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Pharmacological and Pharmacokinetic Characteristics of YM435, a Novel Dopamine DA_1-Receptor Agonist, in Anaesthetized Dogs

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Abstract

Time-course of plasma concentration of unchanged drug of the dopamine DA_1-receptor agonist (–)-(*S*)-4-(3,4-dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride hydrate (YM435), and its effects on blood pressure and renal blood flow were investigated in anaesthetized dogs.

Continuous intravenous infusion of YM435 (0·1–3 $\mu g\ kg^{-1}\ min^{-1}$) rapidly increased renal blood flow and lowered blood pressure in a dose-dependent manner. These effects remained generally stable throughout the infusion period. Following the start of infusion, plasma concentration of unchanged drug also rose rapidly and dose-dependently and remained virtually constant throughout the infusion period. A significant correlation was observed between log YM435 plasma concentration and the increase in renal blood flow ($r = 0{\cdot}93$, $P < 0{\cdot}0001$) and between the former and the reduction in blood pressure ($r = 0{\cdot}93$, $P < 0{\cdot}0001$).

The present results indicate that YM435 produces renal vasodilatation and lowering of blood pressure in a dose-dependent manner and with rapid onset following continuous intravenous infusion, and that these effects are generally stable throughout the period of infusion. These haemodynamic effects of YM435 were in good agreement with the time-course of plasma concentration of unchanged drug.

Dopamine is known to exert diverse effects on the kidney and cardiovascular system via dopamine receptors and α and β-adrenoceptors (Goldberg & Rajfer 1985). Peripheral dopamine receptors are classified into two biochemically and pharmacologically distinct subtypes. Stimulation of the dopamine DA_1 receptor induces vasodilatation, and this vascular relaxant effect is conspicuous especially in the renal and mesenteric vascular beds (Crumley et al 1976). The dopamine DA_2 receptor is located presynaptically at the sympathetic nerve ending and suppresses noradrenaline release (Lokhandwala & Barrett 1983). At low doses, dopamine causes vasodilatation by stimulating dopamine DA_1 receptors in vascular smooth muscles. At somewhat higher doses, dopamine stimulates β-adrenoceptors to evoke positive inotropic and positive chronotropic effects on the myocardium. At high doses, dopamine stimulates α-adrenoceptors to cause vasoconstriction. This lack of selectivity for dopamine DA_1 receptors and additional effects at α- and β-adrenoceptors limits the clinical usefulness of dopamine for treating hypertensive emergencies (Goldberg et al 1977). Indeed, it was reported that intravenous administration of dopamine elevated blood pressure in severely hypertensive patients (McNay et al 1966). However, when dopamine was infused after administration of the α-adrenoceptor blocker phenoxybenzamine, DA_1-mediated vasodilating actions were observed and blood pressure was decreased with enhancement of renal blood flow and sodium excretion.

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In the treatment of an acute elevation of blood pressure, it is frequently necessary to provide prompt and suitable treatment with parenteral medications to prevent damage to vital organs, namely the brain, heart and kidneys, and subsequent death (Vidt 1986). However, it is also reported that acute lowering of blood pressure often leads to deterioration of renal function (Perry et al 1966; Pohl et al 1974). This adverse effect may still be often noted when the blood pressure is decreased from very high levels in hypertensive emergencies including hypertension during and after surgery (Reid & Muther 1987).

(–)-(*S*)-4-(3,4-Dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride hydrate (YM435, Fig. 1) is a potent renal and systemic vasodilator that selectively stimulates dopamine DA_1 receptors (Anan et al 1991, 1996; Yatsu et al 1997a, b). In anaesthetized dogs, YM435 produces a dose-dependent lowering of blood pressure and increase in renal blood flow, by which it increases glomerular filtration rate and water and sodium excretion (Yatsu et al 1997c). Previous study has shown that YM435 is effective in a canine model of acute hypertension (Yatsu et al 1997b). Moreover, YM435 has also been shown to be effective in preserving and improving renal haemodynamics and function in various models of renal dysfunction (Yatsu et al 1991, 1997c). It has been demonstrated that the effects of YM435 appear promptly following the start of continuous intravenous infusion and rapidly disappear after the cessation of infusion (Yatsu et al 1997b). A characteristic feature of the effects of YM435 is their high degree of controllability on intravenous administration. The objectives of this study were to examine, concurrently, the pharmacokinetics and pharmacodynamics of a continuous intravenous infusion of YM435 in anaesthetized dogs and to characterize the concentration–effect relationships and haemodynamic responses.

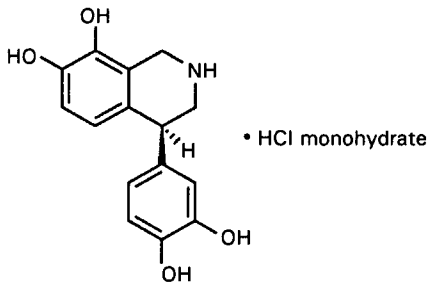

FIG. 1. Chemical structure of YM435.

Materials and Methods

Animal preparation

Mongrel dogs of either sex, 10–13 kg, were used. The animals were anaesthetized by intravenous injection of pentobarbital sodium (30 mg kg^{-1}). A constant level of anaesthesia was maintained by intravenous infusion of pentobarbital sodium at a rate of 3–5 mg kg^{-1} h^{-1}. After endotracheal intubation, artificial respiration was performed by means of a respiration pump (SN-480-4; Shinano Seisakusho, Tokyo) with room air at 18 strokes min^{-1} (20 mL kg^{-1} tidal volume). The right femoral artery was catheterized for measurement of systemic blood pressure with a pressure transducer (AP-200T; Nihon Kohden, Tokyo) and heart rate with a tachometer (AP-600G; Nihon Kohden, Tokyo) triggered by the arterial pulse wave. The left renal artery was exposed by a flank incision using the retroperitoneal approach, and the renal artery was carefully dissected free from surrounding tissue. An electromagnetic blood flow probe (Nihon Kohden, Tokyo) was attached at the renal artery to measure renal blood flow with an electromagnetic flowmeter (MFV-3100; Nihon Kohden, Tokyo). Blood pressure, heart rate and renal blood flow were recorded on a polygraph (RM-6000; Nihon Kohden, Tokyo). Catheters were inserted into the left femoral vein for infusion of YM435 and into the left femoral artery for collection of blood samples to determine plasma concentration of unchanged drug. These experiments were approved by the local animal ethics committee for animal studies and conducted humanely.

Experimental protocol

Six dogs were divided into two groups of three. In one group, a 30-min continuous intravenous infusion of YM435 at 0·1 μg kg^{-1} min^{-1} was performed using an infusion pump (STC-521; Terumo Corporation, Tokyo) after achieving the stabilization of haemodynamic parameters. The cardiovascular parameters were measured and blood samples were obtained immediately before the the start of infusion, at 15 min of infusion and just before the end of infusion. Sixty minutes after the end of infusion, another 30-min intravenous infusion of YM435 was started at 1 μg kg^{-1} min^{-1}, and measurement of cardiovascular parameters and blood sampling were carried out according to the above protocol. The other group of dogs received a 30-min continuous intravenous infusion of YM435 at 0·3 μg kg^{-1} min^{-1}, and after an ensuing 60-min non-infusion period, they received another 30-min intravenous infusion of YM435 at 3 μg kg^{-1} min^{-1}. Measurement of the cardiovascular parameters and blood sampling were performed according to the same protocol as that in the first group.

Analytical measurements

Plasma concentrations of unchanged drug were determined by high-performance liquid chromatography (HPLC) with electrochemical detection as described below. Plasma samples (0·525 mL) were prepared by adding 25 μL 10% L-ascorbic acid aqueous solution to 0·5 mL plasma. To these samples, 0·1 mL of an aqueous solution, the internal standard substance (20 ng), 25 μL of 10% L-ascorbic acid aqueous solution, 0·6 mL of water, and 1 mL of 0·05 M Tris (hydroxymethyl) aminomethane-HCl buffer (pH 9·0) were added. Then, 5 mL of a mixture of ethyl acetate–isopropanol (95:5, v/v) was added and shaken for 20 min. After centrifugation, the ethyl acetate layer was transferred to another tube, 0·2 mL of a citric acid-disodium phosphate buffer (pH 4·0) was added and mixed for 30 s. After centrifugation, the organic layer was discarded, and the aqueous layer was evaporated to dryness at 40°C under reduced pressure. The residue was dissolved by adding 0·2 mL water and 40–60 μL of the resultant solution was injected into the HPLC system, consisting of a solvent delivery pump (L-6000; Hitachi, Tokyo), an autosampler (WISP 710A; Waters), and detector (Coulochem 5100A with 5011 analytical cell, ESA). An octadecyl silanized silicagel column (Nucleosil $_5C_{18}$, 15 cm × 4 mm i.d., Nagel) was maintained at 40°C. The mobile phase was a mixture of 0·05 M citric acid–0·1 M disodium phosphate buffer solution (pH 4·0) containing 0·5 mM sodium octylsulphate and 1 mM EDTA–acetonitrile (88:12, v/v). The mobile phase had a flow rate of 0·75 mL min^{-1}. The determination limit of this method was set at 0·5 ng mL^{-1}.

Drugs and data analysis

YM435 and the internal standard substance, (*R,S*)-7-dihydroxy-8-methyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide were synthesized at Yamanouchi Pharmaceutical Co., Ltd. All other chemicals were the best grade commercially available. All data are expressed as the mean ± s.e.m. Linear correlations were obtained from least-squares analysis. A value of $P < 0·05$ was regarded as significant.

Results

Tables 1 and 2 show the time-courses of the effect of YM435 on blood pressure and renal blood flow and changes in plasma concentration of unchanged drug.

Intravenous infusion of YM435 (0·1 μg kg^{-1} min^{-1}) had little or no effect on mean blood pressure and brought about a slight increase in renal blood flow (Table 1). At 15 and 30 min of infusion at this dose level, the plasma concentration of unchanged drug was 2·5 ± 0·1 and 2·5 ± 0·2 ng mL^{-1}, respectively. Heart rate just before the start of infusion at 0·1 μg kg^{-1} min^{-1} was 142 ± 15 beats min^{-1}, and heart rate at 15 and 30 min of infusion was 138 ± 15 and 136 ± 16 beats min^{-1}, respectively.

Renal blood flow increased markedly and mean blood pressure fell rapidly in response to intravenous infusion of YM435 at 1 μg kg^{-1} min^{-1} started 60 min after cessation of the infusion at 0·1 μg kg^{-1} min^{-1} (Table 1). The percentage change in renal blood flow was greater than that in mean blood pressure. The increase in renal blood flow was 53·6 ± 8·5% and 55·7 ± 4·9% at 15 and 30 min of infusion, respectively;

Table 1. Renal blood flow, mean blood pressure and plasma concentration of unchanged drug during 30-min intravenous infusion of YM435 (0·1 and then 1 $\mu g\ kg^{-1}\ min^{-1}$) in anaesthetized dogs.

	Time after YM435 infusion (min)			
	0·1 $\mu g\ kg^{-1}\ min^{-1}$		1 $\mu g\ kg^{-1}\ min^{-1}$	
	15	30	15	30
Renal blood flow (Δ%)	5·6 ± 3·2	0·7 ± 2·2	53·6 ± 8·5	55·7 ± 4·9
Mean blood pressure (Δ%)	−1·5 ± 1·2	−0·2 ± 2·1	−11·9 ± 1·7	−11·7 ± 1·1
Plasma concn of unchanged drug (ng mL^{-1})	2·5 ± 0·1	2·5 ± 0·2	25·6 ± 1·7	26·1 ± 1·8

The cardiovascular parameters represent the mean % change ± s.e.m. from baseline values (n = 3). Baseline renal blood flow and mean blood pressure in the lower dose (0·1 $\mu g\ kg^{-1}\ min^{-1}$) were 123 ± 10 mL min^{-1} and 130 ± 7 mmHg, respectively, and in the higher dose (1 $\mu g\ kg^{-1}\ min^{-1}$) were 97 ± 10 mL min^{-1} and 137 ± 1 mmHg, respectively.

Table 2. Renal blood flow, mean blood pressure and plasma concentration of unchanged drug during 30-min intravenous infusion of YM435 (0·3 and then 3 $\mu g\ kg^{-1}\ min^{-1}$) in anaesthetized dogs.

	Time after YM435 infusion (min)			
	0·3 $\mu g\ kg^{-1}\ min^{-1}$		3 $\mu g\ kg^{-1}\ min^{-1}$	
	15	30	15	30
Renal blood flow (Δ%)	16·8 ± 7·3	16·2 ± 7·8	56·6 ± 4·4	57·7 ± 2·7
Mean blood pressure (Δ%)	−4·4 ± 1·9	−5·3 ± 4·5	−22·5 ± 1·0	−19·4 ± 1·0
Plasma concn of unchanged drug (ng mL^{-1})	6·3 ± 0·8	6·5 ± 0·8	63·1 ± 8·4	59·4 ± 5·4

The cardiovascular parameters represent the mean % change ± s.e.m. from baseline values (n = 3). Baseline renal blood flow and mean blood pressure in the lower dose (0·3 $\mu g\ kg^{-1}\ min^{-1}$) were 127 ± 14 mL min^{-1} and 131 ± 10 mmHg, respectively, and in the higher dose (3 $\mu g\ kg^{-1}\ min^{-1}$) were 111 ± 2 mL min^{-1} and 137 ± 15 mmHg, respectively.

and the reduction in mean blood pressure was −11·9 ± 1·7% and −11·7 ± 1·1% at these periods, respectively. Plasma concentration of unchanged drug was 25·6 ± 1·7 and 26·1 ± 1·8 ng mL^{-1} at 15 and 30 min of infusion, respectively. Thus, all these parameters showed virtually comparable values at the two time points. The plasma concentration of unchanged drug immediately before the start of infusion at 1 $\mu g\ kg^{-1}\ min^{-1}$, i.e. 60 min after cessation of a 30-min infusion at 0·1 $\mu g\ kg^{-1}\ min^{-1}$, was below the lower limit of detection (< 0·5 ng mL^{-1}). Heart rate just before the start of infusion at 1 $\mu g\ kg^{-1}\ min^{-1}$ was 128 ± 16 beats min^{-1}, and heart rate at 15 and 30 min of infusion was 146 ± 18 and 145 ± 18 beats min^{-1}, respectively.

Renal blood flow clearly increased and mean blood pressure decreased rapidly, but slightly, following the start of intravenous YM435 infusion at 0·3 $\mu g\ kg^{-1}\ min^{-1}$ in the second group of dogs (Table 2). These responses remained generally stable throughout the period of infusion. The percentage change in renal blood flow was greater than that in mean blood pressure. The increase in renal blood flow was 16·8 ± 7·3% and 16·2 ± 7·8% at 15 and 30 min of infusion, respectively. The reduction in mean blood pressure caused by the infusion of YM435 was −4·4 ± 1·9% and −5·3 ± 4·5% at these periods, respectively. Plasma concentration of unchanged drug was 6·3 ± 0·8 and 6·5 ± 0·8 ng mL^{-1} at 15 and 30 min of infusion, respectively. Thus, all these parameters showed virtually comparable values at the two time points. Heart rate just before the start of infusion at 0·3 $\mu g\ kg^{-1}\ min^{-1}$ was 126 ± 3 beats min^{-1}, and heart rate at 15 and 30 min of infusion was 127 ± 4 and 126 ± 9 beats min^{-1}, respectively.

Renal blood flow increased markedly and mean blood pressure fell rapidly in response to intravenous infusion of YM435 at 3 $\mu g\ kg^{-1}\ min^{-1}$ started 60 min after the cessation of the infusion at 0·3 $\mu g\ kg^{-1}\ min^{-1}$ (Table 2). The percentage change in renal blood flow was greater than that in mean blood pressure. Renal blood flow increased by 56·6 ± 4·4% and 57·7 ± 2·7% at 15 and 30 min of infusion, respectively; mean blood pressure decreased by −22·5 ± 1·0% and −19·4 ± 1·0% at these periods, respectively. Plasma concentration of unchanged drug was 63·1 ± 8·4 and 59·4 ± 5·4 ng mL^{-1} at 15 and 30 min of infusion, respectively. Thus all these parameters showed virtually comparable values at the two time points. The plasma concentration of unchanged drug immediately before the start of the infusion at 3 $\mu g\ kg^{-1}\ min^{-1}$, i.e. 60 min after cessation of a 30-min infusion at 0·3 $\mu g\ kg^{-1}\ min^{-1}$, was below the lower limit of detection (< 0·5 ng mL^{-1}). Heart rate just before the start of infusion at 3 $\mu g\ kg^{-1}\ min^{-1}$ was 114 ± 15 beats min^{-1}, and heart rate at 15 and 30 min of infusion was 147 ± 12 and 146 ± 10 beats min^{-1}, respectively.

There was a significant correlation between log plasma concentration of unchanged drug and increase in renal blood flow (Fig. 2A) and also between the former and the reduction in mean blood pressure decrease following infusion of YM435 (Fig. 2B).

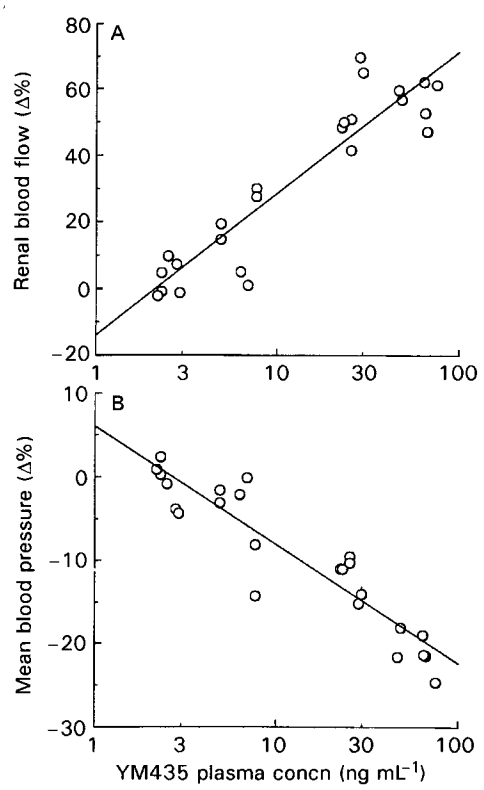

FIG. 2. A. Relationship of percentage increase in renal blood flow by YM435 to log of plasma concentration of unchanged drug. Regression equation (n = 24): Y = 42·7X − 14·0, r = 0·93, $P < 0.0001$. B. Relationship of percentage reduction in mean blood pressure by YM435 to log of plasma unchanged drug concentration. Regression equation (n = 24): Y = −14·2X + 5·9, r = 0·93, $P < 0.0001$.

Discussion

In the present study, continuous intravenous infusion of the dopamine DA_1-receptor agonist YM435 (0·1–3 $\mu g\ kg^{-1}\ min^{-1}$) produced dose-dependent renal vasodilating and hypotensive effects which were rapid in onset and remained generally stable throughout the period of infusion. Plasma concentration of unchanged YM435 also increased rapidly following the start of infusion in a dose-dependent manner and remained practically stable throughout the infusion period. The plasma level of unchanged drug was below the lower limit of detection (< 0.5 ng mL^{-1}) at 60 min after cessation of the infusion, thus providing evidence in support of a rapid elimination of the drug from plasma.

It is known that the vasodilatory actions of dopamine DA_1-receptor agonists are greatest in the renal vascular bed, but resistance in other vascular beds is reduced (Hahn et al 1982; Hughes et al 1986). In this study, although mean blood pressure decreased with all infusion rate of YM435, the increase in renal blood flow reached plateau and renal blood flow did not increase further with the highest dose (3 $\mu g\ kg^{-1}\ min^{-1}$). Taken together, it is conceivable that the primary effect of YM435 seems to be renal arteriolar, and blood pressure decrement is due to diminished peripheral vascular resistance.

Previous study has shown that YM435 does not produce excessive hypotension in a canine model of acute hypertension induced by angiotensin II or noradrenaline (Yatsu et al 1997b). After discontinuation of YM435 infusion, blood pressure rapidly increased toward the level seen before YM435 infusion, but did not rebound to exceed pre-infusion blood pressure values. We previously demonstrated that the haemodynamic effect was produced promptly after the start of YM435 infusion, was maintained throughout the infusion, and returned to baseline within 10 min of termination of infusion in open-chest anaesthetized dogs (Yatsu et al 1997b). Similarly, YM435 showed its effects promptly after the start of continuous intravenous infusion, and, by 10 min after the discontinuation of administration, the pressor response induced by angiotensin II or noradrenaline had returned to similar levels to those seen before the start of YM435 infusion. These previous findings are in good agreement with the present data. The preferred drug for the treatment of hypertensive emergencies, including hypertension during and after surgery, should have a rapid onset and offset of action to lower blood pressure quickly (Palmer & Lassetter 1975; Nabil 1978; Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure 1988). The pharmacokinetic characteristics of YM435, therefore, are considered to be highly suited to blood-pressure control in hypertensive emergencies.

The present data demonstrate that YM435 increases renal blood flow at low doses, namely at low plasma concentrations of unchanged drug, and that the plasma level of the compound increases with increasing dose to eventually exert its blood-pressure-lowering effect. These results are consistent with previous findings that selective stimulation of dopamine DA_1 receptors at lower doses produces renal vasodilatation with no alteration in blood pressure, while stimulation of dopamine DA_1 receptors at higher doses elicits more potent renal vasodilatation, and produces a decrease in blood pressure (Hahn et al 1982; Lappe et al 1986; Hegde et al 1989). YM435 dose-dependently reversed the increase in renal vascular resistance induced by angiotensin II or noradrenaline, indicating that YM435 can preserve blood flow to the kidney as well as control acute hypertension (Yatsu et al 1997b). Furthermore, our previous studies have shown that YM435 is effective in preserving and improving renal haemodynamics and function in various models of renal dysfunction (Yatsu et al 1991, 1997c). It is therefore considered that YM435 may be preferable for the control of acute hypertension in patients with impairment of renal function, because it controls abnormally elevated blood pressure and maintains adequate blood flow in the kidney, which is a vital organ.

The present results indicate that YM435 produces renal vasodilatation and hypotensive effects in a dose-dependent manner, with a rapid onset, following continuous intravenous infusion, and that these effects are generally stable throughout the period of infusion. These pharmacological effects of YM435 are in good agreement with the time-course of plasma concentration of unchanged drug.

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