Hypotensive Effects of YM430, a 1,4-Dihydropyridine Derivative, in Spontaneously Hypertensive Rats and Renal Hypertensive Dogs

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ABSTRACT—The hypotensive effects of YM430 (4(((S)-2-hydroxy-3-phenoxypropyl)amino)butyl methyl 2,6-dimethyl-((S)-4-(m-nitrophenyl))-1,4-dihydropyridine-3,5-dicarboxylate) were evaluated in hypertensive animals. In conscious spontaneously hypertensive rats (SHR), single oral administration of YM430 (10−100 mg/kg) produced a dose-dependent decrease in mean blood pressure (MBP) with slight reflex tachycardia. The hypotensive effect of YM430 reached its maximum about 2 hr after dosing and lasted for over 10 hr. Importantly, the β1-adrenoceptor blocking activity of YM430 had a similar time course to that of its calcium entry blocking activity. In conscious normotensive dogs (NTD: 1–10 mg/kg, p.o.), YM430 decreased MBP without reflex tachycardia, and inhibited isoproterenol (ISO)-induced tachycardia in a dose-dependent manner. In conscious renal hypertensive dogs (RHD: 0.3–3 mg/kg, p.o.), YM430 also produced a sustained hypotensive effect. Furthermore, on repeated oral administration to conscious SHR and NTD, YM430 caused a long-lasting hypotensive effect. This hypotensive activity and inhibition of ISO-induced tachycardia showed neither tolerance, augmentation nor rebound. In conclusion, YM430 has a long-lasting hypotensive effect and behaves as a hybrid compound, combining calcium entry blocking and β1-adrenoceptor blocking activities in vivo. In addition, the degree of the blocking activities of YM430 remains nearly constant in the long-term after oral administration.

Keywords: YM430, Calcium antagonist, β1-Blocker, Antihypertensive, Oral administration

Calcium entry blocking agents are widely recognized as effective drugs in the treatment of hypertension, and appear to have an acceptable safety profile in the majority of patients (1, 2). The mechanism of action of these agents is vasodilation induced by blocking the influx of Ca2+ into smooth muscle cells through direct inhibition of the voltage-gated L-type calcium channel of the cell membrane (3, 4). Despite their good efficacy, however, calcium entry blocking agents, especially 1,4-dihydropyridine derivatives, produce unwanted effects such as reflex sympathetic nerve stimulation due to baroreceptor activation. This reflex sympathetic stimulation may well impair the hypotensive effect by increasing heart rate (HR), cardiac output and plasma renin activity (PRA) (5−7). Moreover, although β-adrenoceptor blocking agents, also widely used in the treatment of hypertension, provide the obvious additional benefit of blocking any reflex-induced increase in HR, they produce unfavorable effects such as bronchoconstriction and peripheral circulatory disturbance (8).

To overcome the incomplete effects of monotherapy with either drug alone, combination therapy of a calcium entry blocking agent with a β-adrenoceptor blocking agent is now common practice. Clinical studies have confirmed that combined treatment has advantages in therapeutic efficacy over monotherapy (5, 9−11).

We previously reported (12, 13) the pharmacological properties of YM430 (4(((S)-2-hydroxy-3-phenoxypropyl)amino)butyl methyl 2,6-dimethyl-((S)-4-(m-nitrophenyl))-1,4-dihydropyridine-3,5-dicarboxylate, Fig. 1) in isolated tissue and in vivo studies. This drug is a novel 1,4-dihydropyridine derivative that combines calcium entry blocking and β-adrenoceptor blocking activities in vivo.
pyridine derivative that possesses calcium entry blocking (pK\textsubscript{Ca} = 8.51, in rabbit aorta) and selective \(\beta_1\)-adrenoceptor blocking (pA\textsubscript{2} = 7.59, in rat atria; pA\textsubscript{2} = 5.59, in guinea pig trachea) activities in one molecule (12). Intravenous administration of YM430 produced hypotensive effects without reflex tachycardia in conscious normotensive dogs (NTD) (13). The rationale outlined above indicate that a drug possessing both activities would have a desirable therapeutic profile in the treatment of hypertension. Thus, the present study was designed to investigate the antihypertensive effects of YM430 in spontaneously hypertensive rats (SHR), NTD and renal hypertensive dogs (RHD) after single and repeated oral dosing. SHR as the animal model of human essential hypertension and RHD as the hypertensive model of dog are generally used.

MATERIALS AND METHODS

**Experimental procedures**

**Conscious SHR:** A total of 54 male SHR of the Okamoto-Aoki strain aged 16–23 weeks and weighing 250–355 g were used. The rats were anesthetized with ether, and a carotid artery and a jugular vein were cannulated (polyethylene catheters: Intramedic PE-50; Clay Adams, Parsippany, NJ, USA) for blood pressure (BP) recording and isoproterenol injection, respectively. BP and HR were recorded at three days after surgical treatment under unrestrained conditions. BP was measured with a transducer (AP-400T; Nihon Kohden, Tokyo) and HR with a cardiotachometer (AT-600G, Nihon Kohden) triggered by the BP pulse wave. YM430 (10–100 mg/kg, p.o.), nifedipine (1–10 mg/kg, p.o.) and atenolol (30 mg/kg, p.o.) were suspended in a 0.5% methylcellulose solution and given by oral gavage at 5 ml/kg. To assess the \(\beta_1\)-adrenoceptor blocking activity of YM430 (100 mg/kg, p.o.), isoproterenol (0.1 µg/kg, i.v.) was injected immediately after measurement of BP, and the increase in HR was measured.

The effects of YM430 (30 mg/kg, p.o., once a day) after 14-day repeated oral dosing were also studied in conscious SHR. BP and HR were measured by the tail-cuff method with a sphygmomanometer (PS-200; Riken Kaibatsu, Tokyo) just before and on the 1st, 3rd, 7th, 14th day of treatment and 1st day of recovery. YM430 was suspended in a 0.5% methylcellulose solution and given by oral gavage at 5 ml/kg.

**Conscious dogs:** Twenty beagle dogs of either sex weighing 8–14 kg were used. The effects of YM430 on HR, PQ-interval and BP were evaluated in conscious NTD and RHD. RHD (two-kidney, one-clip Goldblatt hypertensive dogs) were prepared by constricting the renal artery under GOF anesthesia (N\textsubscript{2}O : O\textsubscript{2} = 2 : 1, 1% halothane) with an adjustable silver clamp placed around the artery to reduce blood flow by 60% to 80%. The animals (systolic BP (SBP) ≥ 160 mmHg and diastolic BP (DBP) ≥ 100 mmHg) were used as RHD four weeks after surgery.

For measurement of BP in both NTD and RHD, a polyvinyl catheter was implanted in the abdominal aorta via a muscular branch of the femoral artery under GOF anesthesia. Animals were used for experiments after a 1-week recovery period. BP was measured in the femoral artery with a pressure transducer and HR with a cardiotachometer triggered by the pulse wave of BP. Both measurements were made while the animal was lying quietly on a bench. The electrocardiogram (ECG) (lead II) was also measured. The \(\beta_1\)-adrenoceptor blocking activity of YM430 was evaluated by its antagonism of isoproterenol-induced (0.5 µg/kg, i.v.) tachycardia just before and 2 hr after oral dosing. YM430 (NTD: 1–10 mg/kg, p.o.; RHD: 0.3–3 mg/kg, p.o.) was prepared as a lactose trituration (×10) and given orally in hard gelatin capsules. The dose ranges of YM430 in NTD and RHD were confirmed by a preliminary experiment. These doses produced similar peak hypotension between NTD and RHD.

The effects of YM430 (10 mg/kg, p.o., once a day) after 10-day repeated oral dosing in conscious NTD were also investigated. The same measurements of HR, PQ-interval, BP and \(\beta_1\)-adrenoceptor blocking activity as described above were made before (for 2 days); on the 1st, 3rd, 5th, 10th day of treatment; and on the 1st day of recovery.

During the experiments, all animals were housed in individual experimental cages, fed a dry-type rat or dog meal, and water was given ad libitum.

All of these experiments were approved by the Animal Ethics Committee of Yamanouchi Pharmaceutical Co., Ltd.

**Drugs**

YM430 was prepared by Yamanouchi Pharmaceutical Co., Ltd. Nifedipine, atenolol and isoproterenol hydrochloride were obtained commercially (Sigma Chemical Co., St. Louis, MO, USA). Isoproterenol hydrochloride was dissolved in 0.9% saline solution containing 0.01% ascorbic acid.

**Data analyses**

Data are expressed as the mean ± S.E.M. Statistical analyses were performed by Student's t-test or one-way ANOVA. P values less than 0.05 were considered to be statistically significant.
Table 1. Age, body weight (B.W.) and baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) before a single oral dosing of YM430 and reference compounds to conscious spontaneously hypertensive rats

| Parameter      | YM430 (mg/kg, p.o.)          | Nifedipine (mg/kg, p.o.) | Atenolol (mg/kg, p.o.) |
|----------------|-------------------------------|--------------------------|------------------------|
|                | 10 (n = 7) 20 (n = 7) 100 (n = 6) | 1 (n = 5) 23 23 20-23 | 30 (n = 5) 3 10 (n = 5) |
| Age (weeks)    | 20               20           23               | 23                     | 20-23                  |
| B.W. (g)       | 305.7 ± 12.2     302.8 ± 11.5   321.6 ± 4.5  | 333.0 ± 2.0            337.0 ± 5.8   319.0 ± 7.8  | 328.0 ± 8.4 |
| HR (beats/min) | 375.6 ± 5.0      370.6 ± 6.7   345.2 ± 16.1  | 350.2 ± 10.9           338.0 ± 6.5   337.6 ± 15.7  | 346.4 ± 9.9 |
| SBP (mmHg)     | 190.8 ± 7.1      214.2 ± 7.2   197.1 ± 10.5  | 208.6 ± 8.9            214.0 ± 10.3   232.6 ± 5.6   | 201.0 ± 12.6 |
| DBP (mmHg)     | 127.7 ± 4.8      140.1 ± 3.5   134.6 ± 7.3   | 135.2 ± 6.7            151.8 ± 8.9   151.8 ± 3.9   | 138.8 ± 5.9 |
| MBP (mmHg)     | 148.8 ± 5.5      164.9 ± 4.7   155.5 ± 7.5   | 159.7 ± 7.3            172.0 ± 9.4   178.7 ± 4.3   | 159.5 ± 8.1 |

Values are the mean ± S.E.M. of the indicated number of animals.

Fig. 2. Time course change in heart rate (HR), mean blood pressure (MBP) and isoproterenol (0.1 μg/kg, i.v.)-induced tachycardia on single oral dosing of YM430, nifedipine or atenolol to spontaneously hypertensive rats. ▲: 1 mg/kg, ■: 3 mg/kg, ○: 10 mg/kg, ●: 30 mg/kg, △: 100 mg/kg. Each point represents the mean ± S.E.M. of 5 to 7 rats.
RESULTS

Conscious SHR (single oral dosing)

Age of animals, body weight and baseline values of HR, SBP, DBP and mean BP (MBP) in each group are shown in Table 1. Values were not significantly different among any group (one-way ANOVA). YM430 at doses of 10–100 mg/kg, p.o. produced a dose-dependent hypotensive effect (Fig. 2). At 100 mg/kg, p.o., maximum decrease in SBP, DBP and MBP were 62.0±9.2, 55.0±7.0 and 57.6±6.8 mmHg, respectively. Increase in HR at that dose was 49.0±11.7 beats/min (Fig. 3). The hypotensive effect at 30 and 100 mg/kg, p.o. reached maximum about 2 hr after dosing and lasted over 10 hr. YM430 at 100 mg/kg, p.o. also inhibited isoproterenol-induced tachycardia, and this effect lasted over 10 hr (Fig. 2). Nifedipine at doses of 1 to 10 mg/kg, p.o. produced a steep decrease in MBP with an increase in HR in a dose-dependent manner. Nifedipine at 3 mg/kg, p.o., a dose that had the same hypotensive activity as YM430 at 100 mg/kg, p.o., produced the maximum HR increase of 94.6±13.9 beats/min (Fig. 3). The increase in HR by YM430 was significantly weaker than that of nifedipine (Fig. 3). Atenolol at 30 mg/kg, p.o. had a little effect on MBP, but caused a decrease in HR and inhibited isoproterenol-induced tachycardia.

Conscious dogs (single oral dosing)

Baseline values for HR, PQ-interval and MBP are shown in Table 2. Values were not significantly different among any group (one-way ANOVA). On the other hand, baseline values of MBP in RHD (136.8±2.6 mmHg: n=16) was significantly higher than that of NTD (114.0±4.2 mmHg: n=11) (P<0.001, Student’s t-test), and we confirmed that the hypertension of RHD was well established. In conscious NTD (1–10 mg/kg, p.o.; Fig. 4) and RHD (0.3–3 mg/kg, p.o.; Fig. 5), YM430 produced hypotensive effects in a dose-dependent manner. In NTD, the maximum decrease in MBP of YM430 at 10 mg/kg, p.o. was 34.0±3.2 mmHg. The hypotensive effect of YM430 reached maximum about 2 to 4 hr after dosing and lasted over 10 hr. In RHD, in contrast, the effect reached maximum at 1 hr after dosing and lasted over 8 hr. In NTD, no change in HR was observed.

![Graph showing maximum change in heart rate (HR) and mean blood pressure (MBP) on single oral dosing of YM430, nifedipine and atenolol to spontaneously hypertensive rats. Each bar represents the mean ± S.E.M. of 5 to 7 rats. *P<0.05, as compared with the YM430 at 100 mg/kg, p.o. by Student’s t-test.](image-url)
Table 2. Baseline values of heart rate (HR), PQ-interval and mean blood pressure (MBP) before single oral dosing of YM430 to conscious normotensive dogs (NTD) and renal hypertensive dogs (RHD)

| Parameter          | NTD (mg/kg, p.o.) | RHD (mg/kg, p.o.) |
|--------------------|-------------------|-------------------|
|                    | 1 (n=3)           | 3 (n=4)           | 10 (n=4)  | 0.3 (n=5) | 1 (n=6) | 3 (n=5) |
| HR (beats/min)     | 112.0±13.6        | 125.0±8.66        | 116.0±10.0 | 103.2±5.4 | 85.3±6.4 | 94.8±9.1 |
| PQ-Interval (msec) | 106.7±7.3         | 96.3±5.5          | 95.0±8.7   | 97.0±4.4  | 91.8±5.2 | 96.0±5.8 |
| MBP (mmHg)         | 127.3±7.3         | 112.0±2.4         | 106.0±7.9  | 135.4±5.0 | 139.0±2.6 | 135.4±6.6 |

Values are the mean±S.E.M. of the indicated number of animals.

Fig. 4. Effects of single oral dosing of YM430 on heart rate (HR), PQ-interval and mean blood pressure (MBP) in conscious normotensive dogs. ○: 1 mg/kg, ●: 3 mg/kg, △: 10 mg/kg. Each point represents the mean±S.E.M. of 3 to 4 dogs.
whereas in RHD, YM430 at the highest dose, which decreased MBP by 29.2±5.7 mmHg, increased HR by 33.0±9.9 beats/min. YM430 had no effect on PQ-interval in either group of animals. YM430 also inhibited iso-proterenol-induced tachycardia in a dose-dependent manner in both groups of animals (Fig. 6).

**Conscious SHR (repeated oral dosing)**
YM430 was orally administered at 30 mg/kg once a day for 14 days to conscious SHR. Baseline values for HR and SBP did not vary (not significant, one-way ANOVA) throughout the dosing period (Table 3). The increase in body weight was not different between the control and

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**Fig. 5.** Effects of single oral dosing of YM430 on heart rate (HR), PQ-interval and mean blood pressure (MBP) in conscious renal hypertensive dogs. ■: 0.3 mg/kg, ○: 1 mg/kg, ●: 3 mg/kg. Each point represents the mean±S.E.M. of 5 to 6 dogs.
YM430-treated group (Fig. 7). YM430 consistently decreased SBP and caused a slight increase in HR by about 60 beats/min on the 1st, 3rd, 7th and 14th day after dosing. The hypotensive effect of YM430 reached maximum about 2 hr after dosing and lasted over 10 hr on each day. This effect returned to baseline at 24 hr after dosing on each day. No tolerance or augmentation of the hypotensive effect was observed throughout the dosing period. After the 14-day treatment, HR and SBP returned to the predosing values (Fig. 8).

Conscious NTD (repeated oral dosing)

Baseline values for HR, PQ-interval and MBP did not vary throughout the dosing period (Table 4). HR tended to decrease, but the difference was not significant (one-way ANOVA). In conscious NTD, YM430 in repeated oral dosing at 10 mg/kg, p.o. for 10 days produced consistent hypotension (about 35 to 45 mmHg) and antagonism of isoproterenol-induced tachycardia (Figs. 9 and 10). A slight elevation (29.0±4.9 beats/min) of HR on day 10 was observed, and PQ-interval was almost constant throughout the dosing period. No long-term diminution of activity was observed. After the cessation of treatment, MBP returned to the predosing values.

Table 3. Body weight (B.W.) and baseline values of heart rate (HR) and systolic blood pressure (SBP) before dosing in 14-day administration of YM430 to conscious spontaneously hypertensive rats

| Parameter | Pretreatment | 1st day | 3rd day | 7th day | 14th day | Recovery |
|-----------|--------------|---------|---------|---------|----------|----------|
| B.W. (g)  | 284.2±8.1    | 284.2±8.1 | 294.2±8.1 | 294.2±8.1 | 315.7±9.4 | 315.7±9.4 |
| HR (beats/min) | 368.3±4.3 | 367.3±5.4 | 354.3±6.3 | 360.0±8.8 | 340.0±11.2 | 337.6±14.1 |
| SBP (mmHg) | 170.6±4.9 | 177.3±5.4 | 173.2±4.6 | 173.5±5.5 | 181.2±4.1 | 181.2±4.1 |

Values are the mean±S.E.M. of 7 rats.
YM430 is a 1,4-dihydropyridine derivative that possesses selective $\beta_1$-adrenoceptor blocking activity. Our previous study of the pharmacological properties of YM430 in vitro showed that this drug behaves as a hybrid compound, combining calcium entry blocking and $\beta_1$-adrenoceptor blocking activities in one molecule (12). In the present study, we sought to determine the hypotensive profile of YM430 in animal models of hypertension, namely SHR and RHD.

YM430 in single oral dosing produced dose-dependent hypotensive effects in SHR with little change in HR. Compared to nifedipine, however, at the dose that in-
Fig. 9. Effects of 10-day repeated oral dosing of YM430 (10 mg/kg, p.o.) on heart rate (HR), PQ-interval and mean blood pressure (MBP) in conscious normotensive dogs. Each point represents the mean ± S.E.M. of 4 dogs.
duced similar hypotension, the increase in HR by YM430 was significantly smaller than that of nifedipine. Calcium entry blocking agents, particularly 1,4-dihydropyridines, are thought to induce a reflex increase in sympathetic tone by producing systemic vasodilation (5–7). Takenaka et al. (14) reported that the reflex tachycardia induced by these drugs was abolished by β-adrenoceptor blocking agents or denervation of baroreceptor afferent nerves. YM430 inhibited isoproterenol-induced tachycardia at a dose that produced marked hypotension. This attenuation of reflex tachycardia during the period of hypotension after YM430 dosing is therefore considered due to the effective N1-adrenoceptor blocking activity of this drug. In addition to this, similar studies (15, 16) have reported that β-adrenoceptor blocking agents used for the treatment of hypertension do not induce an acute decrease in BP. Indeed, atenolol (30 mg/kg, p.o., which is equipotent to YM430 at 100 mg/kg, p.o. in β1-adrenoceptor blocking activity) produced almost no hypotensive activity under the same experimental conditions. Therefore, we did not anticipate that the β1-adrenoceptor blockade of YM430 would contribute appreciably to its immediate hypotensive effect in rats and propose instead that this acute activity of YM430 was solely the result of its calcium entry blocking effect.

On the other hand, both the hypotensive activity and inhibition of isoproterenol (ISO)-induced tachycardia of YM430 reached maximum at 2 to 4 hr and lasted more than 10 hr after dosing. The hypotensive effect of YM430 is mainly caused by its calcium entry blocking effect. Importantly, therefore, the time courses of calcium entry blocking and β1-adrenoceptor blocking activity were very similar after oral administration. These results suggest that these activities of YM430 are maintained in a constant ratio after oral administration and may have therapeutic advantage over the combination of calcium entry blocking agent and β-adrenoceptor blocking agent because the time course of both effects are not always similar.

The hypotensive effect of YM430 was evaluated in a second hypertensive animal model, RHD, and compared to that in NTD as normotensive animals. On the basis of its peak decrease in MBP, YM430 showed a dose-dependent hypotensive effect in NTD and RHD. However, hypotension in RHD was achieved with a dose nearly 3 times smaller than that producing an equal hypotensive effect in NTD. This result suggests that RHD are more sensitive to the hypotensive effects of YM430 than NTD; YM430 in clinical studies may therefore be expected to induce more potent hypotensive effects in conditions of hypertension. Nifedipine, also a 1,4-dihydropyridine calcium entry blocker, is reported (17, 18) to cause more effective hypotension in hypertensive patients than in normal subjects. In animal studies using SHR and Wistar Kyoto rats (WKY), calcium entry blocking agents had more potent hypotensive activity in hypertensive rats than normotensive rats (19, 20). Our data in dogs are consistent with these findings in rats. In contrast, although YM430 inhibited isoproterenol-induced tachycardia in a dose-dependent manner, the doses of YM430 producing equivalent β1-adrenoceptor blocking activity in NTD and RHD were closely similar. In fact, HR at the highest dose of YM430 increased in RHD but did not increase in NTD. This finding is interesting; although the calcium entry blocking activity of YM430 showed higher potency in RHD than in NTD, its β1-adrenoceptor blocking activity did not change. The β1-adrenoceptor blocking activity of YM430 was therefore insufficient to induce complete inhibition of reflex tachycardia at the highest dose in RHD. Thus, at least in RHD, no enhancement of β1-adrenoceptor blocking activity was observed, and the relative potency of β1-adrenoceptor blocking activity to calcium
entry blocking activity of YM430 became weaker. However, in SHR, a similar change in the relative potency might also occur. Further study is necessary to clarify the mechanism of the different sensitivity between calcium entry blocking and β₁-adrenoceptor blocking activity in RHD. In any case, since this unfavorable effect of YM430 recovered to baseline at 4 hr after dosing and was of shorter duration than its hypotensive effect, it is probable that the β₁-adrenoceptor blocking activity of YM430 partially inhibits the tachycardia induced by the reflex increase in sympathetic tone in response to its hypotension.

In this experiment, the hypotensive effects of YM430 might be attributable to unchanged YM430 in plasma, because the time course of this effect is well consistent with that of the plasma concentration of unchanged YM430 in NTD (H. Matsushima et al., unpublished data).

In the next study, we evaluated the hypotensive effects of YM430 during repeated oral dosing in SHR and NTD. In SHR, YM430 produced a long-lasting hypotensive effect with a slight increase in HR. However, this elevation of HR is not as large as that with other 1,4-dihydropyridine calcium entry blocking agents (20). In NTD, YM430 produced a long-lasting hypotensive effect but almost had no effect on HR and atrioventricular conduction time. The β₁-adrenoceptor blocking activity of YM430 as determined by the inhibition of ISO-induced tachycardia occurred at the same dose as that at which its hypotensive effects were produced. YM430 in single daily dosing for both 14 days and 10 days was accompanied by neither the development of tolerance nor augmentation of the hypotensive effect, nor was there β₁-adrenoceptor blocking activity (inhibiting HR), in both SHR and NTD. Therefore, it is suggested that the ratio of calcium entry blocking to β₁-adrenoceptor blocking activities of YM430 appear to remain constant on not only single oral dosing but also repeated administration.

It is reported that a drug such as clonidine which acts on the central nervous system induces rebound hypertension, so called "withdrawal syndrome", accompanied by an acute increase in plasma catecholamine concentration after the cessation of repeated dosing (21). However, since the main mechanism of hypotension of YM430 is its calcium entry blocking effect in the peripheral vascular system, this drug would not potentiate sympathetic nerve activity if its treatment is stopped. In fact, rebound hypertension by YM430 was not observed when repeated dosing was stopped in SHR and NTD.

Sodium retention must be one of the unfavorable effects of a vasodilator such as hydralazine (22, 23). However, YM430 increased urinary volume and sodium excretion after oral dosing in SHR (K. Shibasaki et al., unpublished data), so sodium and water retention might not be induced by YM430. In fact, the increase in body weight by YM430 was almost the same as that in the control group. Therefore, YM430 might be acceptable for the treatment of hypertension with sodium retention.

In general, the dihydropyridine calcium entry blocking agents are vascular selective, while the non-dihydropyridines such as verapamil and diltiazem have more prominent effects on the calcium channels in the sinoatrial node (decreased HR) and myocardium (negative inotropic effect). On the other hand, a β-adrenoceptor blocker such as propranolol suppressed the left ventricular contractility, sinus node activity and AV-conduction in anesthetized dogs (24). Therefore, in combined treatment with a calcium entry blocking agent and β₁-adrenoceptor blocking agent, its effect on the AV-conduction system is a crucial factor. In this study, at the effective hypotensive dose of YM430, no changes in PQ-interval was observed after single and repeated oral dosing in conscious dogs. Therefore, it is suggested that YM430, like other dihydropyridines, is a vascular selective calcium entry blocking agent and depressant effect of YM430 on AV-conduction was not induced by its possession of both calcium entry blocking and β₁-adrenoceptor blocking activities in one molecule.

In conclusion, our results indicate that YM430 is a slow-onset and long-lasting antihypertensive agent that induces a smaller increase in HR than nifedipine. The hypotensive effect of YM430 is attributable to its calcium entry blocking activity, while its attenuated increase in HR results from its β₁-adrenoceptor blocking activity. The drug therefore behaves as a hybrid compound, combining calcium entry blocking and β₁-adrenoceptor blocking activities in vivo. The degree of these blocking activities of this compound remains near-constant after oral dosing. YM430 may represent an effective suitable agent for the treatment of hypertension.

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