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Flecainide is effective against premature supraventricular and ventricular contractions during general anesthesia

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Abstract: The effect of intravenously administered flecainide on premature supraventricular (PSCs) and ventricular contractions (PVCs) which developed under general anesthesia was evaluated. Flecainide was infused intravenously at a rate of 0.2 mg/kg/min until the efficacy of this drug appeared or for 10 min; thus, the maximum dose was determined to be 2 mg/kg. Flecainide was administered to 10 patients who experienced more than 5 supraventricular and/or ventricular contractions/min for a period of more than 5 min (PVCs, 4 patients; PSCs, 6 patients). PVCs in 4/4 cases and PSCs in 5/6 cases disappeared following administration of flecainide. The average dose of flecainide was 1.08 ± 0.17 mg/kg (SE). This dose of flecainide did not affect the heart rate and QRS interval, but caused a transient decrease in systolic blood pressure from 127 ± 6 mmHg (SE) to 114 ± 6 mmHg, a 14% increase in the PQ interval, and a 6.3% increase in the QT interval. These results suggest that flecainide is a promising drug for the treatment of PSCs and PVCs which develop during general anesthesia. Transient hypotension and cardiac conduction disturbances immediately after injection may occur when flecainide is used intravenously.

Key words: Flecainide, Arrhythmia, Premature supraventricular contractions, Premature ventricular contractions

Introduction

Flecainide acetate, a class Ic antiarrhythmic drug according to Williams classification, inhibits the fast sodium channel with slow onset and offset electrophysiological kinetics [1]. Therapeutic indications of flecainide as an antiarrhythmic include premature ventricular (PVC) [2] and premature supraventricular contractions (PSC) [3], ventricular [4] and supraventricular tachyarrhythmia [5], ventricular fibrillation [4], and atrial flutter and fibrillation [6]. Chronic PVCs and PSCs have been effectively treated by oral administration of flecainide [2,3]. Recently, an intravenously formulation of flecainide has been introduced in Japan and clinical trials have been started for chronic arrhythmias. However, no clinical trials have been reported for acute arrhythmias during general anesthesia. Since causes or mechanisms of acute arrhythmias during anesthesia are known to be different from those of chronic arrhythmias [7,8], the efficacy of flecainide as an antiarrhythmic may differ between these two types of arrhythmia. Since the pharmacological characteristics of flecainide differ from those of other antiarrhythmics [9] and its potency has been demonstrated to be stronger than that of lidocaine and procainamide [9] it may be effective for treatment of arrhythmia which is intractable to other agents. In fact, the superiority of orally administered flecainide for the treatement of supraventricular arrhythmias has been demonstrated [3].

The availability of many kinds of antiarrhythmic agents possessing different etiologies or efficacies might be beneficial for anesthesiologists in terms of providing better perioperative anesthetic management. In anticipation of having a new type of antiarrhythmic agent, we evaluated the antiarrhythmic effect of intravenously administered flecainide for acute PSCs and PVCs occurring during general anesthesia.

Patients and methods

With the approval of the Committee for Human Research of Tohoku University Hospital and informed consent from all of the patients, we administered flecainide to ten patients, in whom 5 or more beats/min of PSCs ($n = 6$) or PVCs ($n = 4$) lasting over 5 min appeared during general anesthesia. The patients (six

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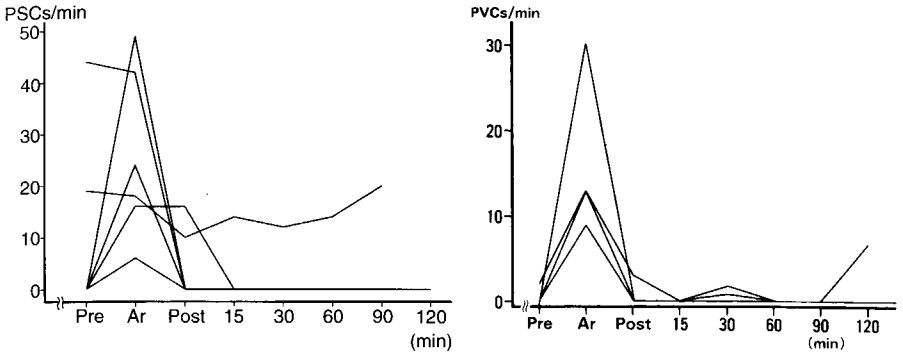

Fig. 1. Effect of flecainide on premature supraventricular contractions (PSCs) and premature ventricular contractions (PVCs). The *vertical axis* shows frequency of PVCs or PSCs per minute and the *horizontal axis* shows time course. Pre, circulatory stable state before flecainide administration; Ar, when arrhythmia developed before flecainide administration; Post, just after completion of flecainide administration

men and four women) ranged in age from 23 to 87 years (64.2 ± 18.6 MSD) and in weight from 42 to 64 kg (52.4 ± 7.6 MSD). The infusion rate of flecainide was 0.2 mg/kg/min and the administration was continued until PSCs or PVCs were suppressed. If arrhythmias were not suppressed by the time the dose of flecainide reached 2 mg/kg, namely, at the end of 10 min infusion, the infusion was stopped.

Electrocardiography (ECG) in each patient was continuously monitored on an oscilloscope and recorded on paper at a speed of 100 mm/s when necessary (Nihon Koden; RMC-1200M, WS-180G). Blood pressure (BP) by the forearm cuff method and heart rate (HR) from ECG were measured before, immediately after (0 min), and at 15, 30, 60, 90, and 120 min after cessation of flecainide infusion. Hematological changes and liver and kidney functions were checked by blood samples to determine whether flecainide caused any adverse effects immediately after and 2 days postoperatively. Flecainide 100 mg dissolved in sodium acetate solution was prepared in a 10 ml ampule by Eisai Co. (Tokyo, Japan) and diluted to 20 ml with 5% dextrose just before the start of intravenous infusion.

All measured data were expressed as mean ± SE except height, weight, and age of patients (mean ± SD) and statistically analyzed by the Wilcoxon test. A P value less than 0.05 was considered to be statistically significant.

Results

Flecainide was administered to six patients with PSCs and to four patients with PVCs which developed during general anesthesia. Type of anesthetics administered when arrhythmias appeared included halothane in one case, isoflurane in six cases and sevoflurane in three cases with 50%–67% of N_2O in oxygen. In one case of PSCs, disopyramide had been orally administered prior to the operation. In the three cases of PSCs which developed during the operation, lidocaine at a dose of 1–2 mg/kg was used unsuccessfully for treatment before the flecainide trial. With the infusion of flecainide (maximum infusion time = 10 min), PVCs disappeared in three of four cases and PSCs in four of six cases immediately after the end of infusion, except in two cases. In one case, PSCs disappeared 17 min after the end of flecainide infusion, and in another case, the frequency of PVCs decreased immediately after and disappeared 15 min after the end of infusion (Fig. 1). The average dosage of flecainide used was 55.0 ± 7.5 mg (SE) (range of 12–90 mg), or 1.08 ± 0.17 mg/kg (SE) (range of 0.3–2.0 mg/kg). PVCs reappeared after 30 min in one case, and after 30 and 120 min in another, although the number of PVCs per minute was less than that before the treatment in both cases (Fig. 1). The PVCs which reappeared were only transient and spontaneously disappeared without further treatment. In one case of PSCs in which PSCs had been chronically presented before the operation (not the case for which disopyramide had been used), flecainide treatment failed.

HR was not affected by flecainide (Fig. 2). Systolic BP decreased immediately after flecainide administration and returned to the preadministration level by 15 min after the end of infusion (Fig. 2). A decrease in

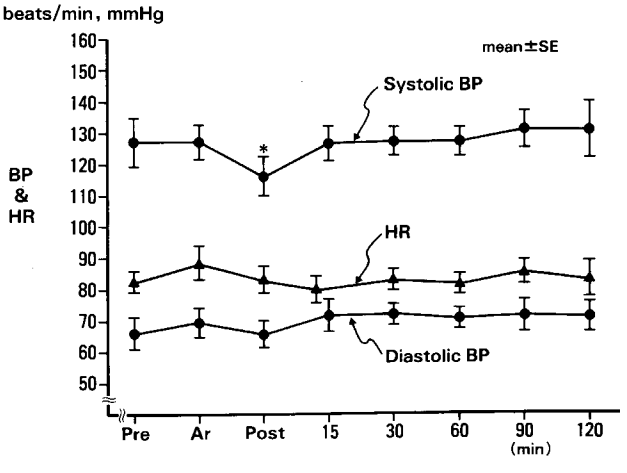

Fig. 2. Effect of flecainide on heart rate (HR) and systolic and diastolic blood pressure (BP). *$P < 0.05$ *vs* Ar

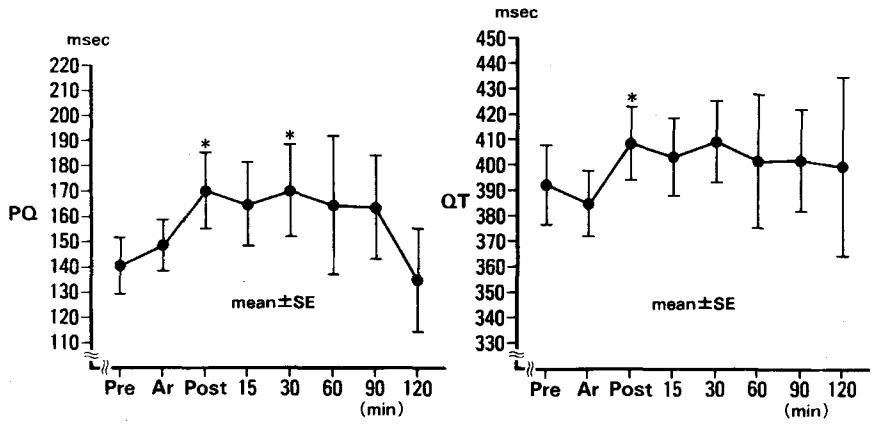

Fig. 3. Effect of flecainide on PR and QT interval. $*P < 0.05$ *vs* Ar

systolic BP below 80 mmHg immediately after administration was observed in two cases, one case of which was treated with ethylephrine and the other of which recovered without any treatment. The mean PQ interval on the ECG immediately after and 30 min after flecainide treatment, and the mean QT interval immediately after flecainide administration, significantly increased by 14.1%, 14.1%, and 6.3%, respectively (Fig. 3). The QRS interval was not changed by flecainide.

Discussion

This is the first report to demonstrate the effectiveness of intravenous flecainide in the treatment of PSCs and PVCs spontaneously and acutely occurring during general anesthesia in humans. The action of flecainide results from inhibition of the fast sodium channel; this agent is thus categorized as a class I antiarrhythmic agent according to Williams classification, similar to lidocaine. However, the marked depression of phase 0 and the relatively unchanged duration of the action potential differs from the action of lidocaine; thus flecainide is defined as class Ic as compared with class Ib in the case of lidocaine [10]. Since the half life of flecainide is long, its antiarrhythmic effect lasts several hours [11]. The antiarrhythmic effect of flecainide has been demonstrated in various arrhythmic models [9,12], and is assumed to be the more potent and uniform than that of lidocaine, procain amide, quinidine, disopyramide, or other class Ic agents [9].

In humans, oral administration of flecainide has been reported to be effective in the treatment of supraventricular arrhythmias, PVCs, and ventricular tachycardias [2,4,5]. Human trials in Japan for patients with chronic arrhythmias have been carried out using the double-blind method, and the efficacy of oral administration was found to be 81% for PVCs and 61% for PSCs [13]. On the other hand, higher efficacy was demonstrated in this study, namely 100% for PVCs and 83% for PSCs. The only case in which flecainide treatment failed was the patient who presented with chronic PSCs. Differences in the characteristics of arrhythmias (acute versus chronic) and in the method of administration (intravenous versus oral) may contribute to this difference in the efficacy. The other significant difference observed in this study was that flecainide is superior to lidocaine in the treatment of PSCs, since PSCs unaffected by lidocaine responded to flecainide treatment. Only a few drugs are known to be effective for the treatment of atrial and supraventricular arrhythmias, and the use of flecainide for such treatment is promising.

ECG changes produced by flecainide in this study consisted of PR and QT prolongation, as previously reported [14]. It has been proved that these ECG changes are mediated by the marked prolongation of Hiss-ventricular conduction time [14]. The prolongation of conduction time differ from the effect of lidocaine (class Ib) and is similar to that of dysopyramide (class Ia). The degree of negative inotropic effect by dysopyramide has been reported to be almost equal to that by flecainide [15,16]. An anesthetic agent has been reported to influence the conduction time [17], and thus the prolongation of the conduction time produced by flecainide may be accelerated under the presence of anesthetics. However, the degree of prolongation of PR and QT intervals in this study did not differ from those in the study of unanesthetized patients [18]. Therefore, the interaction between anesthetic agents and flecainide on the conduction time may be negligible.

Transient hypotension immediately after the injection is the only adverse effect of flecainide observed in this study. Even in unanesthetized patients, it has been reported that severe hypotension occurred in 22% of patients with atrial fibrillation who were treated with intravenous flecainide [19]. A dose-dependent negative inotropic effect [20] is considered to be the major contribution to this depression. Since the decrease in BP is only transient, within 15 min, slow and titrated injection

is recommended for intravenous administration of this drug. Of course caution is necessary when it is used in patients whose cardiac function is severely depressed.

In conclusion, flecainide is a useful antiarrhythmic agent for treatment of PVCs as well as of PSCs which develop during anesthesia and surgery. An adverse reaction following injection of flecainide is transient hypotension.

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