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Short communication

Venodilator effects of pranidipine, a 1,4-dihydropyridine Ca^{2+} channel antagonist, in rats: comparison with nifedipine and amlodipine

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Abstract

The effects of pranidipine, a dihydropyridine Ca^{2+} channel antagonist, on mean circulatory filling pressure, an index of body venous tone, were compared with those of other dihydropyridines (nifedipine and amlodipine) and nitroglycerin in anaesthetized hexamethonium- and norepinephrine-treated rats. In this study, the compounds were used at doses having a equi-hypotensive effect. Intravenous bolus injection of pranidipine (10 and 30 μg/kg) significantly decreased mean circulatory filling pressure in a dose-dependent manner, as did nitroglycerin (30 and 100 μg/kg). Nifedipine (30 and 100 μg/kg), however, did not affect mean circulatory filling pressure. Amlodipine (1000 and 3000 μg/kg) decreased mean circulatory filling pressure only at the higher dose. These results suggest that pranidipine has a greater venodilator effect than nifedipine and amlodipine.

Keywords: Pranidipine (OPC-13340); Ca^{2+} channel antagonist; Circulatory filling pressure, mean; Venodilator effect; (Rat)

1. Introduction

Pranidipine (OPC-13340, methyl 3-phenyl-2 (*E*)-propyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate) is a new potent and long-lasting dihydropyridine Ca^{2+} channel antagonist being developed clinically as an antihypertensive and antianginal drug. We previously reported that pranidipine exerts a potent and long-lasting hypotensive action in several kinds of hypertensive rats and dogs (Nakayama et al., 1990; Mori et al., 1993). Pranidipine increased the blood flow of various arteries such as the coronary, femoral, vertebral and superior mesenteric arteries in anaesthetized dogs (Nakayama et al., 1991). However, there is no information on the effects of pranidipine on body venous tone or compliance. Indirect information on the effects of pranidipine on left ventricular end-diastolic pressure (Ohura et al., 1994) and pulmonary artery wedge pressure (Nishinaka et al., 1994) suggests that pranidipine causes venodilation. The purpose of this study was therefore to determine the effects of pranidipine on body venous tone in rats by the measurement of mean circulatory filling pressure. Mean circulatory filling pressure, an index of body venous tone, was measured during circulatory arrest induced by balloon inflation in the right atrium (Yamamoto et al., 1980). The effects of pranidipine were compared with those of two other dihydropyridine Ca^{2+} channel antagonists, nifedipine and amlodipine.

2. Materials and methods

2.1. Animal preparation

Male Sprague-Dawley rats weighing 270–350 g were anaesthetized with urethane (1.5 g/kg i.p.), and a tracheotomy was performed. Three cannulas (PE-50) were inserted, one into the left femoral artery to record arterial pressure and heart rate, one into the inferior vena cava through the left femoral vein to record central venous pressure, and one into the right femoral vein to infuse hexamethonium and norepinephrine. A saline-filled Fogarty balloon catheter (3F) was inserted into the right atrium via the right jugular vein.

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2.2. Measurement of mean circulatory filling pressure

Mean circulatory filling pressure was determined by the method introduced by Yamamoto et al. (1980). Briefly, the balloon was inflated in the right atrium with 0.2 ml of saline, causing circulatory arrest. Venous pressure increased and arterial pressure decreased immediately, each reaching plateau in 5–7 s. These plateau pressures are referred to as venous plateau pressure and final arterial pressure, respectively. Mean circulatory filling pressure was calculated from the following equation,

mean circulatory filling pressure
= venous plateau pressure
+ 1/60 (final arterial pressure
− venous plateau pressure)

where 1/60 is the arterial-to-venous compliance ratio.

2.3. Experimental protocol

After measurement of the basal values of mean arterial pressure, heart rate and mean circulatory filling pressure, hexamethonium was infused into the right femoral vein at 0.135 mg/kg per min (0.5 ml/h) to exclude the baroreflex activity. About 10 min after the start of hexamethonium infusion, blood pressure was stable at a decreased level; then norepinephrine was additionally infused into the right femoral vein at 2.0 μg/kg per min (0.5 ml/h) to elevate hexamethonium-decreased mean circulatory filling pressure and arterial pressure to the basal level. These drugs were applied throughout the experiment. After stabilization, the three parameters were measured as the control values. Ten and 25 min after measurement of the control values, a low dose and a high dose, respectively, of pranidipine (10 and 30 μg/kg), nifedipine (30 and 100 μg/kg), amlodipine (1000 and 3000 μg/kg), nitroglycerin (30 and 100 μg/kg) and the vehicle (40 and 50% dimethylformamide in saline) were intravenously injected into the left femoral vein ($n = 7$ per group). The test compounds were all used at doses having equi-hypotensive effect. The three parameters were measured at the peak of hypotension. It took about 0.5 min for nitroglycerin, 1 min for nifedipine and 2 min for pranidipine and amlodipine from drug injection to peak hypotension. Hexamethonium used in this study inhibited tachycardiac responses to acetylcholine (2 μg/kg).

2.4. Drugs

Fresh drug solutions were prepared daily. Pranidipine (synthesized at Otsuka Pharmaceutical), amlodipine (extracted from Amlodine, Sumitomo, Japan) and nifedipine (Wako, Japan) were dissolved in 40 and 45% dimethylformamide (Wako, Japan) in saline for the low dose and the high dose, respectively. Nitroglycerin (Millisrol inj., Nippon Kayaku, Japan, 1 mg/2 ml) was used without dilution. Hexamethonium (Wako, Japan) was dissolved in saline. Norepinephrine (Sankyo, Japan, 1 mg/ml) was diluted with saline.

2.5. Statistics

All values were expressed as means ± S.E.M. Comparisons between the vehicle group and the treated groups were performed by two-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test using the Statistical Analysis System (SAS Institute Japan, Japan). In addition, the differences between the pranidipine group and the other Ca^{2+} channel antagonist groups were analyzed by two-way ANOVA, followed by Dunnett's multiple comparison test. Differences were considered to be significant if $P < 0.05$.

3. Results

Table 1 shows the values before and after hexamethonium and norepinephrine infusion. There were no statistical differences in the control values of mean arterial pressure and mean circulatory filling pressure among the groups.

In this study, the compounds were used at doses having an equi-hypotensive effect and there were no statistical differences in the magnitude of hypotension among the test compounds (Fig. 1a). In this condition, nitroglycerin caused a significant decrease in mean circulatory filling pressure compared with the vehicle. Pranidipine also significantly decreased mean circulatory filling pressure in a dose-dependent manner. Nifedipine did not affect mean circulatory filling pressure. Amlodipine decreased mean circulatory filling pressure only at the higher dose. The pranidipine-induced decrease in mean circulatory filling pressure was

Table 1
Basal and control values of mean circulatory filling pressure (MCFP) and mean arterial pressure (MAP) in each group

	MCFP (mmHg)	MAP (mmHg)
Before hexamethonium + norepinephrine (basal)		
Vehicle	6.2 ± 0.1	88 ± 3
Pranidipine	6.1 ± 0.2	79 ± 3
Nifedipine	5.9 ± 0.2	81 ± 3
Amlodipine	5.9 ± 0.3	79 ± 3
Nitroglycerin	6.2 ± 0.3	85 ± 6
After hexamethonium + norepinephrine (control)		
Vehicle	6.2 ± 0.2	86 ± 4
Pranidipine	6.5 ± 0.3	78 ± 3
Nifedipine	6.2 ± 0.4	81 ± 2
Amlodipine	6.4 ± 0.2	79 ± 3
Nitroglycerin	6.3 ± 0.4	84 ± 3

Values are means ± S.E.M. There were no significant differences in the control values of MCFP and MAP among the groups ($n = 7$ per group).

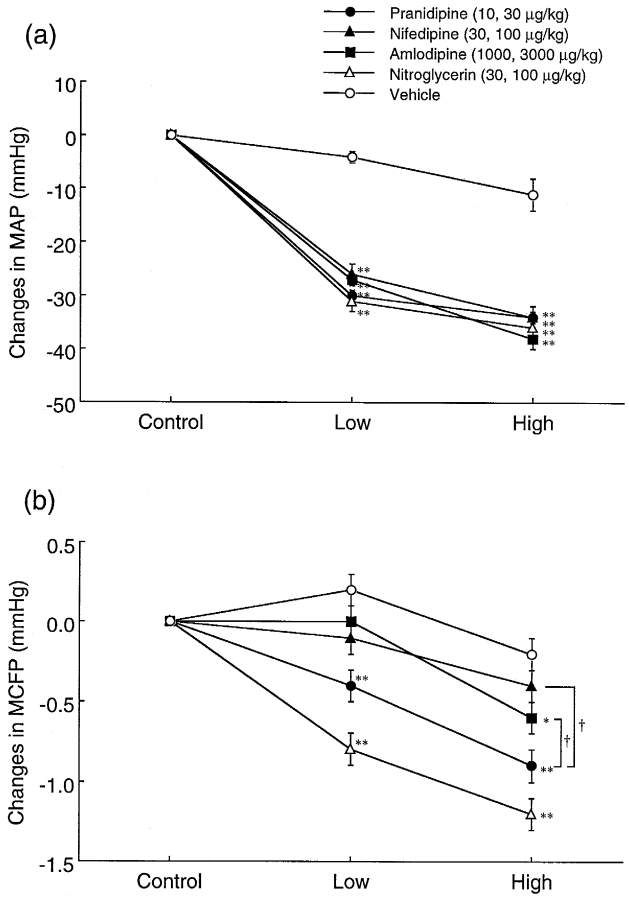

Fig. 1. Effects of pranidipine, nifedipine, amlodipine, nitroglycerin and the vehicle on mean arterial pressure (MAP) (a) and mean circulatory filling pressure (MCFP) (b) represented as changes from control values ($n = 7$ per group). Each point represents the means ± S.E.M. Low: lower dose of each compound; High: higher dose of each compound. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the vehicle-treated group. $^{\dagger}P < 0.05$ compared with the pranidipine-treated group.

significantly greater than the nifedipine- and amlodipine-induced decreases (Fig. 1b). Heart rate was significantly decreased by all of the Ca^{2+} channel antagonists, but not by nitroglycerin (data not shown).

4. Discussion

In this study we examined the effects of pranidipine on mean circulatory filling pressure in comparison with those of nifedipine, amlodipine and nitroglycerin in anaesthetized rats. Mean circulatory filling pressure is widely accepted as an index of venous tone. This is a good method in the sense that the measurement of venous tone relates to the entire venous bed, and it has, therefore, been used by numerous investigators to measure the effects of vasoactive agents on the venous system. Several investigators have reported that venodilators such as sodium nitroprusside, nitroglycerin (D'Oyley et al., 1989), isoprenaline (Abdelrahman and Pang, 1990), α-adrenoceptor antagonists (D'Oyley and Pang, 1990) and calcitonin gene-related peptide (Abdelrahman and Pang, 1992) did not reveal effects on body venous tone in intact animals, unless reflex autonomic nerve activity was attenuated in advance or venous tone was directly elevated by the administration of drugs such as norepinephrine and phenylephrine. Thus, rats were pretreated with a continuous infusion of hexamethonium and norepinephrine to unmask the venodilator effects of the test compounds in this study.

Pranidipine significantly decreased mean circulatory filling pressure in a dose-dependent manner, as did nitroglycerin. Nifedipine did not affect mean circulatory filling pressure. Amlodipine decreased mean circulatory filling pressure only at the higher dose. These compounds were compared at doses having equi-hypotensive effect. These results show that pranidipine has a greater venodilator effect than nifedipine and amlodipine. These Ca^{2+} channel antagonists may have the same Ca^{2+} channel blocking action at the doses used in this study, because they had equi-hypotensive effect. Thus, other mechanisms than Ca^{2+} channel blocking action may be involved in the venodilator effect of pranidipine.

Several investigators examined the effects of Ca^{2+} channel antagonists on mean circulatory filling pressure, and reported that dihydropyridine Ca^{2+} channel antagonists had little effect on it (Ito and Hirakawa, 1984; Waite et al., 1988). In vitro studies also support these results. Nifedipine had little effect on norepinephrine-induced constriction in isolated femoral veins at the doses inhibiting the KCl-induced and norepinephrine-induced constriction in isolated femoral arteries (Yamaura et al., 1994). But Shiramoto et al. (1994) reported that CD-832, a dihydropyridine Ca^{2+} channel antagonist which had a releasable nitrate moiety in its chemical structure, decreased mean circulatory filling pressure in anaesthetized hexamethonium-treated rats. Pranidipine does not have a releasable nitrate moiety, but it does have a unique action on endothelium-dependent relaxation. In the isolated rat aorta, clinical concentrations of pranidipine prolonged the duration of endothelium-dependent relaxation induced by acetylcholine or ATP. This prolongation was not observed with other Ca^{2+} channel antagonists such as nifedipine, nitrendipine, nicardipine, diltiazem or verapamil (Nakayama et al., 1993). Thus, the pranidipine-induced decrease in mean circulatory filling pressure in this study may be related to the enhancement of the action on endothelium-dependent relaxing factor. Ohura et al. (1994) reported that pranidipine suppressed an increase in left ventricular end-diastolic pressure during coronary occlusion and reperfusion in an in vivo porcine model. Nishinaka et al. (1994) reported that pranidipine suppressed the elevation of pulmonary artery wedge pressure on exercise-induced angina in patients. The enhancement of the action on endothelium-dependent relaxing factor may be involved in these effects.

It is well known that edema is often induced by the

administration of Ca^{2+} channel antagonists to patients (Russell, 1988). This side effect seems to be derived from a decrease in the ratio of pre- to post-capillary resistance. Our findings in this study of decreased arteriolar tone but little effect on venous tone following the administration of nifedipine and amlodipine are thus consistent with such clinical findings. Pranidipine, however, decreased arterial pressure and also mean circulatory filling pressure. The effects of pranidipine may clinically contribute to a decrease in the incidence of the side effect.

In conclusion, our results suggest that pranidipine has a greater venodilator effect than nifedipine and amlodipine.

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