Reduction of White Coat Effect By Cilnidipine in Essential Hypertension

Satoshi Morimoto, Kazuo Takeda, Atsuhiko Oguni, Hidenori Kido, Sanae Harada, Jiro Moriguchi, Hiroshi Itoh, Tetsuo Nakata, Susumu Sasaki, and Masao Nakagawa

Stress elevates blood pressure (BP) by increased sympathetic nerve activity. Cilnidipine, a novel dihydropyridine calcium antagonist that has inhibitory actions on N-type as well as L-type voltage-dependent calcium channels, has been reported to attenuate the cold stress-induced increase in plasma norepinephrine and BP in rats. Because white coat effect is associated with an enhanced pressor response to mental stress, we postulated that cilnidipine would attenuate white coat effect in patients with essential hypertension.

Sixty-one consecutive outpatients (50 men, 11 women) with essential hypertension were studied prospectively. Twenty-nine patients were treated with either cilnidipine (n = 15) or nifedipine, a representative L-type voltage-dependent calcium antagonist (n = 14). Gender, age, body mass index, duration of hypertension, target organ damage of hypertension, and BP and heart rate (HR) were not significantly different between cilnidipine and nifedipine groups, and both systolic (SBP) and diastolic BP (DBP) were significantly decreased after treatment in both groups. White coat effects on systolic and DBP and HR were not significantly different between groups before antihypertensive treatment. Cilnidipine, but not nifedipine, significantly reduced white coat effects on SBP and HR. Furthermore, white coat effects on systolic BP and HR were significantly lower after treatment in the cilnidipine group compared with the nifedipine group. These data suggest that cilnidipine may reduce white coat effect in hypertensive patients by N-type calcium channel antagonism. Am J Hypertens 2001;14:1053–1057 © 2001 American Journal of Hypertension, Ltd.

Key Words: Essential hypertension, white coat effect, calcium channel antagonist, cilnidipine.

Stress elevates blood pressure (BP) by increased sympathetic nerve activity and the response to stress is enhanced in hypertensive subjects.1 Sudden changes in BP by stress might be related to the incidence of hypertensive complications.2 Thus, it is important to evaluate the effects of antihypertensive agents on cardiovascular responses to stress.

Dihydropyridine calcium antagonists have been used widely in the treatment of hypertension. Cilnidipine is a novel and unique 1,4-dihydropyridine derivative calcium antagonist that has potent inhibitory actions not only on L-type but also on N-type voltage-dependent calcium channels.3 Cilnidipine depresses the pressor response to acute cold stress by reducing sympathetic nerve activity in rats and humans.4,5

It is known that in most subjects, daytime BP is lower than office BP.6,7 This difference is ascribed to the “white coat effect” (ie, the alerting reaction and pressor response of the patient to the measurement of BP in the clinic environment).8,9 White coat effect is reported to be associated with an enhanced pressor response to stress and might be related to cardiovascular complications of hypertension.10,11 Therefore, it is important to estimate the effects of antihypertensive agents on white coat effect. In the present study, we examined the effects of cilnidipine on white coat effect in patients with essential hypertension.

Methods

Case Selection

Sixty-one consecutive patients (50 men, 11 women) who visited the outpatient clinic of Kyoto Industrial Health Association from September to October 1998 and fulfilled the following criteria were studied prospectively: patients who had been referred to the clinic because of recent detection of BP elevation at a checkup or patients with essential hypertension in which antihypertensive treatment had been withdrawn for at least 4 weeks.
Estimation of White Coat Effect

White coat effect was calculated based on automatic measurements of BP or heart rate (HR) obtained every 2 min using an ambulatory BP recording device, TM-2421 (A&D Company, Tokyo, Japan). In a preliminary study, six subsequent readings provided by the device were 5 mm Hg within the BP values simultaneously obtained with a mercury sphygmomanometer \((n = 3;\) data not shown). The device was placed on one arm of the patient by a nurse in a waiting room at least 10 min before entering the physician’s office, where the patient underwent measurements of BP and HR as described below. In the waiting room, the patient remained quietly in the sitting position. White coat effects on BP and HR were calculated by the following definition: 12

\[
\text{White coat effect} = \text{Maximum BP (HR) value in the office room} - \text{Average BP (HR) value before entering the office room.}
\]

Office BP and HR Measurements

Office BP was obtained in the sitting position by a physician with a conventional mercury sphygmomanometer from the other arm of the patient. The first and fifth Korotkoff sounds were taken to identify systolic and diastolic values, respectively. The HR was measured according to the palpatory method (15–30 sec).

Home BP and HR Measurements

Home BP was measured to determine the indication of antihypertensive medical treatment (ie, patients with white coat hypertension were not treated with antihypertensive drugs and thus were excluded from this study; see Protocol). Home BP and HR were self-measured by the patients in the sitting position in the early morning and in the late evening every day with semiautomatic devices using the oscillometric method. The measurements were registered on special case record forms.

Protocol

The study period consisted of an observation period and subsequent treatment period. On the first day of the observation period (week –4), office BP and white coat effect were estimated. Only patients with essential hypertension who had a SBP of >160 mm Hg or DBP of >90 mm Hg remained to be examined during the following 4 weeks of observation period with the other patients being excluded from the study. During the observation period, the patients measured home BP and HR. On the second visit after the observation period (week 0), office BP and white coat effect were estimated. Again, only those who had an office SBP of >160 mm Hg and/or DBP of >90 mm Hg with home SBP of >140 mm Hg and/or DBP of >90 mm Hg were randomly divided into two groups: oral cilnidipine treatment group (10 mg, once daily) and nifedipine treatment group (20 mg, oral controlled-release nifedipine, once daily) and other patients were excluded from the study. Nifedipine was selected as a control drug for cilnidipine because it is a representative L-type voltage-dependent calcium antagonist widely used in the clinical setting. On the third and fourth visit after 4 and 12 weeks of treatment period, respectively, office BP and white coat effect were again estimated. During the treatment period, increased doses of cilnidipine (20 mg) and controlled-release nifedipine (40 mg) were allowed.

The present study was approved by the ethics committee of Kyoto Prefectural University of Medicine. Informed consent was obtained from all subjects.

Statistical Analysis

Values are expressed as mean ± SE mean. Comparisons between cilnidipine and nifedipine group were made by a \(\chi^2\) test or nonpaired Student’s \(t\) test. Comparisons between each period were made by one-factor ANOVA followed by Fisher’s multiple range test. A \(P\) value < .05 was considered statistically significant.

Results

Of the 61 patients, 32 patients were excluded from the study on the second visit; 24 patients showed average home SBP of <140 mm Hg and DBP of <90 mm Hg, indicating white coat hypertension and were treated without antihypertensive medication. Eight patients dropped out during the observation period. No patients were diagnosed with secondary hypertension. The remaining 29 patients were randomly divided into cilnidipine \((n = 15)\) and nifedipine \((n = 14)\) groups. Gender, age, body mass index, duration of hypertension, target organ damage of hypertension, and BP and HR values were not significantly different between the two groups (Table 1, Fig. 1).

After a short-term (4 weeks) antihypertensive treatment period (on the third visit), SBP and DBP were significantly decreased in both groups (Fig. 1). Neither SBP nor DBP showed significant differences between the two groups after 4 weeks of treatment. The HR was unchanged by treatment and was not significantly different between groups during any time period. White coat effects on SBP and DBP and HR did not differ between the two groups before antihypertensive treatment (Fig. 2). In the nifedipine group, white coat effects on SBP and DBP and HR showed slightly insignificant decreases after 4 weeks of treatment. In contrast, in the cilnidipine group, white coat effects on SBP and HR were significantly decreased by treatment for 4 weeks and the white coat effect on DBP also showed a tendency to be decreased, although it did not achieve a significant difference. In addition, white coat effects on SBP and HR were significantly lower in the cilnidipine group compared with the nifedipine group after 4 weeks of treatment.

After a relatively long-term (12 weeks) antihypertensive treatment period (on the fourth visit), 16 patients were
excluded from the study. In the cilnidipine group, 6 patients required additional administration of different antihypertensive drugs and 3 patients dropped out. In the nifedipine group, 3 patients needed additional administration of different antihypertensive drugs, 1 patient discontinued nifedipine because of decreased BP, and 3 patients dropped out. Therefore, office BP and HR measurements and white coat effects were estimated in 6 and 7 patients in cilnidipine and nifedipine groups, respectively. In both groups, there was a tendency, which did not reach statistical significance, for further decreases in SBP and DBP compared to 4 weeks after treatment (Fig. 1). Neither SBP nor DBP showed significant differences between groups 12 weeks after treatment. There was no significant change

### Table 1. Baseline characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Cl (n = 15)</th>
<th>Ni (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>13/2</td>
<td>12/2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>46.7 ± 1.9</td>
<td>47.1 ± 1.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.8 ± 0.8</td>
<td>23.4 ± 1.1</td>
</tr>
<tr>
<td>Duration of hypertension (mo)</td>
<td>53.2 ± 10.4</td>
<td>51.8 ± 13.4</td>
</tr>
<tr>
<td>Proteinuria (+/-)</td>
<td>2/13</td>
<td>2/12</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.95 ± 0.02</td>
<td>0.94 ± 0.04</td>
</tr>
<tr>
<td>Left ventricular mass (g)*</td>
<td>220.4 ± 15.1</td>
<td>206.5 ± 20.7</td>
</tr>
<tr>
<td>Hypertension stage (I/II/III)†</td>
<td>12/3/0</td>
<td>12/2/0</td>
</tr>
</tbody>
</table>

Cl = cilnidipine group; Ni = nifedipine group.
Average values are expressed as mean ± SE.
* Calculated by echocardiograms according to the formula of Devereux and Reichek.13
† Classified by degree of organ damage.14

---

**FIG. 1.** Office blood pressure (BP) and heart rate (HR) before (weeks –4 and 0) and after (weeks 4 and 12) cilnidipine (Ci) or nifedipine (Ni) treatment; n = 15, weeks –4, 0, and 4 in cilnidipine group; n = 14, weeks –4, 0, and 4 in nifedipine group; n = 6, week 12 in cilnidipine group; n = 7, week 12 in nifedipine group. *P < .05 compared to weeks –4 and 0. SBP = systolic BP; DBP = diastolic BP. Bars represent mean ± SE mean.

**FIG. 2.** White coat effects on SBP and DBP and HR before (weeks –4 and 0) and after (weeks 4 and 12) Ci or Ni treatment; n = 15, weeks –4, 0, and 4 in cilnidipine group; n = 14, weeks –4, 0, and 4 in nifedipine group; n = 6, week 12 in cilnidipine group; n = 7, week 12 in nifedipine group. *P < .05 compared to weeks –4 and 0; †P < .05 compared to nifedipine group at the same period. Bars represent mean ± SE mean. Abbreviations as in Fig. 1.
in HR between 4 and 12 weeks or between groups 12 weeks after treatment. White coat effects showed similar trends as those after 4 weeks (Fig. 2). White coat effects on SBP and HR were significantly decreased by treatment for 12 weeks in the cilnidipine group but not in the nifedipine group, and white coat effects on SBP and HR were significantly lower in the cilnidipine group compared with the nifedipine group.

Discussion

In the present study, we found that cilnidipine, an antagonist of L-type and N-type voltage-dependent calcium channels, significantly decreased white coat effect in patients with essential hypertension. Possible attenuation of white coat effect by antihypertensive drugs including calcium channel antagonists has been reported.15–22

In addition, nifedipine, an L-type voltage-dependent calcium antagonist, has been shown to have central sympathetic inhibitory effects,23,24 which might lead to reduction of white coat effect. Indeed, in this study, nifedipine showed a slight decrease in white coat effect (Fig. 2). However, the reduction of white coat effect by nifedipine therapy did not achieve statistical significance and the white coat effect after cilnidipine treatment was significantly lower than nifedipine treatment (Fig. 2). Therefore, although a slight decrement in white coat effect by L-type calcium channel blockade or BP reduction itself cannot be completely ruled out because of the relatively small number of subjects, our results suggest that cilnidipine reduced white coat effect in hypertensive patients mainly by non-L-type calcium channel antagonism.

A number of studies have indicated 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 norepinephrine from sympathetic nerve endings.25–30 Studies using the whole-cell patch-clamp technique have shown that cilnidipine inhibits N- and L-type voltage-dependent calcium channel activity in rat dorsal root ganglion neurons.3 Cilnidipine, but not nifedipine, suppresses the increase in norepinephrine secretion rate induced by renal nerve stimulation in dogs.25 Cilnidipine depresses the pressor response to acute cold stress by attenuating the increase in plasma norepinephrine concentration4 and white coat effect is considered to be related with an enhanced pressor response to stress.10,11 Therefore, we presume that, in the present study, cilnidipine attenuated norepinephrine release from the sympathetic nerve endings by blocking N-type calcium channels and thereby reduced white coat effect. We did not, however, investigate changes in indices of sympathetic nerve activity such as plasma norepinephrine concentration,31,32 power spectral analysis of HR variability,33 or muscle sympathetic nerve activity34 by the treatment. Further studies are required to test our presumption.

This study has a limitation because nearly all of the subjects were men (Table 1). This study failed to determine the role of cilnidipine in women, who have been observed to have greater white coat effect than men.21,34–36 Interestingly, Loeb et al21 reported that calcium antagonist (either nifedipine or verapamil) reduced white coat effect in women. Because men in the Loeb et al21 study did not have a white coat effect, we cannot directly compare our results.

White coat effect has been historically measured as the difference between office BP and average daytime BP.6,7 However, Parati et al12 have reported that the difference between office BP and average daytime BP measured by ambulatory BP monitoring does not reflect the alerting reaction in the clinic environment. Accordingly, in the present study, we calculated white coat effects based on frequent automatic measurements of BP and HR using an ambulatory BP recording device.

It has been reported that SNX-111, an N-type calcium antagonist, protects against neuronal loss after global cerebral ischemia in rats.37 In addition, several investigators have indicated clinical advantages of cilnidipine in the treatment of hypertension. Saihara et al5 showed that cilnidipine depressed the pressor response to acute cold stress in healthy young volunteers. Minami et al38 reported that cilnidipine produced less sympathetic activation and reflex tachycardia than nifedipine retard in patients with essential hypertension. Sakata et al39 demonstrated by using 123I-metaiodobenzylguanidine cardiac imaging that cilnidipine suppressed cardiac sympathetic overactivity in patients with essential hypertension. Therefore, cilnidipine may be beneficial for long-term treatment of hypertension. However, although some studies have indicated that white coat effect may be related to cardiovascular complications of hypertension,10,11 the benefit of treatment of white coat effect remains to be elucidated. Long-term studies are needed to determine whether the white coat effect reducing action of cilnidipine decreases cardiovascular complications of hypertension.

In summary, we found that cilnidipine, but not nifedipine, significantly decreased white coat effect in patients with essential hypertension. These results suggest that cilnidipine may reduce white coat effect in hypertensive patients by blocking N-type voltage-dependent calcium channel. This might indicate one of the beneficial effects of cilnidipine for long-term treatment of hypertension.

Acknowledgment

The authors thank Dr. Henry L. Keen for assistance in revising the manuscript.

References

7. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G: Relation-
5. Saihara S, Sumio M, Hosono N, Hayashi Y, Kitamura Y, Hashimoto
3. Fujii S, Kameyama K, Hosono M, Hayashi Y, Kitamura K: Effect of
21. Loeb ED, Diamond JA, Krakoff LR, Phillips RA: Sex difference in
20. Parati G, Omboni S, Mancia G: Difference between of
15. Weber MA, Cheung DG, Graettinger WF, Lipson JL: Characteriza-
14. WHO/ISH: 1993 Guidelines for the management of mild hyperten-
11. Devereux RB, Reichek N: Echocardiographic determination of left
10. WHO/ISH: 1993 Guidelines for the management of mild hyperten-
9. Weber MA, Cheung DG, Graettinger WF, Lipson JL: Characteriza-
7. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G: Relation-
5. Saihara S, Sumio M, Hosono N, Hayashi Y, Kitamura Y, Hashimoto
3. Fujii S, Kameyama K, Hosono M, Hayashi Y, Kitamura K: Effect of
0. Parati G, Ulian L, Sampieri L, Palatini P, Villani A, Vanasia A, Mancia G: Attenuation of the “white-coat effect” by antihyperten-