Original Article

Comparison of the Effects of Cilnidipine and Amlodipine on Ambulatory Blood Pressure

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Cilnidipine is a novel and unique 1,4-dydropyridine derivative calcium antagonist that exerts potent inhibitory actions not only on L-type but also on N-type voltage-dependent calcium channels. Blockade of the neural N-type calcium channel inhibits the secretion of norepinephrine from peripheral neural terminals and depresses sympathetic nervous system activity. The purpose of this study was to assess the effect of cilnidipine and amlodipine on ambulatory blood pressure (BP) levels. We performed 24-h ambulatory BP monitoring before and after once-daily use of cilnidipine ($n=55$) and amlodipine ($n=55$) in 110 hypertensive patients. Both drugs significantly reduced clinic and 24-h systolic BP (SBP) and diastolic BP (DBP) ($p<0.005$). However, the reductions of 24-h (−1.19±6.78 *vs*. 1.55±6.13 bpm, $p=0.03$), daytime (−1.58±6.72 *vs*. 1.68±7.34 bpm, $p=0.02$) and nighttime (−1.19±5.72 *vs*. 1.89±6.56 bpm, $p=0.01$) pulse rate (PR) were significantly greater in the cilnidipine group than the amlodipine group. There was no correlation between the degree of daytime SBP change and that of daytime PR change after amlodipine treatment ($r=-0.08$, n.s.), but there was a significant negative correlation between the degree of daytime SBP change and that of daytime PR change after cilnidipine treatment ($r=-0.27$, $p<0.05$). N-type calcium channel blockade by cilnidipine may not cause reflex tachycardia, and may be useful for hypertensive treatment. (*Hypertens Res* 2005; 28: 1003–1008)

***Key Words*: cilnidipine, amlodipine, ambulatory blood pressure, pulse rate**

Introduction

Many studies have reported that calcium antagonists or the combination of a calcium antagonist and an angiotensin blocker improves target organ damages and the clinical outcome in patients with hypertension (*1–6*). Dihydropyridine calcium antagonists have been widely used for the treatment of hypertension in Japan (*7, 8*). Amlodipine avoids sympathetic overactivity or reflex tachycardia because it has a longer biological half-life than short-acting calcium antagonists (*9*). Studies using ambulatory blood pressure (BP) monitoring have demonstrated that amlodipine controls BP levels throughout a 24-h period (*10, 11*).

Cilnidipine is a novel and unique 1,4-dihydropyridine derivative calcium antagonist with potent inhibitory actions against not only L-type but also N-type voltage-dependent calcium channels (*12*). The N-type voltage-dependent calcium channel plays an important role in sympathetic neurotransmission and regulates the release of norepinephrine from sympathetic nerve endings (*13*). It has been reported that once-daily administration of cilnidipine resulted in a safe and more effective BP decrease in essential hypertension without excessive BP reduction or reflex tachycardia than similar administration than once-daily administration of nifedipine (*14*) or nisoldipine (*15*).

We recently showed that the morning BP surge significantly increases the risk of stroke independent of age and 24-

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Received August 3, 2005; Accepted in revised form November 4, 2005.

Table1. Baseline Characteristics of Hypertensive Patients

	Amlodipine (n=55)	Cilnidipine (n=55)	p
Male (%)	36	33	n.s.
Age (years)	63±4.9	61±8.8	n.s.
BMI (kg/m^2)	26±4.0	25±3.4	n.s.
Clinic SBP (mmHg)	170±14	171±16	n.s.
Clinic DBP (mmHg)	97±14	95±15	n.s.
Clinic PR (bpm)	73±15	78±14	n.s.
24-h SBP (mmHg)	147±12	148±13	n.s.
24-h DBP (mmHg)	84±7.7	87±12	n.s.
24-h PR (bpm)	69±7.4	72±8.3	<0.05
Daytime SBP (mmHg)	155±16	155±11	n.s.
Daytime DBP (mmHg)	89±8.5	91±12	n.s.
Daytime PR (bpm)	74±8.9	76±9.2	n.s.
Sleep SBP (mmHg)	134±18	134±17	n.s.
Sleep DBP (mmHg)	76±9.4	78±12	n.s.
Sleep PR (bpm)	60±6.3	62±8.0	n.s.
Morning SBP (mmHg)	153±16	155±14	n.s.
Morning PR (bpm)	72±9.4	72±11	n.s.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. Values are shown as the mean±SD or the percentage.

h BP level in hypertensive patients (*16*). Thus, antihypertensive medication more specific for morning BP in addition to 24-h BP would be useful for the prevention of cardiovascular events in hypertensive patients. Amlodipine, with its long biological half-life, may decrease BP over a 24-h period, including morning BP. In addition, sympathetic nervous activity is activated in the morning, and may contribute to morning BP surge (*17*), and cilnidipine, which causes N-type calcium channel blockade, may decrease morning BP by a sympathetic inhibitory action.

Both cilnidipine and amlodipine have clinical benefits resulting from the unique characteristics of each agent. This study compared the effects of cilnidipine and amlodipine on ambulatory BP and pulse rate (PR) using ambulatory BP monitoring in patients with essential hypertension.

Methods

Study Patients

This study was an open-label, randomized study of the effects of once-daily morning administration of cilnidipine and amlodipine on ambulatory BP. We studied 110 hypertensive outpatients, each of whom had visited our office more than three times and showed a mean clinic systolic BP (SBP) ≥140 mmHg or mean clinic diastolic BP (DBP) ≥90 mmHg on two or more occasions during the run-in period. The studied patients were consecutively selected from among outpatients who met the following criteria. None of the patients had received any antihypertensive medication for at least 1 month before the start of the study. The results of physical and laboratory examinations, which included blood and urine tests, chest X-ray, and a resting electrocardiogram, were normal. All patients had normal renal and liver function. No patient had a past history of coronary artery disease, stroke (including transient ischemic attack), congestive heart failure, or malignancy. Informed consent was obtained from all of the subjects. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan.

Protocol

One hundred and ten patients were recruited for this study. Cilnidipine was administered orally once daily at an initial dose of 10 mg for 4 weeks. If the clinic BP remained high (SBP≥140 mmHg or DBP≥90 mmHg) or the magnitude of the reduction in BP was insufficient (a decrease in SBP <20 mmHg or a decrease in DBP <10 mmHg), the dose was increased to 20 mg once daily for another 4 weeks. Amlodipine were administered orally once daily at an initial dose of 2.5 mg for 4 weeks. We increased the dosage of amlodipine by 2.5 mg once daily when BP was not successfully controlled (as described above). Each patient was studied for a maximum of 16 weeks with a treatment period of up to 8 to 16 weeks.

Twenty-Four-Hour BP Monitoring

The 24-h ambulatory BP monitoring (ABPM) was monitored every 30 min with the use of a cuff-oscillometric device (TM-2425; A&D Co., Tokyo, Japan). The first ABPM was performed at the end of the run-in period and the second ABPM at the end of the treatment period of 8 to 16 weeks: if the clinic BP was controlled as described above, the second ABPM was performed at 8 weeks, and if clinic BP was uncontrolled, the second ABPM was performed at 16 weeks. Nighttime BP was defined as the average BP from the time when the subject went to bed until the time he/she got out of bed, and daytime BP as the average BP recorded during the rest of the day. Morning BP was defined as the mean BP during the first 2 h after awakening.

Statistical Analysis

Values are expressed as the mean±SD. The differences of the baseline characteristics and the change in BP and PR parameters between the cilnidipine and amlodipine groups were compared using an χ^2-test or unpaired t-test. The differences between the values before and after antihypertensive medication within the same group were tested using a paired t-test. A p value <0.05 was considered statistically significant.

Table 2. Blood Pressure and Pulse Rate before and after Treatment

	Amlodipine group ($n=55$)			Cilnidipine group ($n=55$)		
	Before	After	*p*	Before	After	*p*
Clinic SBP (mmHg)	170±14	144±15	<0.001	171±16	143±13	<0.001
Clinic DBP (mmHg)	97±14	85±8.9	<0.001	95±15	83±12	<0.001
Clinic PR (bpm)	73±15	73±14	n.s.	78±14	76±11	n.s.
24-h SBP (mmHg)	147±12	133±10	<0.001	148±13	137±11	<0.001
24-h DBP (mmHg)	84±7.7	77±6.5	<0.001	87±12	80±8.7	<0.001
24-h PR (bpm)	69±7.4	70±6.6	0.07	72±8.3	71±9.4	n.s.
Daytime SBP (mmHg)	155±16	139±11	<0.001	155±11	142±11	<0.001
Daytime DBP (mmHg)	89±8.5	81±7.8	<0.001	91±12	83±8.8	<0.001
Daytime PR (bpm)	74±8.9	76±7.7	<0.1	76±9.2	75±8.5	<0.1
Nighttime SBP (mmHg)	134±18	122±13	<0.001	134±17	126±15	<0.005
Nighttime DBP (mmHg)	76±9.4	71±8.1	<0.001	78±12	74±9.7	0.001
Nighttime PR (bpm)	60±6.3	62±7.0	<0.05	62±8.0	61±8.0	n.s.
Morning SBP (mmHg)	153±16	140±12	<0.001	155±14	146±15	<0.001
Morning PR (bpm)	72±9.4	73±9.6	n.s.	73±11	73±11	n.s.

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.

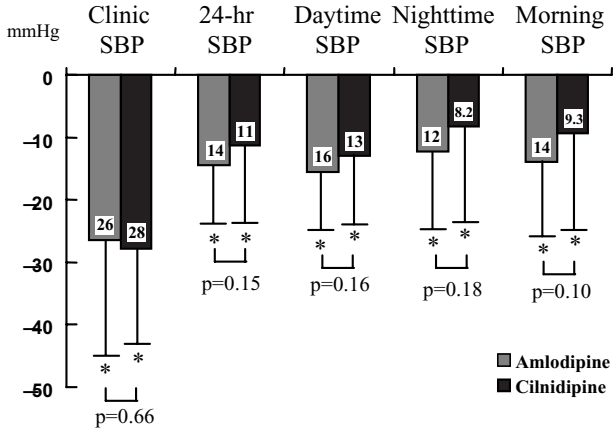

Fig. 1. *Changes in blood pressure after amlodipine and cilnidipine treatment. *p < 0.005 compared to the pretreatment values by paired* t*-test. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

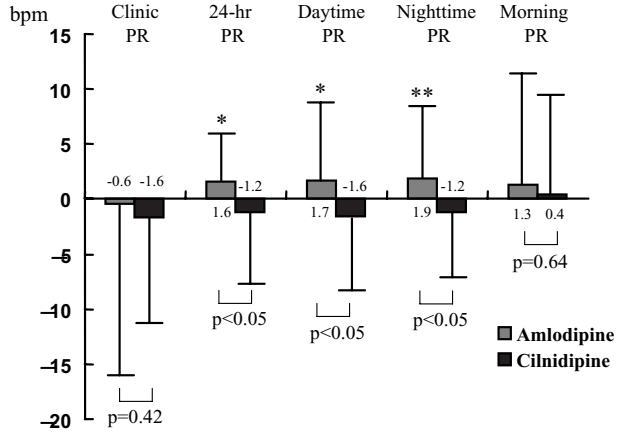

Fig. 2. *Changes in pulse rate (PR) after amlodipine and cilnidipine treatment. *p < 0.1, **p < 0.05 compared to the pretreatment values by paired* t*-test.*

Results

There were no adverse reactions in either the amlodipine or cilnidipine group. All patients in both groups completed the study.

Table 1 shows the characteristics of the 110 hypertensive patients on whom this study was conducted. There were no significant differences between the amlodipine and cilnidipine groups in any clinical characteristic or in the baseline clinic, 24-h, daytime or nighttime BP; however, 24-h PR was significantly higher in the cilnidipine group than in the amlodipine group. Clinic SBP, 24-h SBP, daytime SBP, nighttime SBP and morning SBP decreased significantly in both groups after treatment (Table 2). There were no significant differences in the reduction in any of the BP parameters between the amlodipine and cilnidipine groups (Fig. 1).

Figure 2 shows the effects of amlodipine and cilnidipine on the PR levels. In the amlodipine group, nighttime PR after treatment was significantly higher than that before treatment, and 24-h and daytime PR after treatment tended to be higher than those before treatment. In the cilnidipine group, there was no significant difference in any of the PR parameters between before and after treatment. The 24-h, daytime and nighttime PR showed significantly greater decreases in the cilnidipine treatment group than in the amlodipine treatment group. In the lower-dose amlodipine group (2.5 to 5.0 mg/

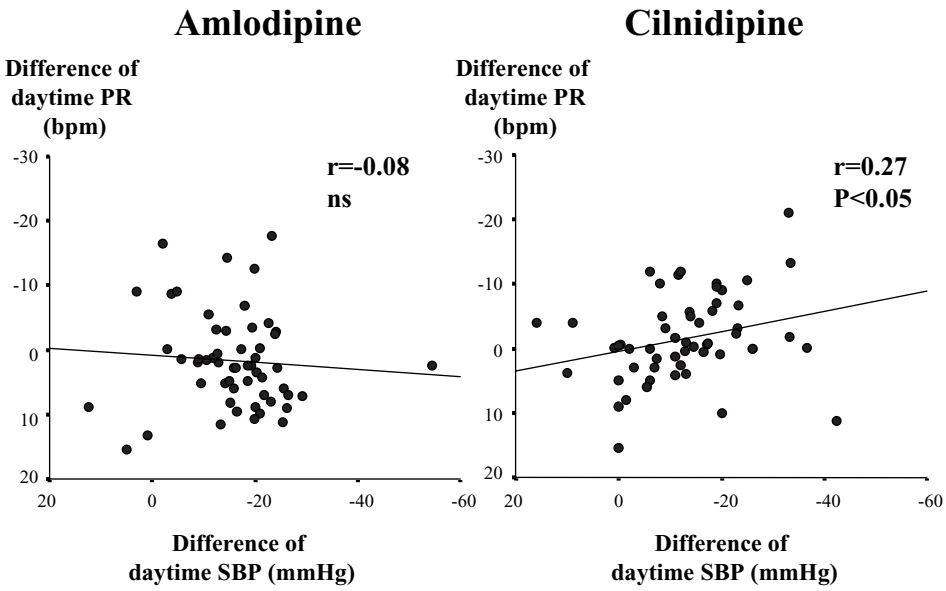

Fig. 3. *Relationship between the change in daytime systolic blood pressure (SBP) and the change in daytime pulse rate (PR) after treatment with amlodipine and cilnidipine.*

day, $n=45$), there were no significant differences in any of the PR parameters between before and after treatment (clinic PR: 73.3±14.5 *vs*. 72.8±14.2 bpm; 24-h PR: 68.9±7.4 *vs*. 69.6±6.2 bpm; daytime PR: 74.4±8.9 *vs*. 75.0±7.0 bpm; nighttime PR: 59.6±6.3 *vs*. 60.9±6.9 bpm; morning PR: 72.1±9.2 *vs*. 72.8±9.7 bpm).

For each group, we also analyzed the correlation between the daytime SBP change and daytime PR change following amlodipine and cilnidipine therapy (Fig. 3). In the amlodipine group, there was no correlation between the degree of daytime SBP change and that of daytime PR change after treatment. In the cilnidipine group, however, there was a significant negative correlation between the degree of daytime SBP change and that of daytime PR change after treatment. There was no relationship among the changes in 24-h, nighttime, or morning SBP, or among the changes in 24-h, nighttime, or morning PR after treatment in either group. At the start of the second ABPM, the mean dose of cilnidipine was 12.2±4.5 mg and that of amlodipine was 5.7±1.8 mg.

Discussion

In this study, once daily use of cilnidipine or amlodipine significantly reduced the ambulatory BP level over a 24-h measurement period, including morning BP. We found that cilnidipine, but not amlodipine, significantly decreased the ambulatory BP level without causing an increase in PR. There have been previous reports that compared the effects of cilnidipine and amlodipine (*18*, *19*) on BP and PR. However, this study was the first to report that cilnidipine treatment achieved a significantly greater decrease in PR than amlodipine treatment in hypertensive patients.

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 (*20*). Therefore, antihypertensive drugs that do not increase the heart rate would seem to be preferable. It has been reported that treatment with short-acting calcium antagonists may not prevent cardiovascular disease (*21*, *22*). A rapid and excessive decrease in BP and an increase in sympathetic activity by the drug have been suggested as possible underlying mechanisms for this unexpected outcome (*23*). Accordingly, long-lasting calcium channel blockers that exert less influence on the sympathetic nervous system are now recommended for treatment of hypertension (*24*). The long-acting nature of amlodipine (which has a half-life of 45 h after a single oral dose (*25*)), leads to a reduction of BP throughout the day and night (*10*), and prevents an increase in sympathetic activity (*26*). In this study, amlodipine significantly increased sleep PR, and tended to increase 24-h and daytime PR. Recently, some studies have reported that amlodipine increased PR, sympathetic activity, and reflex tachycardia *via* a reduction in BP, which are common adverse effects of conventional dihydropyridine calcium antagonists (*27*, *28*). However, in this study, the PR was not changed by low-dose amlodipine (2.5 to 5 mg/day) treatment. Changes of PR by amlodipine treatment might depend on the dose of amlodipine. A recent clinical trial demonstrated that the lowering of BP was associated with a significant fall in cardiovascular events (*29*). Therefore, in hypertensive treatment, it is not clear whether the reduction of PR is more effective in the prevention of cardiovascular events than the reduction of BP.

Cilnidipine is also a long-acting dihydropyridine calcium antagonist, but its half-life (2.1–2.5 h) is shorter than that of amlodipine (*30*). However, in this study, the tendency of amlodipine treatment to increase the PR was not observed with cilnidipine treatment. There was a significant negative correlation between the degree of daytime SBP change and that of daytime PR change after cilnidipine treatment. Both amlodipine and cilnidipine have been applied clinically based on their ability to blockade both the L-type and N-type calcium channels (*18*). Some experimental and clinical studies have suggested that cilnidipine is significantly more selective in blocking the N-type calcium channel than other calcium antagonists (*14, 15, 18, 19, 26, 31, 32*). Blockade of the neural N-type calcium channel inhibits the secretion of norepinephrine from peripheral neural terminals (*12*). Attenuating norepinephrine release from the sympathetic nerve endings by blocking the N-type calcium channels with cilnidipine might cause a decrease in PR. Clinically, Sakata *et al*. demonstrated by using ^{123}I-metaiodobenzylguanidine cardiac imaging that cilnidipine suppressed cardiac sympathetic overactivity while amlodipine had little suppressive effect (*18*). The effect of cilnidipine on PR might be due to not only long-acting effects but also a reduction in sympathetic nerve activity. In this study, we could not prove this hypothesis because we did not measure an index of sympathetic nervous activity.

Recently, some studies have reported that morning BP surge and morning BP level were associated with target organ damage (*33*) and stroke events in hypertensive patients (*16*). The treatment of morning BP is very important (*34–36*). Sudden activation of the sympathetic nervous system is the primary mediator of the morning surge. Whereas arousal from sleep is associated with a slight rise in plasma epinephrine, arising induces a significant rise in both epinephrine and norepinephrine (*37*). We speculated that cilnidipine therapy with its sympathetic inhibitory action was more effective than amlodipine therapy in controlling morning BP in hypertensive patients. However, we failed to show a better reduction in morning BP surge with cilnidipine.

An important issue when evaluating the BP-lowering effect of antihypertensive drugs is the reproducibility of measurement. Generally speaking, there have been problems with the reproducibility of ABPM. Nonetheless, some reports have shown that ABPM was useful for evaluating the BP-lowering effects of antihypertensive drugs (*38, 39*).

In conclusion, N-type calcium channel blockade by cilnidipine may not cause reflex tachycardia, and may be useful for hypertensive treatment.

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