JACC Vol. 16, No. 7
December 1990:1722–7

The Value of Class IC Antiarrhythmic Drugs for Acute Conversion of Paroxysmal Atrial Fibrillation or Flutter to Sinus Rhythm

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In a single-blind randomized study, the efficacy and safety of intravenous propafenone (2 mg/kg body weight per 10 min) versus flecainide (2 mg/kg per 10 min) were assessed in 50 patients with atrial fibrillation or flutter. Treatment was considered successful if sinus rhythm occurred within 1 h. Conversion to sinus was achieved in 11 (55%) of 20 patients with atrial fibrillation treated with propafenone and in 18 (90%) of 20 with atrial fibrillation treated with flecainide ($p < 0.02$). If atrial fibrillation was present ≤24 h, conversion to sinus rhythm was achieved in 8 (57%) of 14 patients in the propafenone group and 13 (93%) of 14 in the flecainide group ($p < 0.05$). Atrial flutter was converted in two (40%) of five patients treated with propafenone and in one (20%) of five with flecainide (p = NS).

Mean time to conversion was 16 ± 10 min in the propafenone group versus 18 ± 13 min in the flecainide group (p = NS). QRS lengthening (83 ± 15 to 99 ± 20 ms) was observed only in the patients treated with flecainide ($p < 0.001$). Patients successfully treated with propafenone showed significantly higher plasma levels than those whose arrhythmia did not convert to sinus rhythm. Transient adverse effects were more frequent in the flecainide group (40%) than in the propafenone group (8%) ($p < 0.01$).

In conclusion, at a dose of 2 mg/kg in 10 min, flecainide is more effective than propafenone for conversion of paroxysmal atrial fibrillation to sinus rhythm. However, considering the propafenone plasma levels and very few adverse effects, the dose or infusion rate, or both, used in the propafenone group may not have been sufficient to achieve an optimal effect. Neither drug seems very effective in patients with atrial flutter.

(J Am Coll Cardiol 1990;16:1722–7)

Propafenone hydrochloride has been classified as a class IC antiarrhythmic agent with weak beta-adrenoceptor antagonist activity. It primarily slows intraatrial and atrioventricular (AV) node conduction (1). Clinically, no substantial increase in atrial refractoriness has been observed. Propafenone is useful for the management of patients with various forms of ventricular and supraventricular tachycardias (1–9). Recent studies have demonstrated that intravenous propafenone is potentially effective in terminating paroxysmal atrial fibrillation and in controlling ventricular response during atrial fibrillation with only minor side effects (10–12). However, the drug seems less effective in patients with atrial flutter (12).

Flecainide acetate is a class IC antiarrhythmic agent currently used in both ventricular and supraventricular arrhythmias (13–25). It slows intracardiac conduction and prolongs the refractory period to a lesser extent (15–17). We (24) have shown in a previous study that flecainide is very effective for immediate conversion of recent onset atrial fibrillation but its use is complicated by drug-related side effects and it seems to be ineffective for atrial flutter.

The value of propafenone as an antiarrhythmic agent for conversion of paroxysmal atrial fibrillation or flutter, as compared with that of more frequently used drugs such as quinidine or flecainide, is not well established. This comparative study was undertaken to determine the efficacy and safety of intravenous propafenone versus flecainide for conversion of atrial fibrillation or flutter to sinus rhythm

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Manuscript received March 19, 1990; revised manuscript received June 13, 1990, accepted July 2, 1990.

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0735-1097/90/$3.50

within 1 h. The relation between plasma levels and effectiveness of both drugs was also studied

Methods

Study patients. Fifty consecutive patients (34 men and 16 women) 27 to 78 years old (mean 59 ± 14) were selected for this study, which was approved by the institutional review board. They were entered into the study if there was atrial fibrillation or flutter lasting <6 months with a ventricular rate >100 beats/min at rest and no signs of heart failure. Exclusion criteria were any previously documented or suspected conduction disturbances of more than first degree AV block, concomitant therapy with class I antiarrhythmic drugs, Wolff-Parkinson-White syndrome, sick sinus syndrome, acute myocardial infarction, hyperthyroidism, cardiac surgery within 2 weeks before the start of the study, left atrial enlargement with atrial fibrillation or flutter lasting >2 days without appropriate anticoagulation therapy, electrolyte imbalance and body weight >100 kg.

Treatment protocol. A complete medical history, physical examination, routine biochemical laboratory testing, chest X-ray film and a 12 lead electrocardiogram (ECG) were performed before administration of the drug. If the chest X-ray film showed signs of cardiac enlargement, additional two-dimensional echocardiography was performed before the start of treatment. The patients were observed for at least 30 min before administration of either drug to allow their condition to stabilize. In seven patients with atrial fibrillation who had qualified for enrollment spontaneous conversion to sinus rhythm occurred before the start of the study. After informed consent was obtained, the patients were randomly assigned to treatment with either intravenous propafenone or flecainide. During 1 h after administration of either drug, the patient's rhythm was continuously monitored. Treatment was considered successful if conversion to sinus rhythm occurred within 60 min after start of the infusion. If sinus rhythm was not restored, patients were treated with direct current cardioversion or with other antiarrhythmic drugs, or both.

A 12 lead ECG was recorded as soon as conversion to sinus rhythm occurred and at 60 min after start of the infusion. The ECG intervals were assessed just before start of the infusion and at 60 min. The RR interval, QRS interval, QT interval, corrected QT interval (QTc = QT/$\sqrt{RR}$) and atrial flutter wave interval, where appropriate, were calculated from a mean of five consecutive beats.

Drug administration and plasma sampling. Propafenone hydrochloride and flecainide acetate, both at a dose of 2 mg/kg body weight, were administered intravenously in 10 min. Plasma samples were collected at 20 and 60 min and also at the time of conversion to sinus rhythm. Determination of plasma levels of both drugs was done by means of high pressure liquid chromatography.

Table 1. Clinical Baseline Characteristics of 50 Study Patients*

	Propafenone Group (n = 25)	Flecainide Group (n = 25)
Mean age (yr)	61 ± 13	58 ± 15
Gender (male/female)	19/6	15/10
Mean heart rate at entry (beats/min)	141 ± 21	137 ± 25
AF/AFl <24 h (no.)	14/2	14/1
Chest X-ray film (mean CTR) (%)	47 ± 7	46 ± 5
Mean left atrial size (mm)	37 ± 7	38 ± 7
Previous AF/AFl	8/1	5/2
Etiology		
No cardiac disease	12	10
Hypertensive heart disease	2	2
Coronary artery disease	7	7
Pulmonary disease	1	1
Valvular heart disease	3	4
Pericardiectomy	0	1
Concomitant drug treatment		
Digoxin	4	3
Beta-blocker	3	6
Calcium antagonist	1	4
Anticoagulant	6	9

*p = not significant. AF = atrial fibrillation; AFl = atrial flutter; CTR = cardiothoracic ratio; NS = not significant.

Statistics. Mean values ± SD were given for continuous variables and were analyzed by means of Student's *t* test for unpaired or paired variables where appropriate. Fisher's exact test was used to compare discontinuous variables.

Results

Patient characteristics (Table 1). The clinical characteristics were fully comparable in both groups. Forty patients with paroxysmal atrial fibrillation and 10 with paroxysmal atrial flutter were entered into the study. Recent onset (≤24 h) atrial fibrillation was present in 28 (70%) and atrial flutter in 3 (30%) patients. Twelve patients (30%) had long-standing (>24 h) atrial fibrillation and 7 (70%) had long-standing atrial flutter. Sixteen patients had previously documented episodes of paroxysmal atrial fibrillation or flutter.

Conversion rate. Conversion to sinus rhythm was achieved in 11 (55%) of the 20 patients with atrial fibrillation treated with propafenone (propafenone group) and in 18 (90%) of the 20 with atrial fibrillation in the group treated with flecainide (flecainide group) ($p < 0.02$). Atrial flutter was converted to sinus rhythm in two (40%) of five in the propafenone group and one (20%) of five in the flecainide group (p = NS). All three patients with atrial flutter converted to sinus rhythm after a brief period of atrial fibrillation.

Duration of the arrhythmia. If atrial fibrillation had been present ≤24 h, the conversion rate was 57% (8 of 14 patients) in the propafenone group and 93% (13 of 14 patients) in the

flecainide group ($p < 0.05$). If atrial fibrillation lasted >24 h, 50% (three of six patients) in the propafenone group had conversion to sinus rhythm as did 83% (five of six patients) in the flecainide group (p = NS). The mean duration of atrial fibrillation (if present >24 h) was 7.7 ± 11.1 days (range 2 to 30) in the propafenone group and 4.2 ± 2.4 days (range 2 to 8) in the flecainide group (p = NS). Atrial flutter had been present <24 h in 3 of the 10 patients. Conversion to sinus rhythm occurred in both patients with recent onset atrial flutter who were treated with propafenone.

Conversion time. The time required for conversion to sinus rhythm in the propafenone group was 16 ± 10 min (range 4 to 40). In the flecainide group it was 18 ± 13 min (range 3 to 47) (p = NS).

Electrocardiographic measurements. In the patients treated with propafenone whose arrhythmia was not converted, slowing of mean ventricular rate from 138 ± 23 to 101 ± 21 beats/min ($p < 0.001$) after 1 h of the infusion was noted. The patients treated with flecainide whose arrhythmia was not converted showed a decrease in ventricular rate from 133 ± 27 to 116 ± 36 beats/min ($p < 0.05$). The propafenone group showed no significant increase (mean 3%) of the QRS interval from 83 ± 11 to 86 ± 12 ms; the QT interval increased from 310 ± 33 to 344 ± 43 ms ($p < 0.001$) and the QTc interval decreased from 473 ± 46 to 416 ± 60 ms ($p < 0.001$). In the flecainide group, the QRS interval significantly increased (mean 16%) from 83 ± 15 to 99 ± 20 ms ($p < 0.001$), the QT interval increased from 314 ± 45 to 370 ± 52 ms ($p < 0.001$) and the QTc interval decreased from 465 ± 57 to 427 ± 55 ms ($p < 0.003$). In both treatment groups with atrial flutter, there was a significant increase in atrial flutter cycle length from 216 ± 22 to 272 ± 59 ms in the propafenone group and from 200 ± 28 to 244 ± 46 ms in the flecainide group ($p < 0.05$ for both).

Cardiac measurements. The mean cardiothoracic index on a chest X-ray film was 0.46 ± 0.06 in patients with successful conversion to sinus rhythm versus 0.47 ± 0.06 in the group without conversion (p = NS). In patients with atrial flutter, the mean cardiothoracic index was 0.50 ± 0.01 in the group with conversion and 0.47 ± 0.05 in the group without conversion (p = NS). In patients with atrial fibrillation, the mean anteroposterior left atrial size on two-dimensional echocardiography was 38 ± 6 mm (range 25 to 48) in the group with conversion and 38 ± 9 mm (range 25 to 55) in the group without conversion (p = NS). Patients with atrial flutter whose arrhythmia converted had a mean left atrial size of 39 ± 3 mm (range 37 to 42) compared with 38 ± 11 (range 27 to 55) in the group without conversion (p = NS).

Previous treatment with class IA agents. Eight of 16 patients with recurrent episodes of atrial fibrillation or flutter had been treated previously with a class IA antiarrhythmic drug. Pharmacologic cardioversion to sinus rhythm was achieved in three of these patients. In three of five patients whose arrhythmia had not been converted during treatment with a class IA agent the arrhythmia converted to sinus rhythm after intravenous administration of either propafenone or flecainide.

Table 2. Adverse Effects During or After Intravenous Propafenone Hydrochloride or Flecainide Acetate

	Propafenone (n = 25)	Flecainide (n = 25)
Dizziness	2	2
Paresthesia	—	5
Dryness of mouth	—	1
Short-lasting hypotension	—	1
Transient conduction disturbance		
Left bundle branch block	—	1
Junctional escape rhythm	—	2

Concomitant use of digoxin. Seven patients were receiving digoxin on entry into the study. Conversion to sinus rhythm was achieved in 5 (71%) of the 7 patients who received digoxin and in 27 (63%) of 43 without the concomitant use of digoxin (p = NS).

Adverse effects. Transient mild adverse effects were noted in 10 patients (42%) in the flecainide group and in only 2 patients (8%) in the propafenone group ($p < 0.01$) (Table 2). Two patients in the flecainide group had more than one drug-related side effect. None of the patients required discontinuation of the intravenous administration and no additional treatment was required.

Plasma levels. Propafenone and flecainide plasma samples were collected in all patients. At the time of conversion to sinus rhythm the mean plasma level of propafenone was 1.26 ± 0.71 mg/liter, at 20 min it was 0.90 ± 0.56 mg/liter and at 60 min 0.56 ± 0.24 mg/liter. The mean plasma level of flecainide at the time of conversion to sinus rhythm was 0.53 ± 0.43 mg/liter, at 20 min it was 0.37 ± 0.23 mg/liter and at 60 min 0.20 ± 0.08 mg/liter. There was a significant difference in plasma levels at 20 and 60 min when the patients with arrhythmia conversion were compared with patients without conversion in the propafenone group (Table 3). In the flecainide group plasma levels in the patients with arrhythmia conversion were also higher, although this difference did not reach statistical significance.

Long-term follow-up. Forty-nine patients remained in sinus rhythm and 1 patient had persisting atrial fibrillation during a mean follow-up period of 11.4 ± 5.2 months. After conversion to sinus rhythm most patients were treated orally with propafenone, flecainide, quinidine, sotalol or digoxin but six patients did not receive any drug therapy. Sixteen of the medically treated patients experienced at least one symptomatic episode of supraventricular tachyarrhythmia during the follow-up period and one patient had daily episodes of atrial fibrillation despite various forms of therapy.

Table 3. Comparison of Plasma Levels in Patients With and Without Conversion to Sinus Rhythm

	With Conversion	Without Conversion	p Value
Propafenone group			
No. of patients	13	12	
Propafenone levels (mg/liter)			
At cardioversion	1.26 ± 0.71	—	
At 20 min	1.15 ± 0.58	0.63 ± 0.41	<0.02
At 60 min	0.65 ± 0.19	0.45 ± 0.23	<0.03
Flecainide group			
No. of patients	19	6	
Flecainide levels (mg/liter)			
At cardioversion	0.53 ± 0.43	—	
At 20 min	0.40 ± 0.13	0.28 ± 0.13	NS
At 60 min	0.21 ± 0.05	0.18 ± 0.05	NS

NS = not significant.

Discussion

Paroxysmal atrial fibrillation is an extremely common tachyarrhythmia in humans, whereas paroxysmal atrial flutter is less common (26,27). These rhythm disturbances are frequently associated with very disturbing palpitation and an increased risk for embolic cerebrovascular events or they may even result in more insidious symptoms related to the loss of contribution of atrial systole to ventricular filling and subsequent cardiac output (28,29). Therefore, the rapid restoration of sinus rhythm in patients with paroxysmal atrial fibrillation or flutter is usually warranted.

Acute therapy of paroxysmal atrial fibrillation or flutter. Control of ventricular response during atrial fibrillation or flutter can usually be achieved by various drugs and sinus rhythm can be restored by direct current countershock in most patients. Chemical cardioversion, especially if the drug is given orally, is seldom achieved rapidly and adverse effects are frequently observed (20). During and shortly after intravenous drug administration overall conversion success rates vary from 6% for verapamil to 58% for procainamide and ≤90% for flecainide (17,24,30). However, the "ideal" cardiovascular drug for restoration of sinus rhythm should be simple to administer, highly effective with a rapid onset of action and devoid of significant cardiac or noncardiac toxicity.

Comparison with previous studies. In a previous report (24) we suggested that patients with recent onset atrial fibrillation and uncompromised left ventricular function can be managed with intravenous flecainide rather than hospitalization for therapy with quinidine or electrical cardioversion. However, transient adverse effects during and shortly after flecainide infusion were still noted in 26% of the patients. Propafenone may be more suitable for the treatment of paroxysmal atrial fibrillation or flutter. Its electrophysiologic effects are similar to those of flecainide but only minor drug-related side effects were reported (8,10,12) when the drug was given intravenously in doses ≤2 mg/kg in the treatment of supraventricular arrhythmias. In this study propafenone was well tolerated with only very few mild transient adverse effects, as contrasted to more persistent side effects during long-term oral therapy (4,5). This finding suggests that formation of metabolites during oral therapy, but not after acute intravenous administration, is probably responsible for these adverse effects.

Major findings of the present study. We report here a controlled randomized study where the efficacy and safety of intravenous propafenone was compared with intravenous flecainide for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm with a defined end-point for therapeutic success within 1 h after drug administration, thereby largely eliminating the bias of spontaneous conversion.

In this study flecainide had an overall conversion rate of 90% in patients with atrial fibrillation; however, the conversion rate was only 20% in patients with atrial flutter. These results are in agreement with previous studies (16,19,24). Propafenone showed a significant lower overall conversion rate of 55% in patients with atrial fibrillation as compared with the flecainide group. However, in propafenone-treated patients with atrial flutter, we found a conversion rate of 40%, although the number of observations was small. Comparable results were obtained by Bianconi et al. (12) who reported an overall conversion rate of 62% in patients with atrial fibrillation and a 33% conversion rate in patients with atrial flutter. Connolly et al. (10) found a conversion rate of 43% in patients with atrial fibrillation after cardiac surgery. In our study conversion to sinus rhythm was achieved very rapidly in both treatment groups. Both propafenone and flecainide caused a significant decrease in the ventricular response at 60 min in the patients without arrhythmic conversion.

If atrial fibrillation lasted ≤24 h it was converted to sinus rhythm in almost all patients (93%) treated with intravenous flecainide. However, a significantly lower conversion rate of 57% was noted with intravenous propafenone in this group of patients. No significant difference in conversion rate (five of six flecainide-treated and three of six propafenone-treated patients) was seen between the two treatment groups if atrial fibrillation lasted >24 h, although both groups had only a small number of patients. Bianconi et al. (12) reported a higher conversion rate of 71% in patients treated with propafenone when the arrhythmia lasted <48 h but only a 26% conversion rate in patients with a longer-lasting arrhythmia. In patients with long-standing atrial fibrillation (median duration 1 month, mean 8.2 months), Vita et al. (11) reported a conversion rate of only 9% in a placebo-controlled study with intravenous propafenone.

Significant QRS widening due to slowing of intraventricular conduction was noted only in the flecainide group,

representing the conduction slowing effect of flecainide in the myocardium. Also, we noted reversible left bundle branch block in one patient. In contrast, patients treated with propafenone, even those with high plasma levels, whose arrhythmia converted to sinus rhythms did not show significant QRS widening. QTc intervals showed a moderate decrease in both treatment groups, which is not surprising as the QTc interval largely represents the refractory period. Neither propafenone nor flecainide substantially increases ventricular refractoriness.

Different conversion rates of class IC drugs. The electrophysiologic mechanisms by which class IC drugs exert their beneficial effects for the conversion of atrial fibrillation or flutter to sinus rhythm remain speculative and have been discussed previously by our group (24) and by Antman et al. (31). The lower efficacy of propafenone, as contrasted with flecainide, deserves further comment. There may be several reasons for the lower efficacy in our propafenone group: 1) The plasma levels at 20 min in the patients with conversion to sinus rhythm were almost twice as high as the plasma levels of the patients without arrhythmia conversion. This significant difference suggests that a high plasma level should be reached quickly to achieve an atrial tissue level sufficiently high for early conversion to sinus rhythm. This tendency was also found in the flecainide group. 2) Apart from the lower efficacy in the propafenone-treated patients, there were also very few adverse effects in this group.

Limitations of the study. The doses of both drugs used in this study were chosen on the basis of previously reported data. In most of these studies no intravenous dose >2 mg/kg body weight have been used for either propafenone or flecainide, in particular when the drug was given at an infusion rate of ≤10 min. However, the present study shows an evident discrepancy between the doses of both drugs tested. Flecainide produced the typical ECG changes of class IC antiarrhythmic agents and transient adverse effects at plasma levels in the "therapeutic" range. In contrast, propafenone caused no significant ECG changes and rare adverse effects with significantly lower plasma levels in the patients whose arrhythmia was not converted. It is obvious that both the pharmacokinetic and pharmacodynamic behavior of propafenone indicate that the optimal effective dose was not attained in this study. Either a higher dosage or a faster rate of administration that leads to sufficiently high tissue levels is probably necessary for greater efficacy. Therefore, a dose-finding study with propafenone to determine the equipotent dosage or the optimal rate of administration, or both, seems warranted.

Conclusions. Intravenous administration of the class IC antiarrhythmic drugs propafenone and flecainide is very useful for immediate conversion of recent onset atrial fibrillation and may be preferable to oral loading with quinidine or direct current countershock necessitating hospitalization. In atrial flutter these drugs exert almost no effect. At a dose of 2 mg/kg in 10 min, flecainide is more effective than propafenone for conversion of paroxysmal atrial fibrillation to sinus rhythm. However, one should use this drug cautiously and only during close ECG monitoring, especially because of its transient adverse effects on cardiac conduction. In contrast, propafenone is almost free of adverse effects but has a lower efficacy than flecainide.

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