

Utilization of Telemetry System to Assess the Cardiovascular Profile of AH-1058, a New Cardioselective Ca²⁺ Channel Blocker, in Conscious Dogs

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ABSTRACT—Cardiovascular effects of a new Ca²⁺ channel blocker AH-1058, 4-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-1-[(*E*)-3-(3-methoxy-2-nitro)phenyl-2-propenyl]piperidine hydrochloride, were assessed in conscious dogs using a new telemetry system. AH-1058 (0.03, 0.1 and 0.3 mg/kg, i.v.) reduced systolic blood pressure and the maximal upstroke velocity of the left ventricular pressure and increased the heart rate in a dose-dependent manner without affecting the diastolic blood pressure; each of these responses lasted for several hours. These results support the previous knowledge that AH-1058 is a long-lasting cardiodepressive drug. The telemetry system provided important information for predicting favorable clinical effects of AH-1058.

Keywords: AH-1058, Ca²⁺ channel blocker, Cardiovascular action

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 recently synthesized Ca²⁺ channel blocker (1–4). AH-1058 has been demonstrated to selectively suppress the sino-atrial nodal activity, atrio-ventricular conduction and ventricular contractility with little effect on the coronary artery and peripheral vascular vessels in dogs (3, 4). Recently, a telemetry recording system with two channels of pressure monitoring has been developed to simultaneously measure both systemic blood pressure and the left ventricular pressure in conscious animals, which allows evaluation of cardiac as well as hemodynamic actions of various drugs in conscious dogs for hours to days. In the present study, we assessed the cardiovascular action of AH-1058 in conscious dogs using this new method, since such information is still lacking.

All experiments were performed according to Guidelines for Animal Experiments, in the Pharmaceutical Research Laboratories, Ajinomoto Co., Inc. Beagle dogs were kept in individual cages, and a 12-h light (7:00–19:00)–dark (19:00–7:00) cycle was used. The telemetry recording system (Dataquest LabPRO System; Data Sciences International, St. Paul, MN, USA) was used for the evaluation of

cardiovascular drug actions in conscious dogs (5, 6). Signals from the 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.

Seven male beagle dogs 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). The chest was opened by an incision at the 6th intercostal space to expose the heart. A pressure recording 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, a subcutaneous pocket was formed in the left flank, and the unit's tabs were sutured in the underlying tissue. Another pressure recording 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 administration was maintained for

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10 days. Experiments were begun four weeks after surgery. AH-1058 in doses of 0.03, 0.1 and 0.3 mg/kg and its vehicle were intravenously given over an interval of 1 week.

The following drugs were used: AH-1058 (Ajinomoto, Tokyo), thiopental sodium (Tanabe Seiyaku, Osaka) and halothane (Takeda Chemical, Osaka). AH-1058 was dissolved in polyethylene glycol 400 / saline (70:30, vol/vol). AH-1058 was intravenously administered in a volume of 0.1 ml/kg.

All values are expressed as the mean \pm S.E.M. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and maximal upstroke velocity of the left ventricular pressure (LVdP/dt_{max}) 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 for repeated measures was employed for statistical analysis by using SuperANOVA (Abacus Concepts Inc., Berkeley, CA, USA), followed by Dunnett's test for statistical analysis between the vehicle-treated group and others. Differences with a *P*-value of less than 0.05 were considered to be statistically significant.

Typical tracings of systemic blood pressure, left ventricular pressure and electrocardiogram are depicted in Fig. 1,

whereas effects of AH-1058 on blood pressure, HR and LVdP/dt_{max} are summarized in Fig. 2. Basal values of SBP and DBP were 130 ± 4 and 70 ± 2 mmHg for the vehicle group, 133 ± 5 and 72 ± 2 mmHg for the 0.03 mg/kg-treated group, 131 ± 6 and 70 ± 3 mmHg for the 0.1 mg/kg-treated group, and 130 ± 5 and 71 ± 3 mmHg for the 0.3 mg/kg-treated group, respectively. Basal values of HR were 88 ± 7 beats/min for the vehicle group, 82 ± 6 beats/min for the 0.03 mg/kg-treated group, 85 ± 7 beats/min for the 0.1 mg/kg-treated group and 85 ± 8 beats/min for the 0.3 mg/kg-treated group, while those of LVdP/dt_{max} were 2.95 ± 0.16 mmHg/ms for the vehicle group, 2.80 ± 0.14 mmHg/ms for the 0.03 mg/kg-treated group, 2.76 ± 0.13 mmHg/ms for the 0.1 mg/kg-treated group and 2.59 ± 0.12 mmHg/ms for the 0.3 mg/kg-treated group. In all parameters, there were no significant differences among basal values for each group. Intravenous administration of AH-1058 in a dose of 0.3 mg/kg significantly reduced SBP, while the drug barely affected the DBP. HR was increased by drug administration in a dose-dependent manner, and statistical differences were detected in the 0.1 and 0.3 mg/kg-treated groups. LVdP/dt_{max} was decreased by the drug administration in a dose-dependent manner, and statistical differences were detected in the 0.03, 0.1 and 0.3 mg/kg-treated

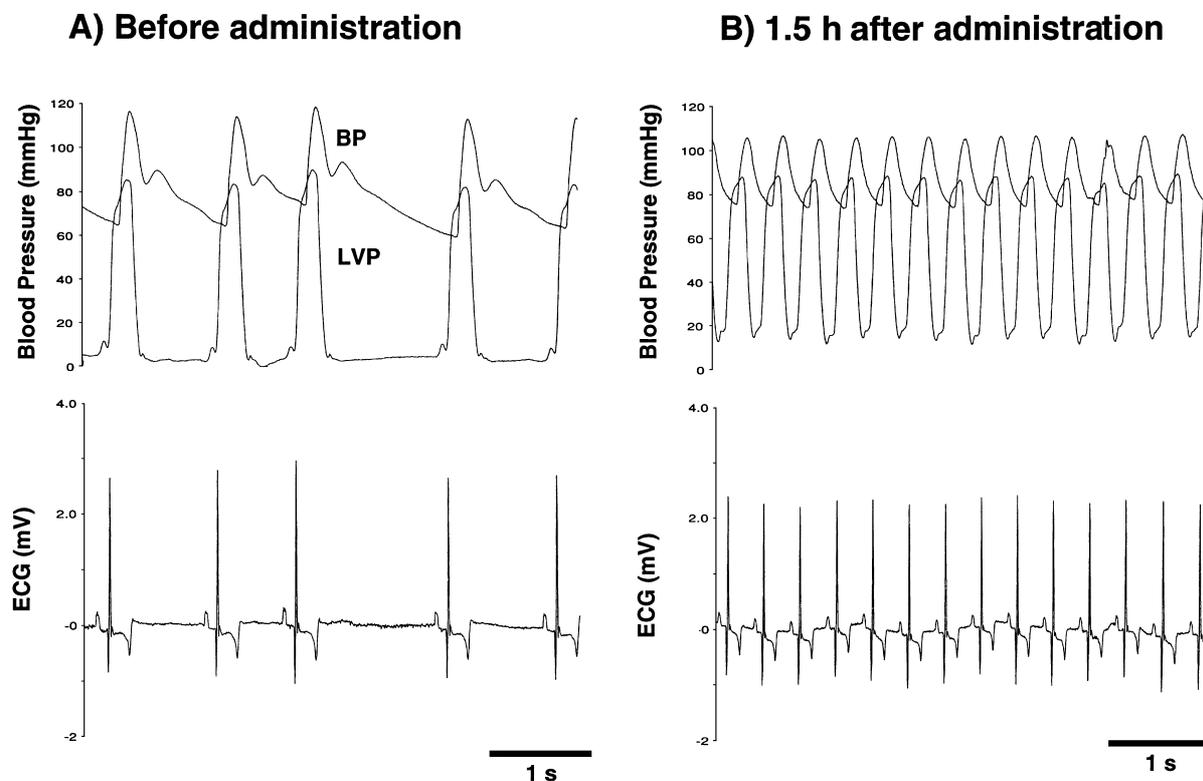


Fig. 1. Typical tracings of systemic blood pressure (BP), left ventricular pressure (LVP) and electrocardiogram (ECG) from a conscious unrestrained beagle dog. A) before administration of AH-1058, B) 1.5 h after administration of AH-1058 in a dose of 0.3 mg/kg (i.v.).

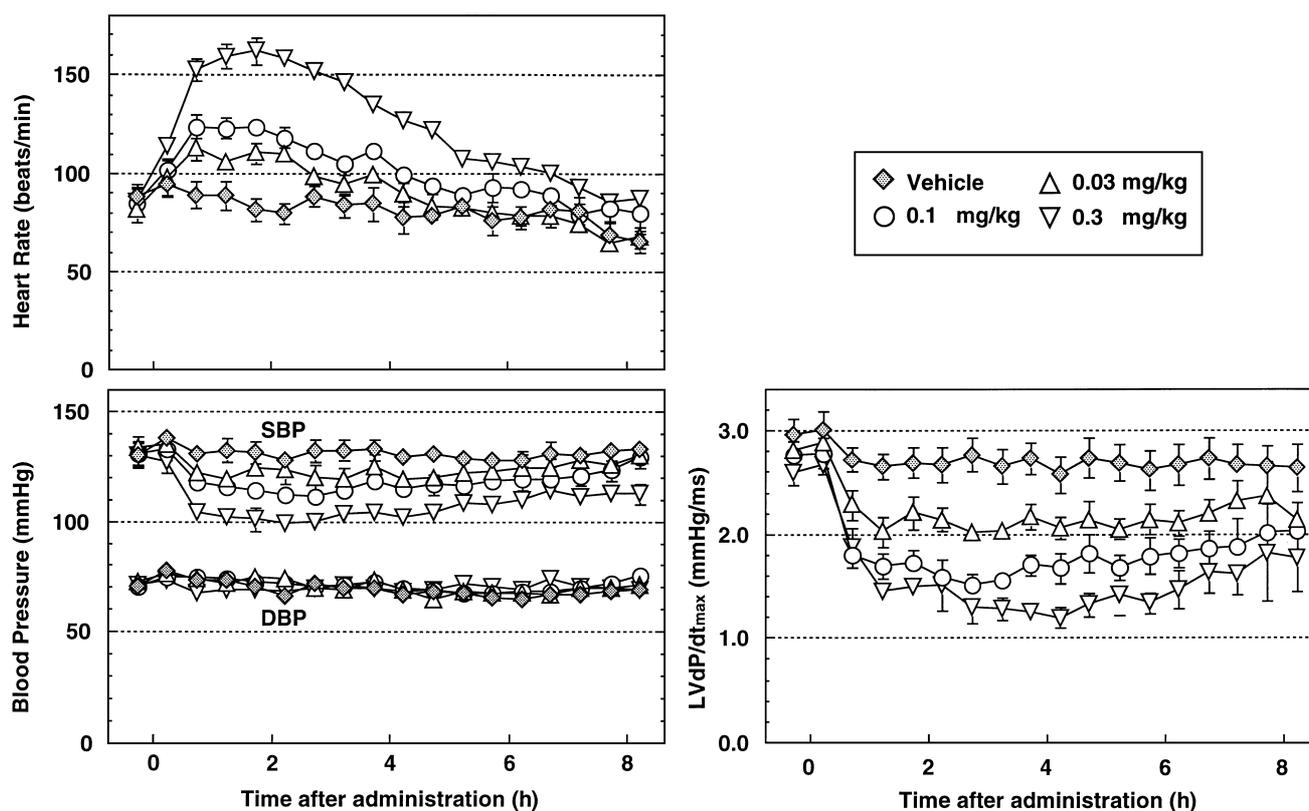


Fig. 2. Effects of AH-1058 (0.03, 0.1 and 0.3 mg/kg) on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and the maximal upstroke velocity of the left ventricular pressure (LVdP/dt_{max}). Data are expressed as the mean \pm S.E.M. (n = 7). Statistically significant differences were detected in the 0.03 mg/kg-treated group (LVdP/dt_{max}), 0.1 mg/kg-treated group (HR and LVdP/dt_{max}) and 0.3 mg/kg-treated group (SBP, HR and LVdP/dt_{max}) compared with the vehicle group.

groups.

As shown in the results, intravenous administration of AH-1058 exerted negative inotropic and SBP reducing action without affecting DBP; each of the maximum actions were detected around 3 h after administration. AH-1058 also increased HR, which was similar in intensity as that induced by other clinically-available Ca²⁺ channel blockers such as amlodipine (7). The tachycardia may be due to a baro-reflex mechanism rather than atropine-like action because we have observed that the drug hardly affects the vagal nerve stimulation-induced bradycardia in a limited number of experiments using anesthetized rats (n = 3).

While the cardiohemodynamic profile of AH-1058 has been previously assessed using isolated or anesthetized canine heart preparations (3, 4), information regarding the time course of the drug action is limited because of the relatively short experimental period that was less than 30 min. Thus, the present study demonstrates that the telemetry system is useful for assessing the time course of the drug action and that the negative inotropic action can be detected in a lower dose than that used in anesthetized dogs (4). The antiarrhythmic action of AH-1058 has been shown to be

long-lasting in the canine coronary ligation-induced arrhythmia model under a conscious state, in which case the antiarrhythmic activity of AH-1058 did not correlate with the plasma drug concentrations (8). Thus, the present cardiovascular action of AH-1058 also may not depend on its plasma concentration although it was not determined in this study. Since no active metabolite modulating Ca²⁺ channels was found by extensive examinations, the current results might be explained by its high lipophilicity allowing it to be readily distributed to the cardiac tissues (1). However, this hypothesis must be further elucidated by measuring the drug concentration in the cardiac tissue.

Another unique observation is that AH-1058 reduced LVdP/dt_{max} at each dose and SBP at the highest dose without affecting DBP unlike verapamil (9, 10), which may be due to its potent and selective negative inotropic action, as previously demonstrated using blood-perfused canine heart preparation (3). However, our previous report using halothane-anesthetized dogs has revealed that AH-1058 decreased mean blood pressure which results from the marked reduction of both SBP and DBP (4), which is in part in contrast with the present result that no change was

detected in DBP. The discrepancy may be associated with the cardiovascular action of anesthetics, because the drugs like halothane and isoflurane modify the cardiovascular action of drugs, especially Ca^{2+} channel blockers, by their non-specific Ca^{2+} channel blocking effects (11). Therefore, the assessment of the cardiovascular drug actions under the conscious state like in the present study may become important to bridge the gap between the clinical effects and the results obtained in anesthetized animals. Further experiments are now going to evaluate the cardiovascular drug's action in both conscious and anesthetized conditions using typical cardiovascular drugs.

In summary, the present results indicate that AH-1058 can decrease the ventricular contraction and SBP without affecting DBP in the conscious state, which may be unique compared with clinically available cardiodepressive drugs such as disopyramide and atenolol that increase peripheral vascular resistance (12, 13). This unique cardiovascular drug profile can be applied for the treatment of certain pathological processes including angina effort, obstructive hypertrophic cardiomyopathy, vasovagal syncope and dissecting aortic aneurysm, in which selective inhibition of the ventricular Ca^{2+} channels would be essential for the drug therapy.

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REFERENCES

- 1 Takahara A, Uneyama H, Sasaki N, Ueda H, Dohmoto H, Shoji M, Hara Y, Nakaya H and Yoshimoto R: Effects of AH-1058, a new antiarrhythmic drug, on experimental arrhythmias and cardiac membrane currents. *J Cardiovasc Pharmacol* **33**, 625 – 632 (1999)
- 2 Tanaka H, Ichikawa T, Matsui S, Okazaki K, Masumiya H, Kawanishi T and Shigenobu K: Calcium channel antagonistic effects of AH-1058, a novel antiarrhythmic drug, on guinea-pig myocardium. *Res Commun Mol Pathol Pharmacol* **104**, 13 – 21 (1999)
- 3 Takahara A, Sugiyama A, Dohmoto H, Yoshimoto R and Hashimoto K: Comparison of cardiovascular effects of a new calcium channel blocker AH-1058 with those of verapamil assessed in blood-perfused canine heart preparations. *J Cardiovasc Pharmacol* **35**, 471 – 478 (2000)
- 4 Takahara A, Sugiyama A, Dohmoto H, Yoshimoto R and Hashimoto K: Electrophysiological and cardiohemodynamic effects of a new type of calcium channel blocker AH-1058 assessed by the canine in vivo model. *Jpn J Pharmacol* **83**, 107 – 112 (2000)
- 5 Truett AA and West DB: Validation of a radiotelemetry system for continuous blood pressure and heart rate monitoring in dogs. *Lab Animal Sci* **45**, 299 – 302 (1995)
- 6 Gelzer ARM and Ball HA: Validation of a telemetry system for measurement of blood pressure, electrocardiogram and locomotor activity in beagle dogs. *Clin Exp Hypertens* **19**, 1135 – 1160 (1997)
- 7 Yamamoto N, Nomura M, Okubo K, Maeda K and Goto T: Pharmacologic characterization of FR172516: a new combined calcium channel-blocking and β -adrenoceptor-blocking agent. *J Cardiovasc Pharmacol* **33**, 587 – 594 (1999)
- 8 Takahara A, Sugiyama A, Dohmoto H, Yoshimoto R and Hashimoto K: Antiarrhythmic and cardiohemodynamic effects of a novel Ca^{2+} channel blocker, AH-1058, assessed in canine arrhythmia models. *Eur J Pharmacol* **398**, 107 – 112 (2000)
- 9 Shiina H, Sugiyama A, Takahara A, Satoh Y and Hashimoto K: Comparison of electropharmacological effects of verapamil and propranolol assessed in the halothane-anesthetized in vivo canine model under the monitoring of monophasic action potential. *Jpn Circ J* **64**, 777 – 782 (2000)
- 10 Taira N: Differences in cardiovascular profile among calcium antagonists. *Am J Cardiol* **59**, 24B – 29B (1987)
- 11 Galleneberg LA, Stowe DF, Kampine JP and Bosnjak ZJ: Effects of nifedipine with isoflurane, halothane, or enflurane on automaticity, conduction, and contractility in isolated guinea pig hearts. *Anesthesiology* **78**, 1112 – 1119 (1993)
- 12 Beltrame J, Aylward PE, McRitchie RJ and Chalmers JP: Comparative haemodynamic effects of lidocaine, mexiletine, and disopyramide. *J Cardiovasc Pharmacol* **6**, 483 – 490 (1984)
- 13 Satoh N, Suzuki J, Bessho H, Kitada Y, Narimatsu A and Tobe A: Effects of betaxolol on cardiohemodynamics and coronary circulation in anesthetized dogs: comparison with atenolol and propranolol. *Jpn J Pharmacol* **54**, 113 – 119 (1990)