Comparison of Electrophysiologic and Hemodynamic Effects of SD-3212, a New Antiarrhythmic Drug, and Flecainide in a Canine Myocardial Infarction Model

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Electrophysiologic and hemodynamic effects of SD-3212, a new antiarrhythmic drug, were examined and compared with those of flecainide, a class Ic antiarrhythmic drug, in a canine myocardial infarction model. The doses of SD-3212 were 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion and 3 mg/kg bolus injection followed by 0.3 mg/kg/min infusion, while those of flecainide were 0.3 mg/kg bolus injection followed by 0.03 mg/kg/min infusion and 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion. SD-3212 at the high dose prolonged the effective refractory period and QT interval, and depressed ventricular delayed conduction. Flecainide at the high dose also prolonged the effective refractory period and depressed ventricular delayed conduction. Flecainide reduced a maximal rate of rise of left ventricular pressure at the high dose, while SD-3212 did not significantly change it. Neither of the drugs significantly affected mean arterial blood pressure or cardiac output. Thus, SD-3212 may produce antiarrhythmic effects with less cardiac depressant effect than flecainide.

Keywords SD-3212; antiarrhythmic drug; electrophysiology; hemodynamics

Class I antiarrhythmic drugs are now frequently used for the treatment of ventricular arrhythmias.²⁾ However, the Cardiac Arrhythmias Suppression Trial (CAST) showed that the class Ic antiarrhythmic drugs encainide and flecainide did not reduce the mortality in patients with ventricular arrhythmias after myocardial infarction.³⁾ Moreover, many investigators demonstrated that class Ic antiarrhythmic drugs actually have a proarrhythmic effect.^{2,4)} SD-3212, (–)-(S)-2-[5-methoxy-2-[3-[methyl-2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one hydrogen fumarate, is a newly synthesized and chemically unique (benzothiazine derivative) antiarrhythmic drug. SD-3212 produces a Na⁺ channel inhibition with a slight Ca²⁺ channel inhibition.⁵⁾ Antiarrhythmic effects of SD-3212 were demonstrated in coronary-ligation and reperfusion-induced arrhythmias and two-stage coronary ligation-induced arrhythmias.^{6–8)} According to the report of Nagashima *et al.*, SD-3212 has antiarrhythmic effects common among class I.⁸⁾ It has been reported that several class I antiarrhythmic drugs, especially those in class Ic, have a depressant effect on the cardiac function.²⁾ In the present study, we examined electrophysiologic and hemodynamic effects of SD-3212 and compared them with those of the class Ic antiarrhythmic drug, flecainide, in a canine myocardial infarction model.

MATERIALS AND METHODS

Mongrel dogs weighing between 8.0–13.0 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. The animal was intubated and ventilated with room air using a positive pressure respirator. A left thoracotomy was performed in the fourth intercostal space and the heart was exposed. After opening the pericardium, the left anterior descending coronary artery (LAD) was

occluded according to the method of Harris⁹⁾ and then several branches of LAD were also occluded. The chest was closed after the complete occlusion, and routine postoperative care was performed including prophylactic antibiotic therapy, *i.e.* intramuscular administration of ceftizoxime every day during postinfarction convalescence.

The measurement of the effective refractory period (ERP) was performed during sinus rhythm or atrial pacing at a cycle length between 350 and 300 ms in 5 animals 5 to 7 d after the LAD ligation. Late diastolic excitation thresholds at test areas were measured and, if they varied by more than 0.5 mA in control state, the data were discarded. For measuring the ERP, premature stimuli with a strength of 1 mA which was about 2–3 times the threshold in the infarcted zones were introduced to the infarcted or the normal zones at progressively shorter coupling intervals. The ERP was defined as the shortest interval at which conduction was successful.

A QT interval in the normal zone was also measured in the electrocardiograms (ECG) of normal zones during atrial pacing. The QT interval was the time between initiation of a rapid deflection and a final slow deflection in the normal zone ECG.

To examine the effect of the drug on the ventricular conduction, intraventricular conduction time of the premature excitation was measured in both normal and infarcted zones as described previously.¹⁰⁾ Atrial pacing was performed at a cycle length between 300 and 350 ms throughout the measurement. Several bipolar electrodes were sutured on the surface of the right and the left ventricles for applying premature electrical stimulations or for recording ventricular bipolar ECG. The time interval between the artifact of the stimulation and the most delayed deflection of the bipolar ECG was measured, and this value was estimated as the conduction time. The

conduction time was measured at the coupling interval of the premature stimulation of 180 ms.

The effects of SD-3212 on the hemodynamic parameters were determined 5 to 7 d after the LAD ligation. Animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg), and ventilation and thoracotomy were performed as described above. Body temperature was maintained at 37–38 °C with a heating pad. The pericardium was opened and the heart was suspended in a pericardial cradle. Two flow probes connected with a 2-channel ultrasonic Doppler flowmeter (Transonic Systems Inc., NY, U.S.A., T201) were placed around the ascending aorta and the proximal left circumflex coronary artery (LCX) to measure cardiac output and blood flow of LCX, respectively. Arterial blood pressure was measured with a pressure transducer (Gould, CA, U.S.A., P50) connected with a fluid-filled polyethylene catheter inserted into the right femoral artery. Left ventricular pressure was measured with a 5F micromanometer-tipped catheter (Millar Instruments, TX, U.S.A., PC350) inserted from the left common carotid artery, and the maximal rate of rise of left ventricular pressure ($LVdp/dt_{max}$) was calculated with an electronic differentiator (Nihon Kohden, Tokyo, Japan, ED-600G). Heart rate was triggered from a standard limb lead II of ECG using a cardi tachometer (Nihon Kohden, AT-600G). All pressure and flow measurements and electrocardiographic signals for analysis were recorded on a multi-channel thermal-array recorder (Nihon Kohden, WS-682G) at a paper speed of 10 mm/min or 50–200 mm/s where appropriate.

After a stabilization period of about 1 h, measurements of control data were performed. Then, a low and a high dose of SD-3212 or flecainide were consecutively administered from the femoral vein. The doses of SD-3212 were 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion (low dose) and 3 mg/kg bolus injection followed by 0.3 mg/kg/min infusion (high dose). The doses of flecainide were 0.3 mg/kg bolus injection followed by 0.03 mg/kg/min infusion (low dose) and 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion (high dose). Measurements after administration of the drug were performed 30–35 min after the start of each infusion. Electrophysiology and hemodynamics were studied in separate animals, and effects of the two drugs were examined in separate animals.

All data are shown as arithmetical means $\pm$ S.E.M. Paired comparisons among pre- and multiple postdrug values were performed by a two-way analysis of variance followed by Dunnett's test. The criterion for statistical significance was $p < 0.05$.

SD-3212 was generously provided by Santen Pharmaceutical Co., Ltd. (Osaka, Japan). For intravenous administration, SD-3212 was dissolved in 10% dimethyl sulfoxide solution in an appropriate concentration. Flecainide was dissolved in a physiological saline. The vehicle did not significantly change any parameter.

RESULTS AND DISCUSSION

Neither of the two drugs affected the excitation threshold. SD-3212 at the low dose did not significantly change the ERP in the normal or the infarcted zone, but the high dose of SD-3212 prolonged the ERP by 28% in the normal zone and 51% in the infarcted zone (Table I). Flecainide at the low dose did not significantly change the ERP in the normal zone, but slightly prolonged the ERP in the infarcted zone. The high dose of flecainide prolonged the ERP by 30% in the normal zone and 29% in the infarcted zone. During atrial pacing, SD-3212 and flecainide at the high doses prolonged the ERP by 43.8 ± 9.0 and $18.8 \pm 5.1\%$ ($n=5$, $p < 0.05$ vs. predrug value) in the infarcted zone, respectively.

SD-3212 significantly prolonged the QT interval. The prolongation with SD-3212 was $3.5 \pm 1.6\%$ ($n=5$) and $13.4 \pm 4.2\%$ of basal values ($n=5$, $p < 0.05$) at the low and the high dose, respectively. Flecainide at the high dose prolonged the QT interval by $3.1 \pm 1.8\%$ ($n=5$).

The ventricular conduction time in the infarcted zone was longer than that in the normal zone, indicating that the conduction in the infarcted zone was delayed. SD-3212 and flecainide at the high dose markedly prolonged the conduction time in the infarcted zone. In two of five animals examined, delayed conduction was blocked by the high dose of either drug. These results are consistent with those reported previously.^{7,8)}

Hemodynamic effects of SD-3212 and flecainide are represented in Table II. Neither drug significantly changed the mean blood pressure, and both at the high dose reduced heart rate. $LVdp/dt_{max}$ was not significantly affected by SD-3212, but it was reduced by flecainide at the high dose. SD-3212 did not significantly change

TABLE I. Effects of SD-3212 and Flecainide on the ERP and Ventricular Conduction Time in Canine Myocardial Infarction Model

	ERP				Ventricular conduction time			
	SD-3212		Flecainide		SD-3212		Flecainide	
	Normal zone	Infarcted zone	Normal zone	Infarcted zone	Normal zone	Infarcted zone	Normal zone	Infarcted zone
Basal value (ms)	162 $\pm$ 10	159 $\pm$ 20	148 $\pm$ 5	126 $\pm$ 11	85 $\pm$ 8	108 $\pm$ 6	85 $\pm$ 5	103 $\pm$ 8
% increase								
Low dose	8 $\pm$ 9	26 $\pm$ 21	8 $\pm$ 4	19 $\pm$ 7	10.6 $\pm$ 4.9	15.1 $\pm$ 8.5	16.3 $\pm$ 4.4	8.5 $\pm$ 5.9
High dose	28 $\pm$ 8 ^{a)}	51 $\pm$ 6 ^{b)}	30 $\pm$ 16	29 $\pm$ 6 ^{b,c)}	23.8 $\pm$ 4.9 ^{a)}	48.5 $\pm$ 8.0 ^{b)}	33.7 $\pm$ 8.2 ^{a)}	49.7 $\pm$ 8.5 ^{b)}

Values are the mean $\pm$ S.E.M. of five or six animals. The low and high doses of SD-3212 are 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion and 3 mg/kg bolus injection followed by 0.3 mg/kg/min infusion, respectively. Those of flecainide are 0.3 mg/kg bolus injection followed by 0.03 mg/kg/min infusion and 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion. a, b) $p < 0.05$ and 0.01 vs. predrug value. c) $p < 0.05$ vs. SD-3212 at high dose in infarcted zone.

TABLE II. Hemodynamic Effects of SD-3212 in Canine Myocardial Infarction Model in Comparison with Those of Flecainide

	Mean blood pressure	Heart rate	LVdp/dt _{max}	Cardiac output	LCX blood flow
Basal value	85.4 ± 6.4 (mmHg)	170.6 ± 12.3 (beats/min)	2716 ± 198 (mmHg/s)	0.62 ± 0.04 (l/min)	15.2 ± 0.9 (ml/min)
SD-3212 (% change)					
Low dose	+8.0 ± 5.1	-14.2 ± 5.2	-0.2 ± 4.6	+3.6 ± 3.7	-11.0 ± 6.3
High dose	+1.8 ± 7.4	-24.6 ± 5.6 ^{a)}	-7.6 ± 12.7	-7.6 ± 12.7	+3.4 ± 16.0
Basal value	81.2 ± 3.2 (mmHg)	162.0 ± 7.1 (beats/min)	2295 ± 140 (mmHg/s)	0.54 ± 0.07 (l/min)	12.0 ± 1.4 ^{c)} (ml/min)
Flecainide (% change)					
Low dose	+7.0 ± 4.2	-2.4 ± 3.2	-5.0 ± 4.6	+6.2 ± 6.9	+5.0 ± 6.1
High dose	+0.8 ± 7.3	-12.2 ± 3.9 ^{a)}	-33.6 ± 4.8 ^{b)}	-16.2 ± 6.2	-13.8 ± 9.0

Changes in the values with the drugs are represented in % of the basal value. Values are mean ± S.E.M. of five animals. a, b) $p < 0.05$ and 0.01 vs. predrug value. c) $p < 0.05$ vs. control for SD-3212. LCX blood flow; blood flow of left circumflex coronary artery. LVdp/dt_{max}; maximum rate of rise of left ventricular pressure. The low and the high doses of SD-3212 are 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion and 3 mg/kg bolus injection followed by 0.3 mg/kg/min infusion, respectively. Those of flecainide are 0.3 mg/kg bolus injection followed by 0.03 mg/kg/min infusion and 1 mg/kg bolus injection followed by 0.1 mg/kg/min infusion.

cardiac output. Flecainide at the high dose slightly reduced cardiac output in all of five animals, although the reduction was not statistically significant ($0.05 < p < 0.1$). Blood flow of LCX was not significantly affected by these drugs.

Previous studies showed that SD-3212 and flecainide produced antiarrhythmic effects at doses of 1–3 mg/kg. In arrhythmias 24 h after coronary ligation, SD-3212 at 3 mg/kg and flecainide at 1 mg/kg reduced a ratio of ventricular beats/total beats by about 80% at about 5–10 min after the administration.^{7,8)} The doses of the two drugs examined in the present study may be antiarrhythmic doses and equipotent. At the high dose both depressed the delayed conduction in the infarcted zone to a similar extent, which may contribute to their antiarrhythmic effects. The ERP was also prolonged by SD-3212 to a greater extent than that with flecainide, which may also contribute to their antiarrhythmic effects.⁸⁾ The QT interval was slightly prolonged by SD-3212 but not by flecainide. Prolongation of the ERP may be partly attributable to a prolongation of repolarization phase with SD-3212. SD-3212 as well as flecainide markedly depressed the delayed conduction in the infarcted zone. Depression of the delayed conduction and prolongation of ERP with these drugs may contribute to their antiarrhythmic action.^{8,10,11)} Some class I antiarrhythmic drugs, especially those in class Ic, have depressant effects on cardiac function.²⁾ SD-3212 did not show any significant depression of ventricular contractility, whereas

flecainide markedly depressed it. Other class Ic antiarrhythmic drugs also have cardiac depressant effects.²⁾ Lower cardiac depression with SD-3212 may be partly attributable to a prolongation of the repolarization phase.

In conclusion, SD-3212 appears to show antiarrhythmic effect with less cardiac depression compared with the class Ic antiarrhythmic drug flecainide.

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