Efficacy and Tolerability of Nilvadipine in Combination with an Angiotensin II Receptor Antagonist in Patients with Essential Hypertension: A Multicenter, Open-Label, Uncontrolled Study

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ABSTRACT

Background: Combination therapy with different classes of antihypertensive drugs often is needed to achieve controlled blood pressure (BP). The combination of an angiotensin II receptor antagonist (AIIA) and a calcium antagonist is a preferred option for reducing uncontrolled BP.

Objective: The aim of this study was to assess the clinical efficacy and tolerability of nilvadipine, a dihydropyridine calcium antagonist, in combination with an AIIA.

Methods: Patients with essential hypertension whose BP was not controlled by an AIIA alone were eligible for this multicenter, open-label, uncontrolled study. One of 3 AIIAs (candesartan cilexetil, losartan potassium, or valsartan) was given for at least 10 weeks before the addition of nilvadipine (daily dose, 4 or 8 mg orally). This combination therapy was given for 8 weeks. BP and heart rate were measured between 2 and 4 weeks before and 0, 4, and 8 weeks after the start of combination therapy. Adverse events were monitored at each visit.

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Results: Thirty-one patients (18 women [58.1%], 13 men [41.9%]; mean [SD] age, 58.5 [10.5] years) were enrolled. At weeks 4 and 8 of combination therapy, mean systolic BP (SBP) and diastolic BP (DBP) were significantly decreased ($P < 0.01$) (at week 8, by 22.0 mm Hg and 12.5 mm Hg, respectively). The mean BP-lowering effect did not differ significantly between the 3 AIIAs tested. Pulse pressure also decreased significantly at week 8, by 9.6 mm Hg ($P < 0.01$). The responder rate (ie, the percentage of patients with DBP < 90 mm Hg or a decrease in DBP ≥ 10 mm Hg) was 72.0% at week 8. Three patients experienced a total of 4 adverse events: mild or severe flushing, mild headache, and mild palpitation. All of these symptoms resolved after nilvadipine treatment was discontinued.

Conclusions: Nilvadipine in combination with an AIIA showed good antihypertensive efficacy and was well tolerated in the hypertensive patients in this study. This combination also significantly decreased pulse pressure, suggesting that this combination therapy also may have a beneficial effect in elderly patients with isolated systolic hypertension. (*Curr Ther Res Clin Exp.* 2003;64:151–166) Copyright © 2003 Excerpta Medica, Inc.

Key words: nilvadipine, angiotensin II receptor antagonist, combination therapy, essential hypertension.

INTRODUCTION

The goal of treatment of hypertension is to prevent the progression of target organ damage by controlling blood pressure (BP), as stated in guidelines recently published in the sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI)¹ and the 1999 guidelines of the World Health Organization–International Society of Hypertension (1999 WHO–ISH).² The JNC VI states that the goal systolic BP (SBP)/diastolic BP (DBP) is $< 140 / < 90$ mm Hg. The 1999 WHO–ISH guidelines state that the goal SBP/DBP is $< 130 / < 85$ mm Hg for young and middle-aged people and up to the upper limit of normal range (140/90 mm Hg) for the elderly.

In Japan, the Japanese Society of Hypertension published guidelines for the treatment of hypertension,³ in which the goal SBP/DBP is $< 130 / < 85$ mm Hg for young and middle-aged people but is less strict (≤ 140 to 160/ < 90 mm Hg) for the elderly (≥ 60 years of age).

In the treatment of hypertension, a first-line drug is selected from among diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (AIIAs), alpha-blockers, and beta-blockers, depending on target organ damage, coexisting disorders, and other factors. However, the percentage of patients whose SBP/DBP is within the normal range (SBP/DBP $< 140 / < 90$ mm Hg) is very low: 27% in the United States,⁴ 5.9% in England,⁴ ~20% in other European countries,⁴ and 10% to 28% in Japan.^{5–7} The guidelines above recommend combination therapy with a different class of antihypertensive drug if the goal BP cannot be achieved with a single drug.

AIAs, the newest major class of antihypertensive drugs, have been reported to have both cardioprotective and renoprotective effects and to be associated with few adverse reactions.^{8–15} Due to their mild BP-lowering effects, it appears to be difficult to achieve the goal BP with AIAs alone.¹⁶ Thus, AIAs frequently are used in combination with another class of antihypertensive drug. Combination therapy with an AIA and a calcium antagonist frequently is used in Japan because these drugs involve different mechanisms in BP-lowering effects. Only 1 report¹⁷ is available on the use of a calcium antagonist in patients treated with an AIA in which the goal BP was not achieved.

In this study, nilvadipine was used as an adjunct antihypertensive drug in patients with essential hypertension whose SBP/DBP could not be controlled by monotherapy with an AIA. The aim of this study was to examine the antihypertensive efficacy and tolerability of this combination therapy.

PATIENTS AND METHODS

Patients were recruited at 12 clinics in Fukuoka, Japan, between August 2001 and August 2002. The study protocol was approved by the institutional review board at Fukuoka University, and written or verbal informed consent was obtained from all patients before they entered the study.

Outpatients of both sexes, aged 30 to 75 years, and having essential hypertension (SBP/DBP $\geq 140/\geq 90$ mm Hg) were eligible for this open-label, uncontrolled study if they had been treated previously with an AIA for at least 8 weeks but did not achieve an SBP/DBP $< 140/< 90$ mm Hg. Furthermore, patients' SBP/DBP had to be $> 140/> 90$ mm Hg both at 2 to 4 weeks before the study and on the day when combination therapy was started, and the difference in BPs at both time points had to be within 30 mm Hg for SBP and within 15 mm Hg for DBP. The selection and the initial dose of AIA were determined by the treating physician, and the dose of AIA was able to be increased before -4 to -2 weeks prior to the start of therapy.

Patients were excluded from the study if they had a history of hypersensitivity to nilvadipine and/or any of the 3 AIAs used in this study (candesartan cilexetil, losartan potassium, or valsartan) or a history of stroke occurring < 1 year before the study. Patients were eligible if stroke occurred ≥ 1 year before the study and their symptoms were stable. Patients with severe cardiac, renal, and hepatic disorders were excluded, as were women who were or might become pregnant or were lactating.

Patients were classified according to whether they met the selection criteria. A registration card was completed immediately after the start of treatment with AIA monotherapy and was sent to the enrollment administrator (Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan) by facsimile or mail.

The dose of the AIA received by each patient at 2 to 4 weeks before combination treatment was started was maintained throughout the study. Nilvadipine was administered orally at 4 or 8 mg/d, divided into 2 doses (morning and

evening) beginning at week 0, based on the judgment of the treating physician. At week 4, if the antihypertensive effect was insufficient (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) and the tolerability was good, the 4-mg dose was increased to 8 mg/d and the 8-mg dose was maintained for the remainder of the study.

BP and heart rate (HR) were measured with the patient in the sitting position at 4 time points: 2 to 4 weeks before the start of combination therapy, at the start of the combination therapy, and 4 and 8 weeks after the beginning of combination therapy (or at the time of discontinuing study participation). The measurements were taken at almost the same time of day throughout the study and only after it was confirmed that the patient had taken the medication in the morning.

The patients were classified by stage of JNC VI using their BP at 0 week of the combination therapy (stage 1: SBP 140–159 or DBP 90–99, stage 2: SBP 160–179 or DBP 100–109, stage 3: ≥ 180 or DBP ≥ 110). The change of stage was followed during the combination therapy.

Responders were defined in 2 ways: (1) an SBP < 140 mm Hg and DBP < 90 mm Hg and (2) DBP < 90 mm Hg or a decrease in DBP ≥ 10 mm Hg. The 2 responder rates were determined at weeks 4 and 8. All other patients were considered *nonresponders*.

Patient-reported adverse events were recorded by the treating physician at each visit and laboratory tests (ie, hepatic and renal function studies) were carried out by a nurse if possible.

Statistical Analysis

BP and HR at weeks 4 and 8 were compared with those at the start of combination therapy within each group (ie, 4-mg and 8-mg nilvadipine) using the Dunnett multiple comparison test. The distribution of BP and pulse pressure was compared between the start of combination therapy and week 8 using the Wilcoxon signed rank test. The level of significance was considered to be $P < 0.05$ (2-tailed).

If the dose of nilvadipine was changed at week 4, the group to which the patient belonged was determined based on the dose of nilvadipine given for 2 weeks before completion of the study.

RESULTS

A total of 31 Japanese patients (18 women [58.1%], 13 men [41.9%]; mean [SD] age, 58.5 [10.5] years) were enrolled in this study. On enrollment, no patients were being treated with any antihypertensive drugs or with drugs other than AIIA monotherapy. Twenty-five patients were included in both the efficacy and tolerability analyses, and the remaining 6 patients were included only in the tolerability analysis. Among the latter 6 patients, 3 were withdrawn due to adverse events. These 3 patients had received 2 mg, 4 mg, or 8 mg of nilvadipine as the initial dose. One patient did not attend the week-4 study visit and dropped out. These patients were confirmed to be well at the next visit and at

follow-up by telephone. Two patients were treated with an inappropriate dose (2 mg/d) of nilvadipine.

Of the AIIAs used in this study, candesartan cilexetil was given to 14 patients (4 mg [4 patients], 8 mg [8 patients], or 12 mg [2 patients]), losartan was given to 9 patients (25 mg [1 patient], 50 mg [7 patients], 100 mg [1 patient]), and valsartan was given to 8 patients (all 80 mg).

Eighteen patients (58.1%) had concomitant diseases: hyperlipidemia (10 patients [32.3%]); mild hepatic disorders (3 patients [9.7%]); and diabetes mellitus, hypothyroidism, hyperthyroidism, retinitis pigmentosa, and ventricular extrasystole (1 patient [3.2%] each).

Table I shows the baseline characteristics of the 25 patients included in the efficacy analysis. The mean prescribed dose of each of the 3 AIIAs was in the medium range before combination therapy was started. At the final assessment, 15 patients were given 4 mg/d (the 4-mg group) and 10 patients were given 8 mg/d (the 8-mg group) of nilvadipine.

Table II and Figure 1 show changes (mean [SD]) in BP and HR. At the start of combination therapy, SBP was 160.0 [9.9] mm Hg (range, 142 to 179 mm Hg) and DBP 98.6 [6.3] mm Hg (range, 90 to 110 mm Hg). Both SBP and DBP had decreased significantly at 4 weeks (by 15.7 and 8.6 mm Hg, respectively) and 8 weeks (by 20.0 and 12.5 mm Hg, respectively) ($P < 0.01$ for all). The HR at the start of combination therapy was not significantly different from those at weeks 4 and 8. Changes in JNC VI¹ BP stage are shown in Table III. The patients with higher BP stages at week 0 showed significant improvement to a lower stage ($P < 0.001$ for all). None of the patients were in stage 3 at week 8 of treatment even though 4 patients were classified as stage 3 before combination therapy.

Table IV shows changes in BP in the 4- and 8-mg/d groups. Both SBP and DBP significantly decreased at weeks 4 and 8 compared with week 0 ($P < 0.01$ for all except SBP and DBP at week 4 in the 8-mg/d group [$P < 0.05$ for both]).

In patients aged < 65 years, SBP/DBP (mean [SD]) at the start of combination therapy (158.9 [8.8]/100.5 [5.8] mm Hg) decreased significantly (to 137.6 [12.0]/88.8 [8.7] mm Hg) at 8 weeks ($P = 0.001$). In patients aged ≥ 65 years, mean SBP/DBP (162.3 [12.3]/94.8 [5.5] mm Hg) also decreased significantly (to 138.6 [7.6]/80.4 [7.3] mm Hg) at 8 weeks ($P = 0.001$) (data not shown).

Table V and Figure 2 show changes in BP by the AIIA given. SBP/DBP decreased significantly at weeks 4 and 8 compared with week 0 ($P < 0.01$ for all except DBP for losartan at weeks 4 and 8 and DBP for valsartan at week 4 [$P < 0.05$ for these]). The differences in SBP and DBP between the 3 AIIAs studied were not significant.

Mean (SD) pulse pressure also decreased significantly, from 61.4 (12.4) mm Hg at the start of combination therapy to 51.8 (10.3) mm Hg at 8 weeks (change, 9.6 mm Hg; $P < 0.01$). Table VI shows changes in the distribution of pulse pressure. Five, 14, and 6 patients had a pulse pressure of ≤ 49 mm Hg, 50 to 69 mm Hg, and ≥ 70 mm Hg, respectively, at the start of combination therapy. These

Table I. Baseline characteristics of patients included in the efficacy analysis (n = 25).

Characteristic	Value
Age, mean (SD), y	57.3 (10.8)
Sex, no. (%)	
Female	14 (56.0)
Male	11 (44.0)
BP, mean (SD), mm Hg	
SBP	160.0 (9.9)
DBP	98.6 (6.3)
MBP	119.0 (5.0)
PP*	61.4 (12.4)
Daily dose of nilvadipine, no. (%) of patients	
4 mg	15 (60.0)
8 mg	10 (40.0)
AllA, no. (%) of patients	
Candesartan cilexetil	12 (48.0)
Losartan potassium	6 (24.0)
Valsartan	7 (28.0)
Daily dose of AllA, mg	
Candesartan cilexetil	
Mean (SD)	7.3 (2.3)
Range	4–12
Losartan potassium	
Mean (SD)	58.3 (20.4)
Range	50–100
Valsartan	
Mean (SD)	80.0 (0.0)
Range	–
Concomitant disease, no. (%) of patients	
Hyperlipidemia	10 (40.0)
Hepatic disorders	2 (8.0)
Diabetes mellitus type 2	1 (4.0)
Hyperthyroidism	1 (4.0)
Retinitis pigmentosa	1 (4.0)

BP = blood pressure; SBP = systolic BP; DBP = diastolic BP; MBP = mean BP; PP = pulse pressure; AllA = angiotensin II receptor antagonist.

*Pulse pressure was calculated as SBP minus DBP.

numbers were 8, 14, and 3 patients at 4 weeks and 9, 15, and 1 patient, at 8 weeks. Thus, the distribution significantly shifted toward a lower pulse pressure.

The responder rate, defined as the percentage of patients with SBP <140 mm Hg, and DBP <90 mm Hg, was 20.0% at week 4 and 40.0% at week 8 (Table VII). The other responder rate, defined as the percentage of patients with DBP <90 mm Hg or a decrease in DBP $\geq$ 10 mm Hg, was 56.0% at week 4 and 72.0% at week 8.

Table II. Mean [SD] changes in blood pressure (BP) and heart rate (HR) 2 to 4 weeks before the study and 4 and 8 weeks after the addition of nilvadipine (n = 25).

Parameter	Pretreatment	Week 0	Week 4	Week 8
BP, mm Hg				
SBP	158.7 (11.3)	160.0 (9.9)	144.3 (13.5)*	138.0 (10.6)*
DBP	98.4 (6.0)	98.6 (6.3)	90.0 (8.3)*	86.1 (9.1)*
MBP	118.5 (5.4)	119.0 (5.0)	108.1 (9.0)*	103.4 (8.4)*
PP	60.4 (12.9)	61.4 (12.4)	54.3 (11.0)*	51.8 (10.3)*
HR, bpm	73.9 (8.2)	75.3 (9.6)	76.3 (8.1)	74.8 (8.4)

SBP = systolic BP; DBP = diastolic BP; MBP = mean BP; PP = pulse pressure.

* $P < 0.01$ versus week 0.

Three of the 31 patients (9.7%) experienced a total of 4 adverse events (severe flushing [1], mild flushing [1], mild headache [1], and mild palpitation [1]) (Table VIII). These symptoms were considered to be treatment related because they resolved soon after the discontinuation of nilvadipine. AIIA therapy was continued in these patients.

In the 17 patients who underwent laboratory testing, because of patient request or preexisting disease other than hypertension, no abnormal values were found.

Figure 1. Mean (SD) changes in blood pressure (BP) and heart rate (HR) with combination therapy with an angiotensin II receptor antagonist and nilvadipine. SBP = systolic BP; MBP = mean BP; DBP = diastolic BP. * $P < 0.01$ versus week 0.

Table III. Changes in blood pressure stage (no. [%] of patients) according to the sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure¹ (JNC VI) after addition of nilvadipine (n = 25).

JNC VI Stage*	Week 0	Week 4 [†]	Week 8 [†]
Normal	0 (0.0)	1 (4.0)	1 (4.0)
High normal	0 (0.0)	4 (16.0)	9 (36.0)
Stage 1	6 (24.0)	13 (52.0)	12 (48.0)
Stage 2	16 (64.0)	6 (24.0)	3 (12.0)
Stage 3	3 (12.0)	1 (4.0)	0 (0.0)

*JNC VI stages: normal = systolic blood pressure (SBP) <130 mm Hg/diastolic blood pressure (DBP) <85 mm Hg; high normal = SBP 130 to 139 mm Hg/DBP 85 to 89 mm Hg; stage 1 = SBP 140 to 159/DBP 90 to 99 mm Hg; stage 2 = SBP 160 to 179/DBP 100 to 109 mm Hg; stage 3 = SBP ≥180/DBP ≥110 mm Hg.

[†]P < 0.001 for all 5 JNC VI stages versus week 0.

DISCUSSION

In pharmacologic therapy for hypertension, a first-line drug is selected from among calcium antagonists, ACEIs, AIIAs, diuretics, alpha-blockers, and beta-blockers. If the antihypertensive effect of the first-line drug is insufficient, a second drug with a different mechanism of action should be added or the patients switched to another drug, as recommended in the JNC VI,¹ the 1999 WHO-ISH guidelines,² and the guidelines for the treatment of hypertension

Table IV. Mean (SD) changes in blood pressure (BP) and heart rate (HR) 2 to 4 weeks before and after the addition of 4 mg/d (n = 15) and 8 mg/d (n = 10) nilvadipine.

Parameter	Pretreatment	Week 0	Week 4	Week 8
BP, mm Hg				
SBP				
4 mg/d	157.0 (10.7)	159.4 (8.4)	140.4 (13.2)*	134.1 (10.0)*
8 mg/d	161.3 (12.2)	160.9 (12.3)	150.1 (12.2) [†]	143.7 (9.2)*
DBP				
4 mg/d	98.9 (5.9)	99.6 (5.6)	88.3 (7.8)*	86.1 (9.4)*
8 mg/d	97.5 (6.3)	97.2 (7.3)	92.5 (8.9) [†]	86.1 (9.0)*
MBP				
4 mg/d	118.3 (4.9)	119.4 (3.9)	105.7 (9.0)*	102.0 (8.5)*
8 mg/d	118.8 (6.3)	118.5 (6.4)	111.8 (8.1)*	105.4 (8.2)*
HR, bpm				
4 mg/d	73.5 (8.5)	75.6 (10.6)	74.1 (8.6)	74.7 (8.5)
8 mg/d	74.4 (8.2)	74.7 (8.1)	80.4 (5.6)	75.0 (8.9)

SBP = systolic BP; DBP = diastolic BP; MBP = mean BP.

*P < 0.01 versus week 0.

[†]P < 0.05 versus week 0.

Table V. Mean (SD) changes in blood pressure (BP) and heart rate (HR) among the 3 angiotensin II receptor antagonists (candesartan cilexetil [$n = 12$], losartan potassium [$n = 6$], and valsartan [$n = 7$]) 2 to 4 weeks before and after the addition of nilvadipine ($n = 25$).

Parameter	Pretreatment	Week 0	Week 4	Week 8
BP, mm Hg				
SBP				
Candesartan	155.2 (13.5)	154.9 (9.6)	142.3 (14.9)*	135.3 (13.1)*
Losartan	157.2 (6.0)	163.0 (9.2)	143.3 (14.7)*	143.3 (7.6)*
Valsartan	166.1 (7.5)	166.1 (6.8)	148.4 (10.5)*	137.9 (6.7)*
DBP				
Candesartan	98.8 (7.2)	100.8 (7.4)	90.5 (11.2)*	86.3 (9.8)*
Losartan	98.2 (4.4)	98.2 (4.6)	89.2 (3.9) [†]	89.3 (8.6) [†]
Valsartan	97.9 (5.7)	95.3 (4.1)	89.9 (5.9) [†]	83.0 (8.2)*
MBP				
Candesartan	117.7 (6.3)	118.8 (6.6)	107.8 (11.8)*	102.8 (10.2)*
Losartan	117.8 (2.5)	119.8 (2.8)	107.3 (5.5)*	107.2 (5.5)*
Valsartan	120.6 (5.6)	118.7 (3.2)	109.4 (6.3)*	101.1 (6.5)*
HR, bpm				
Candesartan	70.9 (6.6)	73.5 (8.4)	74.7 (5.9)	73.9 (7.9)
Losartan	79.5 (6.7)	83.0 (7.5)	82.0 (8.1)	81.8 (6.3)
Valsartan	73.7 (10.1)	71.4 (10.2)	73.6 (9.5)	70.3 (7.9)

SBP = systolic BP; DBP = diastolic BP; MBP = mean BP.

* $P < 0.01$ versus week 0.

[†] $P < 0.05$ versus week 0.

published by the Japanese Society of Hypertension.³ In clinical practice, ≥ 2 drugs often are used as combination therapy based on considerations of target organ damage and concomitant disorders. A sufficient antihypertensive effect produced by a combination of antihypertensive drugs may be associated with the properties of essential hypertension. Essential hypertension involves many disorders of extracellular fluid volume, the neurohormonal system, and calcium metabolic regulation in vascular smooth muscle cells. Thus, a combination of drugs with different mechanisms of action may be effective in achieving goal BP.

In Japan, calcium antagonists or ACEIs have been widely used as first-line drugs. AIIAs also have begun to be used as first-line drugs, perhaps because the accumulated evidence of clinical studies^{8–15,18} has shown that AIIAs have antihypertensive, cardioprotective, and renoprotective effects but produce almost no adverse events. However, the antihypertensive effects of AIIAs appear to be mild, and it is difficult to achieve the goal BP with an AIIA alone.¹⁶ Although more information is needed on the combination of an AIIA and other classes of antihypertensive drugs, the combination of an AIIA and a diuretic has been shown to be effective.¹⁶ Only 1 study¹⁷ has shown combination therapy with

Figure 2. Mean (SD) changes in (A) blood pressure (BP) and (B) heart rate (HR) with 3 angiotensin II receptor antagonists. SBP = systolic BP; MBP = mean BP; DBP = diastolic BP. * $P < 0.05$ versus week 0; † $P < 0.01$ versus week 0.

a calcium antagonist when an AIIA was ineffective in decreasing BP to the desired goal.

In the present study, nilvadipine, a dihydropyridine calcium antagonist, was administered to patients with essential hypertension who had taken AIIA monotherapy for at least 8 weeks but did not achieve an SBP/DBP $<140/90$ mm Hg. Compared with other calcium antagonists, nilvadipine has high selectivity for the brain and coronary arteries.¹⁹ It is highly concentrated in the brain and helps protect the brain by increasing cerebral blood flow.²⁰ Some studies have reported that nilvadipine improved cardiomegaly²¹ and dilated afferent and efferent arterioles in the kidneys.²² This drug mildly and steadily decreases BP and also has antioxidant and antiarteriosclerotic effects.²³ Thus, nilvadipine is widely used in elderly patients who are likely to have many concomitant diseases and cerebrovascular disorders.

Table VI. Changes (no. [%] of patients) in the distribution of pulse pressure (n = 25).

Pulse Pressure, mm Hg	-4 to -2 Weeks Before Study	Week 0	Week 4*	Week 8†
≤49	3 (12.0)	5 (20.0)	8 (32.0)	9 (36.0)
50–59	9 (36.0)	3 (12.0)	10 (40.0)	9 (36.0)
60–69	5 (20.0)	11 (44.0)	4 (16.0)	6 (24.0)
≥70	8 (32.0)	6 (24.0)	3 (12.0)	1 (4.0)

*P = 0.018 versus week 0.

†P = 0.001 versus week 0.

In this study, BP was significantly decreased at 4 weeks of nilvadipine treatment, and significant decreases in SBP ≥ 20 mm Hg and DBP ≥ 10 mm Hg were observed at 8 weeks; no significant change in HR was found. The responder rate, defined as the percentage of patients with DBP < 90 mm Hg or a decrease in DBP ≥ 10 mm Hg, was 72.0% at 8 weeks. MacGregor et al¹⁷ reported that candesartan monotherapy decreased DBP to < 95 mm Hg in 34.5% of patients with moderate to severe essential hypertension (DBP > 100 mm Hg), and the concomitant use of a dihydropyridine calcium antagonist (amlodipine) was associated with a DBP of < 95 mm Hg in 44.3% of patients with uncontrolled BP (DBP > 95 mm Hg), with an overall responder rate of 63.6%. Conlin et al¹⁶ investigated the antihypertensive efficacy of 4 different AIIAs in the treatment of mild to moderate essential hypertension by performing a meta-analysis of 43 published randomized controlled trials. They found that responder rate

Table VII. Responder rates after addition of nilvadipine (n = 25). Values are number of responders/total patients (%).

	Week 4	Week 8
Responder rate defined using SBP and DBP* in patients aged		
≤59 y	1/13 (7.7)	5/13 (38.5)
60–69 y	4/10 (40.0)	5/10 (50.0)
≥70 y	0/2 (0.0)	0/2 (0.0)
Total	5/25 (20.0)	10/25 (40.0)
Responder rate defined using DBP† in patients aged		
≤59 y	4/13 (30.8)	7/13 (53.8)
60–69 y	8/10 (80.0)	9/10 (90.0)
≥70 y	2/2 (100.0)	2/2 (100.0)
Total	14/25 (56.0)	18/25 (72.0)

SBP = systolic blood pressure; DBP = diastolic blood pressure.

*SBP < 140 mm Hg and DBP < 90 mm Hg.†DBP < 90 mm Hg or a decrease in DBP ≥ 10 mm Hg.

Table VIII. Treatment-related adverse events.

Patient Sex and Age, y	Dose Received, mg	Adverse Event	Day of Onset	Treatment	Prognosis	Causal Relationship	Concomitant Drug(s)	Complication
Female, 69	8	Severe flushing	0	Withdrawal	Resolved on withdrawal day	Related	Valsartan	None
Female, 50	2	Mild flushing, mild headache	3	Withdrawal	Resolved on withdrawal day	Related	Losartan potassium, levothyroxine sodium, Chinese medicine	Hypothyroidism
Female, 72	4	Mild palpitation	15	Withdrawal	Resolved 1 day after withdrawal	Unknown	Losartan potassium, pirmenol hydrochloride, ibudflast	Ventricular extrasystole

(percentage of patients with DBP <90 mm Hg or a decrease in DBP $\geq$ 10 mm Hg) for AIIA monotherapy was 48% to 55%, whereas those for combination therapy with an AIIA plus hydrochlorothiazide increased to 56% to 70%, which is smaller than our responder rate of 72.0% at the end of our study. One²⁴ of these 43 randomized controlled trials used amlodipine in addition to valsartan, but the responder rate for combination therapy was not reported. Based on the responder rate in our study, nilvadipine may be as useful as, or superior to, hydrochlorothiazide when administered in combination with an AIIA in treating mild to severe hypertension.

Nilvadipine also significantly decreased pulse pressure. The 20-year Framingham Heart Study²⁵ revealed that not only increased SBP but also increased pulse pressure was a significant risk factor for coronary disease. Increased pulse pressure is associated with arteriosclerosis, age-related changes in the vascular walls, and target organ damage (eg, left ventricular hypertrophy).²⁶ A task force of the European Society of Hypertension²⁷ included decreased pulse pressure in a list of goals for antihypertensive therapy for patients aged $\geq$ 50 years. A 10-mm Hg increment in pulse pressure was associated with a 12% increase in the risk for coronary heart disease, a 14% increase in the risk for congestive heart failure, and a 6% increase in overall mortality in individuals aged $\geq$ 65 years.²⁸ In our study, the distribution of pulse pressure was compared before and after treatment with nilvadipine. This combination therapy decreased the prevalence of a higher pulse pressure, suggesting that nilvadipine decreased DBP but not to a significant degree, and effectively lowered SBP.

A relationship between hypertension and cognitive dysfunction has been reported.²⁹ In particular, interference with the renin-angiotensin-aldosterone system appears to improve cognitive performance, and AIIA has been shown to have a positive effect on not only BP but also impaired cognitive function.³⁰ Although it is not clear whether AIIAs can improve cognitive function in patients with uncontrolled BP, cognitive dysfunction in patients with hypertension did not progress or was improved by effective antihypertensive treatment,³¹ suggesting that well-controlled BP may be necessary to prevent and improve cognitive dysfunction.

Economic concerns also are important in the long-term treatment of hypertension. Combination therapy with nilvadipine and an AIIA can reduce the economic burden on hypertensive patients, in contrast to increasing the dose of AIIA, which can be quite expensive.

Adverse events in this study included flushing, headache, and palpitation. These symptoms resolved soon after discontinuation of nilvadipine. The dihydropyridine calcium antagonists, especially short-acting types, activate the sympathetic nervous system, which is thought to be responsible for decreased BP. Palpitation is one of the typical symptoms associated with the mechanism of action of calcium antagonists. Flushing and headache may be related to the vasodilating action of calcium antagonists. Those symptoms are the common side effects of treatment with dihydropyridine calcium antagonists. No abnormal

changes in liver and renal function were found, as shown by laboratory testing. The frequency of adverse events with combination therapy (nilvadipine plus an AIIA) was almost the same as the frequency found with dihydropyridine calcium antagonists.³²

CONCLUSIONS

Nilvadipine at 4 or 8 mg/d had a significant antihypertensive effect on uncontrolled BP that did not respond to monotherapy with an AIIA. Combination therapy (nilvadipine plus an AIIA) also improved high pulse pressure and appeared to be tolerable, suggesting that this antihypertensive therapy may have a beneficial effect in elderly patients with isolated systolic hypertension.

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