Original Article

The Effect of Combination Therapy with an L/N-Type Ca^{2+} Channel Blocker, Cilnidipine, and an Angiotensin II Receptor Blocker on the Blood Pressure and Heart Rate in Japanese Hypertensive Patients: An Observational Study Conducted in Japan

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Recently, the use of combination therapy with a calcium channel blocker (CCB) and an angiotensin II receptor blocker (ARB) has been rapidly increasing. Although this combination therapy is accepted as a standard treatment hypertension, there have been few large-scale, multicenter studies examining its safety and efficacy. The present study was designed to investigate the safety and efficacy of adding cilnidipine, a dual L/N-type CCB, to the regimen of patients whose blood pressure had been poorly controlled (systolic blood pressure [SBP] >140 mmHg or diastolic blood pressure [DBP] >90 mmHg) by antihypertensive monotherapy with an ARB. The percentage achievement of the blood pressure goals recommended by the JSH 2000 guidelines was also assessed for at least 12 weeks of treatment. A total of 2,920 patients were enrolled in the study at 471 institutions in Japan from February 2003 to July 2004. The incidence of adverse reactions related to cilnidipine was as low as 2.5%. A significant reduction from the baseline was found both in SBP (from 164.1 ± 15.3 to 139.2 ± 15.3 mmHg, $p < 0.0001$) and DBP (from 91.7 ± 11.4 to 79.3 ± 10.7 mmHg, $p < 0.0001$). A total of 31.5% of the patients achieved the blood pressure goals recommended by the JSH 2000 guidelines. Moreover, the heart rate also significantly decreased in these patients, particularly in those with a higher baseline heart rate. Our results indicate that cilnidipine can be used in combination with an ARB to control blood pressure without any significant adverse effects, and also that cilnidipine successfully reduces elevated heart rate, which is a possible risk factor for cardiovascular events. (*Hypertens Res* 2007; 30: 815–822)

Key Words: cilnidipine, heart rate, hypertension, angiotensin II receptor blocker, combination therapy

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Introduction

The Guidelines for the Management of Hypertension for General Practitioners, which were published in Japan in 2000 (JSH 2000) (1), established the following blood pressure goals: <130/85 mmHg for young/middle-aged patients, <140/90 mmHg for elderly patients, and <130/85 mmHg for high-risk patients (with renal disease or diabetes). The new, revised 2004 guidelines of Japanese Society of Hypertension (JSH) (JSH 2004) (2) lowered the blood pressure goal to 130/80 mmHg for high-risk patients. If blood pressure does not reach these goals in hypertensive patients who are under monotherapy, combination therapy with two or more antihypertensive drugs, including the combination of a renin-angiotensin inhibitor and a calcium channel blocker (CCB), is recommended according to the JSH 2000 guidelines.

A previous study (3) assessed the effect of monotherapy with an angiotensin II receptor blocker (ARB) or a CCB, based on the percentage of patients who reached the blood pressure goals recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (4). However, there have been few studies evaluating the efficacy of a CCB added to an ARB regimen in patients with poorly controlled hypertension.

ARB treatment has been added to the list of first-line antihypertensive therapies in the World Health Organization–International Society of Hypertension (WHO/ISH) Guidelines for the Management of Hypertension, revised in 1999 (5), as well as to that of the JSH 2000. Many global, large-scale clinical studies (6–8) have demonstrated the inhibitory effect of ARBs on various conditions, such as cardiovascular events and diabetes onset, which has led to the rapidly increasing use of these agents.

CCBs are among the most commonly prescribed antihypertensive agents in Japan. Since a much larger number of large-scale clinical studies have been conducted for CCBs (9–11) than for ARBs, the safety and efficacy of long-acting CCBs have been well established, and it has also been shown that these drugs confer protection against cardiovascular events through their established antihypertensive action.

Cilnidipine is another antihypertensive agent that has an L/N-type Ca^{2+} channel blocking effect (12, 13). In an animal model of hypertension, this agent has been shown to inhibit calcium influx not only in the vascular smooth muscle cells but also in neural cells. It has also been shown to inhibit the excessive release of catecholamine at the time of blood pressure reduction (14), thereby exhibiting a gradual, strong, and persistent antihypertensive effect without causing reflex tachycardia (15). Clinical trials have demonstrated that 1) cilnidipine administered once daily provides 24-h blood pressure control with antihypertensive activity in patients with hypertension (16); 2) cilnidipine therapy is effective for the treatment of mild-to-severe hypertension; and 3) a consistent

antihypertensive effect of cilnidipine has been observed without increasing heart rate (17). Recently, some studies have also shown that cilnidipine reduces the incidences of proteinuria and albuminuria in hypertensive patients (18–20). Cilnidipine was launched in Japan in 1995, and since then, it has been commonly used as a CCB for the first-line treatment of hypertension.

According to the JSH 2000, if blood pressure does not reach the therapeutic goals in hypertensive patients who are receiving an antihypertensive agent, a combination therapy with two or more antihypertensive agents is recommended. Among these regimens, the combination of a CCB and an ARB is now being considered as a standard treatment method.

Many studies have investigated the safety and efficacy of monotherapy with either an ARB or a CCB (6–11). The purpose of the present study was to evaluate the safety and efficacy of a CCB, cilnidipine, when added to a monotherapy regimen with an ARB from the perspective of the blood pressure goals.

Methods

From February 2003 to July 2004, a total of 2,920 patients, all of whom had been receiving combination treatment with an ARB and cilnidipine were enrolled in this study at various participating cardiovascular and internal medicine departments of hospitals in Japan.

Cilnidipine administered orally once a day after breakfast. The initial daily dose was 5 mg, which was then increased up to 20 mg when the blood pressure did not decrease sufficiently. The duration of the study treatment was set at 12 weeks in principle, but could be discontinued early in the event of adverse reactions.

The patients' demographic characteristics, including sex, age, and the presence and nature of complicated diseases were obtained, and the patients were observed for any changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. In addition, the percentage of patients in whom the target SBP/DBP values were achieved, the schedule of treatment with cilnidipine and ARBs, and the adverse events were assessed. The blood pressure was measured at each clinic visit. Some patients did not visit the clinic every 28 days, but at 12 weeks of treatment with cilnidipine and ARBs, blood pressure and heart rate were measured in all of the patients. Cilnidipine and ARB treatment was continued thereafter in most cases, and measurement of blood pressure and heart rate was performed up to 88 weeks of treatment.

All of the patients were included in the safety analysis. The efficacy analysis was performed in patients who had already been prescribed only an ARB before initiating the combination therapy with cilnidipine and who also did not achieve the established blood pressure goal (140/90 mmHg).

The study was conducted in an actual clinical setting in accordance with Good Post-Marketing Surveillance Practice (GPMSP) as stipulated by the Ministry of Health, Labor

Table 1. Patient Background

Patient background	All patients		Patients included in the efficacy analysis	
	<i>n</i>	Percentage (%)	<i>n</i>	Percentage (%)
Sex				
Male	1,416	48.5	482	48.8
Female	1,481	50.7	517	51.3
Unknown/blank	23	0.8	9	0.9
Age (years)				
<65	1,218	41.7	452	44.8
≥65	1,661	56.9	541	53.7
Unknown/blank	41	1.4	15	1.5
Body mass index (kg/m ²)				
<18	54	1.8	14	1.4
18≤, <25	1,100	37.7	377	37.4
25≤	794	27.2	294	29.2
Unknown/blank	972	33.3	323	32.0
Renal disease or diabetes*				
Nothing	1,847	63.3	677	67.2
Renal disease/diabetes	1,073	36.7	331	32.8
Renal disease	460	15.8	99	9.8
Diabetes	819	28.0	279	27.7
ARB				
Valsartan	1,101	37.7	356	35.3
Candesartan	1,015	34.8	367	36.4
Losartan	549	18.8	195	19.3
Telmisartan	244	8.4	88	8.7
Olmesartan	11	0.4	2	0.2

*The criteria for diabetes or the nephropathy were based on the description of the disease name. ARB, angiotensin II receptor blocker.

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Statistical Analysis

Only patients whose blood pressure and heart rate had been measured on at least 2 separate occasions within the 4 weeks prior to starting therapy were analyzed for efficacy. During the combination therapy, blood pressure and heart rate were measured at every visit. At 4, 8 and 12 weeks of treatment, the means and standard deviations of blood pressure and heart rate were calculated. The blood pressure was statistically analyzed using Dunnett's test for differences between the pre- and post-treatment values. The heart rate value was analyzed using a two-tailed paired *t*-test. The incidence of adverse reactions between the safety analysis and efficacy analysis and the achievement rate of each ARB were analyzed using the χ^2 test. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Patient Demographic Characteristics

A total of 2,920 patients from 471 institutions were included

in this ongoing prospective investigation and all of these patients were included in the safety analysis. Before the combination therapy, 2,123 patients were already receiving ARB, 104 patients were already receiving cilnidipine, 693 patients were not receiving both ARB and cilnidipine. Among these patients, 1,008 patients with poorly controlled blood pressure ($>140/90$ mmHg) despite monotherapy with an ARB were analyzed in order to investigate the efficacy of cilnidipine added to ARB therapy.

Table 1 shows the distribution of the patients with respect to sex, age, body mass index (BMI), the presence of complicated disease (diabetes/nephropathy: the criteria for these diseases were based on the descriptions of the disease name and the types of ARBs used. High-risk patients with renal disease or diabetes accounted for 32.0% of the entire patient population that was included in the efficacy analysis.

The mean baseline blood pressures were 162.9 ± 18.9 mmHg (systolic) and 87.3 ± 12.4 mmHg (diastolic) in the elderly patients, 161.5 ± 18.2 mmHg (systolic) and 95.3 ± 11.7 mmHg (diastolic) in the young/middle-aged patients, and 160.4 ± 19.8 mmHg (systolic) and 87.3 ± 13.6 mmHg (diastolic) in the high-risk patients with renal disease or diabetes.

The doses of cilnidipine at treatment initiation were 5 mg in 500 patients (17.1%), 10 mg in 2,229 patients (76.3%), 15 mg

Table 2. The Status of Adverse Reaction Occurrence

	All cases	Cases included in efficacy analysis
Number of cases	2,920	1,008
Cases of adverse reactions (<i>n</i> (%))	73 (2.50)	33 (3.27)
Episodes of adverse reactions	88	46
System organ class (episodes (%))		
Nervous system disorders	24 cases (0.82)	14 cases (1.39)
Headache	13 (0.45)	8 (0.79)
Dizziness	12 (0.41)	7 (0.69)
Head discomfort	1 (0.03)	0 (0.00)
Cerebral infarction	1 (0.03)	1 (0.09)
Somnolence	1 (0.03)	1 (0.09)
Cardiac disorders	7 cases (0.24)	2 cases (0.20)
Palpitations	6 (0.21)	2 (0.20)
Tachycardia	1 (0.03)	0 (0.00)
Vascular disorders	15 cases (0.51)	9 cases (0.90)
Hot flush	4 (0.14)	1 (0.09)
Flushing	11 (0.38)	8 (0.79)
Orthostatic hypotension	1 (0.03)	0 (0.00)
Gastrointestinal disorders	5 cases (0.17)	2 cases (0.20)
Gingival swelling	1 (0.03)	1 (0.09)
Nausea	1 (0.03)	0 (0.00)
Vomiting	1 (0.03)	0 (0.00)
Dyspepsia	1 (0.03)	0 (0.00)
Abdominal distension	1 (0.03)	0 (0.00)
Abdominal discomfort	1 (0.03)	1 (0.09)
Hepatobiliary disorders	3 cases (0.10)	1 case (0.09)
Liver disorder	1 (0.03)	1 (0.09)
Hepatic function abnormal	2 (0.07)	0 (0.00)
Musculoskeletal and connective tissue disorders	2 cases (0.07)	0 case (0.00)
Musculoskeletal stiffness	1 (0.03)	0 (0.00)
Rhabdomyolysis	1 (0.03)	0 (0.00)
Skin and subcutaneous tissue disorders	4 cases (0.14)	2 cases (0.20)
Pruritus	3 (0.10)	2 (0.20)
Exanthem	1 (0.03)	0 (0.00)
General disorders and administration site conditions	9 cases (0.31)	5 cases (0.50)
Oedema peripheral	4 (0.14)	1 (0.09)
Feeling abnormal	3 (0.10)	3 (0.30)
Malaise	2 (0.07)	1 (0.09)
Investigations	13 cases (0.45)	5 cases (0.50)
Blood creatine phosphokinase increased	1 (0.03)	0 (0.00)
Hypertension	3 (0.10)	2 (0.20)
Hypotension	1 (0.03)	0 (0.00)
Blood pressure decreased	7 (0.24)	3 (0.30)
Blood creatinine increased	1 (0.03)	0 (0.00)

Adverse reaction was totaled using the Medical Dictionary for Regulatory Activities (MedDRA).

in 3 patients (0.1%), 20 mg in 175 patients (6.0%), and unknown or data not entered in 13 patients (0.4%), with a mean dose of 9.7 ± 3.2 mg for all of the patients. The doses of cilnidipine given at the end of observations were 5 mg in 395 patients (13.5%), 10 mg in 2,041 patients (69.9%), 15 mg in 7 patients (0.2%), 20 mg in 283 patients (9.7%), and either

unknown or data not entered in 194 patients (6.6%), with a mean dose of 10.3 ± 3.7 mg for all of the patients. The mean duration of observation was 20.3 ± 2.9 weeks.

The mean dosages of each ARB before the addition of cilnidipine were as follows: valsartan: 80.0 ± 26.0 mg ($n=1,101$); candesartan: 7.0 ± 2.1 mg ($n=1,015$); losartan:

Fig. 1. Changes in the systolic (SBP) and diastolic blood pressure (DBP) after addition of cilnidipine to ARB monotherapy. The data are expressed as the mean $\pm$ SD.

Table 3. Changes in the Blood Pressure Levels and the Percentage of Patients Attaining the Blood Pressure Goals Recommended by the JSH 2000

JSH 2000 SBP/DBP		Number of patients ^a	SBP/DBP (mmHg)			
			Before combination	End of observation (12 weeks or more)		
				Mean $\pm$ SD	Mean $\pm$ SD	JSH 2000 Achieve/Measure ^b %
SBP: 140/DBP: 90	≥ 65 years	378	165.8 $\pm$ 15.8/89.2 $\pm$ 11.2	139.8 $\pm$ 16.0*	77.2 $\pm$ 11.0*	167/346 48.27
SBP: 130/DBP: 85	<65 years	301	162.0 $\pm$ 14.2/95.6 $\pm$ 9.0	138.4 $\pm$ 12.9*	82.4 $\pm$ 8.9*	54/273 19.78
	High-risk patients ^c	313	164.0 $\pm$ 15.3/91.0 $\pm$ 12.5	139.1 $\pm$ 16.4*	78.9 $\pm$ 11.1*	65/292 22.26
Patients in efficacy analysis		992	164.1 $\pm$ 15.3/91.7 $\pm$ 11.4	139.2 $\pm$ 15.3*	79.3 $\pm$ 10.7*	286/911 31.39

SBP, systolic blood pressure; DBP, diastolic blood pressure. * $p < 0.0001$ compared to before combination. ^aExcept patients whose age were unknown. ^bThe number of patients achieving the JSH 2000 goals/the number of patients evaluated in total. ^cRenal disease or diabetes.

49.7 $\pm$ 18.9 ($n = 549$); telmisartan: 37.4 $\pm$ 11.4 ($n = 244$); and olmesartan: 18.2 $\pm$ 4.0 mg ($n = 11$).

Adverse Reactions

The adverse reactions that were reported during the study are summarized in Table 2. A total of 88 adverse reactions occurred in 73 of 2,920 patients (2.5%).

The adverse reactions were classified according to system organ class, with the most commonly observed adverse reactions being nervous system disorders (24 patients, 0.8%), followed in order by vascular disorders (15 patients, 0.5%), investigations (13 patients, 0.4%), general disorders and administration site conditions (9 patients, 0.3%), and cardiac disorders (7 patients, 0.2%). The adverse reactions that had

occurred in more than 5 episodes were headache (13 episodes, 0.4%), dizziness (12 episodes, 0.4%), flushing (11 episodes, 0.4%), decreased blood pressure (7 episodes, 0.2%), and palpitations (6 episodes, 0.2%).

The incidence of adverse reactions in patients included in the efficacy analysis was 3.3% (33 of 1,008 patients) and was not significantly different from that in the patients included in the safety analysis.

Efficacy Results

Changes in the Blood Pressure Levels

The mean blood pressure of the 1,008 patients who were included in the efficacy analysis decreased from 164.1 $\pm$ 15.3 to 139.2 $\pm$ 15.3 mmHg (systolic) and from 91.7 $\pm$ 11.4 to

Fig. 2. a: Changes in the heart rate after addition of cilnidipine to ARB monotherapy. The data are expressed as the mean $\pm$ SD. b: Relationship between the change in the heart rate and the baseline heart rate.

79.3 $\pm$ 10.7 mmHg (diastolic). The blood pressure levels at baseline, 4 weeks, 8 weeks, and 12 weeks of the combination therapy are presented in Fig. 1. Both the systolic and diastolic blood pressure levels significantly decreased within 4 weeks of the combination therapy, and these levels continued to decrease until the end of the study.

Achievement of the Blood Pressure Goals Recommended by the JSH 2000 Guidelines

Of the 1,008 patients who were included in the efficacy analysis, 992 were classified into the following three groups: elderly patients, young/middle-aged patients, and high-risk patients with renal disease or diabetes. The remaining 16 patients were excluded from the analysis because their ages were not available. The percentages of patients in whom blood pressure reached the goals recommended by the JSH 2000 guidelines (<140/90 mmHg, <130/85 mmHg, and <130/85 mmHg for the above patient groups, respectively) are shown in Table 3. Of the 1,008 hypertensive patients, 31.4% achieved a decrease in blood pressure to the target levels, or 48.3% of the elderly patients, 19.8% of the young/middle-aged patients, and 22.3% of the high-risk patients. When we calculated the achievement rate for each ARB combination treatment with cilnidipine, the results were as follows: valsartan: 27.2% (n=312); candesartan: 32.6% (n=334); losartan: 36.5% (n=181); telmisartan: 31.7% (n=82); and olmesartan: 0.0% (n=2). There were no significant differences among these achievement rates.

Changes in Heart Rate

The heart rates measured at baseline and at the end of the observation period are shown in Fig. 2a. Heart rate significantly decreased from 74.2 $\pm$ 10.7 bpm at baseline to 73.0 $\pm$ 10.3 bpm at the end of the observation period. The

patients who showed a higher heart rate at the initiation of the study were further stratified and analyzed, since such patients were likely to have increased sympathetic nervous activity. Heart rate decreased from 79.1 $\pm$ 2.8 to 76.5 $\pm$ 8.2 bpm in the patients with a baseline value of between 75 and 85 bpm, and from 93.6 $\pm$ 7.0 to 84.0 $\pm$ 10.6 bpm in the patients with a baseline value of 85 bpm or more (Fig. 2a). There was a significant negative correlation between the degree of heart rate change and the baseline heart rate (Fig. 2b).

Discussion

In recent years, combination therapy with an ARB and diuretic drugs and/or CCBs has been considered a standard treatment for hypertension (1, 2). However, there have been no studies investigating the effect of combination therapy with an ARB and CCB. The use of a diuretic drug in hypertensive patients may be associated with metabolic adverse effects (21–23), such as potassium depletion, elevated uric acid levels, insulin resistance and increased cholesterol levels. While CCBs have been associated with fewer incidences of such metabolic adverse effects, there is concern about the side effects of an increased heart rate due to the facilitation of the sympathetic nerve activity (13, 24).

Cilnidipine, a dual L/N-type CCB, has been shown to have a consistent antihypertensive effect without increasing the heart rate because it inhibits the secretion of catecholamine (14), and it has also been shown to improve insulin resistance (25, 26). We thus conducted a special investigation in order to evaluate the safety and efficacy of combination therapy with an ARB and cilnidipine.

The incidence of adverse reactions reported during the present study was 2.5%. Of all the patients included in the efficacy analysis, 3.3% reported an adverse reaction, and sim-

Table 4. Dosage of Cilnidipine

Cilnidipine dosage	Start of observation		End of observation	
	<i>n</i>	Mean±SD	<i>n</i>	Mean±SD
5 mg	236	9.1±2.5	190	9.5±2.9
10 mg	845		804	
15 mg	1		2	
20 mg	17		39	
Unknown/blank	6		70	

ilar incidences were found when these adverse reactions were classified according to the system organ class, and no particular tendencies were observed.

Among patients receiving antihypertensive monotherapy using different ARBs, Oparil *et al.* (3) reported that the following percentages achieved the blood pressure goals recommended by the JNC 7 guidelines: for olmesartan, 32.4%; for losartan, 16.1%; for valsartan, 14.5%; and for irbesartan, 25.9%. These findings led to the conclusion that when the blood pressure does not reach the targeted levels with ARB monotherapy, another antihypertensive agent should be added to the treatment regimen.

A total of 1,008 patients in whom the blood pressure had not been adequately controlled despite monotherapy with an ARB were included in the present efficacy analysis. The mean blood pressure levels of these patients at baseline were 164.1±15.3 mmHg for the systolic pressure and 91.7±11.4 mmHg for the diastolic pressure. These patients were then given combination therapy with cilnidipine and an ARB, and the mean blood pressure after 12 weeks of treatment was significantly decreased from the baseline level to 139.2±15.3 mmHg systolic and 79.3±10.7 mmHg diastolic pressure. These findings suggest that patients with poorly controlled hypertension despite ARB monotherapy may therefore respond well to the combination therapy of an ARB and cilnidipine.

However, the percentages of patients in whom the blood pressure reached the goals recommended by the JSH 2000 guidelines were still unsatisfactory: namely, 31.4% of all patients included in the efficacy analysis, 48.3% of the elderly patients (<140/90 mmHg), 19.8% of the young/middle-aged patients (<130/85 mmHg), and 22.3% of the high-risk patients with renal disease or diabetes (<130/85 mmHg). In addition, there were no significant differences between the achievement rates of each ARB combination treatment with cilnidipine. These results may be attributable to the study protocol, which did not allow for excessive increases of the doses of cilnidipine in order to achieve the blood pressure goals. As shown in Table 4, the dose of the drug was maintained at 5 mg in a large number of patients.

These results suggest that aggressive therapy with higher doses of cilnidipine or a combination therapy with more than two antihypertensive drugs should thus be administered in order to achieve the blood pressure goals recommended in

JSH 2004 (2).

Cilnidipine is a long-acting and L/N-type dual calcium channel antagonist which has been commonly used to lower blood pressure without increasing the heart rate. In the present study, the heart rate significantly decreased from 4 weeks of treatment onward in comparison to the baseline level. The Framingham Study (27) revealed that heart rates of 75 bpm or more were associated with an abruptly increased risk for death from cardiovascular events. Curt *et al.* (28) reported that the reflex increase in sympathetic activity induced by short-acting calcium antagonists may therefore be considered a risk factor for mortality. These findings suggest that it is important to decrease high heart rates during the treatment for hypertension. The data also suggest that the higher the baseline heart rate, the more marked the decrease in heart rate with the use of cilnidipine.

Increased sympathetic nervous activity has been strongly implicated in elevated heart rate (29). Increased sympathetic nervous activity depends on norepinephrine release from the sympathetic nerve endings, which is controlled by the N-type calcium channels. Cilnidipine is considered to decrease the heart rate by blocking the N-type calcium channels in the sympathetic nerve endings, thereby inhibiting norepinephrine release and causing an excessive increase in sympathetic nervous activity.

In conclusion, this is the first large-scale study conducted in a multicenter setting to evaluate the safety and efficacy of combination therapy with an ARB and the CCB cilnidipine. Approximately 3,000 and 1,000 patients were included in the safety and efficacy analyses, respectively. The present study demonstrated that combination therapy with cilnidipine and an ARB can be used safely and effectively in hypertensive patients. Moreover, in addition to its antihypertensive effect, cilnidipine can also decrease the heart rate, thereby protecting the heart from damage.

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