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Cardiovascular action of a cardioselective Ca^{2+} channel blocker AH-1058 in conscious dogs assessed by telemetry

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Abstract

AH-1058, 4-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride, is a novel Ca^{2+} channel blocker exerting cardioselective action in isolated or anesthetized canine heart preparations. To clarify the cardiac and hemodynamic action of AH-1058 in conscious dogs, we assessed the effects of the drug on the hemodynamic parameters continuously recorded by telemetry in conscious unrestrained beagle dogs, and its cardiovascular effects were compared with those of verapamil, disopyramide and atenolol. Oral administration of AH-1058 (0.15, 0.3 and 0.6 mg/kg) reduced the systolic blood pressure and maximal upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$), increased heart rate and prolonged the QA interval in a dose-dependent manner whereas the drug did not affect diastolic blood pressure. Verapamil at 10 mg/kg reduced systolic and diastolic blood pressure with little effect on heart rate, $LVdP/dt_{max}$ and QA interval. Disopyramide at 20 mg/kg increased systolic and diastolic blood pressure, decreased $LVdP/dt_{max}$ and prolonged the QA interval with little changes in heart rate. Atenolol at 10 mg/kg decreased $LVdP/dt_{max}$ and prolonged the QA interval with little changes in systolic blood pressure, diastolic blood pressure and heart rate. The time course of the cardiohemodynamic action of AH-1058 was longer than those of the other drugs. These results suggest that AH-1058 is a long-acting cardiodepressive drug, and its hemodynamic profile is obviously different from that of disopyramide and atenolol. This unique cardiovascular profile may be beneficial for the treatment of certain pathological processes in which selective inhibition of the ventricular Ca^{2+} channels would be the target of drug therapy. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: AH-1058; Cardioselective Ca^{2+} channel blocker; Hemodynamics; Telemetry

1. Introduction

AH-1058, 4-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride (Fig. 1), is a recently synthesized cardioselective Ca^{2+} channel blocker, of which the chemical structure is quite different from typical Ca^{2+} channel blockers, including verapamil, diltiazem and nifedipine (Takahara et al., 1999; Tanaka et al., 1999). In the blood-perfused canine heart preparations, AH-1058 has been demonstrated to exert negative chronotropic, inotropic and dromotropic action without affecting the coronary circulation when compared with verapamil (Takahara et al., 2000a). Moreover, in halothane-anesthetized dogs, the drug has been shown to selectively suppress cardiac function without affecting the peripheral vascular vessels (Takahara et al., 2000b). Therefore, AH-1058 is proposed for the treatment of certain pathological processes in which selective inhibition of the cardiac Ca^{2+} channels would be essential for drug therapy.

Assessment of cardiovascular drug actions under a conscious state may be important to estimate the clinical effects. It is because anesthetics including halothane and isoflurane exert a non-specific Ca^{2+} channel blocking action, and indeed cardiovascular actions of Ca^{2+} channel blockers have been reported to be modified by such anesthetics (Galleneberg et al., 1993). In the present study, using a telemetry recording system with two channels of pressure monitoring we assessed the negative inotropic as

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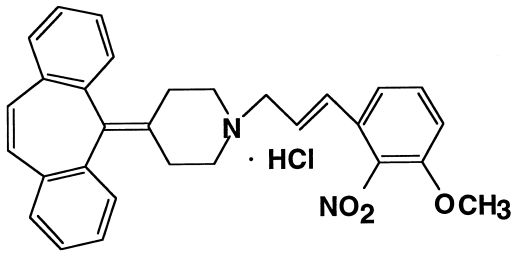

Fig. 1. Chemical structure of AH-1058, 4-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride.

well as hemodynamic action of AH-1058 in conscious unrestrained dogs in comparison with that of a typical Ca^{2+} channel blocker verapamil, a class I antiarrhythmic drug disopyramide and a β-adrenoceptor antagonist atenolol, all of them having been demonstrated to possess negative inotropic action (Beltrame et al., 1984; Taira, 1987; Satoh et al., 1990; Sugiyama et al., 1990).

2. Methods

All experiments were performed according to Guidelines for Animal Experiments, Pharmaceutical Research Laboratories, Ajinomoto. Beagle dogs (Nihon Nosan, Yokohama, Japan) were kept in individual cages, and a 12 h light (7:00–19:00)–dark (19:00–7:00) cycle was used.

2.1. Telemetry system

A telemetry recording system (Data Sciences International, St. Paul, MN, USA) was used for the evaluation of cardiovascular drug actions in conscious dogs (Truett and West, 1995; Gelzer and Ball, 1997). Signals from an implantable transmitter unit (TL11M3-D70-PCP) were received by a cage receiver (RLA 2000) for the measurement of systemic blood pressure, the left ventricular pressure and electrocardiogram (ECG), which was analyzed using a PC-based data acquisition system (DATAQUEST LabPRO SYSTEM). An index of contractility, namely QA interval (Cambridge and Whiting, 1986), which is defined as the time-interval between the Q point of ECG and the beginning of the upstroke of arterial pressure, can be automatically obtained by the computer.

2.2. Surgical implantation of transmitter units

Six male beagle dogs of 8 to 12 months old were initially anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1.0% halothane was inhaled with a volume-limited ventilator (SN-408-3, Shinano, Tokyo, Japan). The chest was opened by an incision at the 6th intercostal space to expose the heart. A pressure catheter (1.2 mm in diameter), which was connected to the implantable transmitter unit, was inserted into the left ventricle of the heart through its apex for recording the left ventricular pressure. Before closing the chest, subcutaneous pocket was formed in the left flank, and the unit's tabs were sutured in the underlying tissue. Another pressure catheter (1.2 mm in diameter) was tunneled subcutaneously from the flank to the groin where the left femoral artery was isolated. The catheter tip was advanced into the abdominal aorta and secured with silk ligature. To monitor the lead II ECG, one lead was routed under the skin terminating near the right axilla, the other was secured in the area of the lower left abdomen. All incisions were closed in routine fashion and antibiotic prophylaxis was maintained for 10 days. Experiments were begun 4 weeks after the surgery.

2.3. Experimental protocol

All drugs were orally administered at 11:00 to the dogs that had been fasted for 18 h. AH-1058 in doses of 0.15, 0.3 and 0.6 mg/kg ($n = 6$), its vehicle ($n = 6$), verapamil in a dose of 10 mg/kg ($n = 4$), disopyramide in a dose of 20 mg/kg ($n = 3$) or atenolol in a dose of 10 mg/kg ($n = 4$) was orally and randomly given at an interval of 1 week. The dose(s) of each drug was determined by the previous reports (Eigenmann and Gerold, 1987; Takahara et al., 2000c; Uchida et al., 1993; Yorikane et al., 1994).

2.4. Drugs

The following drugs were used: AH-1058 (Ajinomoto, Tokyo, Japan), verapamil hydrochloride, disopyramide phosphate, atenolol (Sigma, St. Louis, MO, USA), thiopental sodium (Tanabe Seiyaku, Osaka, Japan), and halothane (Takeda Chemical, Osaka, Japan). AH-1058 was dissolved in polyethylene glycol 400 because of its highly lipophilic chemical property, while verapamil, disopyramide and atenolol were dissolved in distilled water. These drugs were orally administered in a volume of 0.2 ml/kg.

2.5. Data analysis

All values are expressed as means ± S.E. Systolic blood pressure, diastolic blood pressure, heart rate, maximal upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$) and the QA interval were recorded for 10 s every 5 min. Data obtained from all protocols were analyzed in the same manner by calculating the mean values for a 30-min period for each of the dogs. Analysis of variance (ANOVA) was employed for statistical analysis by using SuperANOVA (Abacus Concepts, Berkeley, CA, USA), followed by Dunnett's test for statistical analysis between the vehicle-treated group and others. Additionally, Contrasts was used for statistical analysis between basal values (zero time) and others. Relationship between the QA interval and $LVdP/dt_{max}$ was calculated using the

least square method, and simple correlation coefficient was obtained with Pearson's test. Differences with a P-value of less than 0.05 were considered to be statistically significant.

3. Results

3.1. Cardiohemodynamic effects of AH-1058 in conscious dogs

Effects of AH-1058 on blood pressure and heart rate are summarized in Fig. 2, while those on the QA interval and $\mathrm{LVd}P/\mathrm{d}t_{\max}$ are shown in Fig. 3. Systolic blood pressure and diastolic blood pressure at 0 time were 139 ± 5 and 74 ± 3 mm Hg for the vehicle group, 144 ± 4 and 79 ± 3 mm Hg for the 0.15 mg/kg-treated group, 151 ± 6 and 80 ± 3 mm Hg for the 0.3 mg/kg-treated group, and 140 ± 5 and 74 ± 3 mm Hg for the 0.6 mg/kg-treated group, respectively. Heart rate at 0 time was 61 ± 3 beats/min for the vehicle group, 75 ± 8 beats/min for the 0.15 mg/kg-treated group, 75 ± 5 beats/min for the 0.3 mg/kg-treated group and 69 ± 4 beats/min for the 0.6 mg/kg-treated group. There was no significant difference in each basal value between the groups including the other drug-treated groups. AH-1058 significantly reduced systolic blood pressure in the 0.6 mg/kg-treated group, while the drug barely affected the diastolic blood pressure DBP. Heart rate was significantly increased by the drug in the 0.3 mg/kg-and 0.6 mg/kg-treated groups. The statistically significant changes in systolic blood pressure were observed at 1.5 to 9.5 h in the 0.6 mg/kg-treated group, whereas those in heart rate were at 1 to 5 h (except for 3, 3.5 and 4.5 h) in the 0.3 mg/kg-treated group and at 1 to 6.5 h in the 0.6 mg/kg-treated group.

The QA interval and $\mathrm{LVd}P/\mathrm{d}t_{\max}$ at 0 time were 111 ± 3 ms and 2.62 ± 0.21 mm Hg/ms for the vehicle group, 108 ± 4 ms and 3.03 ± 0.23 mm Hg/ms for the 0.15 mg/kg-treated group, 107 ± 4 ms and 2.97 ± 0.30 mm Hg/ms for the 0.3 mg/kg-treated group, and 110 ± 5 ms and 2.57 ± 0.23 mm Hg/ms for the 0.6 mg/kg-treated

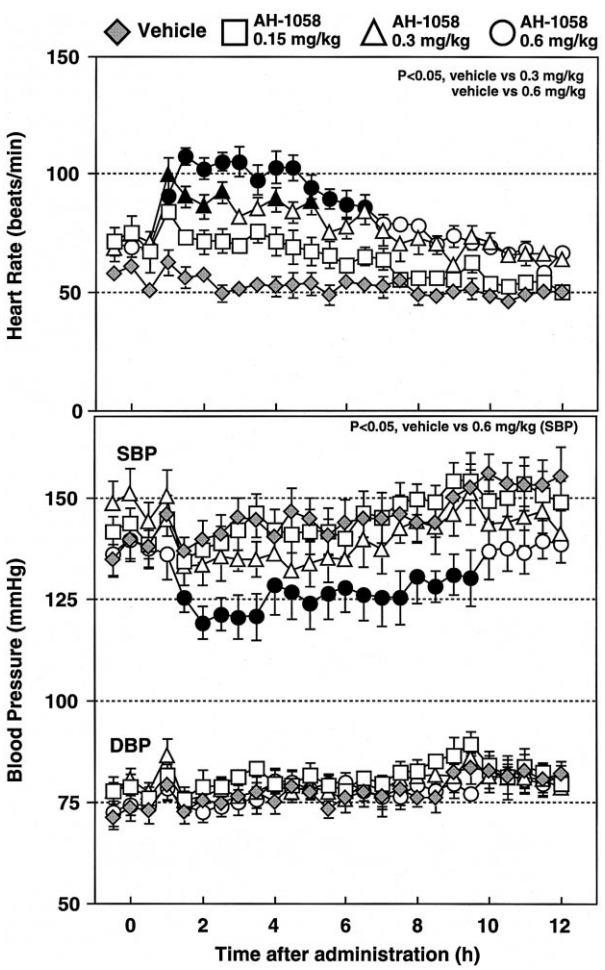

Fig. 2. Effects of oral administration of AH-1058 (0.15, 0.3 and 0.6 mg/kg, $n = 6$) on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR). Data are expressed as means ± S.E. Closed symbols represent significant change from the 0 time values ($P < 0.05$).

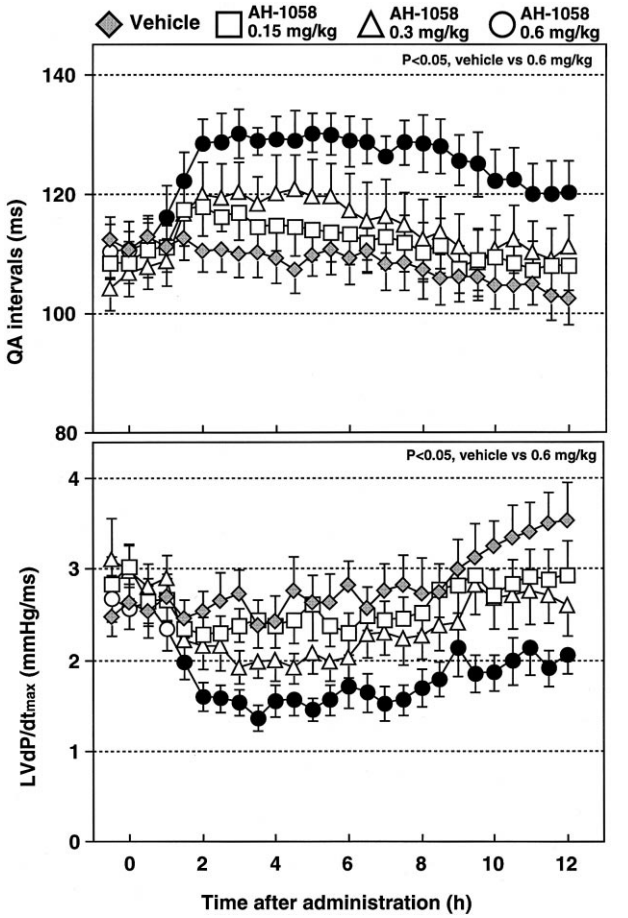

Fig. 3. Effects of oral administration of AH-1058 (0.15, 0.3 and 0.6 mg/kg, $n = 6$) on QA interval and the maximal upstroke velocity of the left ventricular pressure ($\mathrm{LVd}P/\mathrm{d}t_{\max}$). Data are expressed as means ± S.E. Closed symbols represent significant change from the 0 time values ($P < 0.05$).

group, respectively. There was no significant difference in each basal value between the groups including the other drug-treated groups. AH-1058 in dose of 0.6 mg/kg significantly prolonged the QA interval and decreased $LVdP/dt_{max}$. The statistically significant changes in the QA interval were observed at 1 to 12 h in the 0.6 mg/kg-treated group, whereas those in $LVdP/dt_{max}$ were observed at 1.5 to 12 h in the 0.6 mg/kg-treated group. Both parameters in the 0.6 mg/kg-treated group were returned to the basal value at 17 h after administration.

3.2. Cardiohemodynamic effects of verapamil in conscious dogs

Effects of verapamil in a dose of 10 mg/kg on blood pressure, heart rate, QA interval and $LVdP/dt_{max}$ are summarized in Fig. 4. Systolic blood pressure, diastolic blood pressure, heart rate, the QA interval and $LVdP/dt_{max}$ at 0 time were 143 ± 4 mm Hg, 76 ± 6 mm Hg, 66 ± 4 beats/min, 112 ± 4 ms and 2.50 ± 0.19 mm Hg/ms, respectively. An oral administration of verapamil lowered systolic and diastolic blood pressure, of which significant changes were observed at 0.5 to 3.5 h in systolic blood pressure and at 0.5 to 3 h in diastolic blood pressure. Heart rate was significantly elevated at 0.5 and 1 h after administration. The QA interval and $LVdP/dt_{max}$ were not affected by verapamil.

3.3. Cardiohemodynamic effects of atenolol in conscious dogs

Effects of atenolol in a dose of 10 mg/kg on blood pressure, heart rate, the QA interval and $LVdP/dt_{max}$ are summarized in Fig. 5. Systolic blood pressure, diastolic blood pressure, heart rate, the QA interval and $LVdP/dt_{max}$ at 0 time were 152 ± 2 mm Hg, 80 ± 3 mm Hg, 60 ± 1 beats/min, 107 ± 4 ms and 2.91 ± 0.15 mm Hg/ms, respectively. An oral administration of atenolol decreased $LVdP/dt_{max}$, of which significant changes were observed at 0.5 to 6 h. The QA interval was also prolonged at 1 to 6 h in diastolic blood pressure. Slight changes in systolic blood pressure, diastolic blood pressure and heart rate were observed during the experimental period.

3.4. Cardiohemodynamic effects of disopyramide in conscious dogs

Effects of disopyramide in a dose of 20 mg/kg on blood pressure, heart rate, the QA interval and $LVdP/dt_{max}$ are summarized in Fig. 6. Systolic blood pressure, diastolic blood pressure, heart rate, the QA interval and $LVdP/dt_{max}$ at 0 time were 155 ± 4 mm Hg, 83 ± 5 mm Hg, 75 ± 5 beats/min, 108 ± 5 ms and 3.43 ± 0.21 mm Hg/ms, respectively. An oral administration of

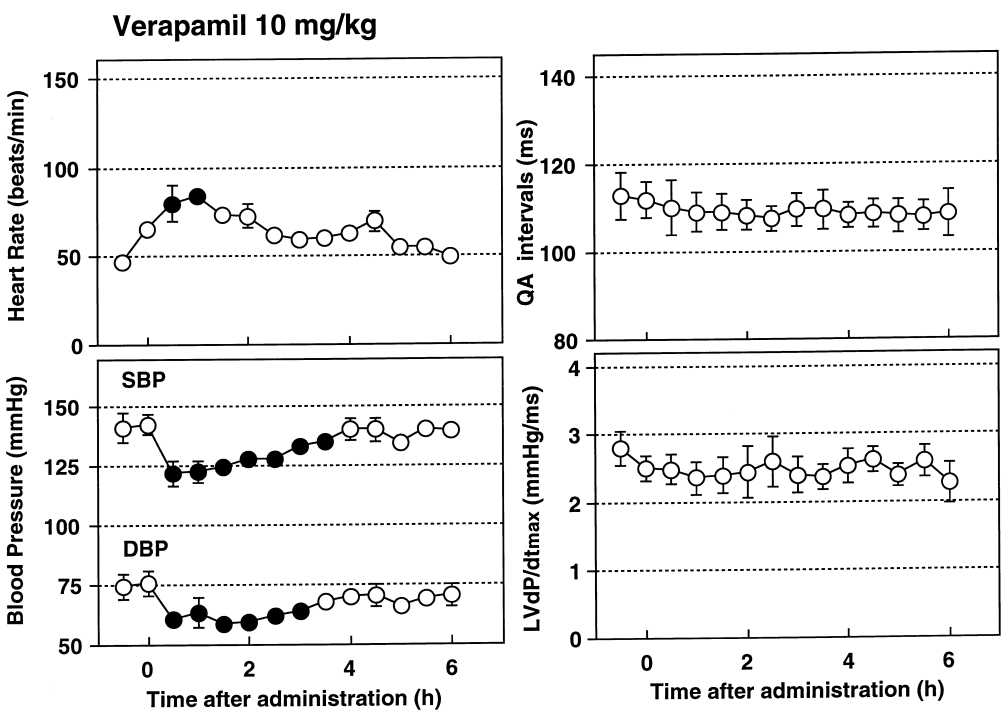

Fig. 4. Effects of oral administration of verapamil (10 mg/kg, $n = 4$) on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), QA interval and the maximal upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$). Data are expressed as means ± S.E. Closed symbols represent significant change from the 0 time values ($P < 0.05$).

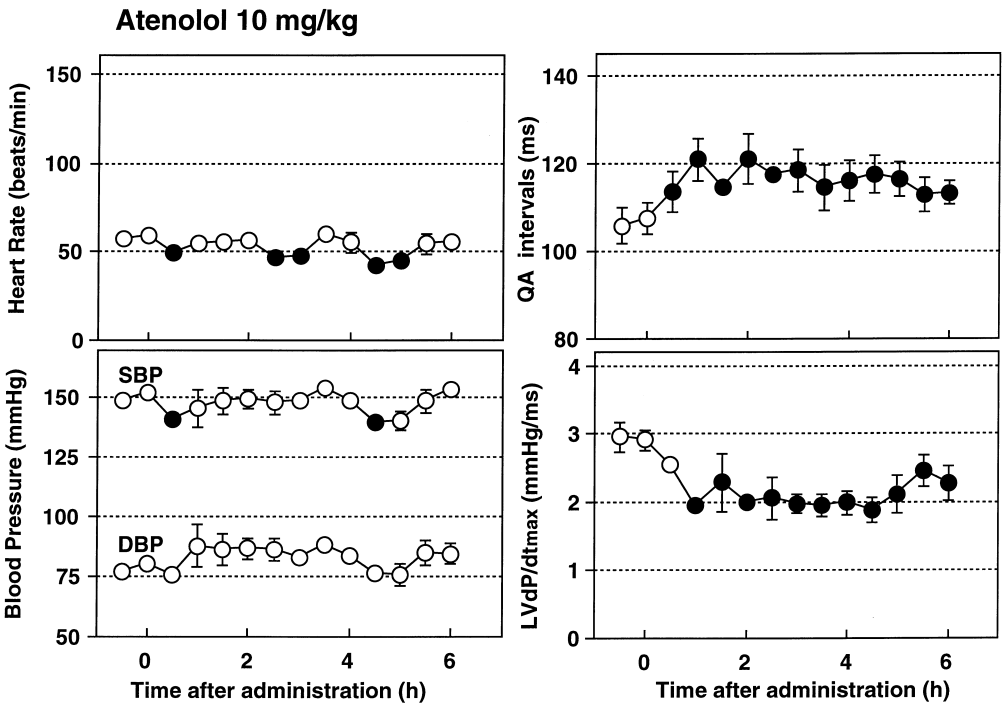

Fig. 5. Effects of oral administration of atenolol (10 mg/kg, $n = 4$) on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), QA interval and the maximal upstroke velocity of the left ventricular pressure ($\mathrm{LVd}P/\mathrm{d}t_{\max}$). Data are expressed as means ± S.E. Closed symbols represent significant change from the 0 time values ($P < 0.05$).

disopyramide elevated systolic and diastolic blood pressure, of which significant changes were observed at 1.5 h in systolic blood pressure and at 1 to 2 h in diastolic blood pressure. $\mathrm{LVd}P/\mathrm{d}t_{\max}$ was significantly decreased at 1.5 h, whereas the QA interval was prolonged at 1 to 2 h. Heart rate was not affected by disopyramide.

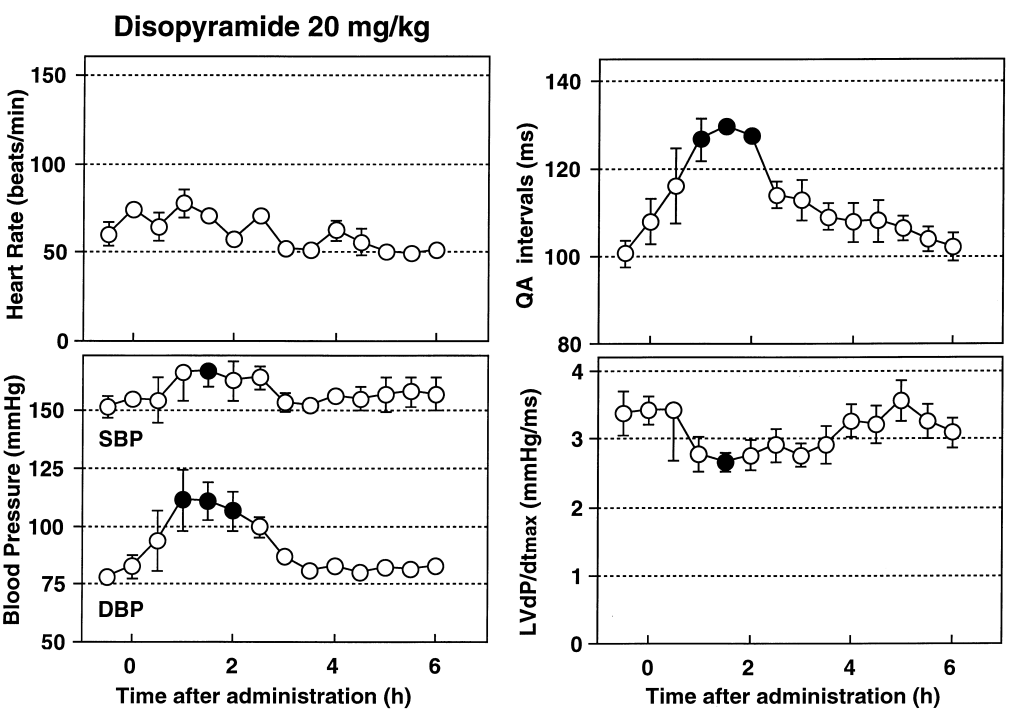

Fig. 6. Effects of oral administration of disopyramide (20 mg/kg, $n = 3$) on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), QA interval and the maximal upstroke velocity of the left ventricular pressure ($\mathrm{LVd}P/\mathrm{d}t_{\max}$). Data are expressed as means ± S.E. Closed symbols represent significant change from the 0 time values ($P < 0.05$).

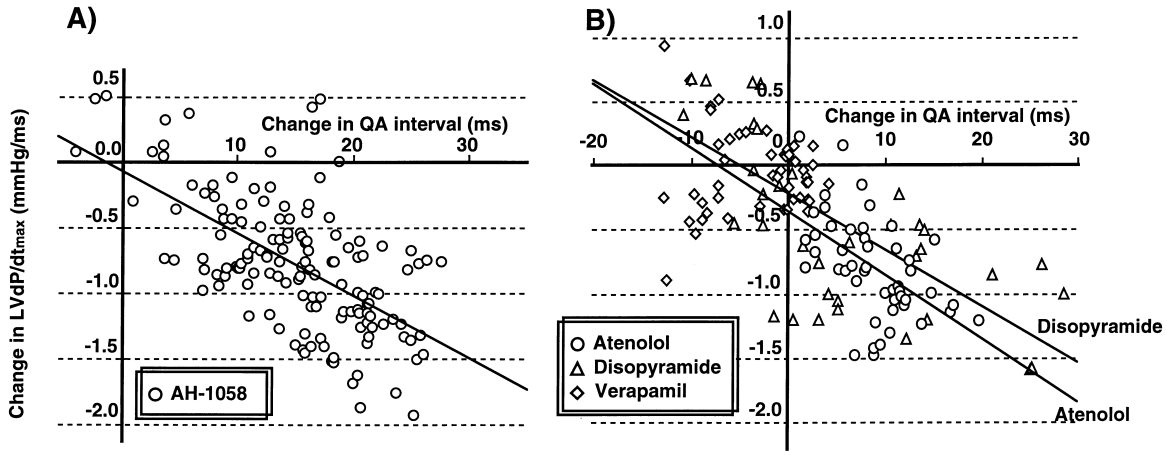

Fig. 7. Correlation between the changes in the QA interval and the maximal upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$). (A) AH-1058 (0.6 mg/kg, $n = 144$), (B) verapamil (10 mg/kg, $n = 48$), atenolol (10 mg/kg, $n = 48$) and disopyramide (20 mg/kg, $n = 36$). Statistically significant correlation was obtained in AH-1058-, atenolol- and disopyramide-treated groups ($P < 0.001$).

3.5. Correlation between QA interval and $LVdP/dt_{max}$ in conscious dogs

The correlation between the changes in the QA interval and $LVdP/dt_{max}$ by AH-1058 (0.6 mg/kg), verapamil (10 mg/kg), atenolol (10 mg/kg) and disopyramide (20 mg/kg), is shown in Fig. 7. All data at each measurement period are plotted in the figure. The changes in the QA interval and $LVdP/dt_{max}$ correlate significantly in AH-1058-($y = -0.048x - 0.057$, $r = 0.618$, $P < 0.001$, $n = 144$), atenolol-($y = -0.050x - 0.351$, $r = 0.538$, $P < 0.001$, $n = 48$) and disopyramide-($y = -0.044x - 0.206$, $r = 0.638$, $P < 0.001$, $n = 36$) treated groups, while significant correlation was not obtained in the verapamil-treated group ($r = 0.070$, not significant, $n = 48$).

4. Discussion

The present study was designed to characterize the cardiovascular profile of a cardioselective Ca^{2+} channel blocker AH-1058 (Takahara et al., 1999, 2000a,b,c) in conscious unrestrained dogs. As demonstrated in this study, the telemetry recording system was analyzed the in vivo cardiohemodynamic action of the cardiodepressive drugs. Both disopyramide and atenolol exerted a negative inotropic action, while systolic blood pressure was increased by disopyramide and not changed by atenolol. Verapamil did not affect cardiac contraction in the present hypotensive dose. On the other hand, AH-1058 exerted negative inotropic action and decreased systolic blood pressure in a dose-dependent manner. AH-1058 increased the heart rate possibly through a baroreflex, which was almost the same intensity as that observed in conscious dogs using other clinically available Ca^{2+} channel blockers such as amlodipine (Yamamoto et al., 1999) and verapamil.

The important observation in the present study is that AH-1058 reduced $LVdP/dt_{max}$ and systolic blood pressure without affecting diastolic blood pressure in contrast to verapamil which has been known to possess less vascular selectivity among Ca^{2+} channel blockers (Taira, 1987). The reduction of $LVdP/dt_{max}$ by AH-1058 can be explained by its potent and selective negative inotropic action, as previously reported using the blood-perfused canine heart preparation (Takahara et al., 2000a), while that of systolic blood pressure without affecting diastolic blood pressure may be explained by the previous observation in anesthetized dogs that AH-1058 reduced cardiac output without affecting total peripheral vascular resistance (Takahara et al., 2000b). Furthermore, as shown in this study, the hemodynamic action of AH-1058 is different from that of the other clinically available cardiodepressive drugs disopyramide and atenolol; i.e. although $LVdP/dt_{max}$ was reduced by both drugs, blood pressure was elevated by disopyramide while unaffected by atenolol, which may reflect that disopyramide and atenolol increase the total peripheral vascular resistance in contrast to AH-1058 (Beltrame et al., 1984; Satoh et al., 1990; Takahara et al., 2000b). These results suggest that AH-1058 become a unique cardiovascular drug exerting the cardiodepressive action hardly affecting peripheral vascular tone in comparison with β-adrenoceptor antagonists or class I antiarrhythmic drugs.

The time course of the AH-1058's effects also deserves comment. The present study shows that cardiovascular action of AH-1058 was slower in onset and longer-lasting than those of verapamil, disopyramide and atenolol. Although the similar time course of the action of AH-1058 has been shown using the canine coronary ligation-induced arrhythmia model, the antiarrhythmic activity of AH-1058 did not correlate with the plasma drug concentrations (Takahara et al., 2000c). The present cardiovascular action of AH-1058 also may not correlate with the plasma concentration although it was not determined in this study. This might be due to its high lipophilicity, which allows it to be readily distributed to the cardiac tissues. However,

this hypothesis must be further elucidated by measuring the drug concentration in the cardiac tissue.

The unique cardioselective profiles of AH-1058 can be applied for the treatment of certain pathological processes. Suppression of the cardiac contractility by AH-1058 may be useful for the treatment of angina pectoris by saving the cardiac energy consumption (Cohn, 1985). The negative inotropic effect can relieve the stenosis of the outflow tract of obstructive hypertrophic cardiomyopathy (Sugimoto et al., 1992; Hamada et al., 1997). Furthermore, the drug can be used for the prevention of vasovagal syncope by reducing cardiac contractility which may decrease the stretch of the cardiac and other centrally located cardiovascular baro-receptors (e.g., aortic arch, pulmonary arteries) resulting in the decrease of afferent neural reflex traffic, otherwise leading to the vagally mediated symptoms (Kapoor, 1997). In addition, AH-1058 may become an alternative in treating dissecting aortic aneurysm by diminution of the force of the left ventricular ejection (Isselbacher et al., 1997). In current therapy for such diseases, β-adrenoceptor antagonists or class I antiarrhythmic drugs have been used. However, most of the class I antiarrhythmic drugs have limitations in their clinical use because of their proarrhythmic and anticholinergic action, while β-adrenoceptor antagonists cannot be administered in patients with asthma or peripheral vascular diseases. Thus, Ca^{2+} channel blockers, with a cardioselective action such as AH-1058, can become a promising drug for controlling cardiac contractility without affecting peripheral vascular tone.

The present study also provided the first information on the correlation between the QA interval and $LVdP/dt_{max}$ in unrestrained conscious dogs. As shown in Fig. 7, the changes in the QA interval by AH-1058, atenolol and disopyramide well correlated with those in $LVdP/dt_{max}$. Moreover, the QA interval was not affected by changes in the heart rate or cardiac loading (Cambridge and Whiting, 1986). Therefore, the QA interval may be used for exploring cardiodepressive action of various drugs in the conscious animal.

In summary, the present results suggest that AH-1058 can be a long-acting cardiodepressive drug and that its hemodynamic action, decrease in the systolic blood pressure without affecting diastolic blood pressure, is obviously different from those of disopyramide and atenolol. This unique cardiovascular profile can be applied for the treatment of certain pathological processes such as angina pectoris, obstructive hypertrophic cardiomyopathy, vasovagal syncope and dissecting aortic aneurysm.

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