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Efficacy of Continuous Infusion of Disopyramide or Verapamil in the Management of Intractable Atrial Fibrillation after Cardiac Surgery

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Abstract

Background and Purpose. Atrial fibrillation (Af) after cardiac surgery is one of the most common sustained arrhythmias. Among these patients with postoperative Af, some patients have an intractable Af refractory to a routine treatment. We examined the efficacy of continuous infusion of disopyramide or verapamil in the management of the intractable Af. *Patients and Methods.* Nine patients (8 males and 1 female, the mean age of 69.8±2.6) who developed an intractable Af after cardiac surgery refractory to diltiazem were studied. Five of nine patients received continuous infusion of disopyramide (group D) and four patients received continuous infusion of verapamil (group V). Patients were continuously monitored with a two-channel (II and V5 leads) ECG with Holter function (M2360A) during surgery and the postoperative period. Changes in cardiac index, corrected QT (QTc) intervals (group D), and other routine hemodynamic variables were assessed. The incidence of return to sinus rhythm and the requirement of vasoconstrictors was compared between the two groups. Therapeutic drug monitoring (TDM) was performed for patients in group D. *Results.* The incidence of return to sinus rhythm was significantly higher ($p<0.05$) in group D (5/5) than in group V (1/4). The mean plasma concentration of disopyramide at the time of return to sinus rhythm was 2.2±0.1 μg/ml, which was well consistent with previous reports. There was no remarkable side effect in group D. Hemodynamic deterioration during the continuous infusion of antiarrhythmic agents was generally mild in group D, but was often severe in group V. The incidence of epinephrine requirement was significantly higher in group V (4/4) than in group D (0/5; $p<0.01$). *Conclusions.* Continuous infusion of disopyramide is more beneficial for the intractable Af than verapamil, in view of the efficacy on return to sinus rhythm and the severity of negative inotropic action. Continuous infusion of disopyramide is also a promising therapeutic option that can be preferentially employed for the post-cardiotomy intractable Af refractory to a routine treatment. TDM of disopyramide associated with a computer-generated arrhythmia trendgram contributed to establishing the validity of the therapeutic approach.

Key words : Atrial fibrillation, Postoperative complication, Disopyramide, Verapamil, Antiarrhythmic therapy, Therapeutic drug monitoring (TDM)

Introduction

Atrial fibrillation (Af) after cardiac surgery is rather common, and is associated with an increase in adverse events in all measurable outcomes of care and increases the use of hospital resources[1]. For example, the estimated incidence of Af after coronary artery

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bypass grafting (CABG) has been reported to range 20 to 30 % of these patients[2]. This is generally a benign problem, however, it can deteriorate hemodynamic conditions in the postoperative critical period and may increase surgical morbidity and the length of hospital stay, and may delay a full and rapid recovery if not treated promptly and effectively[2]. Beta-adrenergic blockers have been reported effective in preventing and terminating Af in the postoperative setting[3,4], but it is not favorably employed for a considerable number of patients with low cardiac functions because of its negative inotropic effects. The routine choice of management for the ventricular rate control in our institute has been a continuous infusion of diltiazem 1-3 μ g/kg/min, whereas in some cases Af is persistent and resistant to treatment. The purpose of this study was to evaluate the efficacy of the continuous infusion of disopyramide or verapamil in the management of the intractable Af.

Patients and Methods

This is a retrospective clinical study in patients who had undergone cardiovascular surgery at Hokkaido University Hospital. Among 206 patients who had been surgically treated for cardiac or major aortic operations between October 1994 and April 1996, 9 patients (4.4%) who developed an intractable Af postoperatively refractory to diltiazem were studied. There were 8 males and 1 female with the mean age of 69.8 ±2.6 (range: 53 to 82) years. The operative procedures for these 9 patients included 2 solitary CABG, 2 CABG associated with peripheral vascular surgery, 2 CABG concomitantly associated with mitral valve replacement (MVR), 2 aortic replacement of the aortic arch, and 1 aortic valve replacement (AVR). Table 1 summarizes the profile of these 9 patients. Adjunctive methods employed for these patients were total cardiopulmonary bypass (CPB) associated with antegrade or retrograde blood cardioplegia for 7 patients undergoing cardiac surgery, and total CPB with selective perfusion of the cerebral branches in 2 patients undergoing the aortic arch replacement. The primary anesthetic was fentanyl in all cases. A pulmonary artery catheter was placed into the pulmonary artery through the internal jugular vein in all patients for continuous monitoring of pulmonary artery and central venous pressures, cardiac index, and oxygen saturation of the mixed venous blood using Vigilance ® (Baxter Healthcare Inc., Irvine, CA). Patients were continuously monitored with a two-channel (II and V5 leads) ECG with Holter function (M2360A, Hewlett-Packard Inc., Imaging Systems Division, Andover, MA) during surgery and the postoperative period. This system stored 24-hour actual waveforms of the two-channel ECG as well as other routine hemodynamic variables from all beds in the intensive care unit (ICU), and allowed for preferred retrospective ECG analysis such as the incidence of supraventricular or ventricular arrhythmias and ST-segment changes within prior 24 hours. A

Table1. A summary of patient profile

Patient	Age	Gender	Diagnosis	Operative procedure	Treatment of atrial fibrillation
1 I. O.	72	M	ASR	AVR	Disopyramide
2 K. F.	82	M	Aortic arch aneurysm	Aortic replacement of the aortic arch	Disopyramide
3 T. I.	65	M	DAA (Stanford A)	Aortic replacement of the aortic arch	Disopyramide
4 S. I.	53	M	MR, EAP	MVR, CABG (1 vessel)	Disopyramide
5 T. I.	73	M	EAP	CABG (4vessels)	Disopyramide
6 K. O.	73	M	EAP, TAA	CABG (4vessels)	Verapamil
7 M. T.	69	M	EAP, ASO	CABG (3vessels),Aortofemoral bypass	Verapamil
8 Y. N.	70	F	EAP, Carotid stenosis	CABG (3vessels),Aortocarotidal bypass	Verapamil
9 T. S.	71	M	EAP, MS	CABG (1vessels),MVR	Verapamil

ASR=Aortic stenosis and regurgitation, AVR=Aortic valve replacement, DAA=Dissecting aortic aneurysm, MR=Mitral regurgitation, EAP=Effort angina pectoris, MVR=Mitral valve replacement, CABG=Coronary artery bypass grafting, TAA=Thoracic aortic aneurysm, ASO=Arterial sclerosis obliterans, MS=Mitral stenosis

12-lead ECG was obtained every 4 to 6 hours as a routine management in the ICU postoperatively.

Among 9 patients who developed an intractable Af refractory to diltiazem, 5 patients were treated with continuous infusion of disopyramide (group D) and 4 patients with continuous infusion of verapamil (group V) . Disopyramide was administrated to patients in group D at a concentration of 0.2 mg/kg/hr, and verapamil was given to patients in group V at a concentration ranging 0.04 to 0.2 mg/kg/hr. In group D patients, plasma concentrations of disopyramide were measured with TDX-analyzer 9520-01 ® (Dainabot Japan Inc., Tokyo, Japan) by fluorescence polarization immunoassay (FPIA). Cardiac index before the occurrence of Af, at the onset of Af, at the time of return to sinus rhythm, and after the cessation of disopyramide or verapamil administration was compared in each group. The effect of disopyramide or verapamil was assessed by the arrhythmia trendgram generated with M2360A. Corrected QT interval in ECG (QTc; msec) was also assessed in the group D. The incidence of return to sinus rhythm and the requirement of vasoconstrictors was compared between the two groups.

Statistical analysis. All continuous variables are presented as the mean ± standard error (SEM). Cardiac index in each group was compared with ANOVA with post-hoc pairwise comparisons (Tukey-Kramer). The QTc intervals in group D were compared with paired-Student's t-test. The chi-square test was used for comparison of dichotomous variables. Differences were considered significant at $p<0.05$.

Results

The incidence of return to sinus rhythm was significantly higher ($*p<0.05$) in group D (5/5) than in group V (1/4). The cardiac rhythm in all 5 cases of group D returned to a regular sinus rhythm in 7.2±2.2 hours after the onset of continuous disopyramide administration (Table 2). There was no cardiac death in group D. The total infusion period of disopyramide ranged 16 to 48 hours, and the mean plasma concentration of disopyramide at the time of return to sinus rhythm was 2.2±0.1 μ g/ml (range; 2.0 to 2.7). Figure 1 summarizes changes in cardiac index in patients treated with disopyramide. The mean cardiac index was 4.0±0.2 (L/min/m^2) before the onset of Af, 3.0± 0.2 at the onset of Af, 3.5±0.1 at the time of return to

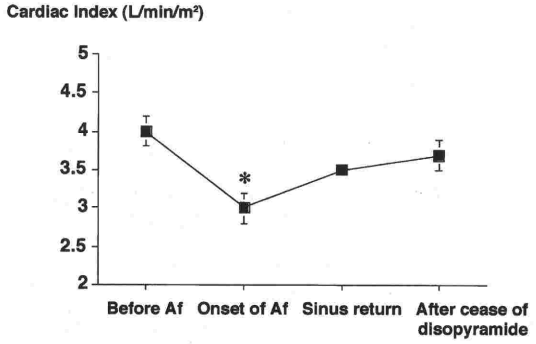

Figure 1. Changes in cardiac index in patients treated with disopyramide.
*$p<0.05$ vs Before Af, Sinus return (=return to sinus rhythm), and After cessation of disopyramide.

Table2. Effects of disopyramide and plasma concentration

Patient	Time from the onset of disopyramide infusion to sinus return	Plasma concentration level at the time of sinus return (μg/ml)	The maximum plasma concentration level (μg/ml)
1 I. O.	10	2.1	2.2
2 K. F.	2	2.7	2.8
3 T. I.	4	2.0	2.9
4 S. I.	6	2.3	2.4
5 T. I.	14	2.1	2.3
mean±SEM	7.2±2.2	2.2±0.1	2.5±0.1

sinus rhythm, and 3.6 ± 0.2 after the cessation of disopyramide administration. The significant decrease in cardiac index was noted only at the onset of Af (*p $<$0.05 vs Before Af, Sinus return, and After cessation of disopyramide). A mild decrease in cardiac index was observed during the period of disopyramide administration, but the decrease did not indicate a clinical significance. Figure 2 shows the comparison of QTc intervals before and after the administration of disopyramide. There was no difference in QTc intervals between the two measurement points, before the onset of Af and at the maximum concentration of disopyramide, which ranged 2.2 to 2.9 μ g/ml (mean;2.5±0.1). No patient developed disopyramide-induced tachyarrhythmias, and no patient required vasoconstrictors due to disopyramide-induced hypotension.

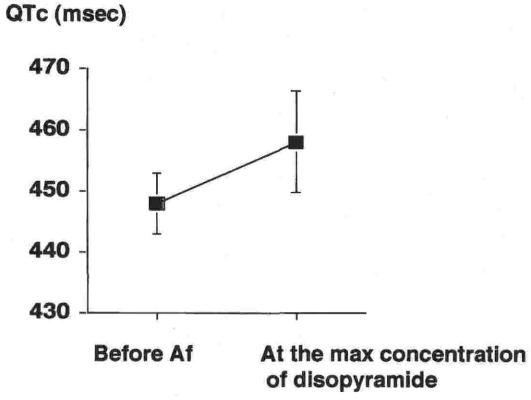

Figure 2. Comparison of QTc time in ECG before and after administration of disopyramide. There was no significant difference between Before Af and At the max concentration of disopyramide.

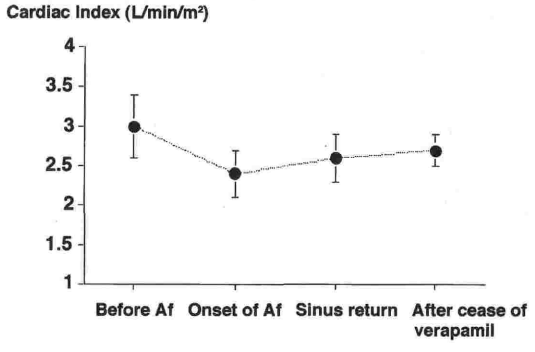

Figure 3. Changes in cardiac index in patients treated with verapamil. There were no significant differences in cardiac index according to the time course.

The continuous infusion of verapamil was employed for 4 patients, however, only one patient showed return to sinus rhythm. The incidence of return to sinus rhythm in group V was significantly lower than that in group D (1/4 vs 5/5; *p$<$0.05 by Fisher's exact test). The rest 3 patients underwent a VVI pacing continuously to maintain hemodynamic conditions. The mean cardiac index in the group V was 3.0±0.4 (L/min/m^2) before the onset of Af, 2.4±0.3 at the onset of Af, 2.6 ±0.3 at the time of return to sinus rhythm, and 2.7± 0.2 after the cessation of disopyramide administration (Fig.3). A marked decrease in cardiac index was found in 1 patient. All 4 patients required a concomitant administration of norepinephrine (**p$<$0.01 vs group D; Fisher's exact test) because of hypotension induced by verapamil.

Figure 4 shows a representative clinical course of the patient in group D, a case of 65-year-old male (patient No.3), who underwent the prosthetic replacement of the aortic arch for Stanford type A acute aortic dissection. The time zero in this figure means the time 22 hrs after ICU admission. Af refractory to diltiazem was developed at 25 hrs after ICU admission (at the time 3 hrs in this figure). A bolus injection of 100 mg disopyramide failed to achieve return to sinus rhythm, at which the plasma concentration of disopyramide was 1.7 μ g/ml. Cardioversion with 50 to 150 J direct current also failed to achieve sinus rhythm at this time. A continuous infusion of disopyramide 10 mg/hr was started in association with VVI pacing. The cardiac rhythm returned to sinus 4 hours after the onset of continuous infusion, at which the plasma concentration of disopyramide was 2.0 μ g/ml. Two hours after return to sinus rhythm, atrial premature contraction (PAC) emerged at a high frequency of 10 to 15/min. An additional bolus injection of 50 mg disopyramide successfully suppressed the PACs, at which the plasma concentration was 2.9 μ g/ml. Twenty minutes later, the infusion dose of disopyramide was increased to 20

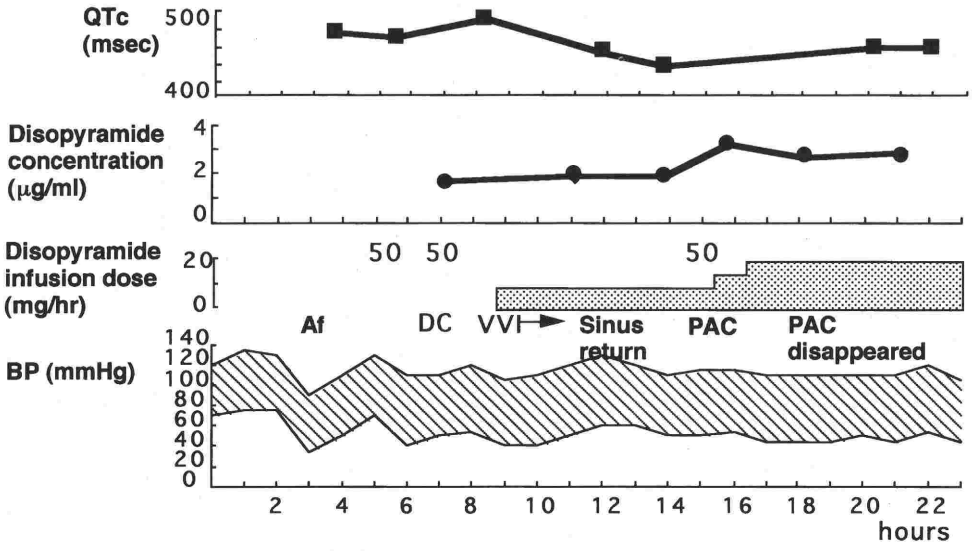

Figure 4. Clinical presentation of patient No.3 (group D) according to the time course.

mg/hr because PAC recurred at the same frequency. One hour after the 20 mg/hr infusion, PAC disappeared at the plasma concentration being 2.8 μg/ml. The recurrence of PAC was not observed afterwards. In this case, disopyramide was at first effective in achieving sinus rhythm at the plasma concentration level of 2.0 μg/ml, which however had to be increased to 2.9 μg/ml enough to suppress recurrence.

Discussion

Atrial fibrillation (Af) after cardiac surgery is one of the most common sustained arrhythmias, and the reported incidence ranged 11% to 36%[5]. Its pathophysiology is unclear, and its prevention and management remain suboptimal[1,6]. Af usually occurs in paroxysms between the second and fifth postoperative day and appears directly related to effects of surgery, including the development of pericarditis, changes in autonomic tone, cold temperature, cardioplegia, myocardial damage, fluid shifts[2,7]. Numerous studies have been made in an attempt to identify incremental risk factors associated with Af after cardiac surgery, because strategies to reduce the incidence of Af should favorably affect surgical outcomes and reduce cost of care[1,6,8~10].

The initial principle of treatment for post-cardiotomy Af is generally aimed at ventricular rate control, because return to sinus rhythm may be difficult to achieve early after surgery[2]. Elective cardioversion by direct current should be delayed for as long as possible after surgery. The therapeutic approach to Af depends on the time course of the arrhythmia, and hemodynamic stability of the patient. Beta-adrenergic blockades have been reported to be the best first option if tolerated[2,4], but they would not be suitable for patients with low cardiac function[11]. We have used a continuous infusion of diltiazem 1-3 μg/kg/min for the ventricular rate control, but some patients had intractable Af refractory to a routine treatment. The post-cardiotomy Af may precipitate significant deterioration of hemodynamic conditions in some cases, and may worsen cardiac functions and develop low output syndrome or other organ dysfunction. Return to sinus rhythm is essential for those patients with significant hemodynamic deterioration due to Af, if ventricular rate control fails to maintain hemodynamic status.

In this study, we employed the continuous infusion of disopyramide or verapamil for those patients with intractable Af. Return to sinus rhythm was seen in all

5 patients treated with disopyramide, however, it was seen in only 1 of 4 patients treated with verapamil. In general, disopyramide increases the Af threshold in the human atrium[12]. Disopyramide has been also reported to be effective for maintaining sinus rhythm after cardioversion of Af[13]. The mean plasma concentration of disopyramide at the time of return to sinus rhythm was 2.2 ± 0.1 μg/ml in this study, but a higher concentration was required to prevent recurrence in some cases. Masuhara and associates reported that the plasma disopyramide concentration higher than 2 μg/ml might be required to achieve the therapeutic effect of disopyramide administered repeatedly[14], which is consistent with our results.

The continuous infusion of verapamil was not effective in achieving return to sinus rhythm when compared with effects of disopyramide. In addition, the vasoconstrictor was necessary for all 4 patients treated with verapamil due to hypotension, and some patients suffered a marked deterioration of hemodynamic status whereas the continuous infusion of disopyramide did not. In view of the efficacy on return to sinus rhythm and the severity of negative inotropic action, continuous infusion of disopyramide seems to be more beneficial for intractable Af than verapamil. In conclusion, continuous infusion of disopyramide is a promising therapeutic option that can be preferentially employed for the post-cardiotomy intractable Af refractory to a routine treatment. Therapeutic drug monitoring of disopyramide associated with a computer-generated arrhythmia trendgram contributed to establishing the validity of the therapeutic approach.

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