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Efficacy and tolerability of oral propafenone *versus* quinidine in the treatment of recent onset atrial fibrillation: A randomized, prospective study

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Abstract

Background: *A prospective, randomized study was conducted to evaluate the efficacy and tolerability of oral propafenone and quinidine for the conversion of paroxysmal atrial fibrillation (AF).*

Methods: *Eighty one consecutive patients (female/male 46/35; mean age 64.0 ± 11.6), admitted to hospital with AF lasting no longer than 48 hours, were randomized in terms of their pharmacological therapy. Forty three patients (55%) were randomly assigned to Group I and received propafenone 600 mg orally as the initial therapy, with an additional dose of 300 mg after eight hours, if the sinus rhythm had not been restored by then. Thirty eight patients (45%) (Group II) received 1 mg digoxin IV followed by an oral loading of quinidine (400 mg followed by 200 mg every two hours).*

Results: *The conversion rate assessed after 24 hours was the same in both groups (Gr. I* vs. *Gr. II: 90.7* vs. *91.4%), with the same number of mild side effects (Gr. I* vs. *Gr. II: 37.2%* vs. *45.7%). No life-threatening adverse events were reported. Propafenone achieved a higher efficacy rate during the first eight hours (83.3* vs. *54.3%; p = 0.01), with a significantly shorter time required to sinus rhythm recovery throughout the study period, with a median time of 165 min (95% confidence interval 120–278)* vs. *360 min (95% confidence inerval 298–650; p < 0.05). There was some indication of greater effectiveness of propafenone than quinidine in early sinus rhythm restoration in patients with: no structural heart disease, in those with an AF duration shorter than 12 hours, and in patients with an ejection fraction > 55%.*

Conclusions: *Although both drugs revealed the same effectiveness, the conversion to sinus rhythm in the group treated with propafenone was observed more quickly despite the longer paroxysmal AF episode duration.* (Cardiol J 2009; 16, 6: 521–527)

Key words: paroxysmal atrial fibrillation, propafenone, quinidine, pharmacological cardioversion

Editorial p. 491

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Introduction

Atrial fibrillation (AF) has been considered a significant medical, social, and pharmaco-economic problem in recent decades. Prolonged life-span among patients with cardiovascular disease, related to higher quality medical care, has resulted in more new cases of arrhythmia [1]. Despite the new strategies involved in the medical therapy of AF, supported by new technologies and the achievements of the pharmacological industry, every year brings many new hospital admissions related to the appearance of arrhythmia or its complications. Despite advances in medical therapy, most patients with paroxysmal AF are managed with medication [2]. The main goal of the medical approach is to restore sinus rhythm (SR), relieve symptoms and reduce the risk of thromboembolic complications. There is no clear-cut superiority of any of the antiarrhythmic agents for patients with new-onset AF [3]. The efficacy of particular medical agents, usually assessed within the first 24 hours of medical therapy, are almost equal for all agents approved for pharmacological cardioversion. The main goal of the medical approach for patients with new-onset AF without significant hemodynamic disturbances is to shorten the time to SR restoration, as well as the safety of the proposed therapy. The goal of our study was to investigate the efficacy and tolerability of standard oral pharmacological therapies in paroxysmal AF involving propafenone and quinidine.

Methods

Inclusion and exclusion criteria

This prospective, randomized, single-center study covered consecutive patients with symptomatic recent onset AF defined as < 48 hours duration. The onset of arrhythmia was considered as the abrupt, well-defined historical appearance of palpitation, with subsequent electrocardiographic evidence of AF. Patient inclusion criteria were: age from 18 to 85 years, mean ventricular rate above 70 beats per minute (calculated over at least 30 R-R cycles), as well as New York Heart Association (NYHA) functional class < II. Exclusion criteria were: documented intolerance, ineffectiveness or contraindications for study drugs, thyroid dysfunction, myocardial infarction in the three months preceding the study, acute myocarditis, cardiac surgery in the 30 days prior to the study, hemodynamic instability defined as symptomatic heart failure or hypotension (systolic pressure < 90 mm Hg), systemic hypertension not responding to treatment (diastolic pressure > 115 mm Hg), valvular heart disease qualified for surgical treatment, R-R intervals exceeding more than 3 s, ventricular rhythm below 70/min (unrelated to drugs reducing ventricular rhythm), bundle branch block, electrocardiogram (ECG) evidence (past or present) of ventricular preexcitation syndrome, QT segment prolongation (a corrected QT interval of more than 480 ms or an uncorrected QT interval of more than 500 ms), hypokalemia (serum potassium level < 3.5 mmol/L), pregnancy and lactation, liver, kidney or central nervous system damage, advanced chronic lung disease, or malignancy. Patients were also excluded from the study if they had been medicated with digitalis or subjected to any antiarrhythmic therapy in the previous 24 hours.

All selected patients were advised of the aim and course of the study and gave their written informed consent prior to inclusion in the trial.

The investigations, approved by the Ethics Committee, were carried out by the Chair and Department of Cardiology at the Medical University of Warsaw.

Study protocol

From 2003 until 2005, consecutive patients admitted to our department with symptomatic recent onset of AF, and who fulfilled the inclusion criteria, were recruited for the study. Eligible patients qualified for pharmacological cardioversion of arrhythmia were randomly assigned to groups. Group I received propafenone 600 mg orally as the initial therapy and an additional dose of 300 mg after eight hours, if the SR had not been restored by then. Group II received digoxin 1 mg IV followed by an oral loading of quinidine (400 mg followed by 200 mg every two hours, with the total dose not exceeding 1400 mg). The exact time of SR restoration was estimated by 24-hour Holter ECG monitoring. The duration of all treatments did not exceed 24 hours. During the study patients were bed resting, continuously monitored and arterial blood pressure was evaluated every hour. Twelve leads ECG (50 mm/s paper speed) were recorded prior to the application of the first dose of the study drug, as well as at the 3rd, 6th, 12th and 24th hour of the study. PR, QRS and QTc intervals were measured according to the Bazet formula, in order to evaluate the time of onset of the effects of the propafenone and quinidine, respectively. SR restoration was also confirmed by standard ECG. At admission two-dimensional and M-mode echocardiograms were recorded to evaluate left atrial dimension, left ventricular end-systolic and end-diastolic diame-

ters, as well as left ventricular ejection fraction. All measurements taken complied with the relevant standards of the American Society of Echocardiography [4].

Safety protocol

Safety was assessed by recording the appearance of clinical proarrhythmic and hemodynamic adverse events, both those reported by the patients and those observed by the investigators. A clinical adverse event was defined as a cardiac or non-cardiac undesirable or unusual experience reported by a patient following study drug administration. A proarrhythmic event was defined as the appearance of a new tachyarrhythmia of any origin and/or new bradyarrhythmia resulting from nodal dysfunction, atrioventricular or other conduction disturbances [5, 6]. Hemodynamic adverse events were considered as any changes in arterial blood pressure or heart failure exacerbation not related to proarrhythmic events that required medical intervention.

Statistical analysis

Summary data is expressed as means ± standard deviation (SD) or absolute numbers and percentages of patients. Analyses were performed in accordance with the intention-to-treat principle. The cumulative risk of AF recurrence was estimated with the Kaplan-Meier product-limit method. The differences between treatment groups were assessed by means of the log-rank test. The early SR restoration predictability was developed based on generalized additive logistic regression. P-value for interaction term was used to assess the significance of the difference in treatment effect. P value < 0.05 was considered statistically significant.

Results

Study group profile and sinus rhythm restoration

The study population consisted of 81 consecutive patients (female/male 46/35; mean age 64.0 ± ± 11.6; 30–83 years) admitted to emergency room with new onset of AF lasting no longer than 48 hours (mean duration time of arrhythmia 12.3 ± ± 11.1 h; 1–47 h). All patients qualified for pharmacological conversion of AF were randomly assigned to two different medical therapy protocols. Forty three patients (55%; female/male 22/21; mean age 62.1 ± 10.7 years; Group I) received propafenone 600 mg orally as the initial therapy. Within the first eight hours, SR was restored in 36 patients (83.3%); seven patients received an additional dose of propafenone 300 mg. At the end of the observational period, 39 study patients (90.7%) were free of arrhythmia with propafenone mean doses of 676.7 ± ± 132.4 mg required for this success rate. Thirty eight patients (45%; female/male 16/19; mean age 66.1 ± 12.4 years; Group II) received 1 mg digoxin IV as an initial therapy, which was followed by an oral loading of quinidine (400 mg followed by 200 mg every two hours with the total dose not exceeding 1400 mg). After eight hours 54.3% of patients treated with quinidine were free from arrhythmia. Recommended therapy was able to restore SR in 35 patients (91.4%) within the first 24 hours of follow-up with quinidine mean doses of 830 ± 430 mg. There was no significant difference in the efficacy of the drugs being studied after 24 hours of follow-up (90.1% *vs*. 91.4%; $p = 0.78$); although propafenone achieved a higher efficacy rate during the first eight hours (83.3% *vs*. 54.3%; $p < 0.01$), with a significantly shorter time required to SR recovery throughout the study period, with median time 165 min (95% confidence interval 120–278 min) *vs*. 360 min (95% confidence interval 298–650 min; $p < 0.05$). Table 1 summarizes the clinical and echocardiographic characteristics of both study groups at the baseline. Figure 1 shows the sinus rhythm conversion rate for both study groups.

Hemodynamic profile and adverse events of study drugs

No life-threatening adverse events were reported during the follow-up. The same number of mild side effects was noted in both groups (Gr. I *vs*. Gr. II: 37.2% *vs*. 45.7%; $p = 0.56$). The potential proarrhythmic effect was observed in 16 study patients; nine (19.6%) on propafenone and seven (20.0%) on quinidine. In one patient (2%) significant bradycardia (< 35'/min) was observed which required atropine administration during propafenone therapy. One patient (2%) in the quinidine group suffered from nausea and vomiting, and required drug discontinuation. Both drugs led to significant blood pressure and heart rate reduction, but within satisfactory ranges, and did not call for medical intervention. No case of significant heart failure exacerbation was observed in any patient (Tables 2, 3). The QRS and QTc lengths were comparable between the study groups in each point of the study. QRS complex duration became significantly longer in the propafenone group starting from the 6th hour of therapy (79 ± 12 *vs*. 86 ± 8 ms; $p < 0.05$), but still remained within normal ranges.

Table 1. The study groups' baseline characteristics.

Parameter	Propafenone	Quinidine	Significance
Number of patients	46	35	NS
Age (years)	62.1 ± 10.7	66.1 ± 12.4	NS
Gender:			
Female	22 (51%)	16 (46%)	NS
Male	21 (49%)	19 (54%)	NS
Mean AF duration [h]	14.5 ± 13.0	9.7 ± 7.7	0.05
First AF episode	14 (32.6%)	12 (34.2%)	NS
History of paroxysmal AF (years)	4.7 ± 4.5	5.6 ± 3.7	NS
AF etiology:			
Ischemic heart disease	26 (60.5%)	17 (48.6%)	NS
Myocardial infarction	8 (18.6%)	6 (17.1%)	NS
CABG	1 (2.3%)	0 (0.0%)	NS
Systemic hypertension	25 (58.1%)	19 (54.3%)	NS
No structural heart disease	36 (83.7%)	27 (77.1%)	NS
Echocardiographic parameters:			
LAsax. [mm]	43.9 ± 5.0	40.0 ± 3.0	NS
LVEDD [mm]	51.0 ± 5.0	51.0 ± 5.0	NS
LVEF (%)	56.4 ± 3.8	52.5 ± 6.2	NS

AF — atrial fibrillation; CABG — coronary artery bypass grafting; LAsax. — antero-posterior left atrial diastolic diameter; LVEDD — left ventricle end-diastolic diameter; LVEF — left ventricular ejection fraction

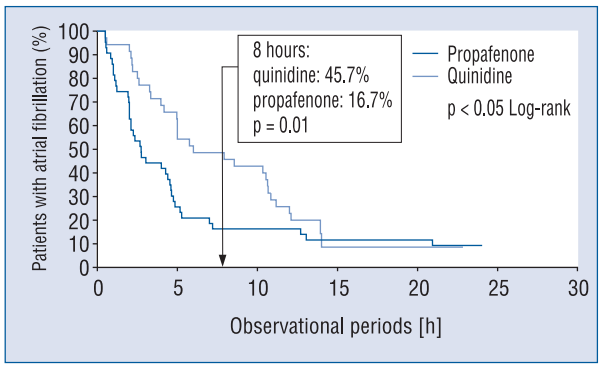

Figure 1. Kaplan-Meier's curves presenting the efficacy of both therapies during 24 hours follow-up.

Parameters affecting early sinus rhythm restoration

Applying logistic regression analysis, we attempted an examination of the impact of the patient's age and gender on the cardioversion's early success, defined as SR restoration up to eight hours of therapy. No statistically significant correlation between the variables in question and the treatment success rate was established ($p > 0.62$ and $p > 0.87$, respectively). To eliminate the impact of the above mentioned variables on the correlation between evaluated parameters, we decided to take them into account while developing the test models.

To find the group of patients in which one of the investigated treatment strategies is better, we ran a series of logistic regression models in subsets of patients with and without factors of interest such as assessed at the baseline clinical and echocardiographic parameters. As shown in Figure 2, there were some trends indicating better effectiveness of propafenone than quinidine in early sinus rhythm restoration in patients with: no structural heart disease, in those with AF duration shorter than 12 hours, and in patients with ejection fraction > 55%. However, these trends did not reach significance (an overlap of confidence intervals between two subgroups for each tested variable). We also found no significant interaction term, but it could be due to our relatively small sample size. The difference in treatment effect could be further investigated in studies with a higher sample size.

Discussion

The main end-point of our study was to evaluate the efficacy and safety profile of an acute oral loading dose of propafenone in restoring SR in patients with recent onset of AF compared to quinidine preceded by digoxin IV bolus in pharmacological cardioversion.

After a 24 hour follow-up period, the effectiveness of both strategies was above 90% and almost

Table 2. Side effects.

	Propafenone	Quinidine	Significance
	No. of patients (%)		
Number of patients	46	35	
Death	–	–	NS
Bleeding complications	–	–	NS
Thromboembolic complications:			
Ischemic stroke	–	–	NS
Pulmonary embolism	–	–	NS
Proarrhythmia:			NS
Ventricular tachycardia	1 (2.3%)	1 (2.9%)	NS
Bigeminy/trigeminy	4 (9.3%)	4 (11.4%)	NS
QTc prolongation	–	–	NS
Atrial flutter	4 (9.3%)	2 (5.7%)	NS
Bradycardia	2 (4.7%)	–	
Somatic symptoms:			NS
Headache	2 (4.7%)	4 (11.4%)	NS
Abdominal pain/dyspeptic symptoms	2 (4.7%)	5 (14.3%)	NS
Hypotension	–	–	NS
Pacemaker implantation	–	–	NS
Total	15 (37.2%)	16 (45.7%)	NS

Table 3. Hemodynamic profile of study drugs.

		Before sinus rhythm restoration	After sinus rhythm restoration	Significance
Heart rhythm [beats/min]	Propafenone	131 ± 21.1	74.6 ± 12.4	0.0001
	Quinidine	124 ± 26.3	75.3 ± 11.8	0.0001
		NS	NS	
Systolic blood pressure [mm Hg]	Propafenone	137 ± 26.3	126 ± 10	0.02
	Quinidine	140 ± 18.4	125 ± 12	0.0003
		NS	NS	
Diastolic blood pressure [mm Hg]	Propafenone	85.2 ± 13.4	79.8 ± 5.91	0.02
	Quinidine	87.1 ± 8.51	78.7 ± 5.94	0.0001
		NS	NS	

equal, as previously discussed [7–9]. However, our data confirms the high efficacy of a single oral loading dose of 600 mg propafenone, with an 83% conversion rate within the first eight hours of therapy. An additional 300 mg of propafenone administered eight hours after the initial dose did not significantly increase the success rate with respect to the other drug.

Thus, a single 600 mg dose of propafenone is effective in most patients with recent onset of AF. The efficacy rate was affected by some parameters, such as no evidence of structural heart disease, preserved left ventricular ejection fraction as well as AF duration shorter than 12 hours. Nevertheless, the homogeneity of our study population and relatively small number of patients with heart disease other than systemic hypertension did not allow us to draw any definite conclusions in this respect. Our study confirmed the high efficacy rate of quinidine. Digoxin given intravenously due to controlled ventricular response during pharmacotherapy with quinidine, a drug with potential cholinolytic effect, has no proven efficacy in SR restoration [10]. Some reported data suggests a high efficacy of the IV administration of digoxin. A higher conversion rate was noted not only during combination with quinidine, but also with other compounds such as propa-

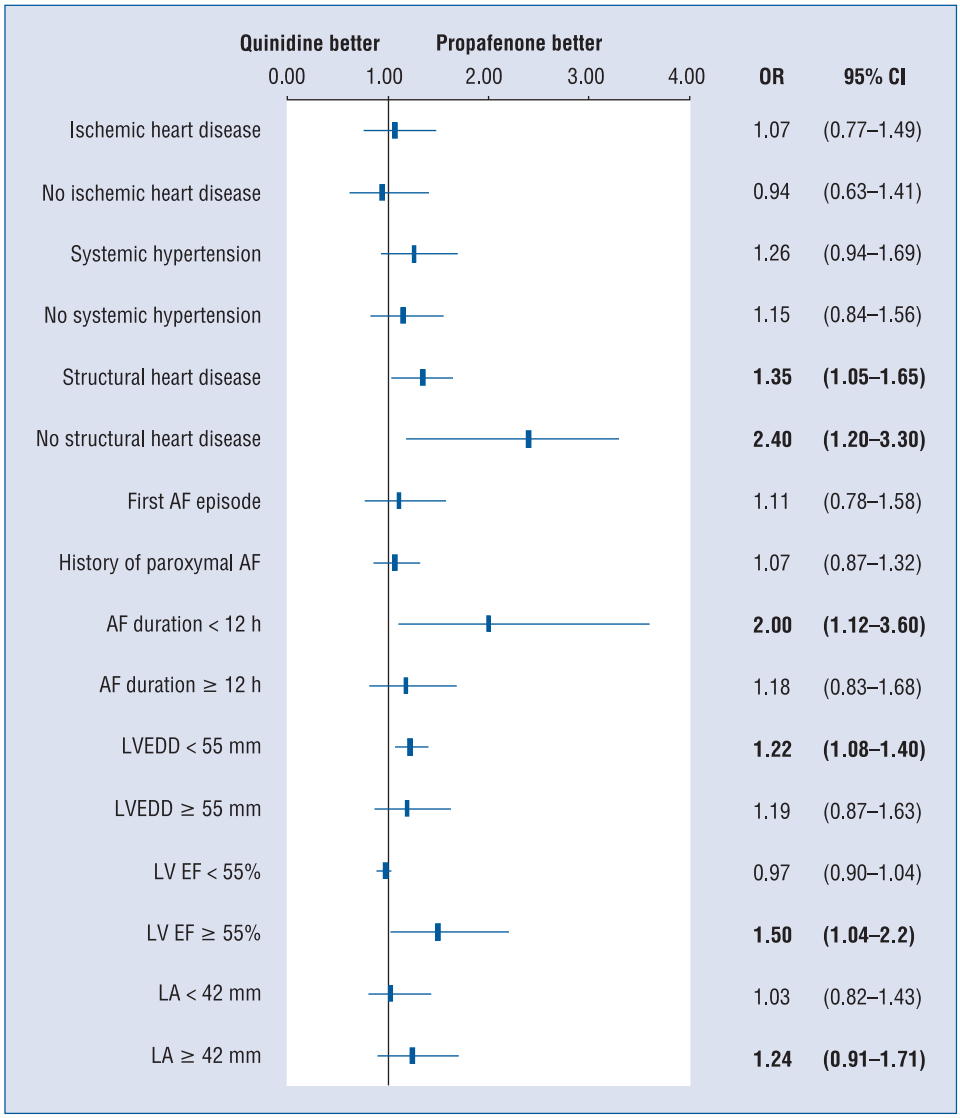

Figure 2. Parameters affecting early sinus rhythm restoration; AF — atrial fibrillation; LA — antero-posterior left atrial diastolic diameter; LVEDD — left ventricle end-diastolic diameter; LVEF — left ventricular ejection fraction; OR — odds ratio; CI — confidence interval.

fenone [11, 12]. However, due to the potential higher rate of proarrhythmic effects and poor evidence supporting a direct antiarrhythmic effect of digoxin, such a combination is now not recommended [10].

The other very important aspect of our study was the tolerability of the proposed therapy. Because of the good short-term prognosis in patients with recent onset AF, safety is an important aspect in the management of arrhythmia. Despite obvious evidence supporting the use of Class IC representatives in the restoration and maintenance of SR, several proarrhythmic events have been reported, mostly during long-term therapy [13–15]. Less attention was paid to the possible proarrhythmic effects of propafenone during acute treatment and there are only a few clinical controlled trials available, with small numbers of patients studied [12, 16–18]. No life-threatening adverse effects were reported during our study. There was one case of bradycardia and non-sustained ventricular tachycardia with mild intensity which constituted no major clinical problems. The therapy was well tolerated without any somatic problems related to the drug.

Our results confirm previously reported data supporting the high efficacy and rapid response to an oral loading dose of propafenone. We think that very good tolerability of 600 mg propafenone given orally as a single dose, as well as the low and acceptable rate of proarrhythmic effect, allow us to recommend this kind of therapy for patients with

paroxysmal AF. In patients with high risk of proarrhythmia, propafenone therapy should be initiated in-hospital manner.

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