Comparison of the Anti-Hypertensive Effects of the L/N-Type Calcium Channel Antagonist Cilnidipine, and the L-Type Calcium Channel Antagonist Amlodipine in Hypertensive Patients with Cerebrovascular Disease

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Abstract

Objectives It is known that the risk of cerebral stroke recurrence in post-stroke patients is comparatively higher than in normal subjects, and it is suggested that autonomic nervous system dysfunctions elevate this risk. We investigated the anti-hypertensive effects of cilnidipine, a Ca antagonist which suppresses sympathetic nerve activation, in hypertensives with chronic-stage cerebrovascular disease in a comparison with amlodipine.

Methods Amlodipine 5-7.5 mg/day, or cilnidipine 5-10 mg/day was administered to 78 hypertensive subjects (greater than 140 mmHg systolic, or 90 mmHg diastolic) undergoing outpatient treatment. Amlodipine or cilnidipine was also administered similarly, to 30 subjects having hypertension associated with a cerebral infarct which occurred more than one month earlier due to cerebral thrombosis or embolism. After 3 months administration, the subjects’ blood pressures and pulse rates were recorded with an ambulatory blood pressure monitor over 24 hours.

Results No difference was recognized in patient age, gender, and systolic and diastolic blood pressure before treatment between the groups. In the cilnidipine groups, no difference in average 24-hour or waking systolic blood pressure values was seen between cerebrovascular disease (CVD) subjects and non-CVD subjects, although in the amlodipine groups, CVD subjects had significantly higher blood pressure values than non-CVD subjects. In the cilnidipine group, the coefficient of variation values of pulse rate were significantly higher in CVD subjects than in non-CVD subjects (p<0.05) .

Conclusion In patients with recent stroke, a Ca antagonist with no sympathetic nerve suppression had weaker blood pressure-lowering effects. Significantly increased pulse rate variability, shown in the CVD subjects administered cilnidipine, suggests that cilnidipine enhanced the parasympathetic function in hypertensive patients with CVD.

Key words: stroke, hypertension, autonomic nervous system, cilnidipine

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Background

Although cerebral stroke mortality has been declining in Japan since the late 1970s, it still surpasses death due to ischemic heart disease, as it does in Korea, Poland and other countries (1). Furthermore, while the dramatic decline in cerebral stroke incidence seen with Hisayama Study from the 1960s to the 1970s can be attributed to the wide-spread use of anti-hypertensive medications, the slowing of this declining incidence since the 1980s has been attributed to an aging population and insufficient anti-hypertension therapies (2). High blood pressure is one of the greatest risk factors for cerebral stroke, and a correlation between lowering
systolic pressure and a lowered risk of cerebral stroke incidence has been reported through meta-analyses of intervention trials (3, 4).

It is recognized that chronic-stage patients with a history of cerebrovascular disease (CVD) have a higher recurrence rate than those who do not, but there is debate as to whether differences in cerebral hemorrhage and ischemic stroke recurrence are blood pressure dependent (5), which complicates this clinical condition and makes blood pressure management all the more delicate. A loss of the lowered nighttime sleeping blood pressure seen in normal subjects, or autonomic nervous system dysfunction, has been reported in chronic-stage CVD (6), and it is thought to be one important risk factor for recurrence. It is recognized that function of not only the sympathetic, but also the parasympathetic system is less activated during this stage (7), and this emphasizes the importance of autonomic nervous system control with respect to preventing the recurrence of cardiovascular events in cerebral stroke patients.

Ca antagonists, widely used as anti-hypertension agents, relieve vascular constriction and lower vascular resistance by binding with vascular smooth muscle L-type Ca channels, and inhibiting the influx of Ca ions into the cell. Because Ca antagonists are powerful blood pressure lowering agents, compared with other anti-hypertension drug classes, they more easily induce a sympathetic nervous system reflex response; an increased incidence of cardiac events has been reported with short-acting Ca antagonist use (8, 9). This led to the design of improved Ca antagonists with longer serum half-lives which has resulted in better control of cardiovascular events in later intervention trials, such as HOT (10) and ALLHAT (11). However, as long as any Ca antagonist exerts its blood pressure lowering effect by lowering vascular resistance, its use in treatment may be problematic depending on the patient’s clinical background, due to the accompanying sympathetic nervous system response (12, 13), no matter how attenuated that response may be.

Cilnidipine is a fourth generation Ca antagonist being used clinically that suppresses L/N-type Ca channels, and the release of noradrenalin from sympathetic nerve endings (14). It has been reported to suppress noradrenalin release from cardiac sympathetic nerves in hypertensive patients upon nuclear cardiology examination (15), improve myocardial diastolic function (16), and suppress heart rate (17). In this report, the effects of cilnidipine in hypertensive patients, both with and without a history of CVD, are compared with the long-acting third generation Ca antagonist amlodipine.

Methods

Target patients and blood pressure measurements

Of a total of 78 hypertensive (greater than 140 mmHg systolic, or 90 mmHg diastolic) outpatients (41 males, 37 females) with no history of cerebrovascular disease, cilnidipine 5-10 mg/day was administered to 33 randomly selected subjects (the CI group: average age 69.9 ± 8.2 years), and amlodipine 5-7.5 mg/day to the remaining 45 subjects (the AM group: average age 65.5 ± 11.1 years). And of a further total of 30 patients (16 males, 14 females) having hypertension with cerebral infarct, due to either cerebral thrombosis or embolism more than 1 month previously, cilnidipine 5-10 mg/day was administered to 13 randomly selected subjects (the CIC group: average age 70.5 ± 7.9 years), and amlodipine 5-7.5 mg/day to the remaining 17 subjects (the AMC group: average age 66.2 ± 9.3 years). Informed consent was obtained before enrollment in the trial. Patient characteristics and blood pressure before treatment are listed in Table 1. These agents were administered once-daily, after breakfast. After 3 months of administration, the patients were fitted with an ambulatory blood pressure monitor (ABPM) (A&D, TM-2421), and their blood pressures and pulse rates were recorded every 15 minutes, for 24 hours.

These observed readings were averaged for 24 hours or for awake periods. No other blood pressure-lowering agent was used during the trial. Average blood pressures and pulses were plotted as mean ± standard deviation, and the short-term variability for these values (100 × blood pressure SD/blood pressure average) was analyzed as “coefficient of variation” of blood pressure. Statistical analyses were carried out using unpaired Student’s t-test. P-values of <0.05 were considered statistically significant, and p-values <0.1 were considered as a trend.

Results

No difference was recognized in patient age, gender, and systolic and diastolic blood pressure before treatment between the groups (Table 1).

Blood pressure and pulse rate measurements over 24 hours

Figure 1 shows blood pressures and pulse rates for each treatment group. Systolic blood pressure averages seen over 24 hours with an ambulatory blood pressure monitor in the hypertensive patients having no cerebrovascular disease (CVD) were 134.9 ± 13.0 mmHg with cilnidipine administration (the CI group), and 132.4 ± 12.3 mmHg with amlodipine administration (the AM group). At the same time, these averages in hypertensive patients having CVD were 135.6 ± 12.7 mmHg with cilnidipine administration (the CIC group), and 139.2 ± 10.3 mmHg with amlodipine administration (the AMC group). There was no significant difference between the CIC and the CI groups, although the AMC group had significantly higher blood pressure values than the AM group. There was also no difference seen between the CIC and CI groups in awake blood pressure averages, although again, the AMC group had significantly higher values compared to the AM group (Fig. 2). No significant differences were seen in diastolic blood pressures,
Table 1. Patient Characteristics and Systolic Blood Pressure (Sys. BP) and Diastolic Blood Pressure (Dia. BP) before Treatment

<table>
<thead>
<tr>
<th>group</th>
<th>number (M, F)</th>
<th>age</th>
<th>Sys. BP</th>
<th>Dia. BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI group</td>
<td>33 (18, 15)</td>
<td>69.9 ± 8.2</td>
<td>146.8 ± 15.8</td>
<td>86.0 ± 9.8</td>
</tr>
<tr>
<td>AM group</td>
<td>45 (23, 22)</td>
<td>65.5 ± 11.1</td>
<td>146.9 ± 17.9</td>
<td>88.5 ± 8.7</td>
</tr>
<tr>
<td>CIC group</td>
<td>13 (7, 6)</td>
<td>70.5 ± 7.9</td>
<td>145.5 ± 16.3</td>
<td>88.8 ± 9.6</td>
</tr>
<tr>
<td>AMC group</td>
<td>17 (9, 8)</td>
<td>66.2 ± 9.3</td>
<td>146.9 ± 9.5</td>
<td>91.5 ± 11.0</td>
</tr>
</tbody>
</table>

No Difference Was Recognized in Patient Age, Gender, and Systolic and Diastolic Blood Pressure before Treatment between the Groups.

CI: Cilnidipine Group (hypertension), CIC: Cilnidipine Group (hypertension with cerebrovascular disease), AM: Amlodipine Group (hypertension), AMC: Amlodipine Group (hypertension with cerebrovascular disease)

**Figure 1.** Effects on systolic blood pressure (Sys. BP), diastolic blood pressure (Dia. BP) and pulse rate (PR) during a 24-hour period as measured by ambulatory blood pressure monitor. In patients with recent stroke, amlodipine, a Ca antagonist with no symptomatic nerve suppression, had weaker blood pressure-lowering effects. CI: cilnidipine group (hypertension), CIC: cilnidipine group (hypertension with cerebrovascular disease), AM: amlodipine group (hypertension), AMC: amlodipine group (hypertension with cerebrovascular disease)

**Figure 2.** Effects on systolic blood pressure (Sys. BP), diastolic blood pressure (Dia. BP) and pulse rate (PR) during awake period measured by ambulatory blood pressure monitor. In patients with recent stroke, amlodipine, a Ca antagonist with no symptomatic nerve suppression, had weaker blood pressure-lowering effects. CI: cilnidipine group (hypertension), CIC: cilnidipine group (hypertension with cerebrovascular disease), AM: amlodipine group (hypertension), AMC: amlodipine group (hypertension with cerebrovascular disease)

**Blood pressure and pulse rate variability**

Regarding blood pressure variability as an autonomic nervous system index, there was a trend toward higher systolic blood pressure coefficient of variation values in the AMC group compared to the AM group (p<0.1), as well as a trend toward higher values compared to the CIC group, over the entire 24-hour period. Coefficient of variation values of pulse rate of CIC group were significantly higher than those of CI group (p<0.05) (Fig. 3).

**Discussion**

It has been suggested that autonomic nervous system dysfunction brought on by organic brain disorders may contribute to the frequent blood pressure variation abnormalities (18, 19) seen in chronic-stage CVD, and especially the loss of a night-time blood pressure dip (20). Such dysfunction is recognized in not only the sympathetic nervous system, but in the parasympathetic nervous system as well, and it has been reported to relate to autonomic nervous system imbalances (21). Such reports would suggest that differing effects will be expressed by differing anti-hypertension agents, even in stable chronic-stage cerebrovascular disease.

Since cilnidipine suppresses not only the L-type but also the N-type Ca channels found on peripheral sympathetic nerve endings which control noradrenalin release, it is thought to be a Ca antagonist with low sympathetic nerve activation when lowering blood pressure. In a comparison with the once-daily administered Ca antagonist nisoldipine,
Cilnidipine demonstrated significantly lower heart rates, especially in the day-time in essential hypertension patients (22). Furthermore, treatment with cilnidipine has also been reported to elicit no change in autonomic nervous system activity, compared with non-treatment in a spectral analysis of heart rate variability which was done in essential hypertension patients (23). In evaluations of myocardial sympathetic nerve function with nuclear medical scans using MIBG, cilnidipine was shown to suppress sympathetic nerve function. This sympathetic nerve suppression is not seen with the long-acting L-type Ca antagonist amlodipine (15).

Treatment with cilnidipine achieved the same 24-hour blood pressure value levels in patients with a history of CVD, as it did in patients with no history of CVD. In patients with recent stroke, a Ca antagonist with no sympathetic nerve suppression had weaker blood pressure-lowering effects. These results suggest the possibility of sympathetic nerve activation in patients having CVD, and that there was a different response to the Ca antagonists used. A certain level of cardiovascular protection has been proven with amlodipine in large-scale intervention trials such as the ALLHAT (11) and VALUE (24), because it has excellent sustained efficacy, and it does not lead to sudden blood pressure drops. However, although baroreflex activation with blood pressure lowering is weak, it does occur, and further studies are needed to investigate the relationship between sympathetic nerve function and hypertension pathology, as sympathetic nerve activity levels may influence the blood pressure values achieved with drug intervention in hypertension accompanied by autonomic nerve dysfunction.

Autonomic nervous system modulation after stroke is thought to be related to not only sympathetic nervous system, but also parasympathetic nervous system dysfunction (21). The autonomic nervous system in chronic-stage stroke as well, has been shown to lower not only sympathetic, but also parasympathetic nervous system function (7). This suggests an important autonomic nervous system role in evaluating blood pressure and heart rate variability, and in particular, it indicates that there is a relationship between heart rate variations and parasympathetic nerve function. Heart rate variation is significant, as it can be used to non-invasively estimate the prognosis. A relationship between lowered heart rate variability and the onset of hypertension was shown by the Framingham Heart Study (25). Furthermore, a correlation was shown between reduced heart rate variability (HRV) and the risk of arrhythmia after myocardial infarction (26). In the present study, significantly increased pulse rate variability was shown in the group administered cilnidipine having CVD. Since the recovery of parasympathetic function after stroke is usually delayed compared to that of sympathetic function (27), sympathetic function is more activated than parasympathetic function after CVD. As cilnidipine suppresses the sympathetic function, cilnidipine may induce the stronger activity of parasympathetic function. Because pulse rate variability (PRV) reflects the parasympathetic function, significantly increased pulse rate variability, shown in the group administered cilnidipine having CVD, suggests that cilnidipine enhanced the parasympathetic function in patients with CVD.

References


