J Anesth (1997) 11:136–140

Journal of
Anesthesia

Possible evaluation of hemodynamic effects of the potassium channel opener KRN2391 on induced hypotension in dogs

NORIKO TASHIRO and SHOHEI TAKEDA

Department of Anesthesiology, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba-ku, Yokohama 227, Japan

Abstract: KRN2391 is potassium channel opener with a nitrate moiety which possesses potent vasodilatory action. The hemodynamic profiles of KRN2391-induced hypotension are still not well understood. The aim of this study was to investigate the potential use of KRN2391 for induced hypotension. Eight dogs were anesthetized with 0.87% halothane in oxygen (1 MAC). After the baseline period, mean arterial pressure (MAP) was reduced to 60 mmHg for 60 min by the infusion of KRN2391. MAP was reduced approximately 50% and was associated with a 80% maximum reduction ($P < 0.01$) in systemic vascular resistance but was not accompanied by a significant change in heart rate. Hypotension induced by KRN2391 was associated with a 224% maximum increase ($P < 0.01$) in cardiac index (CI) and a 136% maximum increase ($P < 0.01$) in stroke volume index (SVI) during induced hypotension. Both CI and SVI remained significantly increased after the termination of drug infusion. Left ventricular maximum dP/dt increased significantly during and after induced hypotension. Right atrial and mean pulmonary artery pressures increased significantly, whereas pulmonary capillary wedge pressure remained unchanged. The results of the present study show that KRN2391 is effective in reducing afterload during induced hypotension, and suggest that the hemodynamic profiles of KRN2391-induced hypotension are a hyperdynamic state as expressed by twofold increases in CI concomitant with the increase in right ventricular filling pressures.

Key words: KRN2391 (potassium channel opener), Induced hypotension, Systemic hemodynamics

Introduction

KRN2391 [*N*-cyano-*N'*-(2-nitroxyethyl)-3-pyridinecarboxamidine monomethanesulfonate] is a recently developed agent with antihypertensive and vasodilatory properties. It has been reported to possess both a potassium channel opening action and a nitrate action [1,2].

KRN2391 causes a preferential increase in coronary artery blood flow and a decrease in peripheral vascular resistance. The preference of KRN2391 for the coronary vasculature is greater than that of nicorandil and nifedipine at equipotent hypotensive doses, and the hypotensive action of KRN2391 is approximately 30 times more potent than that of nicorandil [3]. Nicorandil is also reported to show a dual action of the nitrate-potassium channel opener hybrid type [4,5].

We have recently reported that infusion of KRN2391 produces a decrease in mean arterial pressure in a dose-dependent fashion through a significant reduction of systemic vascular resistance in halothane-anesthetized dogs [6]. KRN2391 is reported to produce an increase in oxygen supply to the heart and a decrease in oxygen consumption [7]. These hemodynamic findings suggest that KRN2391 may have therapeutic value in the perioperative period by inducing hypotension and by controlling hypertension when volatile anesthetics are used during surgery.

However, to our knowledge, no studies have been performed on its use to induce hypotension. Therefore, the aim of the present study was to investigate the potential use of KRN2391-induced hypotension in halothane-anesthetized dogs.

Materials and methods

All experimental procedures and the protocols for this study were approved by the Animal Experiment Ethics Committee of Showa University Fujigaoka Hospital. Eight mongrel dogs weighing 11–20 kg (15.5 ± 3.9 kg, mean ± SD) were studied. Anesthesia was induced with sodium pentobarbital (25 mg·kg^{-1}) intravenously. After tracheal intubation, the animals were mechanically ven-

Address correspondence to: S. Takeda
Received for publication on June 24, 1996; accepted on November 25, 1996

tilated with a Harvard respirator to maintain normocapnia. Anesthesia was maintained with 1.0 MAC halothane (0.87%), delivered through an Ohmeda Vaporizer (BOC Health Care, Windlesham, UK) using oxygen as a carrier gas at a flow of 3–5 l·min^{-1} throughout the observation period. End-tidal halothane and CO_2 concentrations were measured continuously by an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

Instrumentation

Cannulae were installed by a cutdown into the left femoral artery for continuous systemic blood pressure (SBP) monitoring and blood sampling, and into the right femoral vein for drug administration; normal saline was infused at a rate of 7 ml·kg^{-1}·h^{-1} together with the infusion of KRN2391. A 7F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter, Baxter Healthcare, Irvine, CA, USA) was advanced into a pulmonary artery via cutdown of the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for the measurements of right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). CO was measured in triplicate by the thermodilution technique; we used a cardiac output computer (MTC6210, Nihon Kohden, Tokyo, Japan) and injected 5 ml of ice-cold, temperature-monitored, normal saline into the right atrium at end-expiration. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated using standard formulae. CI and SVI were calculated as cardiac output and stroke volume divided by the body surface area (BSA), respectively. The BSA of dog was calculated as 0.112 × body weight$^{2/3}$. SVR was calculated as (MAP − RAP)·CO^{-1} × 80, and PVR as (MPAP − PCWP)·CO^{-1} × 80.

A 7F pigtailed catheter (Schneider, Minneapolis, MN, USA) was passed into the left ventricle via cutdown of the right femoral artery and used for measurement of left intraventricular pressure (LVP). Left ventricular maximum rate of pressure change (LV dP/dt_{max}) was electrically derived from the left ventricular pressure wave signal via an electronic differentiator (EQ601G, Nihon Kohden). Heart rate (HR), calculated from lead II of the electrocardiogram (ECG) using a cardiotachometer (AT601G, Nihon Kohden), was continuously monitored.

Each pressure monitoring catheter was connected to a pressure transducer (Uniflow, Baxter Healthcare). SBP, ECG, LVP, and LV dP/dt_{max} were monitored continuously on a polygraph (RM6200, Nihon Kohden) and recorded with an eight-channel pen recorder (VM-640G, Nihon Kohden). The dogs were fixed supine during the measurements and the zero reference was leveled at the midchest. Both mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were determined electronically. Body temperature, monitored by a thermistor attached to the pulmonary artery catheter, was maintained at 37.0 ± 1.0°C with electric heating pads and lamps.

Experimental protocol

After the completion of surgical preparations, the animals were observed for approximately 60 min to allow hemodynamic variables (SBP, MPAP, and HR) to stabilize. Measurements of baseline values were obtained before the infusion of KRN2391 began. After the baseline measurements had been made, MAP was reduced to 60 mmHg for a 60-min hypotensive period by the infusion of KRN2391. A 0.02% solution of KRN2391 (KRN2391 dissolved in normal saline) was infused into the left femoral vein with an infusion pump (STG-521, Terumo, Tokyo, Japan). Measurements of hemodynamic variables were taken 30 and 60 min after the induction of hypotension, and 10 and 30 min after the termination of KRN2391 infusion, respectively.

Statistical analysis

Values are expressed as mean ± SD. Intragroup differences were analyzed by two-way analysis of variance (ANOVA) from repeated measurements of the same variables followed by Dunnett's test when appropriate. A probability value less than 0.05 was considered statistically significant.

Results

The doses of KRN2391 were increased in a stepwise fashion until the desired MAP was attained. A hypotensive steady state of MAP at 60 mmHg was achieved within 9.0 ± 3.3 min. The mean dose of KRN2391 required to maintain MAP at 60 mmHg for a hypotensive period was 568 ± 275 μg·kg^{-1}, with a range of 340–1200 μg·kg^{-1}.

The baseline values of systemic hemodynamics and the changes in hemodynamic variables during and after hypotension induced by KRN2391 are presented in Table 1. MAP decreased from baseline values of 118 ± 13 mmHg to 60 mmHg ($P < 0.01$) during the hypotensive period. Within 30 min after the termination of KRN2391, MAP was significantly lower than the baseline values. Hypotension induced by KRN2391 was associated with an increase in CI, from baseline values of 2.9 ± 1.0 l·min^{-1}·m^{-2} to a maximum of 6.5 ± 1.9 ($P <$

Table 1. Changes in hemodynamic variables during and after hypotension induced by KRN2391 in halothane-anesthetized dogs ($n = 8$)

	Baseline value	During hypotension		After hypotension	
		30 min	60 min	10 min	30 min
MAP (mmHg)	118 ± 13	60 ± 1**	60 ± 1**	79 ± 7**	104 ± 13**
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 1.0	5.6 ± 2.0**	6.5 ± 1.9**	6.0 ± 1.7**	4.8 ± 1.1**
SVI ($ml \cdot beats^{-1} \cdot m^{-2}$)	19 ± 7	34 ± 8**	38 ± 8**	34 ± 7**	29 ± 5**
RAP (mmHg)	4 ± 1	5 ± 1	6 ± 1*	5 ± 1	5 ± 1
MPAP (mmHg)	16 ± 4	15 ± 5	18 ± 5*	18 ± 6*	18 ± 6*
PCWP (mmHg)	10 ± 4	9 ± 5	9 ± 4	10 ± 5	9 ± 5
HR (bpm)	160 ± 31	162 ± 28	170 ± 28	175 ± 30	165 ± 22
SVR ($dynes \cdot s \cdot cm^{-5}$)	4938 ± 2096	1237 ± 379**	1007 ± 272**	1425 ± 311**	2460 ± 750**
PVR ($dynes \cdot s \cdot cm^{-5}$)	235 ± 70	125 ± 44**	154 ± 35**	153 ± 39**	192 ± 22
LV dP/dt_{max} ($mmHg \cdot s^{-1}$)	3187 ± 693	3700 ± 1126	3925 ± 1025*	3825 ± 1022*	3337 ± 930

MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; RAP, right atrial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; HR, heart rate; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LV dP/dt_{max}, left ventricular maximum dP/dt.
Values are expressed as mean ± SD.
* $P < 0.05$; ** $P < 0.01$ significantly different compared with baseline values.

0.01) $l \cdot min^{-1} \cdot m^{-2}$ at 60 min of the hypotensive period, followed by a significant increase over the baseline values after the termination of infusion. Further, there was a significant increase ($P < 0.01$) in SVI throughout the course of observation. RAP increased significantly at 60 min of the hypotensive period. MPAP increased significantly at 60 min of the hypotensive period and at 10 and 30 min after the termination of induced hypotension. PCWP remained unchanged during and after induced hypotension. HR did not change significantly throughout the course of observation. SVR decreased from baseline values of 4939 ± 2097 $dynes \cdot s \cdot cm^{-5}$ to a nadir of 1007 ± 272 ($P < 0.01$) $dynes \cdot s \cdot cm^{-5}$ at 60 min of the hypotensive period, followed by a decrease below the baseline values after the termination of KRN2391 infusion. PVR decreased significantly during induced hypotension and at 10 min after the termination of induced hypotension. LV dP/dt_{max} increased significantly at 60 min of the hypotensive period and at 10 min after the termination of induced hypotension.

Discussion

The present study demonstrated that the hemodynamic profiles of KRN2391-induced hypotension were a hyperdynamic state which resulted in a 224% maximum increase in CI concomitant with increases in SVI due to afterload reduction and with increases in right ventricular filling pressures, but which was not associated with an increase in HR. MAP was reduced by approximately 50% to 60 mmHg during KRN2391-induced hypotension. The decrease in MAP was mostly due to vasodilatation which produced a 80% maximum reduction in SVR.

The vasodilating effect of KRN2391 has been shown to be due to its potassium channel opening action, because KRN2391 produces an increase in the efflux of ^{86}Rb, which is used as a marker for potassium, in isolated rat aorta [1]. Further, KRN2391-induced relaxation of isolated aorta is partly inhibited by methylene blue and oxyhemoglobin [8], suggesting that KRN2391 may possess in part a nitrate-like vasodilating action in the aorta. Although potassium channel opening is considered to be a major mechanism of the vasodilating effect of KRN2391, the activation of guanylate cyclase due to this agent is mediated in a manner characteristic of nitrovasodilators because of the presence of the nitrate moiety within its structure.

The chemical structure of KRN2391 is very similar to that of nicorandil. In isolated rat aorta constricted by norepinephrine, the vasodilating activity of KRN2391 has been shown to be equal to that of chromakalim [1], while that of nicorandil was about $\frac{1}{20}$–$\frac{1}{40}$ of that of chromakalim in the rat aorta [9] and in the guinea-pig pulmonary artery [10]. Nicorandil is also reported to show the dual mechanisms of a potassium channel opener and nitrate action [4,5]. KRN2391 causes a marked increase in coronary and mesenteric blood flow in comparison with other areas of peripheral blood flow in pentobarbital-anesthetized dogs [11]. In addition, the preference of KRN2391 for the coronary vasculature is greater than that of nicorandil at equipotent hypotensive doses, and KRN2391 dilates the smaller coronary arteries rather than the larger coronary arteries [3].

The hyperdynamic state of the marked increased CI is associated with right ventricular overload due to the increases in RAP and MPAP as observed in the present study. When right ventricular volume increased because of the increases in venous return and in pulmonary pressure, the shared common intraventricular septum would shift into the left ventricular cavity, thus compressing the left ventricle and reducing left ventricular diastolic compliance. However, the increase in left ventricular filling pressure was not elicited by KRN2391 infusion. An interesting observation during KRN2391 infusion was the discrepancy between the increases in RAP and MPAP and the invariance in PCWP. Therefore, KRN2391 may have an unique effect on the pulmonary vasculature. This discrepancy remains to be elucidated and would need further investigation of this unique phenomenon.

The increase in venous return with KRN2391 was consistent with the result of the earlier study which reported that potassium channel openers such as cromakalim and pinacidil produce an increase in venous return [12]. Therefore, it is well recognized that both drugs may be characterized as vasodilators, which preferentially reduce afterload and increase venous return. In contrast, nitroglycerin is known to reduce venous return and consequently cardiac output by increasing venous capacitance [13,14]. It is also reported that the hemodynamic profile of KRN2391 is closer to that of cromakalim than to that of nitroglycerin [15]. On the other hand, Kashiwabara et al. [16] demonstrated that a low dose of KRN2391 selectively dilates veins, while at high doses it loses such selectivity because of its nitrate action and potassium channel opening action, suggesting that the vasodilating properties of KRN2391 at low doses may cause venodilation. However, the results of the present study suggest that KRN2391 may preferentially dilate the arteriolar system more than the venous system during induced hypotension with the doses studied and may behave as an arteriolar vasodilator. Consequently, venodilation due to the nitrate action of KRN2391 may be masked by its potassium channel opening action. The exact mechanisms responsible for the discrepancies in response to preload and afterload of KRN2391-induced hypotension have not been identified. However, a possible explanation for the present findings may be that the different responses of vasodilatory activity related to KRN2391 are caused by the varying sensitivity and density of the potassium channels in the arterial and venous vascular beds, and in the pulmonary vasculature.

When used for induced hypotension, KRN2391 reduced SVR and increased right ventricular filling pressures. The hemodynamic response to KRN2391 is similar to that reported in a previous study in which a strong reduction in afterload as well as increases in RAP, MPAP, and CI were observed during nicardipine-induced hypotension [17]. As the hyperdynamic state exists, a reflex sympathetic activation can oppose the effects of the vasodilating activity of KRN2391 or nicardipine on the venous vascular beds. In contrast to nicardipine- and KRN2391-induced hypotension, hypotension induced by nitroglycerin with both effects on the arterial and venous beds is shown to reduce right and left ventricular filling pressures and to decrease cardiac output, indicating that the decrease in cardiac output results from a reduction in central blood volume due to venous pooling [18].

KRN2391 produces a dose-dependent decrease in arterial blood pressure accompanied by a concomitant increase in HR in pentobarbital-anesthetized dogs [19]. This increase in HR provoked by KRN2391 is inhibited by propranolol [19], indicating that tachycardia is mediated by a reflex sympathetic activation as a consequence of the decreased arterial blood pressure. In contrast to pentobarbital-anesthetized dogs, the tachycardia elicited by KRN2391 was blunted in the presence of 0.87% halothane [6]. In the present study, reflex tachycardia did not occur during KRN2391-induced hypotension in halothane-anesthetized dogs. The differences in our results from those of a previous study [19] may be explained by the different anesthetics used. Seagard et al. [20] have demonstrated that halothane blocks the baroreflex pathways both peripherally and centrally. It is possible that the suppression of the baroreflexes due to halothane on the heart may oppose the tachycardiac effect of KRN2391. The inhibition of reflex tachycardia under our experimental conditions may reflect the beneficial effects of reduced myocardial oxygen demand, or easy induction of hypotension by the infusion of KRN2391.

The index of myocardial contractility used in the present study was LV dP/dt_{max}, which can be altered by a compensating reflex mechanism and affected by various hemodynamic variables such as preload, afterload, and heart rate. The changes in LV dP/dt_{max} may indicate a net change in myocardial performance. We suggest that the increase in LV dP/dt_{max} might result from the increase in right ventricular filling pressure due to increased venous return and the reduction in afterload due to dilatation of the resistance vessels. An additional factor that cannot be excluded may be the reflex-enhanced contractility mediated through catecholamines release. Therefore, the inotropic effect of KRN2391 cannot be adequately evaluated.

In conclusion, KRN2391 at appropriate infusion rates is effective in decreasing afterload and achieving induced hypotension. Our results suggest that the hemodynamic profiles of KRN2391-induced hypotension are a hyperdynamic state because of the marked increase in CI concomitant with the increase in right

ventricular filling pressures. Further studies are needed to determine whether KRN2391 can be used in clinical medicine.

Acknowledgments. The authors gratefully acknowledge Professor Teruaki Tomaru, Department of Anesthesiology, Showa University Fujigaoka Hospital for his helpful comments and Mrs. Yoshie Hirakawa for her excellent secretarial assistance. The KRN2391 was provided by Kirin Brewery, Tokyo, Japan. This research was supported in part by a grant for cooperative research from Showa University.

References

1. Kashiwabara T, Nakajima S, Izawa T, Fukushima H, Nishikori K (1991) Characteristics of KRN2391, a novel vasodilator, compared with those of cromakalim, pinacidil and nifedipine in rat aorta. Eur J Pharmacol 196:1–7
2. Ishibashi T, Hamaguchi M, Imai S (1992) Vasodilating properties of KRN2391: structural basis of a new pyridine-type potassium channel opener with a nitrate moiety. Naunyn-Schmiedeberg's Arch Pharmacol 346:94–101
3. Ogawa N, Fukata Y, Kaneta S, Jinno Y, Fukushima H, Nishikori K (1992) Comparison of KRN2391 with nicorandil and nifedipine on canine coronary blood flow: antagonism by glibenclamide. J Cardiovasc Pharmacol 20:11–17
4. Taira N (1987) Similarity and dissimilarity in the mode and mechanism of action between nicorandil and classical nitrates: an overview. J Cardiovasc Pharmacol 10[Suppl VIII]: S1–S9
5. Taira N (1989) Nicorandil as a hybrid between nitrates and potassium channel activators. Am J Cardiol 63:18J–24J
6. Takeda S, Inada Y, Ozawa Y, Nakamizo N, Tomaru T (1995) Hemodynamic effects of KRN2391 (potassium channel opener) in halothane-anesthetized dogs. J Anesth 9:176–181
7. Ogawa N, Kaneta S, Jinno Y, Kasai H, Nishikori K, Fukushima H (1992) Comparative cardiovascular effects of KRN2391 and other coronary vasodilators in anesthetized open-chest dogs. Arch Int Pharmacodyn 318:36–46
8. Jinno Y, Kasai H, Ohta H, Nishikori K, Fukushima H, Ogawa N (1992) Contribution of cyclic GMP formation to KRN2391-induced relaxation in coronary artery of the pig. Br J Pharmacol 106:906–909
9. Weir SW, Weston AH (1986) The effets of BRL34915 and nicorandil on electrical and mechanical activity and on ^{86}Rb efflux in rat blood vessels. Br J Pharmacol 88:121–128
10. Eltze M (1989) Glibenclamide is a competitive antagonist of cromakalim, pinacidil and RP49356 in guinea-pig pulmonary artery. Eur J Pharmacol 165:231–239
11. Ogawa N, Jinno Y, Kaneta S, Harada K, Fukata Y, Fukushima H (1993) Hemodynamic profile of KRN2391, a novel vasodilator, in anesthetized dogs. J Cardiovasc Pharmacol 21:874–882
12. Gotanda K, Yokoyama H, Satoh K, Taira N (1989) Cardiohemodynamic effects of cromakalim and pinacidil, potassium-channel opener, in the dogs, special reference to venous return. Cardiovasc Drugs Ther 3:507–515
13. Kaneta S, Jinno Y, Miwa A, Fukushima H, Ogawa N (1993) Effect of KRN2391 on venous return: comparison with other vasodilators. J Cardiovasc Pharmacol 22:82–88
14. Ogilvie RI (1978) Effect of nitroglycerin on peripheral blood flow distribution and venous return. J Pharmacol Exp Ther 207:372–380
15. Kaneta S, Yokoyama T, Izumi H, Izawa T, Ogawa N (1994) Cardiovascular effects of KRN2391 in anesthetized dogs: a comparison with cromakalim and nitroglycerin. Arch Int Pharmacodyn 327:184–193
16. Kashiwabara T, Ogawa N, Izawa T, Fukushima H (1994) Differential vasodilator properties of KRN2391, cromakalim, nitroglycerin and nifedipine in rabbit isolated femoral artery and vein. Br J Pharmacol 111:278–282
17. Takeda S, Inada Y, Tashiro N, Matsui K, Tomaru T, Negishi H, Hosoyamada A (1990) Hemodynamic features of hypotension induced by nicardipine in dogs (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 39:1586–1596
18. Lagerkranser M (1982) Cardiovascular effects of nitroglycerin as a hypotensive agent in cerebral aneurysm surgery. Acta Anaesthesiol Scand 26:453–457
19. Takeuchi A, Harada K, Miwa A, Jinno Y, Kaneta S, Yokoyama T, Ogawa N (1994) Effect of KRN2391 on canine ventricular arrhythmia models. Gen Pharmacol 25:53–60
20. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP (1982) Halothane and the carotid sinus reflex: evidence for multiple sites of action. Anesthesiology 57:191–202