Comparison between Cilnidipine and Nisoldipine with Respect to Effects on Blood Pressure and Heart Rate in Hypertensive Patients

Junichi Minami, Toshihiko Ishimitsu, Teruo Higashi, Atsushi Numabe, and Hiroaki Matsuoka

Cilnidipine is a new and unique 1,4-dihydropyridine calcium antagonist that has both L-type and N-type voltage-dependent calcium channel blocking actions. We compared the effects of cilnidipine and another once-daily dihydropyridine calcium antagonist, nisoldipine, on 24-h blood pressure and heart rate in patients with essential hypertension. We enrolled 10 hypertensive outpatients [9 men and 1 woman; age, 55 ± 3 yr (means ± SEM)] in this study. Their ambulatory blood pressure and heart rate were monitored for 24 h at intervals of 30 min with a portable recorder (TM-2425) after 8 wk of treatment with cilnidipine (5 to 20 mg once daily) and after 8 wk of treatment with nisoldipine (5 to 20 mg once daily). The order of the two treatments was randomized. Blood pressure and heart rate measurements for a 24-h period were analyzed for four segments of the day: morning (06:00 to 11:30), afternoon (12:00 to 17:30), nighttime (18:00 to 23:30), and sleeping time (0:00 to 5:30). Blood pressure levels were similar during the two treatment periods for each 6-h segment of the day. Heart rate was significantly higher during treatment with nisoldipine than during treatment with cilnidipine in the morning segment [by 4.1 ± 1.3 beats/min (p < 0.05)] and the afternoon segment [by 6.4 ± 3.6 beats/min (p < 0.05)]. These results suggest that cilnidipine is effective as a once-daily antihypertensive agent and causes reflex tachycardia less than does nisoldipine. (Hypertens Res 1998; 21: 215–219)

Key Words: cilnidipine, calcium antagonist, N-type voltage-dependent calcium channel, heart rate, essential hypertension

Cilnidipine is a new and unique 1,4-dihydropyridine derivative calcium antagonist that has a slow-onset and prolonged duration of hypotensive action (1, 2). Cilnidipine has been shown to attenuate the pressor response to cold stress by reducing sympathetic nerve activity in spontaneously hypertensive rats (SHRs) (3). Studies using the whole-cell patch-clamp technique have shown that cilnidipine has potent inhibitory action on L- and N-type voltage-dependent calcium channels in rat dorsal root ganglion neurons (4). As for the clinical advantages of cilnidipine over other dihydropyridine derivatives in the treatment of hypertension, we have demonstrated that nifedipine retard administered twice daily increased sympathetic nerve activity throughout the entire 24-h observation period, whereas cilnidipine administered once daily produced less sympathetic nerve activation and reflex tachycardia than did nifedipine retard (5). We have also found that the effects of cilnidipine on autonomic nerve activity and heart rate were as small as those of amlodipine, which has a very long biological half-life (6). However, to the best of our knowledge, no study has compared cilnidipine with other once-daily, second-generation dihydropyridines.

The present study was designed to compare the effects of cilnidipine and another once-daily dihydropyridine, nisoldipine, on 24-h blood pressure and heart rate in patients with essential hypertension.

Methods

Patients

Ten outpatients with essential hypertension participated in this study. Informed consent to participate in the study was obtained from all patients after they had been given a detailed explanation of the study protocol. The study protocol was approved by the Ethical Committee of Dokkyo University School of Medicine. The patients each had a systolic blood pressure greater than 160 mmHg or a diastolic blood pressure greater than 95 mmHg, or both, on at least three occasions at the outpatient clinic. The possibility of secondary causes of hypertension was excluded through a comprehensive check-up, including an assessment of their medical history, physical findings, urinalysis, blood chemistry, and endocrinological and radiological findings.

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when needed. All patients had normal renal function as judged from their endogenous creatinine clearance. According to the World Health Organization criteria for organ damage, all patients were classified as having stage I or II hypertension. Five of the patients were newly given a diagnosis of essential hypertension and had not received prior treatment, and the other five were taking antihypertensive medication: calcium antagonists were being received by 2 patients, an angiotensin-converting enzyme inhibitor by 1, an α1-adrenergic receptor blocker by 1, and a diuretic by 1.

**Study Protocol**

This was a randomized cross-over study conducted at one hospital. After the discontinuation of any previous antihypertensive drugs, each patient received cilnidipine for 8 wk and nisoldipine for 8 wk. The allocation of treatment sequence was carried out blindly. Based on the blood pressure level, the drugs were administered orally once daily at an initial dose of 5 or 10 mg for 4 wk. If the office blood pressure remained high (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg) or the magnitude of the reduction in blood pressure was insufficient (a decrease in systolic blood pressure < 20 mmHg or a decrease in diastolic blood pressure < 10 mmHg), the dose was increased to 10 or 20 mg for another 4 wk. On the last day of each treatment period, the 24-h blood pressure was measured.

**Twenty-Four-Hour Ambulatory Blood Pressure Measurement**

The 24-h ambulatory blood pressure was monitored every 30 min with the use of a cuff-oscillometric device (TM-2425, A&D Co., Tokyo, Japan). The device satisfied the criteria of the Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS) (7). The usefulness of this recorder in clinical hypertension research has been reported by us (5, 6, 8, 9) and other investigators (7, 10). Blood pressure and heart rate measurements during a 24-h period were analyzed for four segments of the day: morning (06:00 to 11:30), afternoon (12:00 to 17:30), nighttime (18:00 to 23:30), and sleeping time (0:00 to 5:30). To minimize effects of the patients' physical activity on blood pressure, ambulatory blood pressure monitoring was performed on the same day of the week.

**Statistical Analysis**

Values are expressed as means ± SEM. The statistical analysis was performed using analysis of variance for repeated measures and then Tukey's multiple comparison for each segment of the day. Values of p < 0.05 were considered to indicate statistical significance.

**Results**

All 10 subjects completed the study protocol. Their baseline characteristics are shown in Table 1. Figure 1 depicts the 24-h pattern of blood pressure and heart rate during each treatment period. Figures 2 and 3 respectively depict the 6-h and 24-h average blood pressure and heart rate during each treatment period. Blood pressure levels were similar for the two treatment periods during each 6-h segment of the day. In contrast, heart rate was significantly higher during treatment with nisoldipine than during treatment with cilnidipine in the morning segment [by 4.1 ± 1.3 beats/min (p < 0.05)] and the afternoon segment [by 6.4 ± 3.6 beats/min (p < 0.05)], whereas the 24-h average heart rate did not differ significantly between the two treatment periods.

<table>
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<tr>
<th>Table 1. Baseline Characteristics of the Subjects</th>
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<tr>
<td>Age (yr)</td>
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<td>Men/Women</td>
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<td>Body height (cm)</td>
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<td>Body weight (kg)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Duration of hypertension (yr)</td>
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Values are means ± SEM. BP, blood pressure.
Discussion

The present study demonstrated that cilnidipine and nisoldipine lowered blood pressure to similar extents after treatment for 8 wk in patients with essential hypertension. However, the effects of these drugs on heart rate differed in some respects: heart rate was significantly higher during treatment with nisoldipine than during treatment with cilnidipine in the morning and the afternoon.

A number of investigators have reported that N-type voltage-dependent calcium channels, which are widely distributed in both central and peripheral sympathetic neurons, are intimately involved in sympathetic neurotransmission and regulate the release of noradrenaline from sympathetic nerve endings (11-15). For example, intravenous administration of \( \omega \)-conotoxin GVIA, a specific N-type voltage-dependent calcium channel blocker, inhibits nitroprusside-induced tachycardia in SHRs (16). Cilnidipine has recently been shown to inhibit both N-type and L-type voltage-dependent calcium channels in rat dorsal root ganglion neurons (4). Both types of channels were inhibited by similar concentration ranges: the median inhibitory concentration (IC50) values for cilnidipine block of L-type and N-type calcium channels were 100 nM and 200 nM, respectively. Moreover, Uneyama et al. (17) electrophysiologically examined the inhibitory effects of cilnidipine and various calcium antagonists on N-type voltage-dependent calcium channels by means of conventional patch-clamp techniques and reported that dihydropyridine calcium antagonists, including nisoldipine but not cilnidipine, failed to inhibit N-type voltage-dependent calcium channels. Therefore, it is thought that the N-type voltage-dependent calcium channel blocking action of cilnidipine may, at least in part, contribute to decreasing high sympathetic tone.

As for other advantages of cilnidipine over conventional dihydropyridine calcium antagonists, it has been shown that cilnidipine, but not other dihydropyridine derivatives, attenuates the elevation of both blood pressure and the plasma noradrenaline concentration induced by acute cold stress in SHRs (3). Cilnidipine has also been shown to suppress the increases in noradrenaline secretion rate and antinatriuretic response and the decrease in renal blood flow induced by renal nerve stimulation in dogs, while nifedipine failed to inhibit such responses (18). In addition, it has been suggested that N-type calcium channel blockers are useful for preventing the brain damage caused by ischemia, as described for the synthetic peptide N-type calcium channel inhibitor SNX-111 (19). In light of these experimental findings, cilnidipine may possess additional clinical advantages in the treatment of hypertension over other dihydropyridines. Thus far, however, little is known about the clinical and therapeutic advantages of cilnidipine as compared with other dihydropyridines, particularly other once-daily, second-generation dihydropyridine calcium antagonists. The results of the present study have shown one of the advantages of cilnidipine in the management of
In the present study, heart rate was significantly higher during treatment with nisoldipine than during treatment with cilnidipine in the morning and the afternoon. Since 24-h ambulatory blood pressure and heart rate measurements were not performed during the drug-free period in this study, we could not assess whether cilnidipine reduced the heart rate below the level during the drug-free period. Our previous study, however, demonstrated that after 4 wk of treatment with cilnidipine, the ambulatory heart rate did not differ from that during the drug-free period in the daytime or nighttime in 14 patients with essential hypertension (5). Moreover, we have found that reflex tachycardia and sympathetic activation persist even after chronic treatment with second-generation dihydropyridine calcium antagonists, despite resetting of the baroreflex of heart rate (5, 9). Taken together, these observations indicate that nisoldipine most likely caused reflex tachycardia after 8 wk of treatment, although there is a slight possibility that cilnidipine reduced the heart rate below the level during the drug-free period.

Epidemiological studies have demonstrated that a higher heart rate is associated with a long-term risk of cardiovascular mortality, independent of other cardiac risk factors. For example, Gillman et al. suggested based on 36-yr follow-up data from the Framingham Study that a high heart rate was an independent risk factor for cardiovascular death in patients with hypertension (20). Therefore, anti-hypertensive drugs that do not increase the heart rate would seem to be preferable. The beneficial effects of β-blockers, which reduce the heart rate, in high-risk patients who have had a myocardial infarction have been demonstrated (21, 22). Among calcium antagonists, non-dihydropyridine agents, such as verapamil and diltiazem, that lower the heart rate would seem to be preferable. The beneficial effects of β-blockers, which reduce the heart rate, in high-risk patients who have had a myocardial infarction have been demonstrated (21, 22). Among calcium antagonists, non-dihydropyridine agents, such as verapamil and diltiazem, that lower the heart rate have been shown to reduce cardiac events in patients with myocardial infarction (21, 23, 24). A number of recent prospective trials, such as the Shanghai Trial of Nifedipine in the Elderly (STONE) (25) and the Systolic Hypertension in Europe (Syst-Eur) Trial (26), have demonstrated the beneficial effects of dihydropyridine calcium antagonists on the primary prevention of stroke in elderly hypertensive patients. However, beneficial effects of dihydropyridines on the primary prevention of ischemic heart disease have not yet been demonstrated. Several lines of evidence have suggested a relationship between short-acting dihydropyridine calcium antagonists and the risk of myocardial infarction (27–29). Short-acting calcium antagonists are known to increase sympathetic nerve activation and reflex tachycardia (30). Heart rate is a key determinant of myocardial oxygen consumption (31). In light of these findings, the unique pharmacological profile of cilnidipine may be of value in treating hypertensive patients, particularly those with coexisting ischemic heart disease.

In conclusion, cilnidipine is effective as a once-daily antihypertensive agent and causes less reflex tachycardia than does nisoldipine, another once-daily dihydropyridine. Further investigations are needed to identify other clinical and therapeutic advantages of cilnidipine over other conventional dihydropyridines.

References
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