VASODILATOR AND HYPOTENSIVE EFFECTS OF THE OPTICAL ISOMERS OF NICARDIPINE (YC-93), A NEW \( \text{Ca}^{2+} \)-ANTAGONIST

Toichi TAKENAKA, Iwaki MIYAZAKI, Masaharu ASANO, Saburo HIGUCHI and Hiroo MAENO

Department of Pharmacology and Biochemistry, Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd., Azusawa, Itabashi-ku, Tokyo 174, Japan

Accepted March 29, 1982

Abstract—Vasodilator and hypotensive effects of (+) and (−) nicardipine were investigated in anesthetized dogs. When administered intravenously, (+) nicardipine was 3 times as potent as the (−) isomer in increasing vertebral blood flow and in lowering mean blood pressure. When injected into the vertebral artery, (+) nicardipine was also 3 times as potent as the (−) isomer in increasing vertebral blood flow. Upon both routes of administration, the duration of the action after (+) nicardipine was longer than that after the (−) isomer. However, there were no differences of plasma nicardipine levels after intravenous injection of both isomers to conscious beagle dogs. The LD50 values of (+) nicardipine in mice and rats upon intravenous injection were only 1.5–2 times smaller than those of the (−) isomer. These results indicate that there exists a stereoselectivity of vasodilator and hypotensive actions among the nicardipine isomers.

Racemic nicardipine (YC-93) an asymmetric 1,4-dihydropyridine derivative, is a potent cerebral and coronary vasodilator with hypotensive activity (1–3). The drug appears to act directly on vascular smooth muscle cells through \( \text{Ca}^{2+} \)-antagonistic activity (3, 4), although involvement of cAMP via inhibition of cAMP phosphodiesterase is suggested in its inhibitory action on oxytocin-induced contraction of the rat uterus (5). Recently, racemic nicardipine has been found to be useful in the treatment of cerebral ischemia due to thromboembolism, atherosclerosis, or cerebral hemorrhage (6) and essential hypertension (7). Nicardipine has an asymmetric carbon at position 4 of the dihydropyridine ring and therefore has two optical isomers, i.e., (+) and (−) nicardipine (8). The present study was aimed at determining how (+) nicardipine differs from the (−) isomer in vertebral vasodilator and hypotensive actions and in acute toxicity.

MATERIALS AND METHODS

Vertebral vasodilator and hypotensive effects in anesthetized dogs: Mongrel dogs of both sexes weighing from 12 to 18 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.). The trachea was intubated and artificial respiration was performed with room air in a tidal volume of 20 ml/kg at 18 breaths/min. Blood pressure in the left femoral artery and heart rate were routinely recorded with a pressure transducer (Nihon Kohden, MPU-0.5) and a cardiotachometer (Nihon Kohden, RT-5) on an inkwriting polygraph (Nihon Kohden, RM-85). After the animal was given heparin sodium at a
Effect of intravenous administration on vertebral blood flow and mean blood pressure in anesthetized dogs: In 10 anesthetized dogs, the basal vertebral blood flow, mean blood pressure, and heart rate were 29±3.5 ml/min, 133±5.4 mmHg, and 167±3.6 beats/min, respectively. Changes in vertebral blood flow
duration of the increased vertebral blood flow, and area under the increased vertebral blood flow in anesthetized dogs. Each point is the mean ±S.E.M. of 6 experiments. The isomers were injected into the vertebral artery. In the left side of the figure, the slopes (95% confidence limits) of the vertebral blood flow (y, ml/min) vs log dose (x, µg) regression lines are follows:
y=29.7±20.7 (14.9-26.5) logx (r=0.845, P<0.001) for (+) nicardipine and y=21.2±16.6 (11.5-21.6) logx (r=0.823, P<0.001) for (-) nicardipine.

Fig. 1. Dose-response curves to (+) nicardipine (○) and (-) nicardipine (●) for the increase in vertebral blood flow, duration of the increased vertebral blood flow, and area under the increased vertebral blood flow in anesthetized dogs. Each point is the mean ±S.E.M. of 6 experiments. The isomers were injected into the vertebral artery. In the left side of the figure, the slopes (95% confidence limits) of the vertebral blood flow (y, ml/min) vs log dose (x, µg) regression lines are follows:
y=29.7±20.7 (14.9-26.5) logx (r=0.845, P<0.001) for (+) nicardipine and y=21.2±16.6 (11.5-21.6) logx (r=0.823, P<0.001) for (-) nicardipine.

Fig. 2. Effects of intravenous (+) nicardipine (left) and (-) nicardipine (right) on mean blood pressure (MBP) and vertebral blood flow (VBF) in anesthetized dogs. Each point represents the mean ±S.E.M. of 5 experiments.
flow and mean blood pressure after intravenous injections of the optical isomers of nicardipine are shown in Fig. 2. (+) Nicardipine (0.3–10 μg/kg i.v.) and (-) nicardipine (1–30 μg/kg) lowered mean blood pressure with a concomitant increase in vertebral blood flow. In terms of the peak drug-induced changes in blood pressure and vertebral blood flow, (+) nicardipine appeared to be approximately 3 times as active as the (-) isomer. The duration of the vasodilator and hypotensive actions of (+) nicardipine was longer than that of the (-) isomer. At the doses tested, both isomers slightly increased heart rate (5–26 beats/min).

**Plasma levels of nicardipine in conscious beagle dogs:** Changes in plasma levels of nicardipine after intravenous injections of the optical isomers at a dose of 0.2 mg/kg to conscious beagle dogs are shown in Fig. 3. Peak plasma concentrations, area under the plasma concentration time curves, and apparent plasma elimination half-lives were not significantly different among the two isomers.

**Acute toxicity:** The LD50 values of (+) nicardipine were 1.5–2 times smaller than those of the (-) isomer in mice and rats (Table 1). After intravenous injection of a lethal dose of both isomers to mice and rats, death occurred in most cases within 5 min. The characteristic symptoms by (+) nicardipine in mice and rats were similar to those by (-) nicardipine, which were convulsion, hypoactivity, and dyspnea. At autopsy, both isomers showed pulmonary congestion in mice and rats.

**DISCUSSION**

The stereoselectivity of an action is one important component in the definition of specific drug action. The present study in anesthetized dogs shows that both the optical isomers of nicardipine exhibit vertebral vasodilating and hypotensive activities as has been observed with racemic nicardipine (1). However, (+) nicardipine was about 3 times as active as the (-) isomer in increasing vertebral blood flow and in decreasing mean

![Graph showing plasma levels of nicardipine](image-url)

**Fig. 3.** Plasma levels of nicardipine after intravenous injection of (+) nicardipine (○) or (-) nicardipine (●) at a dose of 0.2 mg/kg to conscious beagle dogs. Each point represents the mean±S.E.M. of 4 experiments.

<table>
<thead>
<tr>
<th>Drug</th>
<th>LD50 (mg/kg i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mouse</td>
</tr>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>(+) Nicardipine</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>(12.3–17.6)</td>
</tr>
<tr>
<td>(-) Nicardipine</td>
<td>31.4</td>
</tr>
<tr>
<td></td>
<td>(28.6–34.5)</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
</tr>
<tr>
<td>(+) Nicardipine</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>(11.4–13.3)</td>
</tr>
<tr>
<td>(-) Nicardipine</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>(17.1–21.0)</td>
</tr>
</tbody>
</table>

| Figures in parenthesis represent the confidence limits at P=0.05. Ten animals were used for each dose.
arterial pressure upon an intravenous injection. A similar difference of potency between the two isomers in vertebral vasodilating activity has also been observed when the drugs were injected into the vertebral artery. In addition, our recent observation in isolated rabbit aorta has demonstrated that (+) and (-) nicardipine inhibited the contraction induced by 80 mM KCl with ED50 values of about $3.0 \times 10^{-9}$ and $1.5 \times 10^{-8}$ M, respectively (unpublished data). Interestingly, the potency ratio between (+) and (-) nicardipine for the production of vasodilation and hypotension in vivo is very similar to that for the inhibition of KCl-induced contraction in vitro. Thus, these results clearly demonstrate that there is a stereoselectivity in the vasodilator and vascular Ca$^{2+}$-antagonistic activities of nicardipine and suggest that nicardipine may cause a vasodilation through action at a specific site, i.e., Ca$^{2+}$-channels as suggested by Terai et al. (4) and Satoh et al. (12) rather than action through nonspecific membrane perturbation in vascular smooth muscles. Similar stereoselectivities with Ca$^{2+}$-antagonists have been reported by Satoh et al. (12) in anesthetized dogs where (-) verapamil was more active than the (+) isomer in increasing coronary blood flow and in decreasing mean arterial pressure and by Jim (13) in guinea-pig ileal smooth muscles where (-) D-600 was more potent than (+) D-600 as an antagonist of Ca$^{2+}$/K$^{+}$ induced responses.

The duration of vasodilative and hypotensive actions of (+) nicardipine was longer than that of the (-) isomer. Thus, the question arises as to whether the metabolic effect contributes to the difference of the duration between the two isomers. However, the pharmacokinetics after intravenous injection of (+) and (-) nicardipine were almost same in conscious beagle dogs. The result suggests that (+) nicardipine may more easily accumulated in the blood vessels than (-) nicardipine and that the accumulation in the tissues may serve as a reservoir that prolongs the effects of the (+) isomer. Based on the LD50 values in mice and rats, (+) nicardipine was only 1.5–2.0 times more toxic than the (-) isomer, suggesting that (+) nicardipine has a significant margin of safety between the effective and toxic doses as compared with the (-) isomer. At present it is not known which isomer of nicardipine is of greater therapeutic value in clinical situations. However, (+) nicardipine with relatively less toxicity and longer durations of vasodilative and hypotensive actions deserves attention as a possibly more suitable vasodilator and antihypertensive drug than the (-) isomer.

REFERENCES
1) Takenaka, T., Usuda, S., Nomura, T., Maeno, H. and Sado, T.: Vasodilator profile of a new 1,4-dihydropyridine derivative, 2,6-dimethyl-4-(3-nitrophenyl - 1,4 - dihydropyridine - 3,5 - dicarboxylic acid 3 - (2 - (N - benzyl - N - methylamino)} ethyl ester 5-methyl ester hydrochloride (YC-93). Arzneim.-Forsch. 26, 2172–2178 (1976)


9) Sakuma, A.: Bioassay-Design and Analysis, p. 110-130, University of Tokyo Press, Tokyo (1964)

10) Higuchi, S., Sasaki, H. and Sado, T.: Determination of a new cerebral vasodilator 2,6-dimethyl - 4 - (3 - nitrophenyl) - 1,4 - dihydropyridine - 3,5 - dicarboxylic acid 3 -{(2 - (N-benzyl-N-methylamino))ethyl ester 5-methyl ester hydrochloride (YC-93) in plasma by electron capture gas chromatography. J. Chromatogr. 110, 301-307 (1975)

