J Anesth (1998) 12:69–75

Journal of
Anesthesia

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Effects of KRN2391-induced hypotension on the endocrine system and carbohydrate metabolism in halothane-anesthetized dogs

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Abstract

Purpose. The hemodynamic profiles of KRN2391-induced hypotension have been reported to be a hyperdynamic state. However, the endocrine effects of KRN2391-induced hypotension remain to be elucidated. We investigated the endocrine and metabolic effects of KRN2391-induced hypotension on the plasma concentrations of catecholamines, aldosterone, cortisol, glucose, and lactic acid and on plasma renin activity.

Methods. Eight dogs were anesthetized with 0.87% halothane in oxygen. After a baseline period, mean arterial pressure (MAP) was lowered to 60 mmHg for 60 min by the infusion of KRN2391.

Results. KRN2391-induced hypotension resulted in a 50% decrease ($P < 0.01$) in MAP due to a 80% reduction ($P < 0.01$) in systemic vascular resistance associated with a 224% increase ($P < 0.01$) in cardiac index. Plasma norepinephrine concentrations increased ($P < 0.01$) after 60 min of hypotension. Plasma epinephrine concentrations and plasma renin activity both increased ($P < 0.05$) during the hypotensive period. Plasma aldosterone concentrations remained unchanged during the hypotensive period, but then increased ($P < 0.05$) after termination of KRN2391. Plasma cortisol concentrations remained unchanged throughout the observation period. Plasma glucose concentrations increased ($P < 0.01$) during the hypotensive period. Plasma lactic acid concentrations increased ($P < 0.01$) throughout the observation period.

Conclusion. KRN2391-induced hypotension activates the sympathetic nervous system and consequently may modulate the renin-angiotensin-aldosterone axis and carbohydrate metabolism.

Key words: KRN2391 (potassium channel opener), Induced hypotension, Catecholamines, Renin-angiotensin-aldosterone axis, Carbohydrate metabolism

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Received for publication on August 11, 1997; accepted on January 29, 1998

Introduction

KRN2391 [*N*-cyano-*N'*-(2-nitroxyethyl)-3-pyridinecarboximidamide 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 [3]. KRN2391 also produces an increase in the oxygen supply to the heart and a decrease in oxygen consumption [4]. These hemodynamic findings suggest that KRN2391 may have therapeutic value in treating ischemic heart disease by controlling hypertension.

KRN2391 produces a dose-dependent decrease in arterial blood pressure accompanied by a concomitant increase in heart rate in pentobarbital-anesthetized dogs [5]. The increase in heart rate provoked by KRN2391 is inhibited by propranolol [5], indicating that tachycardia is mediated by a reflex sympathetic activation as a consequence of the decreased arterial blood pressure. On the other hand, it has been reported that KRN2391 produces a decrease in mean arterial pressure in a dose-dependent fashion through a significant reduction in systemic vascular resistance that is not associated with reflex tachycardia in halothane-anesthetized dogs [6]. These results suggest that the changes in heart rate induced by KRN2391 may be partly due to suppression of the arterial baroreflexes caused by anesthetics.

More recently, we have reported that the hemodynamic profiles of KRN2391-induced hypotension are a hyperdynamic state expressed by a marked increase in cardiac index concomitant with right ventricular filling pressures [7]. A hyperdynamic hemodynamic state is induced by the excessive release of plasma catechola-

mines that results from reflex sympathetic activation due to hypotension caused by various vasodilators. The activation of the sympathetic nervous system is of considerable importance in the regulation of the endocrine system and carbohydrate metabolism, which may modulate systemic hemodynamics.

However, no studies have been performed on the endocrine and metabolic effects of KRN2391-induced hypotension. Therefore, the current study was undertaken to investigate the effects of KRN2391-induced hypotension on the endocrine system and carbohydrate metabolism.

Materials and methods

All experimental procedures and the protocols for this study were approved by the Animal Experimental Ethics Committee of Showa University Fujigaoka Hospital. Eight mongrel dogs weighing 11–20 kg (15.5 ± 1.2 kg, means ± SEM) were fasted overnight and anesthetized with sodium pentobarbital (25 mg·kg^{-1}) given intravenously. After tracheal intubation, the dogs were mechanically ventilated with a Harvard respirator to maintain normocapnia. Anesthesia was maintained with 1.0 minimum alveolar concentrations (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 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 ml·kg^{-1}·h^{-1} together with KRN2391. Arterial blood samples were drawn anaerobically from the femoral cannula. Arterial blood gas was analyzed for pHa, $PaCO_2$, PaO_2, and base excess by a blood gas analyzer (Radiometer ABL 505, Copenhagen, Denmark). A 7F flow-directed pulmonary catheter (Swan-Ganz thermodilution catheter, Baxter Healthcare, Irvine, CA, USA) was advanced into the 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). CO was measured in triplicate by the thermodilution technique; we used a cardiac output computer (MTC6210, Nihon Kohden, Tokyo, Japan) and injected 5 ml cold, temperature-monitored, normal saline into the right atrium at the end of expiration. Heart rate (HR) was calculated from lead II of the electrocardiogram (ECG) using a cardiotachometer (AT601G, Nihon Kohden), which was continuously monitored.

Each pressure-monitoring catheter was connected to a pressure transducer (Uniflow, Baxter Healthcare). SBP and ECG 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 in a supine pasition during the measurements and the zero reference was leveled at the midchest. Mean arterial pressure (MAP) was 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. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated using standard formulas. CI was calculated as CO divided by body surface area (BSA). BSA was calculated as $0.112 \times \text{body weight}^{2/3}$. SVR was calculated as $(MAP\text{-}RAP) \cdot CO^{-1} \times 80$.

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. 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, endocrine, and metabolic variables were taken 30 and 60 min after the induction of hypotension, and 30 min after the termination of KRN2391 infusion, respectively. When arterial blood was drawn, twice the volume of collected blood was replaced by a bolus injection of a hydroxyethyl starch solution into the femoral vein. Blood samples were kept in ice water until centrifugation.

Plasma catecholamine assays

The arterial blood samples were transferred to an ice-chilled centrifuge tube containing 10 mg of sodium ethylenediamine tetraacetic acid (EDTA-2Na). After the blood had been mixed by gentle inversion, the plasma for the catecholamine assays was separated from the blood cells by centrifugation (4000 *g*) at 4°C for 10 min and stored at −80°C until assayed.

Free catecholamines were measured by fully automated high-performance liquid chromatography using a diphenylethylenediamine condensation method (HLC-725 Catecholamine Analyzer, Tosoh, Tokyo, Japan). A 600-μl aliquot of plasma was mixed with 300 μl of a 6% perchloric acid solution by a vortex mixer for deproteination. After 200 μl of 1.5 mol·l^{-1} sodium acetate had been added, the mixture was stirred and centrifuged (14000 *g*) at 4°C for 20 min. The clear supernatant was placed in the autosampler of a high-performance liquid chromatography analyzer. Specifically, the sample was instilled into to a precolumn (TSK precolumn (CA1, 7.5 × 75 mm) with the preparation eluent A (sodium perchlorate, sodium citrate, and sodium azide) using a microprocessor-controlled column-switching device. The eluate was instilled into another precolumn (TSK precolumn CA2, 4 × 60 mm) equilibrated with preparation eluent B (acetonitrile and sodium citrate). Absorbed catecholamine was eluted with analytical eluent C (ethanol and ammonium nitrate) and instilled into an analytical column (TSK gel, catecholpak 6 × 150 mm). The separated catecholamines were subjected to a reaction coil (90°C) with fluorogenic reagent D (diphenylethylenediamine in 50% ethanol solution) as well as reagent E (ethanol, potassium hexacyanoferrate, boric acid, and ascorbic acid), and the catecholamines were converted to diphenylethylenediamine derivatives. The fluorescence intensity of the eluate from the reaction unit was measured in a detector at 470 nm wavelength with an excitation wavelength at 355 nm. The detection limit of both norepinephrine and epinephrine was 5 pg·ml^{-1}. The intraassay coefficients of variation (CV) for measurements of norepinephrine and epinephrine were 0.69%–2.43% and 0.85%–2.73%, respectively. The interassay CV values for measurements of norepinephrine and epinephrine were 2.08%–2.91% and 2.14%–3.54%, respectively.

Measurement of plasma renin activity, plasma aldosterone, and cortisol

Plasma renin activity was measured by a radioimmunoassay (RIA) (Incstar, Stillwater, MN, USA). The plasma was incubated under conditions inhibiting the activity of angiotensinase and angiotensin-converting enzyme, and angiotensin I produced in the plasma by renin was measured by RIA using Gammacoat plasma renin activity ^{125}I-RIA kits. Angiotensin I is expressed as renin activity (ng·ml^{-1}·h^{-1}). The calculated sensitivity was 18 pg per tube. The intraassay and interassay CV values of plasma renin activity were 4.0%–10.0% and 5.6%–6.8%, respectively. Plasma aldosterone concentration was measured by a competitive solid-phase RIA (Daiichi Radioisotope Laboratory, Tokyo, Japan). The plasma and ionized (^{125}I) aldosterone (SPAC-S Aldosterone kit) were added to a tube coated with anti-aldosterone, and the aldosterone concentration was measured by competitive reaction of sample and ^{125}I aldosterone. The detection limit of plasma aldosterone was 25 pg·ml^{-1}. The intraassay and interassay CV values of plasma aldosterone were 1.8%–8.3% and 2.4%–3.2%, respectively. Plasma cortisol concentration was measured by an RIA (Incstar, Gammacoat cortisol ^{125}I-RIA kits). The methodology was the solid-phase radioimmunoassay using a plastic tube coated with antibody raised in rabbit against cortisol. 8-Anilino-1-naphthalene sulfonic acid was used as a cortisol-binding protein inhibitor. The intraassay and interassay CV values of plasma cortisol were 3.5%–5.0% and 4.2%–8.7%, respectively.

Measurement of plasma glucose and lactic acid

Plasma glucose concentration was measured by the glucose dehydrogenase method (Merkeauto glucose, Kantokagaku, Tokyo, Japan). Plasma lactic acid concentration was measured by the lactate oxidase method (Determiner-LA, Kyowa Medics, Tokyo, Japan).

Statistical analysis

Values are expressed as means ± SEM. 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. $P < 0.05$ was considered statistically significant.

Results

The changes in the hemodynamic variables of KRN2391 are presented in Table 1. Hypotension induced by KRN2391 was attributed to the significant reduction in SVR in association with a significant increase in CI but was not accompanied by a significant change in HR. Details of the hemodynamic effects of KRN2391-induced hypotension have been reported elsewhere [7].

The changes in the endocrine system during KRN2391-induced hypotension are presented in Table 2. Plasma norepinephrine concentrations increased ($P < 0.01$) after 60 min of hypotension and then returned to near the baseline values after termination of KRN2391. Plasma epinephrine concentrations increased ($P < 0.05$) during the hypotensive period, followed by an increase over the baseline values after induced hypotension. Plasma renin activity increased after 30 ($P < 0.05$) and 60 min ($P < 0.05$) of hypotension. Plasma aldosterone concentrations

Table 1. Changes in hemodynamic variables during and after KRN2391-induced hypotension

Variable	Baseline value	During hypotension		After hypotension
		30 min	60 min	30 min
MAP (mmHg)	118 ± 5	60 ± 0.3**	60 ± 0.3**	104 ± 5**
HR (bpm)	160 ± 11	162 ± 10	170 ± 10	165 ± 8
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.4	5.6 ± 0.7**	6.5 ± 0.7**	4.8 ± 0.4**
SVR ($dyne \cdot s \cdot cm^{-5}$)	4939 ± 741	1237 ± 134**	1008 ± 96**	2460 ± 265**

Values are means ± SEM.
MAP, Mean arterial pressure; HR, heart rate; CI, cardiac index; SVR, systemic vascular resistance.
** $P < 0.01$ compared with baseline values.

Table 2. Changes in the endocrine system during and after KRN2391-induced hypotension

Variable	Baseline value	During hypotension		After hypotension
		30 min	60 min	30 min
NE ($pg \cdot ml^{-1}$)	36 ± 9	45 ± 11	76 ± 21**	41 ± 11
E ($pg \cdot ml^{-1}$)	80 ± 46	310 ± 133*	342 ± 140*	153 ± 70
PRA ($ng \cdot ml^{-1} \cdot h^{-1}$)	12.8 ± 3.5	21.9 ± 5.7*	22.3 ± 4.2*	16.5 ± 2.9
ALD ($pg \cdot ml^{-1}$)	390 ± 59	388 ± 49	393 ± 46	465 ± 54*
Cortisol ($\mu g \cdot dl^{-1}$)	15.6 ± 2.0	15.1 ± 1.2	15.2 ± 1.3	16.0 ± 1.4

Values are means ± SEM.
NE, Plasma norepinephrine concentration; E, plasma epinephrine concentration; PRA, plasma renin activity; ALD, plasma aldosterone concentration.
* $P < 0.05$, ** $P < 0.01$ compared with baseline values.

Table 3. Changes in carbohydrate metabolism during and after KRN2391-induced hypotension

Variable	Baseline value	During hypotension		After hypotension
		30 min	60 min	30 min
Glucose ($mg \cdot dl^{-1}$)	115 ± 5	155 ± 9**	154 ± 12**	124 ± 10
Lactic acid ($mg \cdot dl^{-1}$)	17 ± 2	27 ± 2**	30 ± 3**	29 ± 3**

Values are means ± SEM.
** $P < 0.01$ compared with baseline values.

remained unchanged during the hypotensive period but then increased ($P < 0.05$) after termination of KRN2391. Plasma cortisol concentrations remained unchanged throughout the observation period.

The changes in carbohydrate metabolism during KRN2391-induced hypotension are presented in Table 3. Plasma glucose concentrations increased ($P < 0.01$) during the hypotensive period. Plasma lactic acid concentrations increased ($P < 0.01$) throughout the observation period.

The changes in arterial blood gases during KRN2391-induced hypotension are presented in Table 4. pHa and BE decreased ($P < 0.01$) progressively during the hypotensive period. $PaCO_2$ and PaO_2 remained unchanged throughout the observation period.

Discussion

The current study demonstrates that the endocrine profiles of KRN2391-induced hypotension are caused by the activation of the sympathetic nervous system, which indirectly modulates the renin-angiotensin-aldosterone axis and metabolic effects.

Table 4. Changes in arterial blood gases during and after KRN2391-induced hypotension

Variable	Baseline value	During hypotension		After hypotension
		30 min	60 min	30 min
pHa	7.40 ± 0.01	7.36 ± 0.01**	7.34 ± 0.02**	7.34 ± 0.02**
$PaCO_2$ (mmHg)	37 ± 1	36 ± 1	38 ± 1	39 ± 2
PaO_2 (mmHg)	539 ± 26	527 ± 16	522 ± 35	551 ± 14
BE ($mEq \cdot l^{-1}$)	−1.5 ± 0.6	−4.1 ± 0.8**	−4.6 ± 1.0**	−3.9 ± 1.0**

Values are means ± SEM.
pHa, Arterial pH; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; BE, base excess.
** $P < 0.01$ compared with baseline values.

The decrease in MAP due to the reduction in systemic vascular resistance caused by KRN2391 was associated with hemodynamic and endocrine evidence of sympathetic activation, as reflected by the increases in cardiac index and plasma catecholamine concentrations. Sympathetic activation due to hypotension is known to elicit increases in heart rate, myocardial contractility, and systemic vascular resistance, together with a decrease in venous capacity, which results in the increase in cardiac index. The mechanism of action of potassium channel openers was thought to be similar to that of calcium channel blockers, because potassium channel openers produced hyperpolarization of cell membranes and thus decreased Ca^{2+} influx through inhibition of the voltage-dependent Ca^{2+} channel [8]. However, it has been demonstrated that KRN2391 has dual vasodilating mechanisms due to both a nitrate and a potassium channel-opening action [1,2]. Although potassium channel opening is considered to be a major mechanism of the vasodilating effect of KRN2391, the activation of guanylate cyclase due to KRN2391 is mediated in a manner characteristic of nitrovasodilators because of the presence of the nitrate moiety within its structure [1].

The concentration of plasma norepinephrine is used as an estimate of the overall activity of the sympathetic nervous activity [9]. After induction of KRN2391-induced hypotension, plasma norepinephrine concentrations showed a slight increase initially and then increased significantly later. As a characteristic of the arterial baroreflex, it is known that the increase in input from arterial baroreceptors, due to the increase in arterial pressure, inhibits sympathetic nerve activity, whereas the decrease in baroreceptor input, due to the decrease in arterial pressure, enhances sympathetic nerve activity. However, the degree of sympathetic activation depends on the magnitude of arterial vasodilation and the sensitivity of the arterial baroreflex. Heart rate did not change significantly, despite profound vasodilation during KRN2391-induced hypotension in halothane-anesthetized dogs, because the sensitivity of the arterial baroreflex was altered by various anesthetics: the sensitivity of arterial baroreceptors is reduced by halothane [10]. Further, it has been reported that steady-state plasma norepinephrine concentrations in excess of $1800 pg \cdot ml^{-1}$ were required to produce measurable hemodynamic or metabolic changes [11]. The effects of KRN2391-induced hypotension on plasma epinephrine, as an estimate of adrenal preganglionic sympathetic nerve activity to the adrenal medulla [12], were examined. The activation of plasma epinephrine by KRN2391 agreed with the results of a previous study using nicardipine [13]; thus, both KRN2391 and nicardipine seem to increase adrenal sympathetic activity in halothane-anesthetized dogs, although it cannot be denied that a direct effect of KRN2391 on adrenal medullary cells may activate the secretion of epinephrine. In addition, the decrease in MAP seems to correlate with the changes in plasma epinephrine concentrations rather than the changes in plasma norepinephrine concentrations. These results suggest that the increase in plasma epinephrine may be compensated for by activation of adrenal sympathetic activity instead of by suppression of plasma norepinephrine due to the reduction of the baroreceptor sensitivity caused by halothane anesthesia.

Increases in plasma renin activity were observed during KRN2391-induced hypotension. With the use of various vasodilating agents, such as nitroprusside [13–17], nitroglycerin [16], and nicardipine [13,17], to induce hypotension, these results also have suggested a role for renin-angiotensin system in blood pressure maintenance. Multiple factors are known to be involved in renin release [18,19]. Plasma renin activity may increase during KRN2391-induced hypotension for several reasons, including the reduction of renal perfusion pressures, increased sympathetic tone, and the opening of potassium channels resulting in the hyperpolarization of the membranes. Hyperpolarization may reduce the possibility of calcium channels opening, thus having

similar effects to calcium channel blockers [20,21]. The decrease in intracellular calcium concentration in the juxtaglomerular cells by KRN2391 may explain the activation of renin release, because calcium ion is an inhibitory signal for renin release [22,23]. KRN2391 administration caused an increase in renin release, ultimately resulting in the formation of angiotensin II, which increased systemic blood pressure by vasoconstriction and plasma aldosterone. However, we could not determine whether increased renin release was caused by a direct effect of KRN2391 on juxtaglomerular cells or by a secondary phenomenon.

Plasma glucose and lactic acid concentrations increased during KRN2391-induced hypotension. In the current study, plasma glucose concentrations increased in parallel with the increases in plasma epinephrine concentrations. Epinephrine acts on hepatocytes to faciliate conversion to glucose by the liver, thus inducing hyperglycemia, increasing lactic acid concentration, and decreasing muscle and hepatic glycogen content [24]. Further, the physiologic thresholds of plasma epinephrine concentrations for the increase in plasma glucose have been shown to be 150–200 $pg \cdot ml^{-1}$ [25], as plasma epinephrine concentration values were more than 310 $pg \cdot ml^{-1}$ during KRN2391-induced hypotension (Table 2). The increased plasma lactic acid concentrations were unlikely to have resulted from overproduction due to enhanced anaerobic metabolism, because the arterial blood gas data did not show pHa values less than 7.34 and base excesses less than −4.6 (Table 4). In addition, we have reported that KRN2391 is a potent vasodilator of the splanchnic organ vasculature in isoflurane-anesthetized dogs, and that blood flow to the liver and pancreas persists even when KRN2391 is infused at rates that reduce MAP to 60 mmHg, suggesting that KRN2391 preserves organ blood flow during induced hypotension [26]. Therefore, the increased lactic acid concentrations seem to be caused by the plasma epinephrine changes associated with sympathetic activation [25].

In conclusion, these findings show that KRN2391 activates the sympathetic nervous system and may modulate the renin-angiotensin-aldosterone axis and carbohydrate metabolism.

Acknowledgments. The authors thank Yoshie Hirakawa for her excellent secretarial assistance. KRN2391 was provided by Kirin Brewery, Tokyo, Japan. This research was supported in part by a grant for cooperative research from Showa University.

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