

Efficacy of Propafenone Hydrochloride in Preventing Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting

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ABSTRACT

Background: Atrial fibrillation (AF) is one of the most common complications after coronary artery bypass grafting (CABG), and the incidence of postoperative AF (PAF) is estimated to range from 10% to 40%. PAF is a serious complication that is related to unstable hemodynamics, development of embolisms, patient discomfort, and increased medical costs associated with the prolongation of hospital stay. Sometimes, immediate attention is also necessary. In this study, we assessed the efficacy of treatment with the antiarrhythmic drug propafenone hydrochloride, which was administered in the early postoperative period, in preventing the development of PAF, and we attempted to identify risk factors for PAF.

Materials and Methods: The subjects were 78 patients who underwent isolated off-pump CABG between July 2007 and October 2008. We conducted the study by dividing the patients into 2 groups, a group of 26 patients who received propafenone hydrochloride (P group) and a control group of 52 patients who did not receive this drug (C group). The patients in the P group were given propafenone hydrochloride (150-450 mg/day orally) for 10 days, starting on the day after surgery, and were observed for the development of AF by means of continuous 12-lead electrocardiographic monitoring. Development of AF was defined as AF that lasted ≥ 30 minutes or as supraventricular arrhythmia that required new treatment even though it did not persist for 30 minutes.

Results: The background factors of the patients in the P and C groups were similar. The operation times and the numbers of distal anastomoses in the 2 groups were similar, and there were no particular differences between the 2 groups with respect to postoperative factors. The incidence of PAF was 35% in the C group and significantly lower in the P group (12%, $P = .0337$). Moreover, multiple logistic regression analysis showed that propafenone hydrochloride was the sole factor that prevented the development of PAF (odds ratio, 0.207; 95% confidence interval, 0.053-0.804; $P = .0229$).

Received November 3, 2009; received in revised form December 26, 2009; accepted January 21, 2010.

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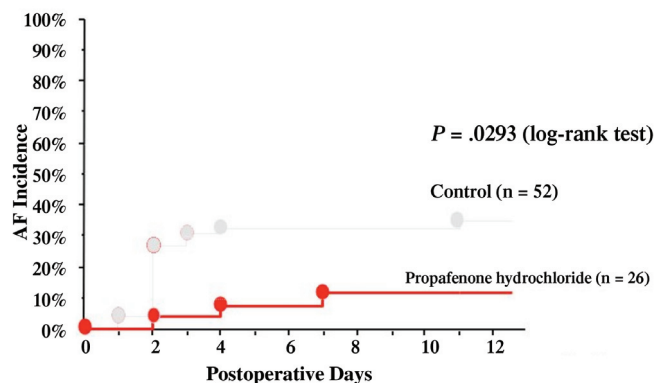
Conclusion: Cases must be carefully considered before administering propafenone hydrochloride, but the results of this study indicate that propafenone hydrochloride may prevent the development of PAF.

INTRODUCTION

Despite improvements in heart surgery techniques and the results of heart surgery in recent years, atrial fibrillation (AF) after heart surgery continues to be the most common postoperative complication. The incidence of postoperative AF (PAF) is estimated to range from 10% to 40% and to occur most often in the first 2 to 4 days after surgery [Aranki 1996; Mathew 1996; Olshansky 1996; Almassi 1997; Hogue 2000; Zaman 2000; Maisel 2001].

PAF is seldom directly linked to cardiovascular death, but in addition to destabilizing hemodynamics, PAF causes postoperative complications, including embolisms. PAF is also said to lead to the prolongation of a patient's hospital stay and to be a cause of patient discomfort.

Propafenone hydrochloride is the only Vaughan Williams class Ic antiarrhythmic drug that possesses a β -blocking action, and although propafenone hydrochloride has been claimed to prevent AF after coronary artery bypass grafting (CABG), there have still been no reports concerning off-pump cases



Kaplan-Meier curve for the incidence of atrial fibrillation (AF) after off-pump coronary artery bypass grafting in the propafenone hydrochloride and control groups.

[Merrick 1995]. In the present study, we investigated whether treatment with propafenone hydrochloride in the early post-operative period prevents the development of AF after isolated off-pump CABG (OPCAB) by comparing a group that received propafenone hydrochloride and a group that did not receive this drug. We also attempted to identify risk factors for the development of AF after OPCAB surgery.

MATERIALS AND METHODS

During the period between July 2007 and October 2008, 104 patients underwent OPCAB surgery, and 25 of these patients were excluded from the study for one of the following reasons: (a) chronic AF prior to surgery, (b) 81 years of age or older, (c) echocardiography or ventriculography results showing a left ventricular ejection fraction <40%, (d) serum creatinine ≥ 1.8 mg/dL, (e) implanted-type defibrillator or pacemaker prior to surgery, or (f) participation in another clinical study in the past. The remaining 79 patients were adopted as the subjects of this study. Propafenone hydrochloride was administered to the 27 patients from whom informed consent was obtained, and they initially formed the propafenone hydrochloride treatment group (P group). One patient in the P group, however, was excluded from the study because of QT prolongation observed immediately after propafenone hydrochloride administration. No improvement was observed, even when the dose was reduced, and treatment was stopped. Consequently, the P group ultimately consisted of 26 patients. The other 52 patients, who did not receive propafenone hydrochloride, served as the control group (C group), and the study was conducted by comparing these 2 groups.

Treatment with propafenone hydrochloride (150-450 mg/day orally) was started on the day after surgery and continued for 10 days. The patients were observed for the development of PAF by means of continuous 12-lead electrocardiographic monitoring. We defined AF as the absence of a P wave before the QRS complex and an arrhythmia that lasted 30 minutes or more; however, when an arrhythmia lasted <30 minutes

and if treatment in the form of the administration of an antiarrhythmic drug, countershock, and so forth, was necessary, AF was considered to have occurred. When administration of an antiarrhythmic drug produced QT prolongation, the dose was reduced as appropriate.

The data are reported as the mean $\pm$ SD or as the number of cases (percent). Differences between the 2 groups for categorical data were analyzed with the χ^2 test or Fisher test. The paired Student *t* test or the Mann-Whitney *U* test was used for the analysis of continuous variables. In addition, the numbers of days after surgery when PAF occurred were calculated by means of Kaplan-Meier curves and were evaluated with the log-rank test. Differences were considered statistically significant at *P* values $\leq .05$. A logistic regression model was used to conduct a multivariate analysis of factors associated with the development of PAF. Variables with *P* values <.1 in the univariate analysis were selected for analysis in the final test model. StatView software (version 5.0 for Windows; SAS Institute, Cary, NC, USA) was used to perform the statistical analysis.

RESULTS

OPCAB surgery was performed in every case, and none of the cases required conversion to on-pump surgery. The propafenone hydrochloride dose in the P group was 150-450 mg/day, as stated above, and the mean dose was 361 ± 128 mg/day. The details of the 26 patients in the P group and the 52 patients in the C group are shown in Table 1. The ages before surgery were similar in the 2 groups (P group, 66.5 ± 10.0 years; C group, 69.1 ± 9.0 years), and the male-female ratios were not significantly different. There were no significant differences between the 2 groups with respect to preoperative concomitant diseases, including hypertension (P group, 85%; C group, 77%) and diabetes (P group, 50%; C group, 48%), nor were there any significant differences between the 2 groups with respect to left ventricular ejection fraction (P group, $64.3\% \pm 10.0\%$; C group, $60.3\% \pm 10.2\%$) or EuroSCORE (P group, 4.1 ± 2.9 ; C group, 5.3 ± 3.7). The

Table 1. Patient Characteristics*

	Propafenone Group (n = 26)	Control Group (n = 52)	P
Age, y	66.5 ± 10.0	69.1 ± 9.0	.2448
Male/female sex, n	21/5	42/10	>.999
Hypertension, n	22 (85%)	40 (77%)	.5572
Diabetes mellitus, n	13 (50%)	24 (48%)	.8727
Hyperlipidemia, n	19 (73%)	40 (73%)	.7091
Old myocardial infarction, n	7 (27%)	14 (27%)	>.999
Prior cerebrovascular accidents, n	4 (15%)	7 (13%)	>.999
Chronic obstructive pulmonary disease, n	0	6 (12%)	.1707
Left ventricular ejection fraction, %	64.3 ± 10.0	60.3 ± 10.2	.1098
No. of diseased vessels	2.6 ± 0.6	2.6 ± 0.6	.8037
EuroSCORE	4.1 ± 2.9	5.3 ± 3.7	.1678

*Data are presented as the mean $\pm$ SD where indicated.

Table 2. Operative Data*

	Propafenone Group (n = 26)	Control Group (n = 52)	P
Total operative time, h	5.4 ± 1.0	5.3 ± 0.7	.6473
Use of internal mammary artery, n	26 (100%)	50 (96%)	.5498
No. of distal coronary anastomoses	4.2 ± 1.2	4.1 ± 1.2	.6636
Target location			
LAD	44% (49/111)	42% (91/215)	.7533
LCX	34% (38/111)	34% (73/215)	.9596
RCA	22% (24/111)	24% (51/215)	.6695
Transfusion, n	8 (31%)	25 (48%)	.1447

*Data are presented as the mean ± SD where indicated. LAD indicates left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 3. Postoperative Morbidity and Mortality*

	Propafenone Group (n = 26)	Control Group (n = 52)	P
Early death (<30 d), n	0	0	—
Atrial fibrillation, n	3 (12%)	18 (35%)	.0337
Mediastinitis, n	1 (4%)	0	.3333
Perioperative myocardial infarction, n	0	0	—
Cerebrovascular accidents, n	0	3 (6%)	.5468
Reexploration for bleeding, n	0	0	—
Intensive care unit stay, d	1.3 ± 0.8	1.9 ± 1.5	.0297
Hospital stay, d	21.6 ± 10.9	25.0 ± 18.9	.1745

*Data are presented as the mean ± SD where indicated.

mean numbers of diseased vessels in the 2 groups were the same (P group, 2.6 ± 0.6 ; C group, 2.6 ± 0.6).

Intraoperative and postoperative factors are shown in Tables 2 and 3. The 2 groups had similar operation times (P group, 5.4 ± 1.0 hours; C group, 5.3 ± 0.7 hours) and numbers of distal anastomoses (P group, 4.2 ± 1.2 ; C group, 4.1 ± 1.2), and no early deaths occurred in either group. The incidence of PAF was significantly lower in the P group (3 cases, 12%) than in the C group (18 cases, 35%) ($P = .0337$), and no postoperative cerebrovascular accidents were observed in the P group. The mean number of days spent in the intensive care unit was significantly lower in the P group (1.3 ± 0.8 days) than in the C group (1.9 ± 1.5 days) ($P = .0297$), and patients in the P group tended to have shorter postoperative hospital stays (21.6 ± 10.9 days) than patients in the C group (25.0 ± 18.9 days), although the difference was not statistically significant.

The incidence of PAF in both groups was highest during postoperative days 2 to 4. The Kaplan-Meier curves also showed a reduced incidence of PAF in the P group, and the difference was significant ($P = .0293$, Figure).

Table 4 summarizes the results of the univariate analysis of PAF occurrences. PAF appeared in 21 patients and did not appear in 57 patients. When the 78 patients were divided into a PAF and a non-PAF group and then compared, no significant

differences were found between the groups with respect to preoperative or postoperative medications (β -blockers, angiotensin receptor blockers, statins), and there were no significant differences with respect to other factors, including sex (PAF group, 17 men [81%]; non-PAF group, 46 men [81%]), patients with renal dysfunction (PAF group, 3 cases [14%]; non-PAF group, 2 cases [4%]), and preoperative left atrial diameter (PAF group, 38.3 ± 5.8 mm; non-PAF group, 36.7 ± 5.9 mm). When propafenone hydrochloride treatment and hypertension (the 2 factors with P values ≤ 0.1) were subjected to a multivariate analysis, propafenone hydrochloride was determined to be the sole factor preventing the development of PAF (odds ratio, 0.207; 95% confidence interval, 0.053–0.804; $P = .0229$), and hypertension was determined to be the sole risk factor for the development of PAF (odds ratio, 8.843; 95% confidence interval, 1.062–73.624; $P = .0438$) (Table 5).

DISCUSSION

AF is one of the most common postoperative complications after CABG, and immediate intervention is sometimes necessary. There have been various opinions regarding the pathogenetic mechanism of PAF, including the following: (a) sympathetic nerve and vagus nerve involvement [Raja 2004],

Table 4. Results of Univariate Analysis of Factors Related to Postoperative Atrial Fibrillation (PAF)*

	PAF Group (n = 21)	Non-PAF Group (n = 57)	P
Preoperative treatment, n			
β-Blockers	8 (38%)	19 (33%)	.6950
Statins	15 (71%)	39 (68%)	.7985
ARBs	11 (52%)	30 (53%)	.9843
Postoperative treatment, n			
β-Blockers	8 (38%)	15 (26%)	.3115
Statins	8 (38%)	28 (49%)	.3862
ARBs	6 (29%)	24 (42%)	.2758
Male sex, n	17 (81%)	46 (81%)	>.999
Hypertension, n	20 (95%)	42 (74%)	.0552
Diabetes mellitus, n	9 (43%)	29 (51%)	.5296
Renal dysfunction, n	3 (14%)	2 (4%)	.1177
COPD, n	2 (10%)	4 (7%)	.6577
Left atrial diameter, mm	38.3 ± 5.8	36.7 ± 5.9	.2833
Left ventricular ejection fraction, %	62.6 ± 12.1	61.3 ± 9.6	.6408
EuroSCORE	5.0 ± 3.5	4.8 ± 3.5	.8105
Transfusion, n	9 (43%)	24 (42%)	.9525
Propafenone hydrochloride use, n	3 (14%)	23 (40%)	.0337

*Data are presented as the mean ± SD where indicated. ARB indicates angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease.

(b) atrial fibrosis, (c) electrophysiological remodeling, (d) inflammation [Jahngiri 2006], (e) mechanical stretching of the atrium that alters the electrophysiological properties of cells, (f) an increase in postoperative intravascular volume produced by interstitial fluid [Chidambaram 1992; Likosky 2004; Engelmann 2005], and (g) intraoperative atrial manipulation and myocardial ischemia. These factors act in combination, making the pathogenic mechanism of PAF very complex.

There has been a variety of reports on risk factors for the development of PAF, including age, sex, hypertension, and prolonged ventilation time [Aranki 1996]. In particular, the elderly have been reported to have a high incidence of PAF because they often have atrial fibrosis or dilatation [Almassi 1997], but there are also reports that claim that old age is not a risk factor [Jidéus 2000]. Moreover, there are reports

claiming that placing patients on pump does not alter the incidence of PAF [Cohn 1999; Siebert 2001]. Thus, there are various opinions regarding risk factors, and no consensus has been reached. In the present study, there was no indication that age, atrial diameter, sex, or renal dysfunction were risk factors for developing PAF, but hypertension was identified as a risk factor.

There have already been many studies on the prevention of PAF. Representative studies include one that demonstrated that postoperative treatment with amiodarone effectively prevents PAF and reduces costs [Zebis 2008] and another study that showed that preoperative statin treatment significantly reduces the incidence of AF after CABG [Marín 2006]. There have been many reports indicating otherwise, however, including a number of recent reports on the usefulness of β-blockers that have even stated that not taking β-blockers preoperatively [Eagle 1999] is a risk factor for PAF. In regard to the timing of treatment with β-blockers, reports have described studies of treatment started before surgery [Leitch 1990; Andrews 1991] or after surgery [Andrews 1991; Zaman 2000].

Propafenone hydrochloride, the drug used in this study, is a propranolol derivative with a half-life of 2 to 3 hours. It is metabolized mainly in the liver. Propafenone hydrochloride is one of a category of drugs whose principal action is sodium channel inhibition, which are grouped in Vaughan Williams class Ic. Propafenone hydrochloride is a potent antiarrhythmic drug that has no significant effect on action potential duration. This drug is also said to have a transient outward current-blocking action [Cahill 2001] as well as a β-blocking action, and good efficacy is suggested even when many other drugs are ineffective. Because there was no significant correlation between β-blocker use and the development of PAF in the present study, the degree to which the β-receptor blocking action of propafenone hydrochloride was involved is unknown. Treatment with propafenone hydrochloride starting in the early postoperative period, however, significantly prevented the development of PAF, and treatment with this drug also appeared to be capable of decreasing the number of postoperative hospital days, although the decrease was not statistically significant. Moreover, the multivariate analysis showed that hypertension was a risk factor and that treatment with propafenone hydrochloride was the sole factor preventing PAF. Even considering that the study included only a small number of patients (ie, it was a “preliminary study”), statistical significance was still achieved. Kowey et al [2004] have reported that high-dose propafenone hydrochloride can suppress the onset of PAF after conventional CABG, and our study is the first to demonstrate the effectiveness of propafenone

Table 5. Results of Multiple Logistic Regression Analysis of Factors Related to Atrial Fibrillation after Off-Pump Coronary Artery Bypass Grafting*

	PAF Group (n = 21), n	Non-PAF Group (n = 57), n	OR	95% CI	P
Propafenone hydrochloride	3	23	0.207	0.053-0.804	.0229
Hypertension	20	42	8.843	1.062-73.624	.0438

*PAF indicates postoperative AF; OR, odds ratio; CI, confidence interval.

hydrochloride after OPCAB. Consequently, the development of PAF was clearly inhibited by the sodium channel inhibitory action and other potent actions of propafenone hydrochloride, including that it has no effect on action potential duration. β -Blockers are generally considered highly effective against PAF, and a synergistic effect of the β -blocking action of propafenone hydrochloride can be expected. Propafenone hydrochloride is considered particularly effective against the sympathetic nerve-dependent type of PAF [Coulmel 1994]. At clinical doses, propafenone hydrochloride has one fourth of the heart rate-inhibiting effect of propranolol, and propafenone hydrochloride can be considered a useful drug for preventing PAF [McLeod 1984].

An ideal method of prevention must be effective in a variety of patient populations, but even in this small study, treatment was discontinued in 1 case because of QT prolongation. Because propafenone hydrochloride has a β -receptor blocking action, it will be necessary to exercise sufficient care in cases with low left ventricular function and in regard to QT prolongation after administration. Careful assessment will be necessary when selecting patients in the future as well.

CONCLUSION

In the present study, propafenone hydrochloride was effective in preventing the development of AF after OPCAB, and hypertension was identified as a preoperative risk factor. A double-blind study appears necessary for further corroboration of the results of this study.

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