Bedtime Administration of Cilnidipine Controls Morning Hypertension

Naoto ASHIZAWA,¹ MD, Shinji SETO,¹ MD, Yoshisada SHIBATA,² PhD,
and Katsusuke YANO,¹ MD

SUMMARY

Morning blood pressure (BP) level plays an important role in the incidence of cardiovascular disease. Recently, Kario, *et al* proposed the usefulness of ME difference (morning minus evening systolic BP) and ME average (average of morning and evening systolic BP) for the evaluation of antihypertensive treatment. Cilnidipine is a novel calcium channel blocker (CCB) that exerts inhibitory actions not only on L-type but also on N-type calcium channels. We investigated the effect of bedtime administration of cilnidipine (10 mg) in addition to the antihypertensive treatment for uncontrolled morning hypertension. Twenty-three hypertensive outpatients (13 males and 10 females; mean age, 66.9 years) with stable antihypertensive medication and uncontrolled morning BP were studied using self-measured BP monitoring in the morning and evening. Morning SBP ($P < 0.001$) and DBP ($P < 0.001$) decreased significantly from 150.2 ± 8.7 and 87.8 ± 9.3 to 132.7 ± 7.4 and 77.5 ± 8.5 mmHg, respectively, after the addition of cilnidipine. Morning heart rate did not change (63.3 ± 7.0 to 64.1 ± 9.4). The evening SBP, but not DBP, decreased significantly after treatment. Both the ME average ($P < 0.001$) and ME difference ($P < 0.01$) significantly decreased from 143.0 ± 9.2 and 14.3 ± 12.4 to 131.3 ± 7.2 and 2.8 ± 9.2 mmHg after treatment, respectively. The microalbuminuria decreased from 39.6 ± 13.2 to 27.3 ± 8.4 mg/g Cr. In conclusion, L-/N-type CCB cilnidipine may be useful for patients with uncontrollable morning hypertension by reducing both ME average and ME difference. (Int Heart J 2007; 48: 597-603)

Key words: L-/N-type calcium channel blocker, Morning hypertension, Microalbuminuria

CARDIOVASCULAR events occur most frequently in the morning^{1,2)} especially within 3 hours after waking.³⁾ An elevated morning blood pressure (BP) level has been associated with target organ damage: left ventricular hypertrophy⁴⁾ and microalbuminuria.⁵⁾ Recent reports demonstrated that morning hypertension measured either by ambulatory BP monitoring (ABPM)⁶⁾ or by self-measured BP

From the ¹ Division of Cardiovascular Medicine, Course of Medical and Dental Sciences, and ² Division of Radiation Epidemiology, Course of Life Sciences and Radiation Research, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan.

Address for correspondence: Naoto Ashizawa, MD, Division of Cardiovascular Medicine, Course of Medical and Dental Sciences, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki City, Nagasaki 852-8501, Japan.

Received for publication May 28, 2007.

Revised and accepted July 19, 2007.

at home⁷⁾ was the strongest independent predictor for future clinical stroke events in elderly hypertensive patients. Moreover, Kario, *et al* showed that morning hypertension with an increase in both Av-ME-BP (average of morning BP and evening BP) and Di-ME-BP (morning BP minus evening BP) was a higher risk for stroke than sustained hypertension.⁶⁾ These facts suggest that antihypertensive medications targeting more specifically morning BP, which can be measured by home monitoring, would decrease the cardiovascular risk of morning hypertension.

Cilnidipine is a long-acting antihypertensive agent with potent inhibitory actions against both L-type and N-type calcium channels. Because blockade of the N-type calcium channel inhibited the secretion of norepinephrine from peripheral neural terminals and reduced sympathetic nerve activity, cilnidipine more effectively decreased BP in essential hypertension without excessive BP reduction or reflex tachycardia compared to other once-daily administration of calcium channel blockers.⁸⁻¹⁰⁾

The purpose of the present study was to evaluate the efficacy of cilnidipine on morning hypertension in currently treated outpatients with essential hypertension.

METHODS

Study population: This study was conducted on 23 outpatients with essential hypertension (13 males and 10 females aged 50-87 years with a mean $\pm$ standard deviation (SD) of 66.9 ± 8.7 years) with stable antihypertensive medication for at least 3 months and morning BP that was not controlled; home morning SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg.

Administration of cilnidipine: After obtaining informed consent, cilnidipine at a dosage of 10 mg once daily at bedtime was administered in addition to the medication the patient was already prescribed.

Blood pressure measurement: Clinic BP was measured after resting for at least 5 minutes in the sitting position, and pulse rate was measured at the same time. Home BP was measured according to the Japanese Society of Hypertension guidelines for the self-monitoring of BP at home.¹¹⁾ Patients were asked to measure their home BP and pulse rate in the morning (morning BP) and in the evening (evening BP) using an automatic arm-cuff device in the sitting position. Morning BP was measured prior to breakfast within 1 hour after awakening, before taking antihypertensive drugs, and after micturition in principle. Evening BP was measured just before bedtime. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg for clinic BP, and SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg for home BP. Av-ME-BP and Di-ME-BP were defined as the

average of morning BP and evening BP, and their difference, ie, morning BP minus evening BP, respectively.⁶⁾

Urinary albumin excretion: Urine was obtained at an outpatient clinic between 9:00 and 11:00 AM, following overnight fasting, and urinary albumin excretion was measured using turbidimetric immunoassay (Mitsubishi Kagaku Bio-Clinical Laboratories Inc., Tokyo) and was adjusted for creatinine.

Statistical analysis: Data are expressed as the mean $\pm$ SD. Statistical analysis was performed using the paired *t*-test. *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics: The baseline characteristics of the patients were as follows. The duration of hypertension ranged from 1 to 35 years with a mean $\pm$ SD of 15.4 ± 10.9 years. There were 3 cases of cerebral vascular accidents, 3 cases of diabetes, 9 cases of dislipidemia, 6 cases of hyperuricemia, and 5 cases of angina pectoris. The number of antihypertensive drugs prescribed to subjects varied from 0 to 3 (mean $\pm$ SD, 1.6 ± 0.8); no drug in 2, monotherapy in 9, and concomitant therapy in 12 (2 drugs in 9 and 3 drugs in 3). The most commonly prescribed antihypertensive drugs were angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors (17 cases, 73.9%), followed by calcium channel blockers (9 cases, 39.1%) and $\alpha\beta$ blockers (2 cases, 8.7%).

Effects of bedtime administration of cilnidipine: The values of home morning BP, evening BP and morning heart rate (HR) before and after the bedtime administra-

Table. Clinical Characteristics Before and After Administration of Cilnidipine

	Before	After	<i>P</i>
Home			
Morning SBP (mmHg)	150.2 ± 8.7	132.7 ± 7.4	< 0.001
Morning DBP (mmHg)	87.8 ± 9.3	77.5 ± 8.5	< 0.001
Morning HR (bpm)	63.3 ± 7.0	64.1 ± 9.4	0.578
Evening SBP (mmHg)	135.9 ± 13.0	129.9 ± 9.6	< 0.05
Evening DBP (mmHg)	75.3 ± 10.4	72.7 ± 10.1	0.107
Evening HR (bpm)	68.8 ± 5.6	71.5 ± 8.3	0.192
Clinic			
SBP (mmHg)	144.3 ± 17.1	137.4 ± 14.4	< 0.05
DBP (mmHg)	84.1 ± 11.0	82.2 ± 11.5	0.225
HR (bpm)	71.2 ± 8.7	66.4 ± 8.8	< 0.005
Urinary Alb. (mg/gCr)	39.6 ± 52.6	27.3 ± 33.7	0.130

Values are mean $\pm$ SD. Alb indicates albumin; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

tion of cilnidipine are shown in the Table. After cilnidipine administration, morning SBP and morning DBP, both of which were poorly controlled at baseline (150.2 ± 8.7 mmHg and 87.8 ± 9.3 mmHg) were reduced to 132.7 ± 7.4 mmHg ($P < 0.001$) and 77.5 ± 8.5 mmHg ($P < 0.001$), respectively. There was no significant change in home morning HR after cilnidipine treatment (from 63.3 ± 7.0 /min to 64.1 ± 9.4 /min, $P = 0.578$). Evening SBP at home was also reduced significantly after treatment (from 135.9 ± 13.0 mmHg to 129.9 ± 9.6 mmHg, $P < 0.05$), although evening DBP and evening HR at home remained unchanged (from 75.3 ± 10.4 mmHg to 72.7 ± 10.1 mmHg, $P = 0.107$, from 68.8 ± 5.6 /min to 71.5 ± 8.3 /min, $P = 0.192$). On the other hand, clinic SBP was significantly reduced after cilnidipine treatment (from 144.3 ± 17.1 mmHg to 137.4 ± 14.4 mmHg, $P < 0.05$), but clinic DBP was not changed (from 84.1 ± 11.0 mmHg to 82.2 ± 11.5 mmHg, $P = 0.225$). Furthermore, clinic HR was significantly decreased (from 71.2 ± 8.7 /min to 66.4 ± 8.8 /min, $P < 0.005$). Urinary albumin excretion tended to decrease, although it was statistically not significant (from 39.6 ± 52.6 mg/g Cr to 27.3 ± 33.7 mg/g Cr, $P = 0.130$). Each arrow in Figure 1 depicts the simultaneous change in Av-ME-SBP and Di-ME-SBP for each subject; the head and the end of each arrow indicate the values of Av-ME-SBP and Di-ME-SBP before and after administration of cilnidipine, respectively. As shown in Figure 2, Av-ME-SBP and Di-ME-SBP were both significantly reduced after administration of cilnidipine (Av-ME-SBP; from 143.0 ± 9.2 mmHg to 131.3 ± 7.2 mmHg, $P < 0.001$, Di-ME-SBP; from 14.3 ± 12.4 mmHg to 2.8 ± 9.2 mmHg, $P < 0.01$).

Figure 1. Av-ME-SBP (average of morning SBP and evening SBP) and Di-ME-SBP (morning SBP minus evening SBP) before and after administration of cilnidipine for each patient were plotted and are indicated by circles and triangles, respectively.

Figure 2. Av-ME-SBP (average of morning SBP and evening SBP) and Di-ME-SBP (morning SBP minus evening SBP) before and after administration of cilnidipine.

DISCUSSION

In this study, the once-daily before bedtime administration of cilnidipine reduced morning hypertension in both systolic and diastolic BP significantly without causing an increase in PR. Evening home systolic BP and clinic systolic BP decreased significantly; moreover, cilnidipine reduced clinic HR.

Self-measured BP at home is a better predictor for cardiovascular disease risk than casual BP. However, it is still controversial as to which BP-monitoring time at home, ie morning BP or evening BP, is the most powerful predictor of cardiovascular events. Very recently two important Japanese studies were reported. Kario, *et al* demonstrated that morning hypertension with an increase in both Av-ME-BP and Di-ME-BP was a higher risk for stroke than sustained hypertension with similar increases in morning and evening BP, suggesting morning hypertension was the strongest independent risk factor for stroke in the elderly.⁶⁾ On the other hand, Asayama, *et al* showed that evening BP and morning BP predicted future stroke risk equally, whereas morning hypertension might be a good predictor of stroke particularly among individuals using antihypertensive medications.¹²⁾

Because evening BP measurement in Japan was performed in the late evening; after consuming alcohol or taking a bath (before bedtime) according to the Japanese guidelines for home BP measurement,¹¹⁾ evening BP might be lower

than morning BP. Taking these situations into consideration, evening BP was also important for controlling hypertensive patients.

Surprisingly, even after administration of once-daily long-acting calcium channel blockers, ACE inhibitors and ARB, the control of morning BP was far from satisfactory according to the J-HOME study.¹³⁾ Morning hypertension consists of nondipper/riser and morning surge, and they cannot be distinguished without using ABPM. Theoretically, adequate lowering of nocturnal BP by long-acting calcium channel blockers and/or ACE inhibitors, ARBs, and thiazide is recommended for the former and decreasing the morning BP using sympathetic inhibitory agent for the latter. For example, bedtime administration oftrandolapril¹⁴⁾ and doxazosin¹⁵⁾ resulted in a safe and effective means of controlling morning hypertension without inducing excessive reduction nocturnally. Cilnidipine was not less effective than amlodipine in reducing clinic and 24-h systolic and diastolic BP, furthermore, cilnidipine did not cause reflex tachycardia.¹⁶⁾ Yamagishi, *et al* reported the usefulness of cilnidipine at a dosage of 10-20 mg once daily after breakfast for morning hypertension and white-coat phenomenon.¹⁷⁾ Our patients were prescribed cilnidipine at a lower dose (10 mg per day) than those of Yamagishi and at bedtime. The morning SBP at home was much more successfully controlled to below 135 mmHg in the current study than in that of Yamagishi (16/23; 70% versus 25/43; 58%) and the SBP reduction rate in our cases was much higher than theirs (from 150.2 mmHg to 132.7 mmHg; -11.7% versus from 146.2 mmHg to 134.3 mmHg; -8.1%). Our results supported the beneficial effects of cilnidipine for morning hypertension; moreover, cilnidipine also reduced evening systolic BP, clinic systolic BP, and clinic HR significantly when administered at 10 mg once daily at bedtime.

Other once-daily administration of dihydropyridine calcium channel blockers such as nifedipine retard⁸⁾ and nisoldipine⁹⁾ induced reflex tachycardia in the morning and the afternoon. Amlodipine never decreases heart rate, and even increases it by activation of the baroreflex arch resulting in an increased sympathetic outflow to the vascular bed and to the heart.^{10,18,19)} As shown in Figure 2, Av-ME-SBP and Di-ME-SBP were both significantly reduced after cilnidipine administration. Since both the Av-ME-SBP and Di-ME-SBP were associated with future stroke events independently of each other,⁶⁾ cilnidipine seemed to be an ideal agent for controlling morning hypertension. Moreover, cilnidipine had a preferable effect on renal function and microalbuminuria although the albumin excretion rate (log-transformed) was not significantly reduced (from 1.35 ± 0.46 to 1.23 ± 0.40 , $P = 0.085$). This beneficial effect of cilnidipine was mainly mediated by nocturnal BP lowering, however, according to recent reports,^{20,21)} the reduction of microalbuminuria with the addition of cilnidipine treatment might not be due to only a BP-lowering effect. We propose the bedtime use of cilnid-

ipine as a new alternative in optimizing the control of morning hypertension.

REFERENCES

1. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989; 79: 733-43. (Review)
2. Shimada K, Kario K, Umeda Y, Hoshide S, Hoshide Y, Eguchi K. Early morning surge in blood pressure. *Blood Press Monit* 2001; 6: 349-53. (Review)
3. Willich SN, Goldberg RJ, Maclure M, Perriello L, Muller JE. Increased onset of sudden cardiac death in the first three hours after awakening. *Am J Cardiol* 1992; 70: 65-8.
4. Kuwajima I, Mitani K, Miyao M, Suzuki Y, Kuramoto K, Ozawa T. Cardiac implications of the morning surge in blood pressure in elderly hypertensive patients: relation to arising time. *Am J Hypertens* 1995; 8: 29-33.
5. Marfella R, Esposito K, Giugliano D. Increase in nocturnal blood pressure and progression to microalbuminuria in diabetes. *N Engl J Med* 2003; 348: 260-4.
6. Kario K, Ishikawa J, Pickering TG, *et al.* Morning hypertension: the strongest independent risk factor for stroke in elderly hypertensive patients. *Hypertens Res* 2006; 29: 581-7.
7. Sakuma M, Imai Y, Tsuji I, *et al.* Predictive value of home blood pressure measurement in relation to stroke morbidity: a population-based pilot study in Ohasama, Japan. *Hypertens Res* 1997; 20: 167-74.
8. Minami J, Ishimitsu T, Kawano Y, Numabe A, Matsuoka H. Comparison of 24-hour blood pressure, heart rate, and autonomic nerve activity in hypertensive patients treated with cilnidipine or nifedipine retard. *J Cardiovasc Pharmacol* 1998; 32: 331-6.
9. Minami J, Ishimitsu T, Higashi T, Numabe A, Matsuoka H. Comparison between cilnidipine and nisoldipine with respect to effects on blood pressure and heart rate in hypertensive patients. *Hypertens Res* 1998; 21: 215-9.
10. Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K. Comparison of the effects of cilnidipine and amlodipine on ambulatory blood pressure. *Hypertens Res* 2005; 28: 1003-8.
11. Imai Y, Otsuka K, Kawano Y, *et al.* Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003; 26: 771-82.
12. Asayama K, Ohkubo T, Kikuya M, *et al.* Prediction of stroke by home "morning" versus "evening" blood pressure values: the Ohasama study. *Hypertension* 2006; 48: 737-43.
13. Obara T, Ohkubo T, Funahashi J, *et al.* Isolated uncontrolled hypertension at home and in the office among treated hypertensive patients from the J-HOME study. *J Hypertens* 2005; 23: 1653-60.
14. Kuroda T, Kario K, Hoshide S, *et al.* Effects of bedtime vs. morning administration of the long-acting lipophilic angiotensin-converting enzyme inhibitor trandolapril on morning blood pressure in hypertensive patients. *Hypertens Res* 2004; 27: 15-20.
15. Kario K, Pickering TG, Hoshide S, *et al.* Morning blood pressure surge and hypertensive cerebrovascular disease: role of the alpha adrenergic sympathetic nervous system. *Am J Hypertens* 2004; 17: 668-75.
16. Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K. Comparison of the effects of cilnidipine and amlodipine on ambulatory blood pressure. *Hypertens Res* 2005; 28: 1003-8.
17. Yamagishi T. Beneficial effect of cilnidipine on morning hypertension and white-coat effect in patients with essential hypertension. *Hypertens Res* 2006; 29: 339-44.
18. Lefrandt JD, Heitmann J, Sevre K, *et al.* The effects of dihydropyridine and phenylalkylamine calcium antagonist classes on autonomic function in hypertension: the VAMPHYRE study. *Am J Hypertens* 2001; 14: 1083-9.
19. Struck J, Muck P, Trubger D, *et al.* Effects of selective angiotensin II receptor blockade on sympathetic nerve activity in primary hypertensive subjects. *J Hypertens* 2002; 20: 1143-9.
20. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertens Res* 2004; 27: 379-85.
21. Katayama K, Nomura S, Ishikawa H, Murata T, Koyabu S, Nakano T. Comparison between valsartan and valsartan plus cilnidipine in type II diabetics with normo- and microalbuminuria. *Kidney Int* 2006; 70: 151-6.