The Antiarrhythmic Effect of Flecainide on Halothane-Epinephrine Induced Arrhythmias in Dogs

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The antiarrhythmic effect of flecainide acetate (FCN), a newly developed class I antiarrhythmic drug, was evaluated on epinephrine (E)-halothane induced arrhythmias in dogs. The arrhythmogenic dose of E (ADE) under 1% of halothane was significantly increased from 0.71 ± 0.08 to 1.08 ± 0.11 and 1.84 ± 0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$ by the administration of 2 and 4 $mg \cdot kg^{-1}$ of FCN, respectively. The arrhythmias induced by ADE in the absence of FCN were stopped by 1.78 ± 0.29 $mg \cdot kg^{-1}$ of FCN in bolus injections. These results suggest that FCN can be used for the treatment of arrhythmias that E contributes to under halothane anesthesia. (Key words: flecainide, antiarrhythmics, halothane-epinephrine)

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Flecainide acetate (FCN) is a new class I antiarrhythmic drug, and its major function is to restrict the fast inward movement of sodium ions (Na^+) at the cell membrane[1–3]. The antiarrhythmic effect of FCN has been shown in animal models, such as in hydrocarbon-epinephrine, oubain, aconitine and coronary ligation-induced arrhythmias[4]. The efficacy of FCN in humen has been reported in ventricular premature contractions, ventricular tachyarrhythmias and supraventricular arrhythmias[5–9].

We examined the effect of FCN on ventricular arrhythmias induced by halothane-epinephrine interaction in intact dogs, expecting the peri-operative use of FCN under inhalational anesthetics.

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Methods

Seven mongrel dogs (weight 9.7 ± 1.0 kg: SDM) were intubated following intravenous injection of thiopental (25 $mg \cdot kg^{-1}$). Respiration was controlled by a volume limited animal ventilator (AIKA R-60) under muscle paralysis with pancuronium bromide to maintain a Pa_{CO_2} at 35–40 mmHg. End-tidal CO_2 concentrations were continuously monitored with a CO_2 analyzer (Hewllet Packard 78356 A). Anesthesia was maintained with 1% of halothane with 100% oxygen. A femoral artery and vein were cannulated for direct measurement of systemic blood pressure (BP) with a pressure transducer (Statham P23ID), and for continuous infusion of epinephrine (E), respectively. Lactated Ringer's solution was infused at a speed of 8 $ml \cdot kg^{-1} \cdot hr^{-1}$ through a cannulated forearm vein throughout the experiment. The left side of the chest was opened and an electromagnetic flow probe connected to a flow meter (MFV-1200 NIHON KO-

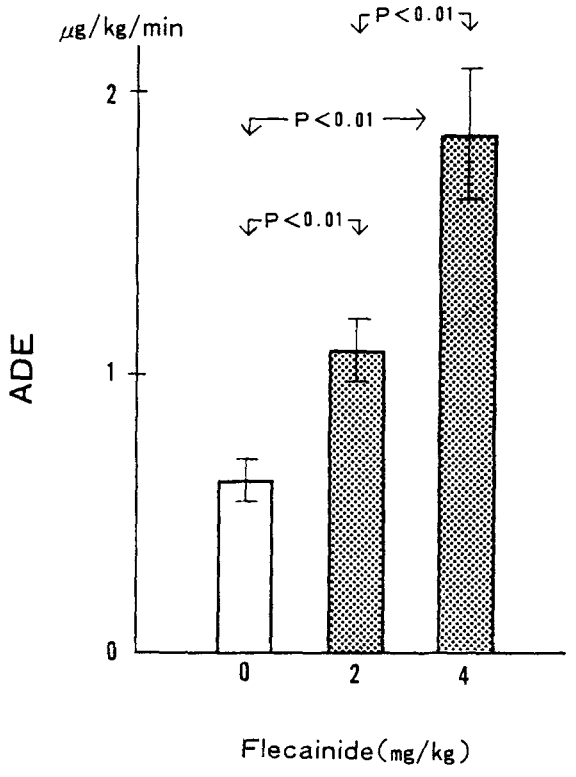

Fig. 1. The effect of flecainide upon the arrhythmogenic dose of epinephrine (ADE) under 1% of halothane in dogs. Mean ± SE.

DEN) was placed on the ascending aorta for measurement of cardiac output (CO). A catheter connected to a pressure transducer was inserted into the left atrium for measurement of left atrial pressure (LAP). Lead II of the ECG was continuously monitored on an oscilloscope and the results were recorded on paper.

After about one hour of stabilization of the circulatory state, E diluted to 25 $\mu g \cdot ml^{-1}$ in normal saline was infused by an infusion pump. The initial speed of infusion was 0.1 $ml \cdot min^{-1}$. If arrhythmias were not induced by 3 minutes-infusion, then the speed was stepwisely increased by 0.1 $ml \cdot min^{-1}$ (0.1, 0.2, 0.3, $\cdots$ $ml \cdot min^{-1}$). When 10/min or more of ventricular arrhythmias were induced by 3 minutes-infusion of E, this rate of infusion was defined as the arrhythmogenic dose of E (ADE) expressed by $\mu g \cdot kg^{-1} \cdot min^{-1}$.

The therapeutic efficacy of FCN on the arrhythmias induced by ADE in the absence of FCN was examined. FCN of 0.5 $mg \cdot kg^{-1}$ was initially injected in bolus. If the arrhythmias did not disappear within one minute, another 0.5 $mg \cdot kg^{-1}$ of FCN was administered. This procedure was repeated until FCN stopped the arrhythmias for more than one minute. The total accumulated doses of FCN to stop the arrhythmias were defined as the anti-arrhythmogenic dose of FCN (AADF).

Two hours after the AADF study, the preventive effect of FCN was evaluated. The dogs were given 2 $mg \cdot kg^{-1}$ of FCN intravenously with a rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$. Five minutes later, ADE was determined by the same procedure used in the absence of FCN, starting at the rate of ADE in the absence of FCN. Two and a half hours following the end of this study, ADE under 4 $mg \cdot kg^{-1}$ of FCN was determined by the same procedure, starting at the rate of ADE under 2 $mg \cdot kg^{-1}$ of FCN.

Paired t-tests were used for statistical analysies; a significant difference was assumed when P was less than 0.05.

Table 1. Cardiovascular states just before arrhythmias are developed

			BPs (mmHg)	BPd (mmHg)	HR	CO ($l \cdot min^{-1}$)	LAP (mmHg)
FCN	0	mean	176.1	116.4	157.0	2.05	18.6
		SE	8.0	6.8	7.1	0.18	1.5
	2 mg $\cdot kg^{-1}$	mean	188.6	126.9	172.0	1.65	23.6*
		SE	6.3	7.0	6.1	0.20	2.4
	4 mg $\cdot kg^{-1}$	mean	197.1**	135.0**	168.6	1.42**	25.6
		SE	5.4	6.6	7.0	0.20	4.2

*$P < 0.05$ vs FCN = 0, **$P < 0.01$ vs FCN = 0

Abbreviations: BPs, systolic blood pressure; BPd, diastolic blood pressure; HR, heart rate; CO, cardiac output; LAP, left atrial pressure; FCN, flecainide.

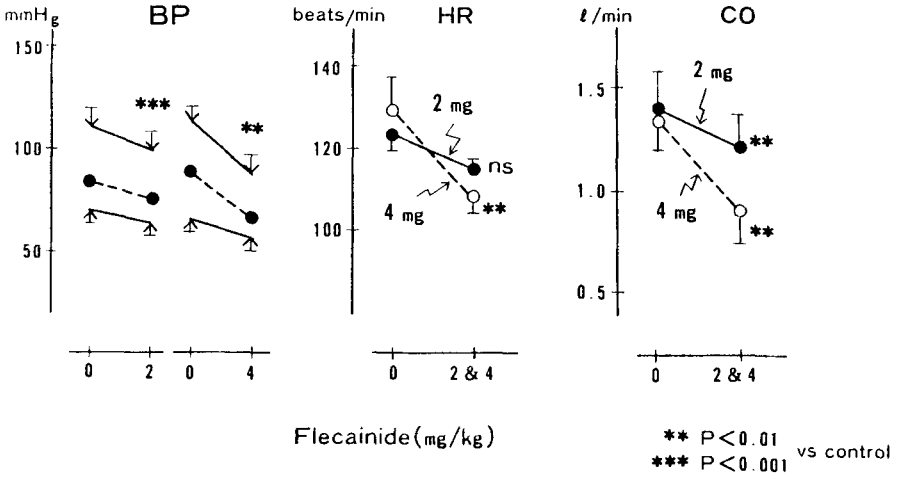

Fig. 2. Cardiovascular changes produced by intravenous flecainide (2 $mg \cdot kg^{-1}$ or 4 $mg \cdot kg^{-1}$) under 1% of halothane in intact dogs. Mean ± SE. **$P < 0.01$; ***$P < 0.001$ vs values in the absence of flecainide (0). Abbreviations: BP, blood pressure; CO, cardiac output; HR, heart rate.

Results

Arrhythmias induced by ADE were stopped by FCN injected intravenously. The antiarrhythmogenic dose of FCN (AADF) for ADE induced-arrhythmias averaged 1.78 ± 0.29 $mg \cdot kg^{-1}$ (SEM), and ranged from 1.0 to 3.0 $mg \cdot kg^{-1}$.

ADE in the absence of FCN under 1% of halothane was 0.71 ± 0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (SEM). ADE increased dose-dependently to 1.08 ± 0.11 and 1.84 ± 0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the presence of 2 $mg \cdot kg^{-1}$ and 4 $mg \cdot kg^{-1}$ of FCN ($P < 0.01$), respectively (fig. 1).

Systemic blood pressure (BP) and left atrial pressure (LAP) just before the development of arrhythmias by ADE were higher and cardiac output (CO) was lower in the presence of FCN (2 and 4 $mg \cdot kg^{-1}$). Heart rate (HR) at this time did not differ in the presence or in the absence of FCN (table 1).

An intravenous injection of 2 mg and 4 $mg \cdot kg^{-1}$ of FCN with a rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ under 1% of halothane decreased BP and CO significantly and dose-dependently. A significant decrease in HR was observed by the administration of a higher dose (4 $mg \cdot kg^{-1}$) of FCN (fig. 2).

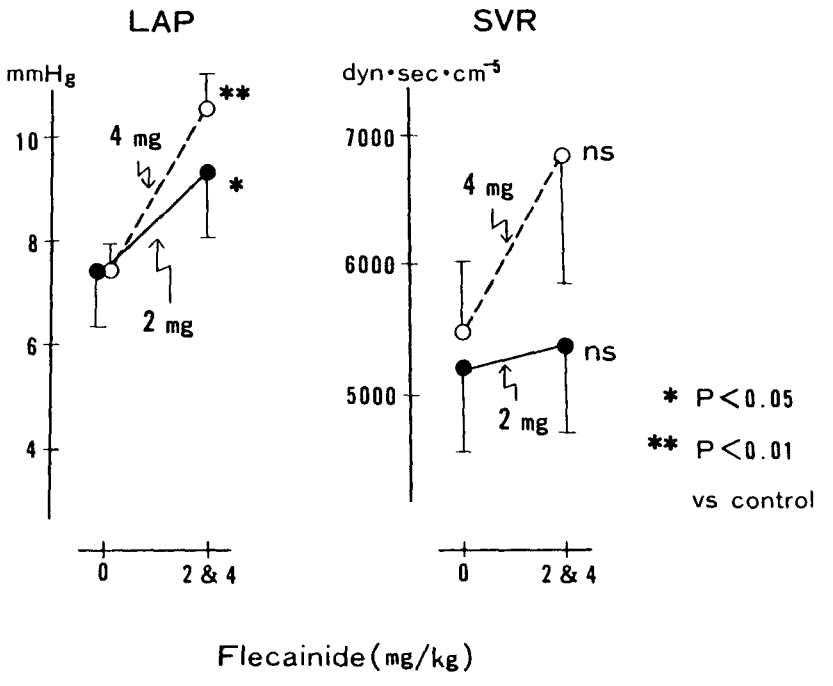

Fig. 3. Changes in LAP (left atrial pressure) and SVR (systemic vascular resistance) produced by intravenous flecainide (2 and 4 mg·kg^{-1}) under 1% of halothane in intact dogs. Mean ± SE. *$P < 0.05$; **$P < 0.01$ vs values in the absence of flecainide (0).

Table 2. ECG changes produced by intravenous injection of FCN

			PQ (sec)	QRS (sec)	QT (sec)	JT (sec)
FCN	0	mean	0.080	0.060	.0.240	0.180
		SE	0.000	0.000	0.006	0.006
	2 mg·kg^{-1}	mean	0.080	0.066	0.260*	0.190
		SE	0.003	0.002	0.006	0.007
FCN	0	mean	0.082	0.058	0.240	0.180
		SE	0.002	0.002	0.006	0.007
	4 mg·kg^{-1}	mean	0.086	0.086*	0.280	0.192
		SE	0.003	0.006	0.019	0.012

*$P < 0.05$ vs FCN = 0
JT is (QT-QRS). FCN is flecainide.

LAP increased slightly but significantly. A change in systemic vascular resistance (SVR) by FCN was insignificant (fig. 3). ECG changes produced by FCN injection are shown in table 2. The QRS and QT interval were significantly prolonged.

Discussion

The present study demonstrates that flecainide (FCN) dose-dependently increases the arrhythmogenic dose of epinephrine (ADE) during halothane anesthesia, and ADE induced arrhythmias are ceased by

the bolus injection of FCN in intact dogs. This suggests that FCN can be used for the treatment of epinephrine related arrhythmias during general anesthesia.

The major action of FCN is the restriction of the fast inward movement of Na^+, hence FCN is categorized as a class I antiarrhythmic drug[1-3]. The electrophysiological characteristics of FCN are the marked depression of the phase 0 of the action potential and the slowing of conduction, especially His-Purkinje conduction time and ventricular activation time[1-4,10]. These changes were observed on ECG in this study. The efficacy of FCN on arrhythmias has been demonstrated in various animal arrhythmic models, including chloroform-induced ventricular fibrillation, hydrocarbon epinephrine-, oubain- and coronary ligation-induced ventricular arrhythmias, and aconitine-induced atrial arrhythmias[4]. We have shown the efficacy on epinephrine halothane-induced arrhythmias in this study. In these animal models, FCN has been assumed to be the most potent and the most uniformly effective agent when compared with lidocane, procainamide, quinidine, disopyramide, encainide, tocainide, mexiletine and lorcainide[4]. In humen, FCN has been used in the treatment of supraventricular arrhythmias, ventricular premature complexes and ventricular tachycardias[5-9].

The increased BP and HR are the important factors in the etiology of arrhythmias induced by E[11]. If the antihypertensive and the negative chronotropic effect of FCN are the causes of the antiarrhythmic effect, BP and HR just before the development of arrhythmias by E in the presence of FCN should be lower than those in the absence of FCN. The present results, however, showed that BP and HR just before the development of arrhythmias were higher and the same in the presence of FCN, respectively. The anti-arrhythmic effect of FCN is, therefore, attributed to a direct effect of this drug, not to an indirect effect through the depression of BP and HR.

One of the unfavorable properties of FCN is cardiovascular depressive action. Although the speed of intravenous injection was relatively slow (2 $mg \cdot kg^{-1} \cdot min^{-1}$) in this study, decreases in BP, CO and HR were observed in the intact dogs. These depressions were accompanied by increased LAP and unchanged SVR. The circulatory depression produced by FCN is, thus, suggested to be mediated by the depression of cardiac function and myocardial contractility. A direct negative inotropic effect of FCN has been demonstrated on isolated heart muscles[1,2]. However, decreases in BP and CO were not obvious when FCN was used for the treatment of arrhythmias in this study. The improvement of cardiovascular instabilities by treatment of arrhythmias may counteract the direct circulatory depression produced by FCN. In humen, intravenous administration of FCN has been reported to reduce BP, CO and ejection fraction, and to increase pulmonary wedge pressure and LVEDP[12-14]. Since the acceleration of cardiac failure has been reported in clinical trials (although there are a few cases[14]), FCN should be administered with caution for patients with failing hearts.

In conclusion, intravenously administered FCN increased ADE and stopped ADE-induced ventricular arrhythmias under halothane anesthesia. FCN can, therefore, be used for the treatment of E related arrhythmias during anesthesia.

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