real emergency-urgency problems), of whom 126 were female (53.9%). Median age was 62 years (range 22-95 years).

Arrhythmia started a median of 3 hours before arriving at the hospital (range 1-72 hours).

Ninety-two patients (39%) arrived at the emergency room during the evening or at night. Sixty-one cases (26%) occurred during the weekend.

The starting symptom was only palpitations in most cases but PAF caused serious hemodynamic problems in 3 patients (1.2%), 2 with valvular disease and 1 with dilated cardiomyopathy.

Median systolic blood pressure was 135 mmHg (range 95-200 mmHg) and mean diastolic blood pressure was 80 mmHg (range 65-110 mmHg). Median ventricular rate was 130 b/min (range 75-200 b/min).

One hundred and seventy-two patients (73.5%) had had previous episodes of PAF.

Eighty-nine patients (38%) were taking antihypertensive drugs, 14 (5.9%) had overt valvular disease, 30 (12.8%) were diabetic, 16 (6.8%) had ischemic heart disease, 5 (2.1%) had suffered from alcohol abuse.

Overall, 137 patients were excluded because of one or more of the following conditions: 14 had overt valvular disease; arrhythmia started at > 48 hours in 2 patients and it was impossible to evaluate the starting time in 14; 15 were older than 75 years, 7 had had an acute myocardial infarction less than 3 months before, 17 were in NYHA functional class > II, 13 had complete bundle branch block, ventricular preexcitation, or sick sinus syndrome, 4 had thyroid, renal or hepatic dysfunction, 70 were on treatment with anti-arrhythmic drugs for the prevention of PAF recurrences, most with sotalol (33 patients), propafenone (21 patients), or amiodarone (8 patients).

Table I. Treatment schedules adopted in the two study groups.

Group A	Group B
2 mg/kg in10 min i.v. → 1 mg/kg in 2 hours i.v.	2 tablets of 300 mg
→ 1 tablet of 300 mg	→ 1 tablet of 300 mg after 6 hours
→ 1 tablet of 300 mg after 8 hours	→ 1 tablet of 300 mg after 8 hours
→ 1 tablet of 300 mg after 8 hours	→ 1 tablet of 300 mg after 8 hours

Ninety-seven patients were randomized to intravenous (Group A, n = 49) or oral (Group B, n = 48) initial load with propafenone.

Baseline characteristics of the two groups are listed in table II. Patients assigned to Group A had slightly but significantly higher baseline values of systolic blood pressure and mean ventricular rate.

Overall, sinus rhythm restoration occurred in 81 patients (83.3%) within 12 hours and in 96 (98.9%) at 24 hours.

Recovery rate resulted significantly greater in Group A at 1 hour (20 patients - 40.8% - vs 3 patients - 6.2%, $p < 0.001$) and 3 hours (30 patients - 61.2% - vs 13 - 27.08%, $p = 0.001$) but not at 6 (32 patients - 65.3% - vs 29 - 60.4%, $p = 0.77$), 12 (41 patients - 83.6% - vs 40 - 83.3%, $p = 0.81$) and 24 hours (48 patients - 97.9% - vs 48 - 100%, $p = 0.99$; Fig. 1). Ventricular rate behavior is shown in table III.

No relation was found between baseline systolic blood pressure values and mean ventricular rate and time of conversion to sinus rhythm ($p = 0.6$ for systolic blood pressure and 0.1 for mean ventricular rate by linear regression analysis).

Two patients experienced asymptomatic hypotension (1 in each group), 1 Group B patient experienced a transient asymptomatic atrial flutter with a 2:1 conduction before converting to sinus rhythm and 1 Group A patient had nausea during infusion. None of the above mentioned side effects needed treatment suspension.

Discussion

Non-valvular PAF is a very frequent arrhythmia. Hospital data certainly underestimate its incidence for various reasons: it is often asymptomatic; some patients

Table II. Patient characteristics in the two study groups.

Variable	Group A	Group B	p
Men/women	28/21	21/27	0.22
Age (years; mean-median, range)	56.3-60 (25-73)	52.7-58 (22-73)	0.18
PAF duration before randomization (hours; mean-median, range)	3-4.1 (1-16)	4-5.1 (1-24)	0.28
Patients with previous episodes of PAF	28	32	0.44
Hypertension	19	13	0.34
Diabetes	5	5	0.76
Cigarette smoking	7	10	0.56
Alcohol abuse	1	1	0.49
Familiarity for ischemic heart disease	7	5	0.81
History of ischemic heart disease	2	3	0.98
History of stroke	1	0	1.0
Systolic blood pressure (mmHg; mean-median, range)	142.1-140 (95-140)	129.4-130 (95-180)	0.0032
Diastolic blood pressure (mmHg; mean-median, range)	82.6-80 (65-100)	80.8-80 (70-100)	0.29
Mean ventricular rate (b/min; mean-median, range)	135-140 (75-200)	107.3-130 (90-200)	0.0026

PAF = paroxysmal atrial fibrillation.

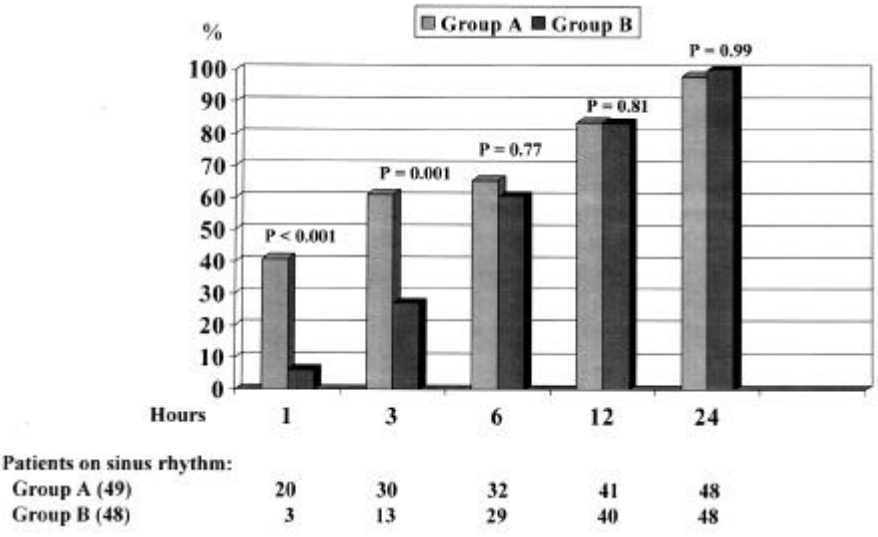

Figure 1. *Conversion to sinus rhythm in the two study groups.*

Table III. Ventricular rate behavior before conversion to sinus rhythm.

Time	Group A (n=, mean-median, range)	Group B (n=, mean-median, range)	p
Baseline	49 135-140 (75-200)*	48 107.3-130 (90-200)*	0.0026
Hour 1	29 111.4-115 (85-125)*	45 112.8-125 (90-155)	0.58
Hour 3	19 106.1-110 (90-120)	35 108.2-115 (90-135)	0.32
Hour 6	17 100.2-105 (90-115)	19 105.6-110 (90-125)	0.11
Hour 12	8 100.6-105 (90-115)	8 99.3-100 (90-115)*	0.79

* $p < 0.01$.

prefer to wait at home for spontaneous cessation and others recur to self-treatment with drugs[1].

In our series, among 234 patients with PAF (valvular and non-valvular) who arrived at the emergency room during the study period, 97 matched the inclusion criteria (41.4%). Current treatment with antiarrhythmic drugs was the main cause of exclusion. The commonest symptom was palpitations.

We elected to study a class 1c drugs because they were faster than other drugs: intravenous amiodarone resulted not different from placebo at 8 hours[7,10,11], and sotalol appeared no better than placebo in some studies [7]. Both propafenone and flecainide have been shown to be rapidly effective[12,13], oral administration resulting not significantly different from intravenous administration[9]. We preferred to test propafenone because of its β-adrenergic blocking activity, compared with flecainide vagolytic properties[1,14,15], and for the large experience with this drug in our institution.

Our data suggest that oral propafenone is quickly effective in cessation of recent-onset atrial fibrillation in patients without clinical evidence of heart disease. A previous study by Boriani et al.[9] compared placebo with oral and intravenous propafenone in the treatment of recent-onset PAF. Exclusion criteria and patient characteristics were similar to those in the present study, but the schedule adopted was different, because further oral doses were not provided after the initial venous infusion nor after the two initial tablets. The results of the two studies are comparable even if we observed a higher conversion rate for intravenous treatment at 1 (40.8 vs 28%) and 3 (61 vs 41%) hours and a lower rate for oral treatment at 3 hours (27 vs 55%). Boriani et al.[9] did not report results after the eighth hour: it is interesting to note that conversion rates in our study continued to grow until 12 and 24 hours especially for Group B (oral treatment), perhaps due to further oral doses of propafenone after the initial load (venous or oral).

Both ways of administration appeared well tolerated and no patient needed suspension. Only 1 Group B patient experienced a transient, asymptomatic atrial flutter with a 2:1 conduction. We did not see any episode of 1:1 flutter or ventricular tachyarrhythmia.

Is the short initial conversion delay observed with oral administration clinically significant? The large interest in the literature for early conversion of PAF is mostly due to two reasons. First, it is well known that PAF implies a significant increase of thromboembolic risk but that this risk is generally low within the first 48 hours[2,3,16], even if not absent[17,18]. Second, the probability of conversion to sinus rhythm is higher if it is attempted when PAF lasts < 48 hours[19,20]. From this point of view the 3-hour delay observed would not be clinically relevant. Furthermore the oral administration appears convenient because it neither needs venous incannulation and fluid infusion, nor continuous ECG monitoring during the early phase. This translates into a substantial cost reduction and nurse assistance request. On the other hand, the intravenous initial load resulted associated with a significantly higher probability of conversion to sinus rhythm at 1 and 3 hours and this could shorten the patients in the emergency room.

Has the time for a home self-treatment of PAF arrived? Oral propafenone is obviously easy to administer and our data seem to confirm that it is safe. Nevertheless drug-induced arrhythmias, though rare, are described[2]. PAF is not generally a life-threatening arrhythmia, especially in patients without clinical evidence of heart disease, and any risk related to a home self-treatment appears unacceptable. On this basis, we believe that oral propafenone could be encouraged as one of the first-choice treatments to convert recent-onset PAF in the emergency room but its use as a home self-treatment cannot be usually recommended.

References

1. Fresco C, Proclemer A. Clinical challenge. II. Management of recent onset atrial fibrillation. PAFIT-2 Investigators. Eur Heart J 1996; 17 (Suppl C): 41-7.
2. Pristowsky EN, Benson W, Fuster V, et al. Management of patients with atrial fibrillation. A statement for healthcare professionals from the subcommittee on electrocardiography

and electrophysiology, American Heart Association. Circulation 1996; 93: 1262-77.
3. Tsai LM, Chen JH, Lin LJ, Teng JK. Natural history of left atrial spontaneous echo contrast in nonrheumatic atrial fibrillation. Am J Cardiol 1997; 80: 897-900.
4. Narayan SM, Cain ME, Smith JM. Atrial fibrillation. Lancet 1997; 350: 943-50.
5. Blackshear JL, Kopecky SL, Litin SC, Safford RE, Hammil SC. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. Mayo Clin Proc 1996; 71: 150-60.
6. Waktare JEP, Camm J. Acute treatment of atrial fibrillation: why and when to maintain sinus rhythm. Am J Cardiol 1998; 81: 3C-15C.
7. Kowey PR, Marinchak RA, Rials SJ, Filart RA. Acute treatment of atrial fibrillation. Am J Cardiol 1998; 81: 16C-22C.
8. Levy S, Breithard R, Campbell RWF, et al. Atrial fibrillation: current knowledge and recommendations for management. Eur Heart J 1998; 19: 1294-320.
9. Boriani G, Capucci A, Lenzi T, Sanguinetti M, Magnani B. Propafenone for conversion of recent-onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. Chest 1995; 108: 355-8.
10. Desai AD, Chun S, Sung RJ. The role of intravenous amiodarone in the management of cardiac arrhythmias. Ann Intern Med 1997; 127: 294-303.
11. Hohnloser SH, Meinertz T, Dammbacher T, Steiert K, Jahnchen E, Zehender M. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo-controlled study. Am Heart J 1991; 121: 89-94.
12. Capucci A, Boriani G, Botto L, et al. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. Am J Cardiol 1994; 74: 503-5.
13. Capucci A, Rosi A, Villani GQ, Aschieri D, Piepolo M. Farmaci di classe 1C in carico orale nella cardioversione della fibrillazione atriale parossistica. G Ital Cardiol 1998; 28: 1422-30.
14. Coumel P, Thomas O, Leenhardt A. Drug therapy for prevention of atrial fibrillation. Am J Cardiol 1996; 77: 3A-9A.
15. Lip GYH, Watson RDS, Singh SP. Cardioversion of atrial fibrillation. BMJ 1996; 312: 115-6.
16. Laupacis A, Albers G, Dalen J, Dunn MI, Jacobson AK, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest 1998; 114: 579S-589S.
17. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol 1995; 25: 452-9.
18. Weigner MJ, Caulfield TA, Danias PG, Silverman DI, Manning WJ. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. Ann Intern Med 1997; 126: 615-20.
19. Gilligan DM, Ellenbogen KA, Epstein AE, et al. The management of atrial fibrillation. Am J Med 1996; 101: 413-21.
20. Wijffels MCEF, Kirchof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995; 92: 1954-68.