Original Article

Efficacy of Azelnidipine on Home Blood Pressure and Pulse Rate in Patients with Essential Hypertension: Comparison with Amlodipine

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Recently it has been recognized that not only blood pressure (BP) but also pulse rate (PR) assessed in the setting of the patient's home by a home BP monitoring device has higher predictive power for cardiovascular events than similar measurements made in the office setting. In this study, we compared the efficacy of azelnidipine to that of amlodipine in lowering morning BP and reducing PR in outpatients with essential hypertension. Patients were assigned to receive once daily administration of azelnidipine 8–16 mg/day ($n=54$) or amlodipine 2.5–5 mg/day ($n=54$) for 8 weeks. Morning BP and PR were evaluated by assessing patients' self-monitored BP and PR in the home environment. The mean reductions of morning systolic/diastolic BP (SBP/DBP) in the azelnidipine and amlodipine groups were similar ($-24.1 \pm 11.8/-14.1 \pm 10.7$ vs. $-20.4 \pm 11.7/-12.2 \pm 7.7$ mmHg). However, whereas azelnidipine decreased mean PR by -6.4 ± 8.3 beats/min ($p < 0.05$ vs. baseline), amlodipine did not cause significant reduction of this parameter (-2.1 ± 8.2 beats/min). Although neither drug changed PR in patients in whom baseline PR was < 70 beats/min, azelnidipine significantly lowered PR in patients whose baseline PR was > 70 beats/min. These results suggest that oral azelnidipine administration may be an effective therapy in the setting of chronic morning hypertension as well as for home PR control. (*Hypertens Res* 2006; 29: 767–773)

Key Words: morning hypertension, home blood pressure, home pulse rate, azelnidipine, L-type calcium channel blocker

Introduction

Hypertension is an established risk factor in the prognosis of cardiovascular diseases and organ damage. Recent research suggests that home-measured blood pressure (BP) has a higher predictive power for onset of cardiovascular events than readings made in the office setting (1–4). On the other hand, as shown by the Framingham Study (5), there is a positive correlation between clinical pulse rate (PR) measurements and cardiovascular disease mortality after adjustment for BP. Recently, it was reported that PR values recorded at home also predict the risk of cardiovascular disease mortality (6).

Azelnidipine is a unique, long-acting L-type calcium channel blocker that does not induce reflex tachycardia, probably because it elicits a gradual fall in BP (7, 8). Twenty-four-hour BP monitoring has shown that the hypotensive effect of azelnidipine is similar to that of amlodipine despite the difference of plasma half-life between these 2 drugs (approximately 8 h vs. approximately 39 h, respectively) (9). In addition, azelnidipine decreases 24-h PR by 2 beats/min whereas amlodipine significantly increased this parameter by 4 beats/min. The present study was conducted to evaluate the efficacy of azelnidipine in ameliorating morning BP surge and high PR at home in previously treated and new patients with essential hypertension.

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Methods

Subjects

In this single-blind, randomized clinical study, evaluation of morning BP and PR at home and office BP and PR was prospectively conducted in 108 outpatients with hypertension (46 males and 62 females; mean age, 59.9 years) defined as morning systolic blood pressure (SBP) ≥ 135 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg. Forty patients were already receiving antihypertensive medication and 68 were newly diagnosed patients. Existing medication, including antihypertensive drugs, was not changed during the study period. The subjects provided informed consent, and the study received the permission of our institutional ethics committee.

Drugs Administration

Azelnidipine and amlodipine were administered at a dosage of 8–16 mg and 2.5–5 mg, respectively, once daily after breakfast. Both treatments began at low dose; if the BP target (home SBP < 135 mmHg) was not achieved, higher doses were subsequently given. In patients already taking antihypertensive drugs, test agents were added to their existing prescriptions. Newly diagnosed patients were placed on monotherapy with the test agents.

Blood Pressure and Pulse Rate Measurement

At each visit, office BP and PR were measured at least twice after subjects had rested for 5 min. Home BP was measured according to the Japanese Society of Hypertension guidelines for self-monitoring of BP at home (10). All subjects were asked to measure and record their BP and PR once each morning and evening for a period of 8 weeks. Morning measurements of BP and PR were made within 1 h of waking, before breakfast and before taking any drugs, with the subjects seated and having rested for ≥ 2 min. Evening measurements of BP and PR were made similarly just before going to bed. Home BP and PR were measured using an HEM401C automatic device (Omron Healthcare Co., Kyoto, Japan), which utilizes the cuff oscillometric method to generate a digital display of SBP/DBP and PR values. This device has been previously validated (11) and satisfies the criteria of the Association for the Advancement of Medical Instrumentation. The arm circumference of patients was < 34 cm in the majority of cases; thus a standard arm cuff was used in this study.

Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg for office BP and SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg for home BP measurements.

Table 1. Clinical Characteristics of Patients

Variable	Azelnidipine	Amlodipine
<i>n</i>	54	54
New/currently treated patients	29/25	39/15
Sex (M/F)	23/31	23/31
Age (years)	58.0 $\pm$ 12.2	61.7 $\pm$ 12.1
BMI (kg/m ²)	23.8 $\pm$ 3.6	24.1 $\pm$ 3.5
Past complications (<i>n</i>)		
Cerebral infarction	1	—
Angina pectoris	2	1
Hyperlipidemia	12	4
Diabetes mellitus	7	6
Hyperuricemia	—	1
Duration of antihypertensive medication (years)	2.4 $\pm$ 1.8	3.0 $\pm$ 1.7

M, male; F, female; BMI, body mass index.

Statistical Analysis

BP and PR values measured at home (average 5 days' data) and in the office were compared before and after administration of study medication. All data are expressed as the mean $\pm$ SD. Statistical analysis was performed by paired Student's *t*-test for intra-group comparison and by unpaired *t*-test for comparison between the 2 groups. *p* values < 0.05 were considered statistically significant.

Results

Patients

Baseline characteristics of patients are shown in Table 1. There was no significant difference in gender, population, age, body mass index (BMI), medical history, and complications between the two groups. Twenty-nine of 54 patients in the azelnidipine group and 39 of 54 patients in the amlodipine group had not received previous antihypertensive therapy. Among those who were already on antihypertensive medication, mean duration of prior therapy was 2.4 $\pm$ 1.8 years in 25 of 54 patients enrolled in the azelnidipine group and 3.0 $\pm$ 1.7 years in 15 of 54 patients in the amlodipine group. The most commonly prescribed antihypertensive agents were angiotensin II receptor blockers, followed by β -blockers, calcium channel blockers, and others.

All patients completed the trial and demonstrated good drug compliance. There were no adverse events observed in this trial.

Blood Pressure

Table 2 shows pretreatment and posttreatment values of BP in the two study groups as measured at home and in the office. Both groups had poorly controlled baseline morning BP at

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

	Azelnidipine group					
	All patients		Newly diagnosed patients (n=29)		Currently treated patients (n=25)	
	Before	After 8 weeks	Before	After 8 weeks	Before	After 8 weeks
Home (morning)						
SBP (mmHg)	160.1±16.6 [#]	136.0±13.7**	159.3±16.1	133.2±12.9**	159.3±16.1 [#]	133.2±12.9**
DBP (mmHg)	97.5±11.4	83.3±10.2**	98.7±11.2	81.9±10.5**	96.0±11.6	85.0±9.7**
PR (beats/min)	74.6±12.6	68.2±10.5**	78.6±14.1	69.8±12.0**	70.0±8.9	66.2±8.3*
Office						
SBP (mmHg)	165.5±20.0	137.3±16.0**	165.8±19.9	138.2±16.8**	164.2±20.4	136.3±15.2**
DBP (mmHg)	99.1±14.8	81.9±11.4**	100.0±12.2	83.6±12.0**	98.0±17.6	79.9±10.6**
PR (beats/min)	79.3±14.3	73.1±11.5**	81.0±16.3	75.7±11.8**	77.3±11.5	70.2±10.7**
	Amlodipine group					
	All patients		Newly diagnosed patients (n=39)		Currently treated patients (n=15)	
	Before	After 8 weeks	Before	After 8 weeks	Before	After 8 weeks
Home (morning)						
SBP (mmHg)	154.8±14.1	134.3±11.5**	156.1±14.2	135.0±10.9**	150.3±13.4	132.5±13.2**
DBP (mmHg)	95.4±10.0	83.2±8.9**	96.3±9.8	83.7±8.3**	93.2±10.6	81.7±10.5**
PR (beats/min)	76.3±9.3	74.3±9.3	78.1±9.4	76.1±9.8	71.5±7.3	69.5±5.8*
Office						
SBP (mmHg)	157.3±14.6 [#]	134.1±12.1**	159.3±15.1	133.8±13.2**	152.1±11.8 [#]	134.7±8.9**
DBP (mmHg)	96.0±11.1	81.9±8.0**	97.8±10.3	82.3±7.9**	91.1±11.9	80.7±8.4**
PR (beats/min)	78.5±11.4	75.6±10.5	80.9±11.1	77.2±10.3	72.1±9.8	71.4±10.1

* $p < 0.05$ vs. baseline; ** $p < 0.001$ vs. baseline; [#] $p < 0.05$ vs. amlodipine; values are expressed as the mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.

home (azelnidipine group, 160.1±16.6/97.5±11.4 mmHg; amlodipine group, 154.8±14.1/95.4±10.0 mmHg). After treatment with azelnidipine and amlodipine, morning BP at home was reduced to 136.0±13.7/83.3±10.2 and 134.3±11.5/83.2±8.9 mmHg, respectively (both $p < 0.001$). Office BP was also observed to decrease significantly after treatment with azelnidipine (from 165.5±20.0/99.1±14.8 to 137.3±16.0/81.9±11.4 mmHg; $p < 0.0001$) and amlodipine (from 157.3±14.6/96.0±11.1 to 134.1±12.1/81.9±8.0 mmHg; $p < 0.0001$). The mean reductions of morning SBP/DBP at home were 24.1±11.8/14.1±10.7 mmHg and 20.4±11.7/12.2±7.7 mmHg in the two groups, respectively. Figure 1a and b respectively show the mean reduction of morning SBP/DBP in newly diagnosed patients (26.9±12.0/17.5±12.7 mmHg and 21.4±11.0/12.5±7.5 mmHg in the two groups, respectively) and in previously treated patients (21.8±11.4/11.0±7.1 mmHg and 17.9±13.4/11.5±8.4 mmHg, respectively). The mean reductions of evening SBP/DBP in the azelnidipine and amlodipine groups were not significantly different (19.1±9.9/11.2±9.0 and 17.6±7.2/10.7±4.9 mmHg, respectively).

Pulse Rate

Table 2 shows PR values before and after treatment with azelnidipine and amlodipine as measured in the morning at

home and in the office. In the azelnidipine group, morning PR at home was significantly ($p < 0.001$) reduced from 74.6±12.6 beats/min at baseline to 68.2±10.5 beats/min at the end of the study. In addition, the pretreatment and post-treatment office PR values were 79.3±14.3 beats/min and 73.1±11.5 beats/min, respectively ($p < 0.001$). However, amlodipine had no significant effect on either home or office PR.

As shown in Table 3, azelnidipine decreased mean morning PR at home by -6.4 ± 8.3 beats/min ($p < 0.001$ vs. baseline), whereas the reduction achieved by amlodipine (-2.1 ± 8.2 beats/min) was not significant. Azelnidipine yielded a significantly lower morning PR at home compared with amlodipine in those with a morning PR ≥ 70 beats/min at baseline. Neither test drug produced a significant change of PR among patients whose morning PR at home was < 70 beats/min at baseline. However, the mean reductions of morning PR in the azelnidipine group were significantly larger than those in the amlodipine group. In addition, the mean reduction of evening PR at home in the azelnidipine group was significantly larger than that in the amlodipine group (5.2 ± 9.7 vs. 1.8 ± 5.3 beats/min, respectively, $p < 0.05$).

Figure 2 shows that in all groups there were significant and negative correlations between morning PR at home before and after administration. In newly diagnosed patients, azelnidipine induced a markedly greater reduction in morning PR

Fig. 1. Effects of azelnidipine and amlodipine on home morning blood pressure (BP) and pulse rate (PR) after 8 weeks of treatment. Mean reductions of systolic blood pressure (SBP), diastolic blood pressure (DBP), and PR relative to the baseline values were compared between the two drugs (azelnidipine, closed column; amlodipine, open column). *a*: Newly diagnosed patients (azelnidipine, $n=29$; amlodipine, $n=39$). *b*: Currently treated patients (azelnidipine, $n=25$; amlodipine, $n=15$). * $p < 0.01$ vs. baseline; ** $p < 0.001$ vs. baseline; # $p < 0.01$ vs. amlodipine.

Table 3. Effects of Azelnidipine and Amlodipine on Change of Home Morning PR (Δ PR)

Subgroup	Azelnidipine			Amlodipine		
	<i>n</i>	Δ PR (beats/min)	<i>p</i> value	<i>n</i>	Δ PR (beats/min)	<i>p</i> value
All patients	54	$-6.4 \pm 8.3^{\#}$	<0.001	54	-2.1 ± 8.2	0.07
Baseline PR						
<70 (beats/min)	15	$-1.9 \pm 6.6^*$	0.10	9	6.6 ± 11.1	0.61
≥ 70 (beats/min)	39	$-8.2 \pm 8.5^{\#}$	<0.0001	45	-3.8 ± 6.3	0.002

* $p < 0.05$; # $p < 0.01$ vs. amlodipine. PR, pulse rate.

than amlodipine (-8.7 ± 8.6 vs. -2.1 ± 9.5 beats/min, $p=0.0042$), whereas in previously treated patients azelnidipine and amlodipine reduced morning PR to a similar extent (-3.8 ± 7.3 vs. 2.0 ± 2.9 beats/min, $p=0.36$). Azelnidipine and amlodipine increased morning PR in 5 of 29 (17%) and in 16 of 39 (41%) newly diagnosed patients, respectively, and in 8 of 25 (32%) and 6 of 15 (40%) previously treated patients, respectively.

Figure 3 shows scatter plots of morning SBP and PR at home in the azelnidipine and amlodipine groups. At baseline,

53 of 54 patients (98%) in both groups exhibited morning SBP ≥ 135 mmHg and/or morning PR ≥ 70 beats/min. At the end of the study, in the azelnidipine and amlodipine groups, morning SBP was <135 mmHg in 29 (54%) and 30 cases (56%), respectively, and morning PR was <70 beats/min in 27 (50%) and 12 cases (22%), respectively. Furthermore, in the two groups 13 (24%) and 8 cases (15%), respectively, achieved both morning SBP <135 mmHg and home PR <70 beats/min.

Fig. 2. Correlations between home morning pulse rate (PR) before administration and changes of home morning PR. *a:* New patients in the azelnidipine group. *b:* Currently treated patients in the azelnidipine group. *c:* New patients in the amlodipine group. *d:* Currently treated patients in the amlodipine group.

Discussion

In the present study, azelnidipine produced significant reductions of morning BP and PR in the home environment in patients with essential hypertension. Although the reductions of mean BP by azelnidipine and amlodipine were similar, only azelnidipine also significantly decreased home PR.

Using an ambulatory BP monitoring (ABPM) unit, Kuramoto *et al.* (9) showed that both azelnidipine and amlodipine achieve stable hypotensive effects lasting ≥ 24 h following once-daily administration. On the other hand, whereas azelnidipine slightly decreased PR, amlodipine had the opposite effect. Other studies have also indicated that amlodipine's effect on PR ranged from no change to a significant increase (12, 13). Eguchi *et al.* (14) showed that amlodipine is effective at lowering BP in older hypertensives, although it may increase ventricular ectopic beats, especially when given at high dose.

Several studies have reported positive relationships

between clinical PR measurements and cardiovascular disease mortality. For example, in the Framingham Study (5) mortality was highest in patients whose clinical PR was >85 beats/min. Home PR values also predict the risk of cardiovascular disease mortality: subjects with a home PR ≥ 70 beats/min have higher risk of cardiovascular mortality than those with normal PR even if they have a normal home SBP of <135 mmHg (5).

In this study, baseline morning BP in the azelnidipine group was significantly higher than that in the amlodipine group. Only a small number of cases achieved both morning SBP <135 mmHg and home pulse rate <70 beats/min, and the number of such cases was not significantly different between the two groups. However, the mean reductions of morning and evening PR in the azelnidipine group were significantly larger than those in the amlodipine group.

A major disadvantage of standard dihydropyridine antihypertensive drugs is their tendency to produce reflex tachycardia. Elevated sympathetic cardioacceleratory drive results in increased PR and increased myocardial oxygen demand, and

Fig. 3. Distribution of home systolic BP (SBP) and home pulse rate (PR) in the azelnidipine (left) and amlodipine (right) groups before (open circles) and after (closed circles) 8-week administration. Morning SBP was controlled to < 135 mmHg in 29 cases (54%) in the azelnidipine group and in 30 cases (56%) in the amlodipine group. Home PR was controlled to < 70 beats/min in 27 cases (50%) and 12 cases (22%), respectively. Following administration, 13 (24%) and 8 (15%) patients had morning SBP < 135 mmHg and home PR < 70 beats/min in the azelnidipine and amlodipine groups, respectively.

this may lead to aggravation of myocardial ischemia. Azelnidipine is a long-acting L-type calcium channel blocker with high lipid solubility that might explain its strong BP-lowering effect with minimum reflex tachycardia (7, 8). The exact mechanism by which azelnidipine effects calcium and other channels and thereby reduces BP and/or PR remains unclear. Shokoji *et al.* (15) examined the effects of azelnidipine and amlodipine on renal sympathetic nerve activity in spontaneously hypertensive rats and concluded that azelnidipine possesses sympathoinhibitory effects, which may contribute to its lack of effect on PR in hypertensive patients. Over-activation of the sympathetic nervous system, especially α -adrenergic nerves, contributes to “morning surge” and abnormal nighttime BP patterns such as “riser” and “non-dipper” patterns, whereas bedtime administration of an α -adrenergic blocker provides better BP control from night to morning (16). In older hypertensives, high morning BP surge is associated with stroke risk independent of ambulatory BP, nocturnal BP falls, and silent infarct (17). As an at least partial explanation for the reduction of PR observed in the present study, it is possible that azelnidipine possesses stronger sympathoinhibitory effects compared with other calcium channel blockers, including amlodipine.

As for other possible mechanisms, azelnidipine has been reported to elicit stronger anti-oxidative action than other calcium channel blockers and inhibits tumor necrosis factor (TNF)- α -induced activator protein-1 activation and interleu-

kin-8 expression in human umbilical vein endothelial cells by suppressing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated reactive oxygen species generation (18). Since nitric oxide (NO) production is decreased due to endothelial injury and the increase in oxidative stress in hypertensive patients, azelnidipine’s strong anti-oxidative properties may confer important benefits in the treatment of hypertension, PR control, and prevention of atherosclerosis (19). Further study is needed to shed light on the underlying mechanisms of azelnidipine on BP and PR control in hypertensive patients.

In conclusion, once-daily administration of azelnidipine effectively controlled both morning BP and office BP while reducing PR in the home and office settings. These findings suggest that azelnidipine may be a useful antihypertensive agent for patients with morning hypertension.

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