CARDIOVASCULAR MEDICINE

Propafenone added to ibutilide increases conversion rates of persistent atrial fibrillation

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Objective: To assess the effectiveness and safety of pharmacological conversion of persistent atrial fibrillation (AF) with a combined propafenone plus ibutilide regimen.

Methods and results: 100 consecutive patients (66 men, mean (SD) age 65 (10) years) with persistent AF (mean (SD) duration 99 (92) days) admitted for elective pharmacological cardioversion were randomly assigned to treatment with either intravenous ibutilide (1 mg plus an additional 1 mg, if required; n = 51) or oral propafenone (600 mg) plus intravenous ibutilide at the same dose (n = 49). Success rates were 41.1% (21 of 51 patients) for ibutilide alone and 71.4% (35 of 49 patients) for propafenone plus ibutilide (p = 0.0044). However, cardioversion occurred earlier in the ibutilide alone group (55 (20) minutes) compared with the combination group (81 (32) minutes, p = 0.0019). A comparable increase in the QTc interval was observed in both groups but one case of sustained torsade de pointes, requiring electrical cardioversion, was observed in the propafenone plus ibutilide group. No other complications were noted during the hospitalisation period.

Conclusion: Concurrent administration of propafenone plus ibutilide for pharmacological cardioversion of persistent AF is safe and more effective than ibutilide alone.

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, with an increasing prevalence over the past few decades.^{1,2} Although control of the ventricular response may be an acceptable treatment in certain subgroups of patients, restoration and maintenance of sinus rhythm remains the preferred strategy in many patients.³⁻⁵ This strategy offers several potential benefits, such as prevention of electrical and structural remodelling of the atria, improved haemodynamic function, amelioration of symptoms, and improvement in the quality of life.³⁻⁶ If this strategy is favoured, most patients are managed with electrical cardioversion, because the pharmacological conversion of persistent AF of relatively long duration is often ineffective.^{7,8} However, pharmacological conversion obviates the need for general anaesthesia and may be associated with lower periprocedural complications and increased cost effectiveness.^{9,10} Therefore, the development of effective drugs for pharmacological conversion of persistent AF is appealing.

Propafenone and ibutilide are two of the most effective antiarrhythmic agents for cardioversion of acute onset AF, but their effectiveness in cases of persistent AF of long duration is modest.^{7,8,11-13} We hypothesised that the combination of these two agents with different pharmacological profiles can improve the success rates in such cases. In the present study, we compared the effectiveness and safety of treatment with propafenone plus ibutilide, versus ibutilide alone, on cardioversion of persistent AF.

METHODS

Study population

Consecutive patients older than 18 and younger than 80 years of age scheduled for elective pharmacological cardioversion of persistent AF were screened. Patients with a duration of the arrhythmia (determined by available ECGs) of over one month but less than one year were considered eligible for the study. Furthermore, pharmacological or electrical cardioversion had not been attempted before. The study protocol

complies with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients underwent clinical assessment, transthoracic two dimensional and Doppler echocardiographic studies, and laboratory investigations. Patients with thyroid dysfunction (including subclinical hyperthyroidism, defined as thyroid stimulating hormone below 0.5 µU/ml), significant valvular heart disease, left atrial diameter greater than 55 mm, advanced heart failure (New York Heart Association class III or IV), or left ventricular ejection fraction less than 40% were excluded. Exclusion criteria were also acute pericarditis, recent acute coronary event or revascularisation, recent infection, malignancies, autoimmune or inflammatory diseases, severe asthma or chronic obstructive pulmonary disease, renal failure, or hepatic failure. Patients with pacemakers, sick sinus syndrome, conduction disturbances, known pre-excitation, history of ventricular arrhythmias or torsade de pointes, QTc over 500 ms, systolic blood pressure lower than 90 mm Hg, electrolyte disturbances, or concurrent intake of QT prolonging drugs were also excluded.

All patients were fully anticoagulated with acenocumarol, targeted at an international normalised ratio above 2.5, for a minimum of three weeks before hospital admission. Heart rate was controlled with β blockers, diltiazem, digoxin, or any combinations of these medications.

Study protocol

The patients were admitted about 24 hours before the scheduled cardioversion and all medications except anticoagulants were discontinued. Clinical assessment was repeated and informed consent was obtained. Patients were randomly assigned to treatment in one to one fashion to either ibutilide or to propafenone plus ibutilide. Treatment in the first group consisted of ibutilide, given at an initial dose of 1 mg intravenously for 10 minutes and a second dose of 1 mg, administered 10 minutes after cessation of the first dose, if this was ineffective. Treatment in the second group consisted of 600 mg oral propafenone, followed by

intravenous ibutilide, at the same dose as in the first group. For the onset of action of propafenone (which is about 90 minutes after oral intake) to coincide with the maximum pharmacological effect of ibutilide (reported to be about 40 minutes after cessation of the infusion) oral propafenone preceded ibutilide administration by 20 minutes.^{13 14} The infusion of ibutilide had been scheduled to be terminated in case of serious arrhythmias or conduction disturbances. All patients were continuously monitored in the coronary care unit for at least six hours after treatment. A 12 lead ECG at a paper speed of 25 mm/s was obtained at baseline, five minutes after infusion of the first dose and five minutes after infusion of the second dose of ibutilide (if required), and at one hour intervals thereafter, until the end of the six hour observation period. A 12 lead ECG was repeated 24 hours after drug administration and the conversion was considered successful when sinus rhythm was present. Patients who successfully converted to sinus rhythm were subsequently discharged from the hospital, whereas those who were not restored to sinus rhythm were scheduled for electrical cardioversion on the next day. Oral treatment for the prevention of AF recurrences (sotalol, amiodarone, or propafenone initiated on the second day after cardioversion) was left to the discretion of the referring physician.

One experienced cardiologist blinded to the patients' characteristics and outcome analysed all ECGs. The QT interval was measured as the interval in milliseconds between the first deflection of QRS and the point of return of the T wave to the isoelectric line. Measurements were obtained from three consecutive complexes in each lead and the resulting average was finally accepted. The leads in which the end of the T wave could not be identified with certainty were excluded from analysis. When a prominent U wave was present, the nadir between the T and U waves was regarded as the end of T wave. The QTc interval was calculated by Bazett's formula ($QTc = QT/\sqrt{RR}$). To assess intraobserver variability, the baseline and post-cardioversion ECG tracings of 10 randomly selected patients were re-examined 10 days after the initial evaluation. Intraobserver variation was less than 5%.

Statistical analysis

Continuous variables are expressed as mean (SD) and were compared by *t* test for independent variables. Categorical variables are expressed as percentages and were compared by χ^2 after Yates's correction. Differences within groups were compared by *t* test for dependent variables. All data were statistically analysed with the Statistica 6.0 software program (StatSoft Inc, Tulsa, Oklahoma, USA). Significance was defined at an α level of 0.05.

Table 1 Baseline characteristics of the two groups

	Ibutilide (n = 51)	Propafenone plus ibutilide (n = 49)	p Value
Age (years)	66 (9)	65 (11)	0.77
Men	34 (66%)	32 (65%)	0.83
AF duration (days)	98 (83)	99 (100)	0.95
Hypertension	27 (52%)	28 (57%)	0.82
Diabetes	7 (13%)	5 (10%)	0.87
Coronary artery disease	10 (19%)	8 (16%)	0.86
LA size (mm)	36 (12)	43 (17)	0.15
LVEF (%)	58 (6)	59 (10)	0.60
HR (beats/min)	92 (13)	95 (11)	0.62
QTc interval (ms)	399 (28)	398 (26)	0.90
Drugs for rate control			
Digoxin	38 (74%)	37 (75%)	0.90
β Blockers	22 (43%)	21 (42%)	0.86
Diltiazem	7 (13%)	5 (10%)	0.87

Values are expressed as mean (SD) or as number (%).

AF, atrial fibrillation; HR, heart rate; LA, left atrial; LVEF, left ventricular ejection fraction.

RESULTS

Patient characteristics

The study population consisted of 100 patients (66 men, mean (SD) age 65 (10) years) having persistent AF for a mean duration of 99 (92) days, with a median of 60 days. The clinical and demographic characteristics, as well as the echocardiographic findings, were comparable between the two groups (table 1).

Restoration of sinus rhythm

Sinus rhythm was restored in 21 of 51 patients (41.1%) in the ibutilide group and in 35 of 49 (71.4%) patients in the propafenone plus ibutilide group. This difference was highly significant ($p = 0.0044$). No patient in the propafenone plus ibutilide group converted to sinus rhythm before the infusion of ibutilide, and one patient in the ibutilide group converted 18 minutes after the onset of the infusion and did not require a second dose. Cardioversion occurred earlier ($p = 0.0019$) in the ibutilide group (55 (20) minutes after the onset of ibutilide administration) than in the ibutilide plus propafenone group (81 (32) minutes after the onset of ibutilide administration). Timing of conversion to sinus rhythm in the combination group displayed two distinct peaks at 50 and 110 minutes after the onset of ibutilide administration (fig 1). No relapses of AF were recorded in either group during the 24 hour hospitalisation period. Moreover, no significant differences in demographic and clinical characteristics were found between patients who successfully converted to sinus rhythm and those who remained in AF (table 2).

Figure 1 Timing of conversion to sinus rhythm (expressed in minutes after the onset of ibutilide administration) in patients who received ibutilide or propafenone plus ibutilide.

Table 2 Predictors of conversion success in the study population

	Conversion (n = 56)	No conversion (n = 44)	p Value
Age (years)	65 (11)	64 (9)	0.71
Men	36 (64%)	30 (68%)	0.84
AF duration (days)	86 (76)	115 (107)	0.12
Hypertension	29 (51%)	26 (59%)	0.59
Diabetes	7 (12%)	5 (11%)	0.89
Coronary artery disease	8 (14%)	10 (22%)	0.40
LA size (mm)	37 (6)	42 (8)	0.15
LVEF (%)	59 (9)	57 (8)	0.41
Baseline HR (beats/min)	96 (12)	90 (15)	0.41
Baseline QTc interval (ms)	400 (27)	395 (26)	0.67
QTc interval increase (ms)	22 (21)	42 (57)	0.12

Values are expressed as mean (SD) or as number (%).

QT interval prolongation

The QTc interval was significantly prolonged in both groups, from 399 (28) ms to 427 (64) ms ($p < 0.001$) in the ibutilide group and from 398 (26) ms to 426 (39) ms ($p < 0.001$) in the propafenone plus ibutilide group. This increase was comparable between the two groups ($p = 0.99$).

Complications and safety profile

One patient in the propafenone plus ibutilide group experienced an episode of sustained torsade de pointes, about 45 minutes after the onset of ibutilide infusion. The patient's QTc interval increased from 407 ms to 520 ms after the infusion of the second dose of ibutilide, despite normal serum electrolyte concentrations. She was successfully cardioverted with a 300 J direct current monophasic shock, although a significant bradycardia ensued requiring external transthoracic pacing. No other significant complications were observed during the hospitalisation period.

DISCUSSION

Pharmacological conversion of persistent AF is highly effective when initiated within seven days after the onset of the arrhythmia.^{7–8} According to the current recommendations for pharmacological cardioversion of AF of more than seven days' duration, only dofetilide has a class I indication; amiodarone and ibutilide have a class IIa and flecainide and propafenone have a class IIb indication.⁷ Previous reports have shown low success rates for pharmacological cardioversion of persistent AF of over seven days' duration.^{7–9} As a result, the majority of patients with persistent AF of long duration are managed with electrical direct current cardioversion. This method is associated with high success rates and shorter monitoring time. However, the development of effective pharmacological treatments for cardioversion obviates the need for sedation or general anaesthesia and may be a more cost effective approach for such patients.^{9–10}

Propafenone is a class Ic antiarrhythmic agent that slows conduction in the atrial tissue by blocking the fast sodium current. Its effectiveness is well established, reaching up to 87% success rates when administered during the first hours after the initiation of the arrhythmia.^{7–8–11} In contrast, propafenone is much less effective in cardioversion of persistent AF, with reported success rates ranging between 4–9.3%.¹¹ Of note, Kochiadakis *et al*¹² have reported that this rate can reach 40% after one month of continuous oral administration.

Ibutilide, a class III antiarrhythmic agent, increases the action potential duration by blocking the rapid component of the delayed rectifier potassium current and by enhancing the slow inward sodium current.^{13–15} Ibutilide can cause significant QT interval prolongation, leading to the development of

torsade de pointes, although this complication is relatively rare. Although ibutilide is more effective in conversion of atrial flutter (AFL), it is also considered one of the most potent agents for cardioversion of recent onset AF, with success rates of up to 80%.^{7–8} These rates decrease significantly, to the range of 30–40%, in patients with persistent AF lasting more than four days.^{16–20} Abi-Mansour *et al*¹⁸ reported an efficacy rate of 28% in patients with AF duration of three hours to 90 days; further analysis, however, showed mean arrhythmia duration of 13.6 days for patients successfully converted to sinus rhythm, compared with 35.4 days for those who remained in AF. Similarly, Eversole *et al*²⁰ studied patients with arrhythmia duration ranging from one hour to 11 months and found a conversion rate of 17% in the subgroup of patients with arrhythmia duration greater than 96 hours. A recent study indicated that ibutilide successfully cardioverted 41.5% of patients with persistent AF lasting 328 (416) days (the series with the longest duration published so far), but these patients had sinus node disease with implanted dual chamber pacemakers.²¹ In accordance with these studies, we report a successful cardioversion rate for ibutilide alone of 41.1% in patients with persistent AF with a mean duration of 98 (83) days.

The efficacy of ibutilide when combined with other antiarrhythmic drugs has not been adequately investigated. Ibutilide in patients with persistent AF, who were treated with long term amiodarone, was associated with 39% success rate within 30 minutes of administration.²² However, these agents belong to the same antiarrhythmic class, sharing common antiarrhythmic actions. In the present study, we evaluated the effectiveness of ibutilide combined with a class Ic antiarrhythmic agent. We showed that the concurrent administration of propafenone and ibutilide is superior to administration of ibutilide alone. The success rate of 71.4% found in our study is the best result achieved by a pharmacological approach and compares favourably with the 70–90% success rate of traditional external, direct current cardioversion.⁹

Very recently, two further studies investigated a similar pharmacological approach in patients with AF or AFL.^{23–24} In the first study, the effects of ibutilide were investigated in 56 patients with AF or AFL (mean duration 64 (44) days) who were pre-treated with propafenone.²³ The authors reported a conversion rate of 62.5% within a four hour observation period after ibutilide administration; only one patient developed two asymptomatic, self terminating episodes of torsade de pointes.²³ Although only 7% of the total group had chronic AFL, the authors did not provide separate information on the success rates in the two subgroups, namely chronic AF and AFL.²³ In the second report, 48 patients with persistent AF (mean duration 32 (54) days) and 23 patients with AFL receiving propafenone or flecainide underwent pharmacological cardioversion with ibutilide.²⁴ The success rate for patients with persistent AF was 47.9% with a trend towards higher conversion rates in those with arrhythmia duration of seven days or less.²⁴ Only two of the 71 patients with AF or AFL developed torsade de pointes.

To our knowledge, our study is the largest so far to investigate the role of the combination of a class Ic agent with ibutilide for cardioversion of persistent AF. In contrast with the two recent reports,^{23–24} our patient population was homogeneous, consisting only of patients with persistent AF of relatively long duration. Moreover, three important methodological differences exist between our study and the two recently published reports.^{23–24} Firstly, our study directly compared ibutilide alone versus propafenone plus ibutilide. Secondly, in our study, propafenone was started at the beginning of the cardioversion process, whereas in the other two studies the patients were already pre-treated for a

relatively long period.^{23–24} Since propafenone exerts rapid electrophysiological effects, pre-treatment does not appear to be justified.^{11–14} Lastly, pre-treatment with either propafenone or flecainide was previously used²⁴; although these drugs belong to the same antiarrhythmic class, significant differences in the acute success rates have been reported.⁸

The two distinct peaks of AF conversion observed in the propafenone plus ibutilide group merit attention. The first peak, observed about 50 minutes after ibutilide administration, probably represents the peak pharmacological action of ibutilide, whereas the second peak, around the 110th minute after ibutilide administration, is most likely secondary to the synergistic action of propafenone and ibutilide. Given the pharmacokinetics of these two agents, one can speculate that even higher conversion rates can be achieved with the combined administration, if oral propafenone precedes the administration of intravenous ibutilide by about 60 minutes.^{11–13–14}

Our study, being free of the methodological limitations of the two previously published reports, provides more solid evidence for superior results with combined propafenone and ibutilide administration compared with ibutilide alone.^{23–24} The risk for proarrhythmic or other side effects was comparable between the two regimens. Previous reports indicate an overall incidence of 4.3% of torsade de pointes, including 1.7% of the sustained form, in ibutilide treated patients.^{13–18–20} The meticulous investigation for factors precipitating proarrhythmia and the low percentage of patients with structural heart disease in our population may account for the low incidence of adverse reactions seen in our study.

Study limitations

We feel that our study adds to the current understanding of pharmacological conversion of persistent AF. However, apart from the timing of propafenone administration, discussed earlier, a few potential limitations may be apparent. Firstly, our study was not placebo controlled and, therefore, the effectiveness of each treatment arm, beyond that of placebo, cannot be directly assessed. Secondly, no data on long term sinus rhythm maintenance are available. Lastly, the low incidence of proarrhythmia may be due to the strict exclusion criteria applied in our study protocol; thus, extrapolation to patients with significant structural heart disease should be made with caution.

Conclusion

Our study indicates that, in selected patients with persistent AF of relatively long duration undergoing elective pharmacological cardioversion, propafenone can be safely added to ibutilide to increase sinus rhythm restoration rates. Further studies examining the optimal timing of propafenone administration before ibutilide infusion are needed. Moreover, the effectiveness and safety of this regimen should be evaluated in other patient groups. Finally, comparison of this strategy with electrical cardioversion constitutes a subject for future research.

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