Effects of Semotiadil Fumarate, a Novel Calcium Antagonist, on Blood Pressure and Heart Rate in Conscious Spontaneously Hypertensive Rats

Akira Kanda and Hiroo Hashimoto*

Daiichi Pharmaceutical Co., Ltd., Exploratory Research Laboratories II, Tokyo R & D Center, 16-13, Kita-Kasui 1-chome, Edogawa-ku, Tokyo 134, Japan

Received February 1, 1993 Accepted July 6, 1993

ABSTRACT—The acute antihypertensive effects of orally administered semotiadil, a novel calcium antagonist, were compared with those of nifedipine and diltiazem in conscious, unrestrained spontaneously hypertensive rats (SHRs). Semotiadil (10 and 30 mg/kg) produced a dose-dependent hypotension that persisted for 18 hr at 30 mg/kg. Diltiazem (30 and 100 mg/kg) and nifedipine (1 and 3 mg/kg) also exhibited hypotension dose-dependently, but their durations of actions were shorter than that of semotiadil. Semotiadil caused a slight increase in heart rate, while diltiazem and nifedipine caused a bradycardia and a marked tachycardia, respectively. These results suggest that semotiadil has a beneficial property as an antihypertensive drug.

Keywords: Semotiadil, Antihypertensive effect, Spontaneously hypertensive rat

Calcium antagonists have been used for the treatment of hypertension as first choice drugs (1). There are three major calcium antagonists, i.e., nifedipine, diltiazem and verapamil; the former one is classified as a dihydropyridine (DHP)-type drug and the latter two, as non-dihydropyridine (non-DHP)-type drugs. It is well known that DHP calcium antagonists have less cardio-depressant effect than a vasodilatory one and non-DHP calcium antagonists show almost equieffectiveness on cardio-depressant (e.g., inhibition of sinoatrial (SA) automaticity and inhibition of atrioventricular (AV) nodal conduction) and vasodilatory effects (2). Such pharmacological features are considered to reflect some of the clinically observed untoward effects of these drugs; namely, DHP calcium antagonists cause reflex tachycardia (3), and non-DHPs induce bradycardia and AV block (4). Semotiadil (semotiadil fumarate, SD-3211) is a novel non-DHP type calcium antagonist that shows more vasoselective action than diltiazem (5, 6) and verapamil (5). Because of this peculiar property, the drug is expected to exert less cardio-depressant effect and to become a beneficial antihypertensive drug (6). It has been shown that semotiadil produces little change in heart rate when administered to conscious hypertensive rats (7) and dogs (8). In addition, semotiadil shows longer-lasting antihypertensive action than diltiazem (7, 8) and nicardipine (7). However, there have been no reports in which these effects of semotiadil were evaluated successively for 24 hr after dosing in conscious, unrestrained hypertensive animals. In this study, therefore, we investigated the 24-hr effects of semotiadil on blood pressure and heart rate in conscious and unrestrained SHR. Moreover, we compared such effects with those of diltiazem and nifedipine, a prototype non-DHP and DHP calcium antagonist, respectively.

Experiments were carried out on male SHR (Okamoto-Aoki strain, 310–410 g). Each rat was anesthetized with ether, and the left femoral artery was cannulated for direct measurement of blood pressure. The cannula was filled with sodium heparin (50 U/ml) to prevent blood coagulation. The rats were kept in individual cages under constant temperature (23 ± 1°C), humidity (55 ± 15%) and photoperiod (7:00 AM to 7:00 PM), and they were allowed food and tap water ad libitum. Next day, after the initial values of blood pressure and heart rate were recorded, semotiadil (10 or 30 mg/kg), nifedipine (1 or 3 mg/kg) or diltiazem (30 or 100 mg/kg) was orally administered at about 10:00 AM. For the control group, the vehicle for these drugs (0.5%
methylcellulose) was administered. Thereafter, measurements of blood pressure and heart rate for 24 hr were carried out. Blood pressure was continuously recorded on an oscillographic recorder (8K21; Nihondenki-San-ei, Tokyo) through a strain amplifier (6M82, Nihondenki-San-ei), and heart rate was determined with a cardio tachometer (1321, Nihondenki-San-ei) triggered by pulse of blood pressure. Semotiadil fumarate was synthesized at Santen Pharmaceutical Co., Ltd. (Osaka). Nifedipine and diltiazem hydrochloride were purchased from Sigma (St. Louis, MO, USA). These drugs were suspended in the vehicle described above. Values were given as means±S.E.M. Differences from the initial values were analyzed by Student's t-test; and in the case of a comparison with the control group, the Kruskal-Wallis test was applied. A P value less than 0.05 was regarded as statistically significant.

Initial values of mean blood pressure and heart rate before administration are shown in Table 1. There was no significant difference among the initial values for each group.

Changes in mean blood pressure after administration of semotiadil, diltiazem or nifedipine are shown in Fig. 1. The vehicle of the drugs exerted little effect on this parameter. Semotiadil produced a dose-dependent decrease in mean blood pressure. At 10 mg/kg, the maximum fall in mean blood pressure was 23.6±6.6 mmHg, and a significant hypotension compared with the initial value was observed until 10 hr after administration. At 30 mg/kg, semotiadil showed a maximum hypotension of 52.4±9.4 mmHg 30 min after administration. At this dose, significant decreases in mean blood pressure compared with both the initial value and the control group were observed for 10 and 18 hr, respectively. Eighteen hours after the administration, a 21.4±7.4 mmHg fall in mean blood pressure was still seen. Thus, the antihypertensive effect of semotiadil emerged immediately and persisted for a long time. Diltiazem also exerted an antihypertensive effect dose-dependently. The maximum decreases in mean blood pressure were 43.8±6.6 mmHg and 59.4±14.6 mmHg at 30 and 100 mg/kg, respectively. At both doses, however, the duration of action was short. Substantially, significant hypotension lasted only for 6 hr; and even at 100 mg/kg, a fall in mean blood pressure of more than 20 mmHg could be observed only until 8 hr after administration. Lower doses of nifedipine produced almost equi hypotension as higher doses of the other two calcium antagonists. The maximum falls in mean blood pressure of 21.0±3.8 and 59.8±5.2 mmHg were obtained at 1 and 3 mg/kg, respectively. On the other hand, the duration of antihypertensive action was very short. At 1 mg/kg, significant hypotension was observed for only 2 hr; and even at 3 mg/kg, such a response lasted for only 4 hr.

Figure 2 shows the effects of the three calcium antagonists on heart rate. The vehicle caused a slight increase in heart rate presumably due to the excitation of the animals by administration by gavage. After administration of both doses of semotiadil, the heart rate was increased, but only to a small degree. The increases induced by both doses were significant as compared with the respective initial values, but not significant as compared with the control group. Four hours after the administration when significant hypotensions still persisted (Fig. 1), the changes in heart rate were not significant at both doses. In contrast, diltiazem decreased the heart rate at either dose; especially, 30 mg/kg of this drug produced significant decreases compared with both the initial value and the control group. Nifedipine markedly increased the heart rate in a dose-dependent manner. At both doses, the increases were significant as compared with not only the initial values but also the control group.

The present study clarified that semotiadil produced a long-lasting antihypertensive effect in the unrestrained SHR whose blood pressure was recorded for a successive 24 hr. At 30 mg/kg, the dose that reduced the mean blood pressure by about 50 mmHg, a significant fall was observed until 18 hr after administration. The duration of action of semotiadil was apparently longer than that of diltiazem or nifedipine. By use of indirect tail-cuff plethysmography, Takada et al. (7) have reported the antihypertensive effects of semotiadil (30 mg/kg, p.o.) and diltiazem (100 mg/kg, p.o.) in conscious SHR. In their report, the effects of both drugs were observed from 1 hr after administration, and the degree of hypotension was similar to the present results from 1 hr after administration. Compared with the control, the duration of significant

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<th>Vehicle</th>
<th>Semotiadil 10 mg/kg</th>
<th>Semotiadil 30 mg/kg</th>
<th>Diltiazem 30 mg/kg</th>
<th>Diltiazem 100 mg/kg</th>
<th>Nifedipine 1 mg/kg</th>
<th>Nifedipine 3 mg/kg</th>
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<tbody>
<tr>
<td>MBP (mmHg)</td>
<td>192.2±6.9</td>
<td>194.0±10.8</td>
<td>182.2±4.6</td>
<td>188.0±1.7</td>
<td>191.0±1.7</td>
<td>197.3±6.7</td>
<td>199.5±7.6</td>
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<td>HR (beats/min)</td>
<td>354.0±15.2</td>
<td>356.0±2.5</td>
<td>346.0±14.6</td>
<td>346.0±11.4</td>
<td>344.2±11.8</td>
<td>352.3±14.2</td>
<td>363.3±22.6</td>
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hypotension produced by semotiadil and diltiazem was 9 and 3 hr, respectively, in their study. In the present study, significant hypotension of semotiadil and diltiazem compared with the control lasted for 10 and 4 hr, respectively. Therefore, the changes in blood pressure within 10 hr after the administration of drugs were similar to those observed by the indirect method. Nishimura et al. (5) have observed using isolated rabbit aorta that the calcium antagonistic effect of semotiadil can not be reversed easily by washout in contrast with that of diltiazem. Therefore, one reason for the long duration of the antihypertensive effect of semotiadil may be the tight binding of this drug to the vascular tissue.

In this study, it was demonstrated that increases in heart rate induced by semotiadil were small and transient as compared with decreases in blood pressure. Although Takada et al. (7) have described that this drug scarcely changes the heart rate in conscious SHR using the indirect tail-cuff method, the initial values of heart rate (383 – 403 beats/min) are higher than our results (344 – 363 beats/min). In our study, the activity of the sympathetic nervous system seems to be lower because the rats were not warmed, and this condition probably brings about lower initial values of heart rate. Thus, it is highly likely that the heart rate tends to increase more easily by excitation of animals after administration of drugs by gavage in this condition.

Fig. 1. Changes in mean blood pressure (MBP) induced by semotiadil, diltiazem and nifedipine in conscious unrestrained SHRs. Each point represents the mean ± S.E.M. of values obtained from five rats. *P < 0.05, **P < 0.01, compared to the initial values. †P < 0.05, ‡P < 0.01, compared to the control group.

Fig. 2. Changes in heart rate (HR) induced by semotiadil, diltiazem and nifedipine in conscious unrestrained SHRs. Each point represents the mean ± S.E.M. of values obtained from five rats. *P < 0.05, **P < 0.01, compared to the initial values. †P < 0.05, ‡P < 0.01, compared to the control group.
study. The slight but significant increases in heart rate observed in the control animals after administration of vehicle may support this consideration. On the other hand, diltiazem clearly decreased the heart rate, showing the characteristic of a non-DHP calcium antagonist (4). Thus, the effect of semotiadil on heart rate is qualitatively different from that of diltiazem, although both drugs are classified as non-DHP-type drugs. In isolated, blood-perfused canine heart preparations, Yoneyama et al. (9) have demonstrated that semotiadil produces less inhibition of SA automaticity than AV nodal conduction, and the profile of semotiadil is different from that of diltiazem which shows equieffective inhibitory action on SA automaticity and AV nodal conduction. Such a characteristic of semotiadil would bring about the difference from diltiazem in the effect on heart rate in vivo. The chronotropic effect of semotiadil was also distinguishable from that of nifedipine, a DHP calcium antagonist, which markedly caused tachycardia. Thus, semotiadil has less effects on heart rate compared with both diltiazem and nifedipine. This property would be attributed to the fact that semotiadil exerts a more vasoselective effect than diltiazem and a more cardioselective one than nifedipine (5).

Recently, new calcium antagonists showing long-lasting effects have appeared, but most of them are DHP-type drugs (10–14). Semotiadil is a non-DHP-type drug, and from the present study, it was clarified that this drug possesses a long-lasting antihypertensive effect and exerts only a weak influence on heart rate. Semotiadil would be expected to be a useful antihypertensive drug, belonging to the group of non-DHP calcium antagonists.

REFERENCES