Original Article

Beneficial Effect of Cilnidipine on Morning Hypertension and White-Coat Effect in Patients with Essential Hypertension

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Home blood pressure has a higher predictive power for cardiovascular events than office blood pressure, and there is a particularly close association between morning blood pressure at home and the incidence of cardiovascular events and mortality in the early morning. In this study, we evaluated the efficacy of a long-acting N-type and L-type calcium channel blocker, cilnidipine, in reducing morning blood pressure at home and in ameliorating the white-coat effect. Fifty-eight subjects diagnosed with both essential hypertension and morning hypertension (43 currently being treated, 15 new patients) were prescribed cilnidipine at a dosage of 10–20 mg per day for 8 weeks. After the addition of or a change to cilnidipine, the morning systolic blood pressure (SBP) was controlled to less than 135 mmHg in 25 (58%) out of the 43 patients currently receiving antihypertensive medication. The office SBP in 24 out of those 25 patients was also maintained under 140 mmHg. In the 15 newly treated patients, the morning SBP of 12 patients (80%) was controlled to less than 135 mmHg after administration of cilnidipine. At baseline, 17 patients showed a clear white-coat effect, in which the difference between office blood pressure and home blood pressure was 20/10 mmHg or more. The white-coat effect was depressed significantly after cilnidipine administration. These results suggest that cilnidipine may serve as a useful antihypertensive medication in the treatment of morning hypertension, and also attenuate the white-coat effect in patients with essential hypertension. (*Hypertens Res* 2006; 29: 339–344)

Key Words: morning hypertension, home blood pressure, white-coat effect, cilnidipine, N-type calcium channel

Introduction

Hypertension is an established risk factor in the prognosis of cardiovascular diseases and organ damage. It may be feasible for patients with hypertension or at high cardiovascular risk to receive a blood pressure-lowering medication in order to achieve reduction in risk of stroke and cardiovascular complications (1). Previous cross-sectional and prospective cohort studies have also indicated that home blood pressure has a higher predictive power for cardiovascular event onset than office blood pressure, suggesting the importance of home blood pressure measurements in clinical practice (2, 3). The

circadian rhythm of blood pressure is regulated by numerous physiologic systems and other internal factors, and, importantly, a steep rise in blood pressure in the morning coincides with activation of the sympathetic nervous system (4). Cilnidipine is a long-acting antihypertensive agent that lowers blood pressure by inhibiting L-type calcium channels directly associated with vascular tone, and N-type calcium channels related to sympathetic nervous activity. Because it acts specifically on N-type calcium channels, cilnidipine is expected to achieve a better reduction in morning blood pressure than other classes of calcium channel blockers, and to attenuate the white-coat effect caused by the hyperactivity of sympathetic nerves. The present study evaluated the efficacy of cilnidipine

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Table 1. Clinical Characteristics of Patients

Variable	Total patients (<i>n</i> =58)	Currently treated patients (<i>n</i> =43)	New patients (<i>n</i> =15)
Sex (female/male)	23/35	16/27	7/8
Age (years)	61.7±11.4	61.7±12.1	61.6±9.3
BMI (kg/m ²)	24.4±3.6	24.6±3.7	23.7±3.3
Duration of antihypertensive medication (years)	—	3.9±4.4	—
Stratification of hypertension by office blood pressure			
High normal	20	19	1
Mild	20	14	6
Moderate	13	9	4
Severe	5	1	4
Past illness and complication			
Cerebral infarction	10	8	2
Angina pectoris	6	5	1
Hyperlipidemia	16	10	6
Diabetes mellitus	20	15	5
Hyperuricemia	1	0	1
White-coat effect	17	9	8

Patients are classified into 4 groups according to the Guidelines for the Management of Hypertension (JSH 2004); “high normal” with systolic blood pressure 130–139 mmHg or diastolic blood pressure 85–89 mmHg, “mild” with 140–159 mmHg or 90–99 mmHg, “moderate” with 160–179 mmHg or 100–109 mmHg, and “severe” with ≥180 mmHg or ≥110 mmHg, and white-coat effect is defined by the difference between office blood pressure and home blood pressure in the morning (systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg). BMI, body mass index. Values are presented as the mean±SD.

Table 2. Blood Pressure and Pulse Rate before and after Cilnidipine Therapy

	Before		After 8 weeks	
	Home	Office	Home	Office
Currently treated patients (<i>n</i> =43)				
SBP (mmHg)	146.2±10.6	146.3±16.8	134.3±9.3***	130.8±14.5***
DBP (mmHg)	88.7±6.9	87.5±11.4	82.0±6.9***	78.4±9.4***
PR (pulse/min)	71.5±11.8	74.7±14.6	68.0±9.0**	72.6±11.1
New patients (<i>n</i> =15)				
SBP (mmHg)	150.3±12.6	163.7±20.7 [#]	131.3±11.0***	133.8±14.5***
DBP (mmHg)	95.1±7.4	99.5±12.8	83.0±6.4***	80.5±9.4***
PR (pulse/min)	69.7±8.7	81.0±16.0 [#]	66.2±9.4	72.4±16.0**

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. Values are expressed as the mean±SD. ***p*<0.01 and ****p*<0.001 vs. before administration, and [#]*p*<0.05 vs. home blood pressure or home pulse rate in the morning.

on morning hypertension and the white-coat effect in currently treated patients or new patients with essential hypertension.

Methods

Subjects

The present study was conducted prospectively on 58 outpatients with hypertension (23 males and 35 females; mean age: 61.7 years; range: 37–88 years) whose morning blood pressure at home was ≥135/85 mmHg (≥135 mmHg and/or ≥85

mmHg). Forty-three patients were currently receiving antihypertensive medication and 15 were newly diagnosed patients. Informed consent for the study was obtained from each participant.

Administration of Cilnidipine

Cilnidipine was administered at a dosage of 10–20 mg once daily after breakfast. For currently medicated patients, cilnidipine was either added to a previous prescription or substituted for the current medication. The new patients were placed on monotherapy with cilnidipine.

Fig. 1. Distribution of systolic blood pressure (SBP) in currently treated patients (left) and new patients (right) before (open circles) and after (closed circles) 8-week administration of cilnidipine. Morning SBP was properly controlled (<135 mmHg) in 25 currently treated patients (58%) and in 12 new patients (80%).

Blood Pressure Measurement and Statistical Analysis

Office blood pressure was measured after 5 min in a state of rest at each visit, and pulse rate was measured at the same time. Home blood pressure was measured according to the Japanese Society of Hypertension guidelines for self-monitoring of blood pressure at home (5). Patients were asked to measure their home blood pressure and pulse rate once every morning in the seated position prior to breakfast within 1 h after waking up, using an automatic arm-cuff device. Hypertension was defined as $\geq 140/90$ mmHg (≥ 140 mmHg and/or ≥ 90 mmHg) for office blood pressure and $\geq 135/85$ mmHg for home blood pressure. White-coat effect was defined as the difference of at least 20 mmHg for systolic blood pressure (SBP) and/or 10 mmHg for diastolic blood pressure (DBP) between office and home blood pressure. Data are expressed as the mean $\pm$ SD. Statistical analysis was performed by Student's paired or unpaired *t*-test, and values of $p < 0.05$ were considered to be statistically significant.

Results

Blood Pressure Control for Currently Treated Patients

The mean duration of antihypertensive medication prior to cilnidipine administration was 3.9 ± 4.4 years (range: 0.2–24 years) for the 43 currently treated patients (Table 1). Twenty-four cases were receiving antihypertensive monotherapy; 19 cases were on concomitant therapy. The most commonly prescribed antihypertensive agents were angiotensin II receptor

blockers or angiotensin-converting enzyme inhibitors (31 cases, 72%), followed by calcium channel blockers (17 cases, 40%), α -blockers (9 cases, 21%) and others (10 cases, 23%). A history of cerebral infarction was identified in 8 cases, angina pectoris in 5, hyperlipidemia in 10, and diabetes in 15.

The values of morning blood pressure at home and office blood pressure before and after cilnidipine administration are shown in Table 2. After cilnidipine administration, morning blood pressure at home and office blood pressure, both of which were poorly controlled at baseline ($146 \pm 11/89 \pm 7$ mmHg and $146 \pm 17/88 \pm 11$ mmHg, respectively), were reduced in a parallel fashion to $134 \pm 9/82 \pm 7$ mmHg and $131 \pm 15/78 \pm 9$ mmHg, respectively (both $p < 0.001$). There was also a significant decrease of the pulse rate at home after treatment (from 72 ± 12 pulse/min to 68 ± 9 pulse/min, $p < 0.01$). Figure 1 depicts the distribution of SBP values before and after cilnidipine administration in currently treated patients. After cilnidipine administration, the morning SBP at home was successfully controlled to below 135 mmHg in 25 cases (58%).

Blood Pressure Control for New Patients

The baseline characteristics of the newly treated patients are shown in Table 1. A history of cerebral infarction was identified in 2 cases, hyperlipidemia in 6, diabetes in 5, and angina pectoris and hyperuricemia in 1 case each.

The proportion of new patients assessed as having “moderate” or “severe” hypertension (8 cases, 53%) was higher than that in currently treated patients (10 patients, 23%). Morning blood pressure at home and office blood pressure were $150 \pm 13/95 \pm 7$ mmHg and $164 \pm 21/100 \pm 13$ mmHg at base-

Fig. 2. Distribution of morning blood pressure at home in all patients ($n=58$) before (open circles) and after (closed circles) 8-week administration of cilnidipine. The control rate of morning blood pressure ($<135/85$ mmHg) at home was 52%.

line, respectively, and office SBP was significantly higher than that at home ($p<0.05$). After cilnidipine administration, both morning blood pressure at home and office blood pressure were reduced to similar levels of $131\pm11/83\pm6$ mmHg and $134\pm15/81\pm9$ mmHg, respectively (both $p<0.001$, Table 2). The office pulse rate, which was higher than the morning pulse rate at baseline (81 ± 16 vs. 70 ± 9 , $p<0.05$), was significantly decreased to 72 ± 16 pulse/min ($p<0.01$) after cilnidipine administration, although no significant reduction in the morning pulse rate was observed. The distribution of SBP values before and after cilnidipine administration in new patients is shown in Fig. 1. After cilnidipine administration, the morning SBP was reduced to below 135 mmHg in 12 cases (80%).

Morning Blood Pressure at Home for All Patients

The values of morning blood pressure at home in all patients before and after cilnidipine administration are presented in Fig. 2. Both the SBP and DBP fell into a target range of below 135/85 mmHg in 30 (52%) out of 58 patients after 8 weeks of administration.

Efficacy of Cilnidipine on the White-Coat Effect

The white-coat effect, which is defined by the difference between the office blood pressure measurement and morning blood pressure measurement at home, was observed in 9 already treated patients and 8 new patients (Table 1). After cilnidipine administration, both the morning blood pressure at home and the office blood pressure fell to similar levels of $134\pm11/82\pm6$ mmHg and $141\pm14/85\pm7$ mmHg, respec-

tively (both $p<0.001$), with a significant attenuation of white-coat effect (Table 3, Fig. 3). Although the office pulse rate was much higher than the home pulse rate (83 ± 15 pulse/min vs. 72 ± 11 pulse/min, $p<0.05$), the two values declined significantly to similar levels after treatment (74 ± 14 pulse/min and 67 ± 10 pulse/min; $p<0.001$ and $p<0.01$, respectively; Table 3).

Discussion

In the present study conducted among patients with essential hypertension, cilnidipine produced a significant reduction in morning blood pressure at home. Importantly, the morning SBP values in both 58% of currently treated patients and 80% of new patients were reduced to the target level of under 135 mmHg, and the pulse rate also tended to decline after administration of cilnidipine once daily for 8 weeks, confirming previous reports on the efficacy of cilnidipine at suppressing higher blood pressure in the early morning and also higher blood pressure in early morning risers (6, 7). However, the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) study, which was conducted to evaluate current blood pressure control at home and in the office among medicated essential hypertensive patients, demonstrated that subjects with adequately controlled blood pressure accounted for 34% of 3,400 patients based on the criteria for home blood pressure ($<135/85$ mmHg) or 19% of the 3,400 patients based on the criteria for both home and office blood pressures ($<135/85$ mmHg and $<140/90$ mmHg) (8, 9). After cilnidipine administration in this study, home blood pressure in the morning was reduced to within the target range of below 135/85 mmHg in 30 cases (52%), and in 27 (47%) of the total cases, both the home and office blood pressures were controlled to below 135/85 mmHg and 140/90 mmHg, respectively, implying that cilnidipine might have an appropriate blood pressure-lowering effect in the morning in both currently treated and new patients.

Several reports have emphasized that the long-acting characteristic of antihypertensive agents is important to achieve sufficient morning blood pressure control (10–12). Cilnidipine administered once daily elicits a good reduction in early morning blood pressure and suppresses morning rise in blood pressure (6, 7). It is presumed that cilnidipine prolongs vascular dilation for a period of 24 h because of its highly lipophilic characteristic, although the plasma half-life after repeated administration at a dosage of 10 mg is not sufficient (8.1 h) (13–15).

Numerous physiologic systems, including the autonomic nervous system and renin-angiotensin-aldosterone system, regulate the circadian pattern of blood pressure, which falls during the nighttime, rises sharply during the awakening period, and remains elevated throughout the day (4, 16, 17). Over-activation of the sympathetic nervous system, especially the α -adrenergic nerves, contributes to “morning surge” and abnormal nighttime blood pressure patterns, such

Table 3. Blood Pressure and Pulse Rate in Patients with White-Coat Effect before and after Cilnidipine Therapy (n=17)

	Before		After 8 weeks	
	Home	Office	Home	Office
SBP (mmHg)	148.4±11.8	173.6±11.5 ^{###}	134.4±10.8 ^{***}	141.1±13.6 ^{***}
DBP (mmHg)	93.9±7.7	105.2±9.8 ^{###}	82.0±5.5 ^{***}	85.4±7.2 ^{***}
PR (pulse/min)	71.6±10.9	82.5±15.1 [#]	67.0±9.6 ^{**}	73.6±13.9 ^{***}

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. Values are expressed as the mean±SD. ^{**} $p<0.01$ and ^{***} $p<0.001$ vs. before administration, and [#] $p<0.05$ and ^{###} $p<0.001$ vs. home blood pressure or home pulse rate in the morning.

Fig. 3. White-coat effect changes on systolic blood pressure (SBP; open column) and diastolic blood pressure (DBP; closed column) before and after 8-week administration of cilnidipine (n=17). Vertical bars denote SD.

as the “inverted-dipper” or “non-dipper” pattern, whereas bedtime administration of an α -adrenergic blocker provides better blood pressure control from night to morning (18). Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors are also known to reduce morning blood pressure by suppressing the activity of the renin-angiotensin-aldosterone system (19). Cilnidipine is known to suppress the release of catecholamines from sympathetic nerve endings by blocking the N-type calcium channels distributed widely in sympathetic nerves; in this way, it attenuates sympathetic nerve hyperactivity accompanied by a reduction of blood pressure in the awakening period (7, 20). This implies that cilnidipine may contribute to a certain extent to the control of blood pressure in the early morning, and to the reduction or normalization of sympathetic nerve activity through its specific blocking action. Furthermore, Kario *et al.* reported that sympathetic activation due to perceived stress at work might increase ambulatory blood pressure levels throughout the day (21), while home stress may induce additional sympathetic activation at home. In this sense, cilnidipine, a long-acting dihydropyridine calcium channel antagonist with the ability to inhibit sympathetic nerve hyperactivity, is considered to be a useful drug to treat morning hypertensive patients.

The white-coat effect, or persistently elevated blood pressure in the office compared to the blood pressure level outside of the clinical setting, is quite common in medicated hypertensive patients (22, 23), whereas the blood pressure measurements taken in the office may lead to an inaccurate diagnosis of hypertension. When cilnidipine were administered to 17 subjects who showed the white-coat effect, this triggered reaction was apparently eliminated in 13 cases (76%). This finding may be partly attributed to the ability of cilnidipine to suppress catecholamine release from sympathetic nerve endings.

Despite numerous studies on the subject, it remains uncertain whether the white-coat effect has a deleterious effect on prognosis, with the common opinion being that patients with such an alerting reaction should not be treated with antihypertensive agents. However, recent studies have indicated a considerable association between the existence of a white-coat effect and cardiovascular mortality or target organ damage (24–26). Furthermore, recent studies have demonstrated the beneficial effect of cilnidipine on cardiac sympathetic nerve activity and cardiovascular morbidity (27–29). These observations underscore the need to pay close attention to the white-coat effect in hypertensive patients, and suggest that possible antihypertensive medication to ameliorate the white-coat effect should be taken into account, especially in patients with a clinical alerting reaction.

In conclusion, the once-daily administration of cilnidipine effectively controlled both morning blood pressure and office blood pressure in patients with morning hypertension and attenuated the white-coat effect with a good reduction of pulse rate. These findings suggest that cilnidipine may be a useful antihypertensive agent to medicate patients with morning hypertension and morning surge.

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