Effects of Amlodipine and Cilnidipine on Cardiac Sympathetic Nervous System and Neurohormonal Status in Essential Hypertension

Kazuyuki Sakata, Manabu Shirotani, Hiroshi Yoshida, Ryuzou Nawada, Kazuhiko Obayashi, Kiyonori Togi, Narimasa Miho

Abstract—N-Type calcium channel antagonists may suppress sympathetic activity. The purpose of this study was to assess the effects of amlodipine and cilnidipine on the cardiac sympathetic nervous system and the neurohormonal status of essential hypertension. $^{123}$I-metaiodobenzylguanidine (MIBG) cardiac imaging was performed and blood samples were taken to determine plasma renin activity and plasma norepinephrine concentration before and 3 months after drug administration in 47 patients with mild essential hypertension. Twenty-four of the patients were treated with 5 to 10 mg/d of amlodipine; the other 23 were treated with 10 to 20 mg/d of cilnidipine. For comparison, 12 normotensive subjects were also studied. No significant differences were found in the basal characteristics between the 2 hypertensive groups. In both hypertensive groups, both the systolic and diastolic blood pressures were significantly reduced to similar levels 3 months after drug treatment. Before the drug treatment, the 2 hypertensive groups had a significantly higher washout rate and lower heart-to-mediastinum (H/M) ratio compared with the normotensive subjects. The H/M ratio significantly increased ($P<0.05$) in combination with a decreased washout rate ($P<0.02$) after drug treatment in the cilnidipine group. In the amlodipine group, a significant decrease in washout rate ($P<0.04$) was noted, without an increase in the H/M ratio. However, no significant changes were found in plasma renin activity and plasma norepinephrine concentration in either group. Thus, in patients with essential hypertension, cilnidipine suppressed cardiac sympathetic overactivity and amlodipine had a little suppressive effect. Cilnidipine may provide a new strategy for treatment of cardiovascular diseases with sympathetic overactivity. (Hypertension. 1999;33:1447-1452.)

Key Words: calcium channels ▪ amlodipine ▪ cilnidipine ▪ sympathetic nervous system ▪ plasma ▪ renin ▪ imaging

Calcium antagonists are now widely used for the treatment of various types of hypertension. Despite their ability to lower the high blood pressure effectively, calcium antagonists do not always protect against cardiovascular complications because the use of short-acting calcium antagonists is associated with increased risk of acute myocardial infarction and mortality1 and does not reduce the incidence of cardiac events.2 Doubt about the use of calcium antagonists has arisen from their effects on neurohormonal status of patients, because neurohormonal activation is considered to be an important variable in the unexpected results obtained with short-acting calcium channel blockers.3

Sympathetic overactivity plays a major role in the pathophysiology of hypertension.4–7 To lessen or avoid the further neurohormonal activation caused by short-acting calcium channel blockers, third-generation dihydropyridine-based calcium antagonists have been developed that have potential clinical benefits: gradual onset of action and a long duration of effects. However, a recent report on an increase in cardiovascular complications associated with the treatment of long-acting calcium antagonists in hypertension has cast doubt on their usefulness,8 although a large clinical trial with long-acting calcium antagonists showed beneficial effects on cardiovascular mortality and/or morbidity.9 Therefore, a large number of studies have investigated the effects of antihypertensive drugs on the sympathetic nervous system, using muscle sympathetic activity,10 heart rate variability,11,12 and plasma norepinephrine concentration.13 However, sympathetic activity obtained from these methods has been shown to be not always consistent with cardiac sympathetic activity.14,15 To understand the relationships among hypertensive heart disease, cardiovascular complications due to hypertension, and the sympathetic nervous system, it is important to evaluate cardiac sympathetic activity, because the sympathetic outflow is not necessarily uniformly distributed across the organs16 and the cardiac sympathetic nervous system is associated with the prognosis of heart failure,17 a major cardiac complication of hypertension.

Recently, $^{123}$I-metaiodobenzylguanidine (MIBG), an analog of guanidine that shares the same neuronal transport and storage mechanisms as norepinephrine, was used to evaluate cardiac sympathetic activity and innervation of the left
venticle.7,17,18 Using MIBG imaging, we demonstrated that a clinical dosage of nitrendipine did not affect the cardiac sympathetic nervous system in essential hypertension.7 However, the effect of other third-generation dihydropyridine-based calcium antagonists on cardiac sympathetic activity remains unknown. Among the third-generation dihydropyridine-type calcium antagonists, amlodipine19 and cilnidipine (FRC-8653),20 which is a newly synthesized dihydropyridine type of organic calcium channel blocker that has been developed as a slow-onset and long-lasting antihypertensive drug in Japan,21 have been shown to have a potent inhibitory action on the peripheral neuronal N-type calcium channel. Recently, cilnidipine has been shown to exert a substantial beneficial effect toward significantly reducing fatal events in a subgroup of patients with nonischemic dilated cardiomyopathy22 that involved cardiac sympathetic overactivity.18 Although these agents may suppress sympathetic activity by blocking the N-type calcium channel, clinical effects of these drugs on the cardiac sympathetic nervous system remain unknown.

Using MIBG imaging in patients with essential hypertension, we assessed the effects of amlodipine and cilnidipine on the cardiac sympathetic nervous function. We also assessed the effects of these drugs on plasma renin activity and plasma norepinephrine concentration.

Methods

Patients

We selected 47 patients >39 years of age (range, 40 to 75 years of age) with mild essential hypertension who had no organic heart disease and normal cardiac function assessed by exercise 201Tl cardiac scintigraphy and echocardiography. According to the Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee,23 mild hypertension is defined as persistent resting blood pressure between 90 and 105 mm Hg and/or systolic blood pressure between 140 and 180 mm Hg. All hypertensive patients in this study met these criteria. Patients were allocated randomly into 2 groups; 24 received oral amlodipine (5 to 10 mg/d), and 23 received oral cilnidipine (10 to 20 mg/d). We also selected 12 normotensive subjects without organic heart disease and normal cardiac function assessed by exercise 201Tl cardiac scintigraphy and echocardiography. For statistical analysis, the patients treated with cilnidipine were compared with the normotensive subjects. Subjects underwent MIBG imaging within 2 weeks before and 3 months after the start of drug treatment. All hypertensive patients were newly diagnosed and had not received any antihypertensive therapy except for diet therapy before the first MIBG imaging was done. Informed consent was obtained from each patient. This study protocol was approved by the ethics committee of Shizuoka General Hospital.

Echocardiography

Echocardiograms were recorded using an SSD-870 echocardiograph (Aloka Co, Ltd) that had a 3.5-MHz transducer with the patient in the supine position and turned 30° on the left side. M-mode echocardiograms were recorded under 2-dimensional guidance, and the tracing was recorded at a paper speed of 100 mm/s. Measurements were obtained to the nearest millimeter for at least 4 cardiac cycles during quiet respiration, and the average values were used for analysis. All echocardiograms were recorded with the patient in the same position and in the same intercostal and left ventricular area, just below the tip of the mitral leaflets. All measurements, including the left ventricular mass and left ventricular mass index, were made by the same observer as previously described.7

MIBG Scintigraphy

After subjects fasted overnight, each was administered a 111-MBq IV dose of commercially available MIBG (Daichi Radioisotopes Labs, Ltd). A 5-minute static acquisition was made in the anterior view at 15 minutes and at 3 hours after the injection of MIBG. Cardiac images were acquired after each static acquisition with a 3-head gamma camera ( Toshiba GCA 9300A/HG) equipped with parallel-hole, high-resolution collimators. Energy discrimination was provided by a 15% window centered at 159 keV. Data processing was performed on a Toshiba GMS 5500A system.

Left ventricular MIBG activity and washout rate were measured by placing a square region-of-interest over the left ventricle and taking the peak count density; this procedure was repeated over the upper mediastinum. The heart-to-mediastinum (H/M) ratio on the delayed image was calculated to quantify cardiac MIBG uptake as a fraction of the mean count per pixel in the heart divided by that in the upper mediastinum.7 The myocardial washout rate was defined as the percentage change in activity from the initial to the delayed images within the left ventricle and was calculated as follows: Washout Rate (%) = [(A−B)/A]×100, where A is the average count per pixel in the left ventricle on the initial image and B is the average decay-corrected count per pixel in the same region on the delayed image. Decay correction was performed with the assumption that the half-life of the radionuclide [(1/2)] was 13 hours.

Hormonal Analysis

After each subject had rested in the supine position for 30 minutes in a warm, quiet, darkened room between 8 and 9 AM before MIBG imaging, blood pressure was measured and venous blood samples were drawn from an indwelling catheter inserted into the median cubital vein. Blood samples were stored at −70°C. The plasma norepinephrine concentration was determined by high-performance liquid chromatography, and plasma renin activity was determined using a GammaCoat125I plasma renin activity radioimmunoassay kit (INCSTAR) as described previously.7,24

Statistical Analysis

Data are expressed as mean±SD. Comparisons among 3 groups (normotensive subjects, patients treated with amlodipine, and patients treated with cilnidipine) were performed by ANOVA followed by a Bonferroni multiple comparison test. Statistical evaluation was also performed by ANOVA for repeated measurements, which included the effects of amlodipine and cilnidipine and comparisons between groups. If significant differences were detected by ANOVA, a paired t test was performed on the relevant data pairs. A χ2 or Fisher exact test was used to determine the significance of differences in the observed occurrence rates. Probability values <0.05 were considered significant.

Results

Table 1 shows the baseline clinical characteristics of the hypertensive patients and normotensive subjects. No significant differences existed with regard to age, body mass index, and coronary risk factors among the 3 groups, and no difference in blood pressure levels existed between the 2 hypertensive groups. In addition, the echocardiographic findings were comparable across the 3 groups.

Table 2 shows the changes in blood pressure, heart rate, plasma renin activity, and plasma norepinephrine concentration before and after drug treatment. None of the parameters were significantly different between the 2 drug-treated groups before and 3 months after drug treatment. In both groups, drug treatment significantly lowered both the systolic and diastolic blood pressure, although heart rate did not change significantly. In addition, plasma norepinephrine concentration and plasma renin activity did not change significantly after drug administration in either group.
In the 2 hypertensive groups before drug treatment, the washout rate was significantly higher (6.8 ± 5.7 in the normotensive subjects versus 17.9 ± 6.7 in the amlodipine group, \( P < 0.0001 \), and 20.1 ± 8.6 in the cilnidipine group, \( P < 0.0001 \)) and the H/M ratio was significantly lower (2.31 ± 0.24 versus 2.06 ± 0.30, \( P < 0.01 \), and 2.01 ± 0.19, \( P < 0.002 \), respectively) compared with the normotensive group. The Figure shows the scintigraphic variables before and 3 months after drug treatment in the 2 hypertensive groups. In the cilnidipine group, the H/M ratio significantly increased (2.01 ± 0.19 versus 2.12 ± 0.22, \( P < 0.05 \)) after drug treatment, but the ratio did not significantly change in the amlodipine group (2.06 ± 0.30 versus 2.05 ± 0.23, \( P = \) NS) (Figure). In contrast, the washout rate significantly decreased in both the cilnidipine (20.1 ± 8.6 versus 16.1 ± 8.5, \( P < 0.03 \)) and amlodipine (17.9 ± 6.7 versus 14.9 ± 8.5, \( P < 0.04 \)) groups.

Twelve of the normotensive subjects underwent a second MIBG imaging 3 months after the first imaging. The H/M ratio was 2.31 ± 0.24 at the first and 2.30 ± 0.19 at the second test (\( P = \) NS), and the washout rate was 6.8 ± 5.7 and 6.4 ± 6.1 (\( P = \) NS), respectively. Correlation analysis revealed high reproducibility of both the H/M ratio (\( r = 0.91, P < 0.001 \)) and washout rate (\( r = 0.94, P < 0.0001 \)).

**Discussion**

The most significant findings of the present study with MIBG imaging were that without affecting plasma norepinephrine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amlodipine</th>
<th>Cilnidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>Before</td>
<td>158 ± 12</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>130 ± 21*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>Before</td>
<td>104 ± 25</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>83 ± 6*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>Before</td>
<td>77 ± 6</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>Before</td>
<td>1.25 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>1.49 ± 0.71</td>
</tr>
<tr>
<td>Renin, nmol/L</td>
<td>Before</td>
<td>0.44 ± 0.73</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>0.24 ± 0.23</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HR, heart rate. Values are mean ± SD.

*\( P < 0.001 \), vs value before drug treatment. There was no significant difference in any variable between the 2 groups.

**TABLE 1. Distribution of Clinical Variables**

<table>
<thead>
<tr>
<th>Group Characteristic</th>
<th>Normotensive Subjects (n = 12)</th>
<th>Hypertensive Patients Treated With Amlodipine (n = 24)</th>
<th>Hypertensive Patients Treated With Cilnidipine (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56 ± 10</td>
<td>63 ± 9</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Men/Women, n</td>
<td>7/5</td>
<td>14/10</td>
<td>16/7</td>
</tr>
<tr>
<td>Smoking, n</td>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Hypercholesteremia, n</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>FH, n</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hyperuricemia, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8 ± 2.1</td>
<td>22.7 ± 2.7</td>
<td>23.2 ± 3.5</td>
</tr>
</tbody>
</table>

**TABLE 2. Changes in Hemodynamics, Plasma Norepinephrine Concentration, and Plasma Renin Activity**

Comparison of H/M ratio MIBG uptake and washout rate before and 3 months after drug treatment in hypertensive patients treated with amlodipine (n = 24) and cilnidipine (n = 23). Values are expressed as mean ± SD.
Calcium Antagonist and Cardiac Sympathetic Activity

concentration and renin activity, cilnidipine significantly increased MIBG uptake with a significant decrease in washout rate but amlodipine significantly decreased washout rate without a change in MIBG uptake in essential hypertension. These findings suggested that without affecting neurohormonal status, cilnidipine suppressed enhanced cardiac sympathetic activity but amlodipine had little suppressive effect on cardiac sympathetic activity.

Sympathetic overactivity is considered to be a hallmark of hypertensive cardiovascular disease morbidity and mortality because chronic activation of the sympathetic nervous system has been shown to produce adverse effects on the myocardium and the peripheral circulation. These effects are believed to contribute to cardiac and vascular structural alterations that may advance disease progression.

Third-generation dihydropyridine-based calcium antagonists are more favorably accepted than nifedipine because many studies have demonstrated that sympathetic activation by these drugs is less than that caused by short-acting dihydropyridines. However, essential hypertension is a chronic disease that requires long-term medical attention, and it is anticipated that additional long-term sympathetic activation due to antihypertensive drugs may adversely affect cardiovascular disease morbidity and mortality in patients with essential hypertension. Therefore, a desirable calcium antagonist for the treatment of hypertension should have the potential to suppress sympathetic overactivity, as is demonstrated by β-blockers and angiotensin-converting enzyme inhibitors.

Possible Clinical Value of N-Type Calcium Channel Antagonist

Nowycky et al demonstrated the existence of 3 types of voltage-dependent calcium channels, L-, N-, and T-type, on the basis of electrophysiological characterization. Recently, increasing attention has been focused on N-type and T-type calcium channel antagonists, which seem to have the potential to suppress norepinephrine release from the presynaptic site. ω-conotoxin has been reported to block L- and N- but not T-type calcium channels, and neurotoxin has been reported to inhibit depolarization-evoked norepinephrine release. These findings suggest that depolarization-induced norepinephrine release from the sympathetic nerve endings may be triggered mainly by calcium influx through N- rather than T-type calcium channels.

Recently, amlodipine and cilnidipine have been demonstrated to inhibit N-type calcium channels. However, in human clinical studies, the effect of this type of drugs on sympathetic activity is controversial. In addition, the effects of these drugs on cardiac sympathetic activity remain unknown. On MIBG imaging, MIBG washout and uptake rates reflect cardiac sympathetic activity. In subjects with essential hypertension, enhanced MIBG washout rate and decreased MIBG uptake are found, which indicates cardiac sympathetic overactivity. In the present study, in the presence of essential hypertension, a clinical dosage of cilnidipine improved MIBG kinetics, as demonstrated by a reduction in enhanced MIBG washout and an increase in reduced MIBG uptake, similar to the effects of enalapril. These findings suggest that cilnidipine could suppress cardiac sympathetic overactivity in essential hypertension effectively, despite that cilnidipine lowers the systemic blood pressure to a degree similar to that produced by amlodipine. In contrast, a clinical dosage of amlodipine (5 to 10 mg), which effectively lowered blood pressure, decreased the cardiac MIBG washout rate significantly but did not affect MIBG uptake. This suggests that amlodipine affected cardiac sympathetic activity but did not suppress cardiac sympathetic overactivity effectively. However, amlodipine did not induce an increase in plasma norepinephrine concentration, probably as a result of baroreceptor-mediated activation of sympathetic nervous system. These findings indicate that amlodipine does not cause obvious changes to the sympathetic nervous system, although amlodipine appears to suppress baroreceptor-mediated sympathetic activation and to have a tendency to suppress cardiac sympathetic overactivity. Thus, N-type calcium channel antagonists can suppress or have a tendency to suppress cardiac sympathetic overactivity without affecting neurohormonal status in essential hypertension.

Calcium Antagonists and Renin Activity

Both sympathetic and plasma renin activity are known to increase in response to a rapid decrease in blood pressure after administration of dihydropyridine calcium antagonists. Also, calcium antagonists can increase renin activity resulting from direct action on the juxtaglomerular apparatus. The increased renin activity seems to be harmful for patients treated with calcium antagonists because increased renin activity enhances angiotensin II production, which exerts various deleterious actions. Evidence has accumulated that links high levels of plasma renin activity to metabolic imbalances in hypertension. In addition, heart failure patients with a high level of activation of the renin-angiotensin system and who show further an increase in plasma renin activity after therapy respond poorly to long-treatment with vasodilator drugs. Thus, increased plasma renin activity alone appears to be unfavorable with hypertension, in addition to causing cardiac complications. Although various long-acting calcium antagonists have been reported to increase plasma renin activity, both amlodipine and cilnidipine did not increase plasma renin activity.

Clinical Implications

Cardiovascular disease patients with sympathetic activation have a high mortality rate. Decreased MIBG uptake and increased MIBG washout (which suggest cardiac sympathetic overactivity), as shown on MIBG imaging, are associated with an unfavorable prognosis. We expect that cilnidipine (which affects MIBG kinetics in a manner similar to enalapril) could improve the prognosis in such patients, as has been the case with angiotensin-converting enzyme inhibitors. Cilnidipine suppresses cardiac sympathetic overactivity without affecting plasma renin activity, in addition to exerting a weak negative inotropic effect. Thus, it appears that cilnidipine can be used favorably in patients with heart failure. On the other hand, amlodipine had no detrimental effect on the cardiac sympathetic system and the neurohormonal status of essential hypertension. Although we demon-
stratized that cilnidipine had beneficial effects on cardiac sympathetic function and neurohormonal status in patients with essential hypertension, further investigations are needed to determine whether long-term treatment with cilnidipine is more beneficial to patients with essential hypertension or other cardiovascular diseases than are other calcium antagonists, and especially than angiotensin-converting enzyme inhibitors and β-blockers.

Conclusions

In essential hypertension, cilnidipine improved MIBG kinetics and amlodipine had a little effect on it; these drugs did not affect plasma norepinephrine concentration and renin activity. These results suggest that, in essential hypertension, cilnidipine may suppress cardiac sympathetic activity but amlodipine has little suppressive effect. Thus, the use of N-type calcium channel antagonists appears to be safe and beneficial for long-term treatment of essential hypertension. In particular, the unique character of cilnidipine may provide a new strategy for treatment of cardiovascular disease with sympathetic overactivity.

Acknowledgments

The authors are grateful to Mamoru Mochizuki, NMT; Takemii Tanaka, NMT; Atsushi Fukui, NMT; Seiya Ito, NMT; and Kouji Nishio, NMT, for their excellent technical assistance. We are also indebted to Chinoi Kurata, MD, Hamamatsu University School of Medicine, Hamamatsu, Japan, for critically reviewing the manuscript.

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Hypertension. 1999;33:1447-1452
doi: 10.1161/01.HYP.33.6.1447

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