Haemodynamic effects of hypotension induced by KRN2391 and nicardipine in isoflurane anaesthetized dogs

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Purpose: The investigational agent, KRN2391, is a potassium channel opener with a nitrate moiety which possesses potent vasodilatory action. We compared the haemodynamic effects of KRN2391-induced hypotension with those of nicardipine.

Methods: Sixteen dogs were anaesthetized with isoflurane 1.3% in oxygen (1 MAC). After the baseline period, mean arterial pressure (MAP) was decreased to 60 mmHg for 60 min with an infusion of either KRN2391 (n=8) or nicardipine (n=8).

Results: The KRN2391- and nicardipine-induced hypotension resulted in maximal decreased systemic vascular resistance of 35% and 25%, increases in cardiac index of 145% and 197%, and stroke volume index of 150% and 212%, respectively, ($P < 0.01$). There was no change in heart rate. Nicardipine was associated with increases ($P < 0.01$) in both right atrial and mean pulmonary artery pressures, whereas these variables remained unchanged with KRN2391. Pulmonary capillary wedge pressure decreased with KRN2391 ($P < 0.01$), but not with nicardipine.

Conclusion: While both drugs were equally able of inducing hypotension, our results show that the haemodynamic profile of KRN2391- and nicardipine-induced hypotension was a hyperdynamic state expressed by the marked increase in cardiac index with varying changes in right and left ventricular filling pressures, and suggest that KRN2391 may be a useful vasodilator for induced hypotension.

Objectif : Le KRN2391, un composé présentement à l'étude porteur d'une fraction moléculaire nitrate, exerce une activité vasodilatatrice puissante par ouverture des canaux potassiques. Nous avons comparé les effets hémodynamiques de l'hypotension induite par le KRN2391 avec ceux de la nicardipine.

Méthodes : Seize chiens ont été anesthésiés à l'isoflurane 1,3% (1 MAC). Après la période d'équilibration, la pression artérielle moyenne (PAM) a été réduite à 60 mmHg avec une perfusion de KRN2391 (n=8) ou de nicardipine (n=8).

Résultats : L'hypotension induite par le KRN2391 et la nicardipine a fait baisser la résistance vasculaire systémique respectivement de 35% et 25%, augmenter l'index cardiaque de 145% et 197% et la fraction d'éjection indexée de 150% et 212% ($P < 0,01$). Par contre, la fréquence cardiaque n'a pas changé. La nicardipine était associée à des augmentations ($P < 0,01$) des pressions auriculaires droites et artérielles pulmonaires moyennes, alors que ces variables ne changeaient pas avec le KRN2391. La pression capillaire bloquée diminuait avec le KRN2391 ($P < 0,01$) mais pas avec la nicardipine.

Conclusion : Alors que les deux médicaments ont la même capacité d'induction hypotensive, nos résultats montrent que le profil hémodynamique de l'hypotension produite par le KRN2391 et la nicardipine indique un état hyperdynamique qui se manifeste par une augmentation importante de l'index cardiaque et des changements variables des pressions de remplissage des ventricules droit et gauche. Ces résultats suggèrent aussi que le KRN2391 pourrait être utilisé pour induire l'hypotension délibérée.

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This research presented in part at the 11th World Congress of Anaesthesiologists, Sydney, Australia, April 14-20, 1996 and was supported by a Grant from Showa University.

Accepted for publication June 15, 1997.

THE recently synthesized investigational hypotensive agent, KRN2391 [N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboxamide mono methanesulfonate], has antihypertensive and vasodilatory properties. The vasodilating mechanism of KRN2391 is thought to be based on its dual effects as a nitrate and a potassium channel opener.^{1,2} Further, it has been shown that KRN2391 possesses different vasorelaxant properties from those of cromakalim, nitroglycerin, and nifedipine.³

Intravenous administration of KRN2391 produced an increase in coronary blood flow and a decrease in mean arterial pressure in pentobarbital anaesthetized dogs⁴ and it is reported to produce an increase in oxygen supply to the heart and a decrease in oxygen consumption.⁵ We reported that KRN2391 decreases mean arterial pressure in a dose-dependent fashion by a reduction of systemic vascular resistance, and that KRN2391-induced reflex tachycardia may be suppressed by halothane anaesthesia in dogs.⁶ From these observations, the haemodynamic profile of KRN2391 may make it acceptable for induced hypotension during surgery with volatile anaesthetic agents.

Nicardipine is a calcium channel blocker that possesses potent systemic and coronary vasodilating activities. Its use is mainly for perioperative haemodynamic control such as systemic hypertension, vasospastic conditions, and myocardial protection.⁷ Recently, it has been reported that nicardipine-induced hypotension has been used in orthopaedic surgery using fentanyl⁸ and isoflurane anaesthesia.⁹

It is possible that different mechanisms of vasodilating activity are induced by KRN2391 and nicardipine, resulting in different systemic haemodynamic changes. The objectives of this study were to compare the haemodynamic effects of KRN2391 and nicardipine-induced hypotension.

Methods

All experimental procedures and the protocols for this study were approved by the Animal Experimental Ethics Committee of Showa University Fujigaoka Hospital. Sixteen healthy adult mongrel dogs of both sexes weighing between 12 and 18 kg (14.6 ± 1.8 kg, means $\pm$ SD) were fasted overnight and anaesthetized with sodium pentobarbital ($25 \text{ mg}\cdot\text{kg}^{-1}$) *iv*. After tracheal intubation, the lungs were mechanically ventilated with a Harvard respirator to maintain normocapnia. Anaesthesia was maintained with 1.0 MAC isoflurane (1.3%) via an Ohmeda Vaporizer (BOC Health Care, Windlesham, U.K.) using oxygen as a carrier gas at a flow rate of 3–5 $\text{l}\cdot\text{min}^{-1}$ throughout the experimental period. End-tidal isoflurane and CO_2 concentrations were measured con-

tinuously by an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

Instrumentation

Cannulae were placed 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 $7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ together with the infusion of the hypotensive drugs. A 7-F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter, Baxter Health Care, Irvine, U.S.A.) 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 measurement of right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). The CO was measured in triplicate, by the thermodilution technique; we used a cardiac output computer (MTC6210, Nihon Kohden, Tokyo, Japan) and injected 5 ml ice cold, temperature monitored, normal saline into the right atrium at end-expiration.

Heart rate (HR), was calculated from lead II of the ECG using a cardi tachometer (AT601G, Nihon Kohden), which was continuously monitored.

Each pressure monitoring catheter was connected to a pressure transducer (Uniflow, Baxter Health Care). Blood pressure and ECG were monitored continuously on a polygraph (RM6200, Nihon Kohden) and recorded with an eight-channel pen recorder (VM-640G, Nihon Kohden). The animals were fixed in the supine position during the measurements, and the zero reference was leveled at the midchest. 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 $37.0 \pm 1.0^\circ\text{C}$ with electric heating pads and lamps. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulae.

Experimental protocol

The 16 dogs were divided randomly into two groups: The KRN2391 group ($n=8$) received KRN2391, 0.02%, and the nicardipine group ($n=8$) nicardipine, 0.2%, dissolved in normal saline.

After completion of surgical preparations, the animals were observed for approximately 60 min to allow haemodynamic variables (SBP, MPAP, and HR) to stabilize. Measurements of baseline values were obtained before infusion of the hypotensive drugs. After base-

line measurements had been made, MAP was reduced to 60 mmHg for 60 min by infusion of KRN2391 or nicardipine. The solutions were infused into the left femoral vein with an infusion pump (Model STG-521, Terumo, Tokyo, Japan). Measurements of haemodynamic variables were taken 30 and 60 min after induction of hypotension, and 10 and 30 min after termination of drug infusion.

Statistical analysis

Values are expressed as means $\pm$ SD. Intragroup differences were analyzed by a two-way analysis of variance from repeated measurements of the same variables followed by Dunnett's test when appropriate. Intergroup differences of values in each of the phases (baseline, during and after induced hypotension) between the KRN2391 and nicardipine groups were analyzed by Student's unpaired *t* test if the *F* test was significant. A *P* < 0.05 was considered statistically significant.

Results

There were no differences in baseline systemic haemodynamic values between the KRN2391 and nicardipine groups (Table I). The mean doses of KRN2391 and nicardipine required to maintain MAP at 60 mmHg for 60 min were $5.5 \pm 4.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $18.3 \pm 10.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively.

Mean arterial pressure decreased from baseline values of 109 ± 13 mmHg and 106 ± 10 mmHg in the KRN2391- and nicardipine groups to 60 mmHg (*P* < 0.01) at 60 min of the hypotensive period, respectively. Within 30 min after termination of drug infusion, MAP gradually returned towards the base-

line values but the values at 30 min were lower than baseline values in both groups (Figure 1, top). Cardiac index in the nicardipine group increased from baseline values of $2.7 \pm 0.6 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ to a maximum of 5.2 ± 0.9 (*P* < 0.01) $\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ at 60 min of the hypotensive period and plateaued at approximately 192% of baseline values for up to 30 min after termination of infusion. Cardiac index in the KRN2391 group increased from baseline values of $2.9 \pm 0.5 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ to a maximum of 4.2 ± 0.9 (*P* < 0.01) $\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ at 60 min of the hypotensive period and then gradually recovered to near baseline values by 30 min after termination of infusion (Figure 1, middle). The changes in SVI were similar to the changes in CI during and after induced hypotension in both groups, respectively. Systemic vascular resistance in the KRN2391 group declined from baseline values of $4158 \pm 901 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ to a nadir of 1448 ± 378 (*P* < 0.01) $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ at 60 min followed by a reduction (*P* < 0.01) below the baseline values after termination of infusion. Systemic vascular resistance declined from baseline values of $4700 \pm 1051 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ to a nadir of 1253 ± 313 (*P* < 0.01) $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ at 60 min followed by a reduction (*P* < 0.01) below the baseline values after termination of infusion in the nicardipine group. Systemic vascular resistance was lower (*P* < 0.01) in the nicardipine group than in the KRN2391 group 30 min after induced hypotension was terminated (Figure 1, bottom). Pulmonary vascular resistance and HR did not change significantly throughout the course of observation in both groups, respectively. Right atrial pressure in the KRN2391 group remained unchanged throughout the course of observation. Right atrial pressure in the nicardipine group increased (*P* < 0.01) at 60 min followed by an increase (*P* < 0.01) after induced hypotension (Figure 2, top). The changes in MPAP were similar to the changes in patterns of RAP during and after induced hypotension in both groups, respectively (Figure 2, middle). Pulmonary capillary wedge pressure in the KRN2391 group decreased (*P* < 0.01) during the hypotensive period followed by a decrease 10 min after termination of infusion. In contrast, PCWP in the nicardipine group did not change during and after induced hypotension. Pulmonary capillary wedge pressure was lower (*P* < 0.05) in the KRN2391 group than in the nicardipine group at 60 min (Figure 2, bottom).

TABLE I Baseline values of MAP, CI, SVI, HR, SVR, PVR, RAP, MPAP, and PCWP in the KRN2391 and nicardipine groups

	KRN2391 (n=8)	Nicardipine (n=8)
MAP (mmHg)	109 ± 13	106 ± 10
CI ($\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$)	2.9 ± 0.5	2.7 ± 0.6
SVI ($\text{ml}\cdot\text{beats}^{-1}\cdot\text{m}^{-2}$)	16 ± 4	17 ± 5
HR (bpm)	147 ± 12	149 ± 9
SVR ($\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$)	4158 ± 901	4700 ± 1051
PVR ($\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$)	271 ± 44	346 ± 123
RAP (mmHg)	4 ± 1	3 ± 1
MPAP (mmHg)	16 ± 3	17 ± 4
PCWP (mmHg)	8 ± 1	9 ± 4

Values are means $\pm$ SD

MAP = mean arterial pressure; CI = cardiac index; SVI = stroke volume index; HR = heart rate; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; RAP = right atrial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure

Discussion

The results of the present study demonstrated that the haemodynamic profiles of KRN2391- and nicardipine-induced hypotension produced a hyperdynamic state

FIGURE 1 Effect of KRN2391 (n=8, solid circles) and nicardipine (n=8, open circles)-induced hypotension on mean arterial pressure (top), cardiac index (middle), and systemic vascular resistance (bottom) in isoflurane anaesthetized dogs.

* $P < 0.05$, ** $P < 0.01$ vs baseline

† $P < 0.01$ different from KRN2391 and nicardipine (These values were compared at predetermined identical times)
Values are means $\pm$ SD

FIGURE 2 Effect of KRN2391 (n=8, solid circles) and nicardipine (n=8, open circles)-induced hypotension on right atrial pressure (top), mean pulmonary artery pressure (middle), and pulmonary capillary wedge pressure (bottom) in isoflurane anaesthetized dogs.

* $P < 0.05$, ** $P < 0.01$ vs baseline

† $P < 0.05$ different from KRN2391 and nicardipine (These values were compared at predetermined identical times)
Values are means $\pm$ SD

expressed by an increase in CI with varying change in right and left ventricular filling pressures.

Calcium channel blockers produce vasodilatory effects by blocking voltage-dependent transmembrane Ca^{2+} entry. The mechanism of potassium channel openers was thought to be similar to that of calcium channel blockers, because potassium channel openers hyperpolarize cell membranes and decrease Ca^{2+} influx through inhibition of the voltage-dependent Ca^{2+} channel.¹⁰ However, KRN2391 has dual vasodilating mechanisms due to both nitrate and potassium channel opening actions.^{1,2} Although potassium channel opening is considered to be the major mechanism of the vasodilating effect of KRN2391, activation of guanylate cyclase by KRN2391 is mediated in a manner characteristic of nitrovasodilators because of the presence of the nitrate moiety within its structure.¹

The hypotension associated with both KRN2391 and nicardipine was demonstrated to be profound vasodilation of the resistance vessels. However, neither drug dilated the capacitance vessels, because right ventricular filling pressures remained unchanged during KRN2391 infusion, while nicardipine increased these variables. The lack of venodilatation may have contributed to the increase in venous return. Concomitant with the lack of venodilatation, the reduction in afterload was responsible for the increase in CI in the present study. The marked increase in CI during KRN2391- or nicardipine-induced hypotension was in contrast to the haemodynamic profile of hypotension induced by sodium nitroprusside¹¹ or nitroglycerin,¹² which act on both the resistance and capacitance vessels, resulting in reduction of preload and afterload and a decrease in CI. Further, the increases in the right ventricular filling pressures with nicardipine were accompanied by an increase in left ventricular filling pressure. Right and left ventricular filling pressures did not increase during KRN2391 administration. Our results suggest that the difference of left ventricular filling pressure between KRN2391 and nicardipine may be due to the different responses related to KRN2391 and nicardipine caused by the varying sensitivity and density of the potassium channels or calcium channels in the pulmonary vasculature. In addition, the pulmonary vasculature dilatation may be due to the nitrate action caused by KRN2391. These differences between KRN2391 and nicardipine in their effects on capacitance vessels and pulmonary vasculature should be considered when these drugs are used clinically. Both KRN2391 and nicardipine may be beneficial in maintaining venous return and cardiac output, and can be used safely in patients with hypovolemia. In contrast, nicardipine should not be used in the presence of congestive heart failure and pulmonary hypertension

because of the lack of venodilation or the overload of pulmonary vasculature. As a hyperdynamic state exists, reflex sympathetic activation may be elicited, leading to release of catecholamines. It has been reported that the hormonal effects of nicardipine-induced hypotension were provoked by the activation of the sympathetic nervous system.^{8,13,14} Another explanation for the present findings may be that the reflex sympathetic activation can oppose the effects of the vasodilating activity of KRN2391 or nicardipine on the venous vascular beds.

Hypotension induced by either KRN2391 or nicardipine was not associated with changes in HR. It has been demonstrated that nicardipine caused an increase in HR in alert humans which was mediated by a reflex sympathetic stimulation as a consequence of the decreased arterial blood pressure.^{15,16} Moreover, Bernard *et al.*⁸ reported that reflex tachycardia occurred in patients anaesthetized with fentanyl during nicardipine-induced hypotension. Similar to nicardipine, it has been reported that administration of KRN2391 ($3\text{--}30\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) produced a dose-dependent decrease in blood pressure associated with an increase in HR in pentobarbital anaesthetized dogs. This increase in HR elicited by KRN2391 is inhibited by the β -adrenergic blocker (propranolol),¹⁷ suggesting that the tachycardia was mediated by a reflex sympathetic activation. In contrast, the tachycardiac properties of either KRN2391 or nicardipine were blunted in the presence of isoflurane even though MAP decreased. It has been reported that reflex tachycardia did not occur during nicardipine-induced hypotension in halothane anaesthetized dogs¹⁸ or in patients anaesthetized with isoflurane.⁹ These differing results may have been due to the choice of anaesthesia. Seagard *et al.*^{19,20} demonstrated that halothane and isoflurane block the baroreflex pathways, centrally and peripherally. Therefore, it is possible that the suppression of the baroreflexes due to the volatile anaesthetics on the heart could counteract the tachycardiac properties of KRN2391 and nicardipine. In addition, Hysing *et al.*²¹ reported that the interactions between nicardipine and isoflurane are mainly the result of the isoflurane-induced inhibition of reflex tachycardia elicited by nicardipine.

There were haemodynamic differences of SVR between KRN2391 and nicardipine after drug discontinuation. We observed prolonged hypotension after the nicardipine-induced hypotension which is in agreement with the findings of Bernard *et al.*^{8,9} and Takeda *et al.*¹⁸ who reported prolonged hypotension after the infusion of nicardipine had been terminated. Our results demonstrated that nicardipine resulted in less evanescent effect than KRN2391, and suggested that KRN2391 may be more useful than nicardipine in clinical use.

In conclusion, our results showed that the haemodynamic profile of KRN2391- and nicardipine-induced hypotension produced a hyperdynamic state expressed by an increase in CI with varying change in right and left ventricular filling pressures, and it is suggested that KRN2391 may be a useful vasodilator for induced hypotension because of prompt recovery from hypotension.

Acknowledgment

The authors gratefully thank Yoshie Hirakawa for her excellent secretarial assistance. KRN2391 provided by the Kirin Brewery Co., Ltd. (Tokyo, Japan) was used for this study.

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