

Randomized Placebo-Controlled Trial of Propafenone for Treatment of Atrial Tachyarrhythmias After Cardiac Surgery

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Fourteen patients with atrial fibrillation or flutter and a ventricular rate of ≥ 120 beats/min occurring after cardiac surgery entered a double-blind placebo-controlled conditional crossover trial of intravenous propafenone. Patients randomly received either propafenone (2 mg/kg body weight) or placebo during a 10 minute intravenous infusion. If 20 minutes after the initiation of this infusion there was no conversion to sinus rhythm, the patient received a second intravenous infusion over 10 minutes (either propafenone or placebo, whichever was not given first). The electrocardiogram was recorded continuously throughout the study.

Fourteen patients received propafenone and 10 received placebo. No patient's rhythm converted to sinus

rhythm after placebo. In six patients (43%) ($p < 0.001$), the arrhythmia converted to sinus rhythm between 5 and 10 minutes after the end of the propafenone infusion. After propafenone, the ventricular response to atrial fibrillation or flutter decreased significantly from 141.6 ± 15.2 to 116.0 ± 15.5 beats/min. Ventricular rate did not change after placebo. The mean propafenone plasma concentration was 3.46 ± 2.17 mg/liter. The only side effect of propafenone noted was a decrease in systolic blood pressure of 9 ± 9 mm Hg. Propafenone was useful for management of atrial fibrillation after cardiac surgery both for control of rapid ventricular response and for conversion to sinus rhythm.

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Propafenone is an investigational antiarrhythmic agent that is useful for the control of both atrial and ventricular arrhythmias including ventricular tachycardia (1), ventricular premature beats (2) and atrioventricular (AV) node reciprocating tachycardia (3). Although there is fragmentary evidence indicating that propafenone may be useful in atrial fibrillation (4,5), there have been no placebo-controlled trials of propafenone for this arrhythmia. Propafenone prolongs atrial refractoriness and slows intraatrial and AV node conduction (1). These properties should be beneficial for treatment of atrial fibrillation or flutter, both for promoting conversion to sinus rhythm and for slowing the ventricular response.

Atrial fibrillation and flutter occur frequently after open heart surgery (6,7). These arrhythmias are usually of short duration and revert spontaneously, but in some patients hemodynamic compromise may necessitate prompt intervention. Although digoxin (8), verapamil (9) and beta-ad-

renergic blockers (10) can slow ventricular rate, they rarely convert the arrhythmia to sinus rhythm. Sodium channel blocking drugs such as disopyramide (7) and procainamide (11) convert some patients' arrhythmias to sinus rhythm; however, they do not decrease the ventricular response in atrial fibrillation.

In this report, we present the results of a double-blind placebo-controlled conditional crossover trial of propafenone for control of ventricular rate and for conversion of atrial fibrillation or flutter complicating open heart surgery.

Methods

Study patients. Patients who had had open heart surgery within 3 weeks and who developed atrial fibrillation or atrial flutter with a mean ventricular response of ≥ 120 beats/min were eligible for inclusion in this study. In one patient who qualified for the study, the ventricular response to atrial fibrillation decreased to 116 beats/min in the minute preceding drug administration. This patient was included in the analysis.

Patients were excluded from the study for the following reasons: 1) age < 21 years or > 75 years; 2) history of myocardial infarction within 1 month; 3) receipt of beta-

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blocker or calcium antagonist or other antiarrhythmic drugs (except digoxin); 4) systolic blood pressure <90 mm Hg; 5) congestive heart failure; 6) severe obstructive pulmonary disease; and 7) unwillingness or inability to give written informed consent, or extubation not yet performed.

Baseline data obtained at the initiation of the protocol included history and physical examination, blood chemistry values, hematologic profile, urinalysis and electrocardiogram (ECG) with a rhythm strip and at least 5 minutes of continuous ECG recording.

Study design. A double-blind randomized placebo-controlled conditional crossover design was used. Initially, each patient received drug A (propafenone [2 mg/kg body weight] or placebo) intravenously over 10 minutes. If the patient's arrhythmia did not revert to sinus rhythm within 20 minutes of the start of the infusion of drug A, then drug B (placebo or propafenone [2 mg/kg], whichever was not given as drug A), was administered intravenously over 10 minutes. Patients whose arrhythmia was converted to sinus rhythm within 20 minutes of the start of drug A did not receive drug B. The ECG (lead MCL₁) was recorded continuously from 5 minutes before the start of the infusion of drug A until 10 minutes after the end of the infusion of drug B. A continuous ECG rhythm strip was saved for later analysis of heart rate. Blood pressure was measured by sphygmomanometer at 1 minute intervals during drug infusions, at 10 minute intervals for 90 minutes and then every 4 hours for 24 hours.

Conversion to sinus rhythm was attributed to the drug if it occurred during drug infusion or within 10 minutes of the end of the infusion. Ten minutes after the end of the second drug infusion, the study ended and treatment by the referring physicians was resumed. Ventricular response to atrial fibrillation or flutter was determined by counting the QRS complexes in 1 minute of the continuous rhythm strip. Venous blood samples were obtained within 5 minutes of the

end of each drug infusion. Plasma was then extracted and frozen for later analysis of propafenone plasma concentration by a gas chromatographic method.

Data analysis. A Fisher's exact test was used to compare the rates of conversion to sinus rhythm between propafenone and placebo. Paired Student's *t* tests were used to evaluate the effects of propafenone and placebo on the ventricular response in atrial fibrillation and on blood pressure. An unpaired Student's *t* test was used to compare propafenone plasma concentrations in responders and nonresponders. This protocol was approved by the Ethics Committee of our hospital.

Results

Clinical features. Fourteen patients were studied between 2 and 17 days after cardiac surgery (Table 1). All patients were alert and extubated at the time of study. They were all men ranging in age from 25 to 72 years. The mean duration of atrial fibrillation or flutter before drug administration was 8.4 hours (range 1 to 28). Six patients had received intravenous digoxin (0.25 to 1.0 mg during the 24 hours before study). In all cases, at least 4 hours had elapsed between the administration of any digoxin and the administration of study drugs.

Incidence of conversion to sinus rhythm. All 14 patients received propafenone, 6 as drug A and 8 as drug B. Only 10 patients received placebo because 4 patients who received propafenone as drug A (that is, first) had conversion to sinus rhythm and, therefore, did not receive drug B. Table 2 shows the rates of conversion to sinus rhythm for propafenone and placebo. No conversion to sinus rhythm occurred after administration of placebo. In six patients (43%) conversion to sinus rhythm occurred between 5 and 10 minutes after receipt of propafenone ($p < 0.001$).

Table 1. Clinical Characteristics of 14 Male Patients

Patient No.	Age (yr)	Type of Surgery	Days Postop	Arrhythmia	Duration of Arrhythmia (h)	Received Digoxin	Hours Since Last Dose of Digoxin
1	62	CABG	3	AF	1.5	No	—
2	72	CABG/AVR	2	AF	6	Yes	5
3	56	CABG	2	AF	3.5	No	—
4	57	CABG	3	AF	28	No	—
5	53	CABG	3	AF	8	Yes	10
6	66	CABG	5	AF	10	Yes	13
7	62	CABG	2	AF	7	Yes	6
8	60	CABG	5	AF	12	Yes	4
9	67	CABG	17	AFL	5	No	—
10	57	CABG	2	AF	4	No	—
11	70	AVR	2	AF	1	No	—
12	59	CABG	2	AF	6	Yes	5.5
13	47	AVR	2	AF	1	No	—
14	25	ASD	15	AFL	24	No	—

AF = atrial fibrillation; AFL = atrial flutter; ASD = repair of atrial septal defect; AVR = aortic valve replacement; CABG = coronary artery bypass graft surgery; Postop = postoperative.

Table 2. Rate of Conversion to Sinus Rhythm in 14 Male Patients

	Drug A	Drug B	Total
Propafenone	4 of 6	2 of 8	6 of 14
Placebo	0 of 8	0 of 2	0 of 10
			($p < 0.001$)

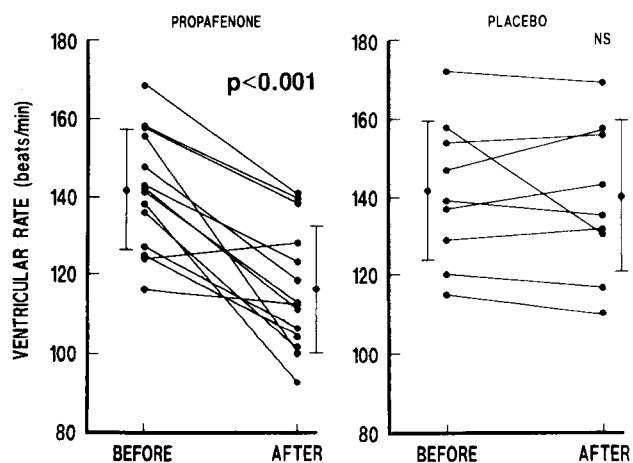
Effect on ventricular response. The effect of propafenone on the ventricular response to atrial fibrillation or flutter is shown in Figure 1. Ventricular rate recorded 5 minutes after the end of the drug infusion was used for this analysis because this was the time of maximal slowing of ventricular rate and because in all patients with conversion to sinus rhythm the conversion occurred between 5 and 10 minutes after the infusion. After propafenone, the ventricular response to atrial fibrillation or flutter decreased from 141.6 ± 15.2 to 116.0 ± 15.5 beats/min ($p < 0.001$). After placebo, it decreased from 142 ± 17 to 140 ± 19 beats/min ($p = \text{NS}$).

Two patients in this study had atrial flutter, and neither had conversion to sinus rhythm. Propafenone decreased the ventricular response by 35 beats/min in one patient and increased it by 7 beats/min in the other.

Blood pressure. There was a small but statistically significant ($p < 0.01$) reduction in systolic arterial blood pressure of 9 ± 9 mm Hg during propafenone infusion that caused no symptoms and did not require treatment. No other side effects were observed.

Plasma concentrations. The mean propafenone plasma concentration in all patients, obtained 1 to 5 minutes after drug infusion, was 3.46 ± 2.17 mg/liter. There was no significant difference between the mean propafenone plasma

Figure 1. The effects of propafenone ($n = 14$) and placebo ($n = 10$) on ventricular response to atrial fibrillation or flutter. Each line represents one patient before and after receiving propafenone or placebo. The dot and bars in the margins represent mean \pm standard deviation.



concentration in the patients who did and did not have conversion to sinus rhythm.

Discussion

Atrial fibrillation and flutter are frequent complications of cardiac surgery. In a prospective study (7) of 1,247 consecutive patients, 24% developed a postoperative atrial tachyarrhythmia. Although prophylactic propranolol reduces the incidence of postoperative atrial tachyarrhythmias to between 5 and 20%, these arrhythmias remain a problem (6,12,13). Because acute atrial fibrillation and flutter frequently terminate spontaneously within 24 hours, investigations of the effects of antiarrhythmic drugs on conversion of atrial tachyarrhythmias after cardiac surgery should be placebo controlled. However, few placebo-controlled studies of antiarrhythmic drugs for postsurgical atrial fibrillation have been performed (9,14).

The present data document for the first time that intravenous propafenone is beneficial and safe for the acute management of atrial fibrillation. Propafenone significantly slowed the ventricular rate in atrial fibrillation or flutter and resulted in prompt conversion to sinus rhythm in 43% of patients.

Previous studies on antiarrhythmic agents. There are two placebo-controlled studies of intravenous verapamil for atrial fibrillation occurring after cardiac surgery. Plumb et al. (9) reported that low dose intravenous verapamil (0.075 mg/kg) decreased ventricular response to atrial fibrillation from 150 ± 22 to 102 ± 14 beats/min and high dose verapamil (0.15 mg/kg) decreased the response from 139 ± 14 to 97 ± 13 beats/min. Hwang et al. (14) reported a similar decrease in ventricular response using the same dose of verapamil. Verapamil was not effective for conversion to sinus rhythm in either study.

Gray et al. (10) evaluated esmolol, a new ultrashort-acting beta-blocker, in 11 patients with atrial fibrillation or flutter occurring after open heart surgery in a nonrandomized noncontrolled study. Esmolol caused a $30 \pm 11\%$ decrease in ventricular response. Although 5 of the 11 patients had conversion to sinus rhythm during the 24 hour esmolol infusion, no placebo group was available for comparison.

Gavaghan et al. (7) reported a large nonrandomized trial of disopyramide and digoxin for control of atrial fibrillation and flutter after cardiac surgery. Sixty percent of patients had conversion to sinus rhythm during the 14 hour study period. There was, however, a high incidence of side effects (19%). Four patients with atrial flutter developed 1:1 AV node conduction in spite of prior digitalization, and one patient developed ventricular tachycardia.

In a randomized trial (15) of sotalol versus disopyramide and digoxin for atrial tachyarrhythmia after cardiac surgery, there was no difference in the overall rate of arrhythmia conversion between sotalol and digoxin/disopyramide, but conversion occurred significantly earlier with sotalol. Sev-

enteen of 20 patients receiving intravenous sotalol developed hypotension (systolic blood pressure decrease of ≥ 20 mm Hg or to < 90 mm Hg).

Because of important differences in design between this and other studies, it is not possible to compare propafenone with most other drugs for conversion of postoperative atrial fibrillation. Only verapamil has been evaluated by placebo-controlled trial for postoperative atrial tachyarrhythmias, and it was not effective for conversion to sinus rhythm.

Plasma concentrations of propafenone. These did not differ significantly between patients with and without conversion to sinus rhythm. It is known that propafenone plasma concentrations decrease very rapidly immediately after a bolus infusion as a result of distribution of drug out of the central compartment (16). Therefore, propafenone concentrations measured in our study may not reflect the plasma concentration at the exact time of conversion.

Role of digoxin. Six patients in our study had received digoxin before receiving propafenone. Although no interaction between propafenone and digoxin has been reported, it is possible that some of the effects attributed to propafenone in this study were caused by an effect of propafenone on digoxin plasma concentrations. However, this is unlikely because propafenone had similar effects in patients who had and had not received digoxin.

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