In vitro and in vivo Vasodilatory Activity of Barnidipine and Its Enantiomers

Osamu Inagaki,* Masaharu Asano, and Toichi Takenaka

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305–8585, Japan. Received August 24, 1998; accepted October 30, 1998

Barnidipine, (3′S)-1-benzyl-3-pyrrolidinyl methyl (4S)-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, is a dihydropyridine calcium antagonist with asymmetric carbons at the dihydropyridine C-4 and the pyrrolidine C-3′ positions. In this study, the vasodilatory activity of barnidipine and its 3 optical isomers were compared in vitro and in vivo to assess the steric effects of these asymmetric carbons. All these enantiomers produced concentration-dependent relaxations on KCl (40 mM)-induced contractions in isolated guinea pig aorta with a potency order of barnidipine > (3′R,4R)=(3′R,4S) > (3′S,4R). The potency ratio between barnidipine and the (3′S,4R) enantiomer was 118. All enantiomers increased coronary blood flow after intra-arterial administration to anesthetized coronary-perfused dogs. The potency order almost agreed with that obtained in vitro, although the potency ratio between barnidipine and the (3′S,4R) enantiomer was only 15. These 4 enantiomers showed stereoselectivity for time course changes as well. The onset and disappearance of blood flow increase after intracoronary administration of barnidipine were slower than those of other enantiomers. The duration for barnidipine was longer than those for other dihydropyridine calcium antagonists such as nifedipine or nitrendipine. The present study suggests stereoselectivity for the C-4 dihydropyridine and to a lesser degree for the C-3′ of pyrrolidine in an ester moiety. The steric effects of these carbons were observed not only in the potency of vasodilatory activity but also in its duration.

Key words barnidipine; stereoselectivity; 1,4-dihydropyridine; enantiomer

Calcium antagonists of the dihydropyridine type are potent peripheral vasodilators which are currently used in the management of hypertension.1–3 The prototype of dihydropyridine calcium antagonist (i.e., nifedipine) is an achiral molecule, but when the ester groups carry different substitution, a chiral center appears in the 4-position of the dihydropyridine ring. Most of these chiral calcium antagonists have shown more potent vasodilator activity than nifedipine. In addition, long duration of action has been claimed for these new calcium antagonists, which improves their clinical usefulness by avoiding fluctuations in blood pressure or the requirement for multiple dosages per day.4,5

The chiral 1,4-dihydropyridines offer an exciting research opportunity to study calcium channels. Many studies on the stereoselectivity of 1,4-dihydropyridine have been conducted.6–7 For example, the (+)-enantiomer of nicardipine shows 3 times greater vasodilatory and hypotensive activities in anesthetized dogs,9 and the (+)-enantiomer of PN 200-110 is 30 times more potent in increasing the cardiac output of anesthetized cats.8 Steric effects on biological activity have been evaluated mainly on the C-4 position of the dihydropyridine ring. The (S) configurations of nitrendipine, nimodipine, Bay e 6627 and PN 200-110 have been reported to contribute greater calcium antagonistic activity than their (R) configurations.6,9 Moreover, some of the enantiomers produce opposite effects, e.g., the (S) enantiomer of Bay K 8644 or 202-791 activates voltage-dependent calcium channels whereas the (R) enantiomer blocks them.6,10

After screening numerous 1,4-dihydropyridine-3,5-dicarboxylates, we selected barnidipine hydrochloride, (3′S)-1-benzyl-3-pyrrolidinyl methyl (4S)-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (Fig. 1) as our new dihydropyridine calcium antagonist. Barnidipine possesses 2 asymmetric carbons, at dihydropyridine C-4 and pyrrolidine C-3′. The absolute configuration of barnidipine was determined to be (S)-1,4-dihydropyridine-C4 and (S)-pyrrolidine-C3 by X-ray crystallographic study.11 Barnidipine is one of 4 enantiomers, the others being (3′S,4R), (3′R,4S) and (3′R,4R). Barnidipine has been shown to possess more potent inhibitory activity in [3H]nitrrendipine binding to rat cerebral membranes than any of the other 3 enantiomers or other dihydropyridines such as nifedipine or nitrendipine.11 In the present study, the in vitro and in vivo vasodilatory activities of barnidipine and its 3 optical isomers were compared to assess the steric effect of the asymmetric carbon in the ester moiety. Barnidipine was once called mepirodipine or YM-09730-5 and its chemical and pharmacological profiles have been described under these names.

MATERIALS AND METHODS

Contraction in Isolated Aorta Male guinea pigs weighing 320–480 g were sacrificed by exsanguination under light anesthesia with ethyl ether. The thoracic aorta was rapidly removed and placed in oxygenated Krebs solution of the following composition: NaCl 118.4 mM, KCl 4.7 mM, MgSO4 1.2 mM, KH2PO4 1.2 mM, CaCl2 2.5 mM, NaHCO3 25 mM and glucose 11.1 mM. The aorta was cut into helical strips (3×15 mm) after the removal of excess fat and connective tissues.

* To whom correspondence should be addressed.

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Fig. 1. Chemical Structure of Barnidipine
and was mounted vertically in organ baths containing 30 ml Krebs solution under a resting tension of 2.0 g. The preload was maintained throughout the experiments and periodically readjusted as needed. The tissue bath solution was maintained at 37°C and aerated with a 95% O₂/5% CO₂ gas mixture. The aorta preparations were allowed to equilibrate in Krebs solution for at least 90 min before the experiments started. Tonic contraction was induced with 40 mM KCl. When the contractions reached a steady state, concentration-response curves for the test drugs were obtained by stepwise cumulative increases in their concentration. A new dose was added immediately after the response to the previous dose reached a new steady state. Isometric tension was recorded through a force-displacement transducer (SB-1T, Nihon Koden, Tokyo, Japan) connected to an amplifier (RP-5, Nihon Koden, Tokyo Japan) and recorded on a recorder (TO-N₃, Fujisoku, Tokyo, Japan).

Coronary Blood Flow in Anesthetized Dogs Adult mongrel dogs of either sex weighing 8—15 kg were used. Anesthesia was induced by a single intravenous injection of sodium pentobarbital (30 mg/kg) and maintained by intravenous infusion of the same anesthetic at a rate of 3—5 mg/kg/h. The trachea was intubated, and the animal was ventilated artificially with room air in a volume of 20 ml/kg at 18—20 breaths/min with the use of a respirator (Shimano Seisakusyo, Tokyo, Japan). A thoracotomy was performed at the left fourth intercostal space. After an intravenous injection of heparin (1000 unit/kg), arterial blood from the distal end of a cannula in the left common carotid artery was led to the circumflex branch of the left coronary artery by an extracorporeal loop. A servocontrolled pump (Model 1251D, Harvard Apparatus, U.S.A.) was incorporated in the circuit to maintain a constant perfusion pressure of 120 mmHg by means of a pump controller (SCS-22, Data Graph Co., Tokyo, Japan). An extracorporeal electromagnetic flow probe (FF-type, Nihon Koden, Tokyo, Japan) was inserted in the circuit to record coronary blood flow. A catheter was placed in the left femoral artery and arterial blood pressure was measured with a pressure transducer (MU-0.5, Nihon Koden, Tokyo, Japan) connected to the catheter. Heart rate was measured with a cardiometer (AT-600G, Nihon Koden, Tokyo, Japan) triggered by the pulse wave of the arterial pressure. All recordings were made on a Nihon Koden multichannel recorder (RM-600). The drug solutions were administered directly into the rubber tube connected close to the coronary artery cannula insertion point. Drugs were injected in a volume of 0.1 ml for a period of 10 s. Four to 5 doses of one isomer were evaluated in a single dog and given in increasing order after coronary blood flow returned to baseline or near baseline levels.

Materials Barnidipine hydrochloride, its optical isomers, nicardipine hydrochloride, and nitrendipine were prepared by Yamanouchi Pharmaceutical Co., Ltd. Nifedipine was purchased from Sigma Chemical (MO, U.S.A.). These compounds were dissolved in distilled water containing 20% ethanol and 20% polyethylene glycol 400, then diluted with 0.9% saline solution to the prescribed concentration.

Statistical Analysis The data are expressed as the mean±S.E.M. Comparison among the groups was performed using one-way analysis of variance (one-way ANOVA) followed by Shift’s test. A probability of less than 0.05 was considered to be statistically significant. The regression analysis of the linear portion of the log-concentration response curves were used for the calculation of IC₅₀ (values 1.2±0.1 g) in isolated guinea pig aorta. The developed tension induced by KCl (40 mM) were 1.4±0.2 g, 1.3±0.3 g, 1.2±0.2 g and 1.0±0.2 g in the barnidipine, 3'R,4'R, 3'R,4'S and 3'S,4'R groups, respectively. Relaxation responses were expressed as a percentage of the KCl-induced contractions. Each point indicates the mean±S.E.M. of 3 to 7 experiments.

RESULTS

Contraction in Isolated Aorta and Atria The addition of KCl (40 mM) into the Krebs solution induced a tonic contraction of 1.2±0.1 g in isolated guinea pig aorta. The developed tension did not vary significantly between groups. The cumulative administration of solvent did not cause a significant change in the developed tension throughout the experiment (data not shown). Barnidipine and the three other enantiomers produced concentration-dependent relaxation in isolated guinea pig aorta (Fig. 2). The inhibitory activity, however, was stereoselective. Barnidipine, the (3'S,4'S) enantiomer, had the most potent relaxant effect among the 4 enantiomers, and the rank order of potency was barnidipine >(3'R,4'R)=(3'R,4'S)>(3'S,4'R). IC₅₀ values are presented in Table 1. Comparison of IC₅₀ values showed that the potency of barnidipine was 15, 22 and 118 times more potent than that of (3'R,4'R), (3'R,4'S) and (3'S,4'R) enantiomers, respectively.

In addition, the relaxant effect of barnidipine on vascular smooth muscle in isolated guinea pig aorta was more potent.
Table 2. Initial Values of Coronary Blood Flow (ml/min) in Coronary-Perfused Dogs

<table>
<thead>
<tr>
<th>Calcium antagonist dose (µg i.a.)</th>
<th>0.03</th>
<th>0.1</th>
<th>0.3</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnidipine (3'S,4S)</td>
<td>28.8±4.1</td>
<td>29.0±4.3</td>
<td>32.4±5.2</td>
<td>29.8±4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3'R,4R</td>
<td>25.4±2.6</td>
<td>25.2±2.1</td>
<td>26.2±2.1</td>
<td>25.2±2.2</td>
<td>27.4±2.1</td>
<td></td>
</tr>
<tr>
<td>3'R,AS</td>
<td>28.6±2.5</td>
<td>25.8±2.7</td>
<td>25.8±2.2</td>
<td>25.4±2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>30.0±3.7</td>
<td>31.0±4.2</td>
<td>31.6±2.8</td>
<td>33.8±4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>29.6±2.4</td>
<td>30.2±2.6</td>
<td>31.2±2.8</td>
<td>33.6±3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>32.0±5.3</td>
<td>32.2±5.4</td>
<td>32.6±5.5</td>
<td>33.4±5.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±S.E.M. of 5 animals.

Table 3. Increase in Coronary Blood Flow in Coronary-Perfused Dogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>ED_{100} (µg)</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnidipine (3'S,4S)</td>
<td>0.60 (0.44–0.92)</td>
<td>1</td>
</tr>
<tr>
<td>3'R,4R</td>
<td>3.0 (2.3–4.4)</td>
<td>1/5.0</td>
</tr>
<tr>
<td>3'R,AS</td>
<td>1.7 (1.4–2.0)</td>
<td>1/2.8</td>
</tr>
<tr>
<td>3'S,4R</td>
<td>9.1 (5.9–17.1)</td>
<td>1/15.0</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>0.73 (0.53–1.05)</td>
<td>1/1.2</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.90 (0.67–1.28)</td>
<td>1/1.5</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.67 (0.41–1.15)</td>
<td>1/1.1</td>
</tr>
</tbody>
</table>

Values are calculated from 5 animals. Figures in parentheses indicate 95% confidence limits.

Fig. 3. Concentration–Response Curves of the Peak Increase in Coronary Blood Flow by (A) Barnidipine and Its Enantiomers and (B) Nicardipine, Nifedipine and Nitrindipine in Anesthetized, Coronary-Perfused Dogs

The circumflex branch of the left coronary artery was perfused with arterial blood from the carotid artery via an extracorporeal loop, and the drug solution was administered directly into the loop in a volume of 0.1 ml. The increases in blood flow were expressed as a percentage of the baseline value. Each point indicates the mean±S.E.M. of 5 experiments.

than that of the other calcium antagonists tested. Comparison of IC_{50} values showed that the potency of barnidipine was 7, 8 and 13 times greater than those of nicardipine, nitrindipine and nifedipine, respectively (Table 1).

Coronary Blood Flow in Anesthetized Dogs The coronary vasodilating activity of each enantiomer was also evaluated in anesthetized coronary-perfused dogs. The initial coronary blood flow values are shown in Table 2. There was no significant difference between any of the groups. Changes in coronary blood flow after direct administration of the enantiomers into the coronary artery are shown in Fig. 3A. The 4 enantiomers all produced dose-dependent increases in coronary blood flow after intra-arterial injection to anesthetized dogs. Heart rate and systemic arterial blood pressure were not affected at the doses used. In terms of the peak increase in coronary blood flow, barnidipine showed the most potent vasodilatory activity of the 4 isomers. Comparison of ED_{100} values demonstrated that the coronary vasodilatory effect of barnidipine was 2.8, 5.0 and 15 times more potent than that of the (3'R,4S), (3'R,4R) and (3'S,4R) enantiomers, respectively (Table 3).

These 4 enantiomers exhibited stereoselectivity for the time course change as well as the potency of the increase in coronary blood flow (Fig. 4). The time to reach the maximum increase after intra-arterial injection of barnidipine was about 2–3 min, whereas that of the other enantiomers was within 1 min. Thus, the onset of action after barnidipine was slower than that of the other enantiomers. Furthermore, the duration of coronary vasodilatory activity of barnidipine was the longest among these enantiomers. The increase in coronary blood flow lasted for more than 2 h after the administration of 1 µg. In order to take into account the kinetics of the coronary vasodilatory activities of these 4 enantiomers, the areas under the increased blood flow curves (AUC) after intracoronary administration of each isomer were calculated by the trapezoidal method. The AUC after the injection of 0.1 µg of barnidipine was about the same as that after the injection of 1 µg of (3'R,4S) and greater than that after 3 µg of (3'R,4R) and 10 µg of (3'S,4R), respectively (Fig. 5A). Thus, the vasodilatory effect of barnidipine was more than 100 times greater than that of (3'S,4R) enantiomer under the indicated conditions.

The time course changes in coronary blood flow after intracoronary administration of barnidipine was compared with those of other dihydropyridine calcium antagonists such as nifedipine, nitrindipine and nicardipine (Fig. 6). These dihy-
Fig. 4. Time-Course of the Increase in Coronary Blood Flow after Administration of Barnidipine and Its Enantiomers in Anesthetized, Coronary-Perfused Dogs

The increases of blood flow were expressed as a percentage of the baseline value. Each point indicates the mean±S.E.M. of 5 experiments.

diarylpyridines increased the coronary blood flow in the same dose range as barnidipine. The time to maximal coronary vasodilation after an injection of barnidipine was about 2 to 3 min, whereas that after the other diarylpyridine calcium antagonists was less than 1 min. Thus, the onset of action after barnidipine was slower than that of the other calcium antagonists. Furthermore, the duration of action of barnidipine was clearly the longest among the antagonists tested. For example, the effect of barnidipine, nitrendipine, nifedipine and nifedipine at 1 μg i.a. lasted for about 120, 25, 20 and 10 min, respectively.

DISCUSSION

Barnidipine possesses 2 asymmetric carbonas in the C-4 position of the diarylpyridine ring and in the C-3' of the pyrrolidine ring in the ester substituent. To investigate the stereospecific effect of the asymmetric carbon in the ester substituent on vasodilatory activity, we conducted an in vitro experiment on the relaxant effect of barnidipine and its 3 optical isomers and an in vivo experiment on the coronary vasodilatory effect of these isomers in anesthetized dogs.

Enantiomers of Bay K 8644 and 202-791 are reported to produce vasoconstriction.\(^{2,10}\) In the case of barnidipine, however, all enantiomers produced a relaxant effect on 40 mM KCl-induced contraction in isolated guinea pig aorta without showing further contractions. Thus, the activation of calcium channels was not observed. The potency order of this relaxing effect was barnidipine > (3'R,4R) = (3'S,4R) > (3'S,4R). In the case of the (S) configuration for the asymmetric carbon in the diarylpyridine ring, the isomer with the (S) configuration of the pyrrolidine configuration in the 3-position of the pyrrolidine ring showed more potent relaxation activity than that of the (R) configuration. In contrast to the (R) configuration at the diarylpyridine C-4, the (R) configuration at the C-3' of the pyrrolidine
ring is preferable to the (S) configuration in the relaxation activity. These results show that the configuration at the pyrrolidine ring C-3' also influences calcium antagonistic activity, although less pronouncedly than the configuration at the dihydropyridine ring C-4.

The potency order in relaxation activity is consistent with the previous findings concerning [3H]nitrendipine binding, except that between the (3'R,4R) and (3'R,4S) enantiomers. In a [3H]nitrendipine binding study, the Kd value of the (3'R,4S) enantiomer was about 4 times smaller than that of the (3'R,4R) enantiomer, whereas their IC50 values in the present relaxation study showed almost the same potency. This could have been due to the reproducibility of the measurements, which could have masked a small difference on the logarithmic scale. Nevertheless, we confirmed, in the relaxation study, that the potency ratio of barnidipine to the (3'S,4R) enantiomer was 118 times, a difference of two orders of magnitude as found in the previous [3H]nitrendipine binding study.

After the intracoronary injection of barnidipine and its enantiomers into coronary-perfused dogs, all enantiomers increased coronary blood flow. In this coronary perfusion system, the perfusion pressure is kept constant by the surroutcontrolled pump. Consequently, the increase in coronary blood flow represents in vivo coronary vasodilation at the cardiac vascular. Barnidipine showed the most potent in vivo vasodilatory activity among the 4 enantiomers. The potency order of the enantiomers in the peak-increase in coronary blood flow was barnidipine > (3'R,4S) = (3'R,4R) > (3'S,4R), and this order is consistent with that in the [3H]nitrendipine binding study. Stereoselectivity was observed not only in the potency of the increase but also in time course changes. Regarding time course changes, the onset of action of barnidipine was slower than that of other enantiomers, and its duration was much longer than that of other enantiomers. The increase in coronary blood flow by barnidipine lasted about 2h after the administration of a 1μg dose. These data indicate that the steric effect of dihydropyridine calcium antagonists is observed also in the kinetics of vasodilatory activities.

Although the potency order of the enantiomers in the peak increase in coronary blood flow is almost compatible with that in the relaxation study of the isolated aorta and that in the previous [3H]nitrendipine binding study, this in vivo difference in potencies was much smaller than the difference observed in vitro. For example, the potency ratio of barnidipine to the (3'S,4R) enantiomer in vitro was 118, whereas that in vivo was only 15. Briand et al. reported that (+) PN 200-110 was only 10-fold more potent than the (−) isomer in lowering blood pressure in vivo, whereas the difference in potency in vitro was over 100 times. They suggested that, when the kinetics of the hypotensive effects were taken into account, the in vivo difference in potency was close to that observed in vitro. Consequently, we calculated the AUC values for the increased coronary blood flow by barnidipine and its enantiomers. As shown in Fig. 5A, the AUC showed dose-dependent increases. Barnidipine is over 10, 30 and 100 times more potent than the (3'R,4S), (3'R,4R) and (3'S,4R) enantiomers, respectively, in increasing the AUC. This difference in the AUC was closer to that observed in vitro [3H]nitrendipine binding study than the difference in peak-increase (Fig. 3A).

The discrepancy between the in vitro and in vivo difference in the potency of vasodilatory activities was observed on other dihydropyridine calcium antagonists as well. The in vitro potency of barnidipine was about 10 times more potent than those of nifedipine, nitrendipine and nicardipine in the present study. This in vitro difference is consistent with that reported in the [3H]nitrendipine binding study. However, the in vivo dose–response curve of barnidipine for a peak increase was almost the same as those of nifedipine, nitrendipine and nicardipine in the coronary perfusion study (Fig. 3B). The duration of the barnidipine was longer than that of other dihydropyridine calcium antagonists tested (Fig. 6), and consequently, the dose–AUC curve of barnidipine was shifted about 10-fold to the left of the other dihydropyridines (Fig. 5B).

The long duration of barnidipine could be explained by its slow association and dissociation from dihydropyridine binding sites. The sustained occupancy of barnidipine on dihydropyridine binding sites was suggested in both in vitro and ex vivo studies. Yamada et al. demonstrated the sustained occupancy of barnidipine on calcium antagonist receptors after oral administration to spontaneously hypertensive rats.
They also reported that the in vitro blockade of cardiac (+)-[3H]PN 200-110 binding sites induced by barnidipine was not reversed by repeated washout with Tris–HCl buffer. Nakayama et al. showed that the suppression of K⁺-induced contractions by barnidipine remained, even after washings at 20 min intervals for more than 3 h in pig coronary arteries. The slow onset and long duration of new dihydropyridine calcium antagonists such as lacidipine have often been attributed to the high lipophilicity of these compounds. A membrane bilayer pathway has been advocated as a mechanism for the action of these drugs. This mechanism proposes drug partitioning into the lipid bilayer followed by lateral diffusion to its specific binding site on calcium channels. The persistence of the drug in the lipid compartment would contribute to its long-lasting vasodilatory effect. According to this explanation, barnidipine, the (3'S,4S) enantiomer, and its (3'R,4R) enantiomer should have the same duration of effects, because mirror-image optical isomers are expected to have the same lipophilicity. However, the duration of increased coronary blood flow by barnidipine is far longer than that by its (3'R,4R) enantiomer, even at the equivalent effective doses. Therefore, in the case of barnidipine, the lipophilicity might not be the main cause for its long duration. Shimada et al. suggested, using his ion channel binding model analysis, that the mechanism of the long-lasting anti-hypertensive effect of new calcium antagonists is due to their high binding affinity at ion-channel sites. Our finding supports his suggestion concerning the point that the order of the duration of increased coronary blood flow by dihydropyridines agrees well with the order observed in the in vitro [3H]nitrendipine binding study. The high binding affinity of barnidipine for calcium channels may contribute to its long duration of action.

It is well established that the use of simple and convenient treatment regimens improves patients' compliance, and physicians are becoming interested in using drugs that are effective when administered once or twice daily. Barnidipine showed a long-lasting antihypertensive effect in Japanese essential hypertensive patients. In addition, some dihydropyridine derivatives with a long duration are reported to cause favorable effects on the myocardium. Gross et al. demonstrated in dogs that amloidipine improved myocardial contractility during reperfusion after 45 min of ischemia. Satoh et al. showed that azelnidipine significantly enhanced the recovery of contractile function from myocardial stunning caused by 20 min ischemia. A recently reported case-controlled study indicated that patients taking long-acting calcium antagonists were found to be at no increased risk of a cardiovascular event compared with those on β-blocker monotherapy, whereas patients taking short-acting calcium antagonists were found to be at significantly greater risk of a cardiovascular event compared with those on β-blocker or long-acting calcium blocker monotherapy. Therefore, the long duration of barnidipine is preferable in the treatment of hypertension.

In conclusion, these results show that the configuration of an asymmetric carbon in the ester moiety as well as the dihydropyridine C-4 influences calcium antagonistic activity. The steric effect of these carbons was observed not only in the vasodilatory activity but also in its duration. Finally, barnidipine showed longer duration of vasodilatory action than its other enantiomers and other dihydropyridine calcium antagonists.

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