Effects of the T/L-type Calcium Channel Blocker Benidipine on Albuminuria and Plasma Aldosterone Concentration

A Pilot Study Involving Switching from L-type Calcium Channel Blockers to Benidipine

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Summary

Albuminuria and a high plasma aldosterone concentration (PAC) are prognosis factors predicting a poor outcome for cardiovascular disease. We examined here the effects of benidipine, a T/L-type calcium channel blocker (CCB), on albuminuria and PAC.

Thirty-one patients with essential hypertension who received an L-type CCB and achieved the target blood pressure (BP) indicated by the Treatment Guidelines of the Japan Society of Hypertension (JSH2009) were investigated. The L-type CCB under treatment was switched to benidipine at a dose in which equivalent BP reduction was expected. BP and estimated glomerular filtration rate at 6 months after switching to benidipine were not significantly different from those at baseline. The urinary-albumin-creatinine ratio (UACR) decreased significantly by 36.9% (P = 0.001). No significant change was observed in plasma renin activity (P = 0.063). The PAC of all patients decreased significantly by 11.8% (P = 0.002). When analyzed by daily doses of benidipine, the PAC appeared to have decreased in patients who received 4 mg per day of benidipine (n = 14), although statistical significance was not reached (P = 0.096). The PAC in patients who received 8 mg per day of benidipine (n = 17) was significantly reduced by 13.2% (P = 0.017).

In hypertensive patients whose BP is controlled by L-type CCB, switching to the T/L-type CCB benidipine maintained BP control and reduced UACR. In addition, the high dose of benidipine reduced the PAC independent of BP control. These results suggest the T/L-type CCB benidipine may contribute to cardio-renal protection in addition to lowering BP. (Int Heart J 2014; 55: 519-525)

Key words: Cardio-renal interaction, Hypertension

Calcium channel blockers (CCBs) include T/L-type and N/L-type CCBs in addition to L-type CCBs.12 Long-acting CCBs with inhibitory effects on T- and N-type calcium (Ca) channels are reported to reduce intraglomerular pressure and albuminuria by dilating the efferent arteries of the glomeruli.13 In addition, the T-type Ca channel is expressed on the glomerular layer of the adrenal cortex and is suggested to be partly involved in the production of aldosterone.14 Aldosterone has been considered a hormone mainly related to reabsorption of sodium and water in the kidney. In recent years, aldosterone has been shown to be involved in cardiovascular organ dysfunction and has received intense attention as an independent prognostic factor for cardiovascular disease.15

On the other hand, benidipine has been shown to strongly inhibit T-type Ca channels and the production of aldosterone in several basic studies.6-8 However, its clinical significance has not been adequately investigated.

We hypothesized that by switching from an L-type CCB to the T/L-type CCB benidipine in patients with essential hypertension who were treated with an L-type CCB, a reduction of urinary excretion of albumin and decline of plasma aldosterone concentration (PAC) may occur.

The aim of this study was to investigate in patients with essential hypertension whose blood pressure (BP) was under control with an L-type CCB if and how switching to the T/L-type CCB benidipine influences the urinary albumin-to-creatinine ratio (UACR) and PAC.

Methods

Study design and population: This study was a 6-month prospective, single-center, open-label study switching from L-type CCBs to the T/L-type CCB benidipine without a washout period. The primary endpoints were changes of the UACR and PAC at 6 months after switching to benidipine versus baseline.
The study population consisted of patients who were on L-type CCB (nifedipine sustained release formulation [nifedipine CR], amlodipine) therapy for at least 6 months and had achieved the target BP at the office according to the Treatment Guidelines of the Japan Society of Hypertension (JSH2009). In these patients, the L-type CCB was switched to the equivalent antihypertensive efficacy of benidipine. When switching from an L-type CCB to benidipine, the following conversion was used as guidance for equivalent BP reduction effects (Nifedipine CR 20 mg switched to benidipine 4 mg. Nifedipine CR 40 mg switched to benidipine 8 mg. Amlodipine 5 mg switched to benidipine 4 mg. Amlodipine 7.5 mg and 10 mg switched to benidipine 8 mg). Since the purpose of this study was to evaluate the non-antihypertensive effects of benidipine, patients whose dosage of benidipine was changed or concomitant antihypertensive drugs were added, suspended, increased, or decreased were excluded from the analysis.

The exclusion criteria included (1) history of side effects by benidipine, (2) hepatic impairment, (3) presence of malignancy, (4) secondary hypertension, and (5) those who did not give informed consent for this study. Diabetes was defined as fasting plasma blood sugar concentrations ≥ 126 mg/dL and HbA1c ≥ 6.5% (according to the National Glycohaemoglobin Standardisation Programme [NGSP]) or current treatment with antidiabetic agents. A diagnosis of dyslipidemia was made when the low-density lipoprotein cholesterol level was 140 mg/dL or above, the triglyceride level was 150 mg/dL or above, the high-density lipoprotein cholesterol level was less than 40 mg/dL, or if the patient was already on lipid-lowering agents. Coronary artery disease was defined as a history of documented myocardial infarction, prior coronary revascularization intervention (coronary artery bypass graft surgery or percutaneous coronary intervention), or the presence of ≥ 50% stenosis in 1 or more of the coronary arteries identified during cardiac catheterization.

BP was measured at the outpatient department at fixed times after the medications were administered. BP measurement was carried out according to the JSH2009 guidelines. BP was measured monthly using a sphygmomanometer (Nippon Colin, Tokyo) in duplicate with the patient in the sitting position after a 5-minute rest. Patients, particularly those with dietary restrictions, were given the same guidance on how to maintain their diet before and after the study period.

All study participants provided written informed consent, and the Surugadai Nihon University Hospital Ethics Committee approved the study design and purpose.

**Laboratory measurements:** To assess urinary albumin excretion, we measured the urinary concentrations of albumin and Cr in an early morning spot urine sample. Plasma renin activity (PRA) and PAC were measured by radioimmunoassay at a contract laboratory (SRL Co., Ltd., Tokyo) at baseline and at the end of the study with the subject in the sitting position after a 20-minute rest. Estimated glomerular filtration rate (eGFR) was calculated by using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula modified by a Japanese coefficient.

**Statistical analysis:** We performed all of the statistical analyses using the SPSS Windows version 12.0 software program (Statistical Package for the Social Sciences, SPSS Ins., Chicago, IL). Data are expressed as the mean ± standard deviation (SD) for continuous variables or medians and interquartile range (IR) for variables of a skewed distribution. Comparison of continuous variables was conducted using the paired t-test and nonparametric pairwise comparison was assessed by Wilcoxon’s signed-rank test. To analyze the change in blood pressure by switching from an L-Type CCB to benidipine, Dunnett’s multiple comparison was performed. Because the plasma aldosterone concentration exhibited a normal distribution, regression analysis was performed using linear regression and Pearson’s correlation coefficients. UACR and plasma renin activity were not normally distributed, therefore, non-parametric correlation coefficients (Spearman’s [P]) were used. A P value less than 0.05 was considered to indicate statistical significance.

**Results**

**Subjects:** Demography and changes of laboratory profiles of 31 patients are shown in Table. There were 24 patients switched from amlodipine (mean daily dose: 6.0 ± 2.8 mg) and 7 patients switched from nifedipine CR (mean daily dose: 34.3 ± 15.1 mg). Mean daily dose of benidipine after switching from L-type CCBs was 6.2 ± 2.0 mg.

<table>
<thead>
<tr>
<th>Table. Patient Characteristics and Changes in Laboratory Profile (n = 31)</th>
<th>Baseline</th>
<th>After switching</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 9.6</td>
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<td>-</td>
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<tr>
<td>Male/female</td>
<td>16/15</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>3 (9.7)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dyslipidemia, n (%)</td>
<td>21 (67.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (12.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>4 (12.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-platelets, n (%)</td>
<td>13 (41.9)</td>
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<tr>
<td>ACEIs, n (%)</td>
<td>6 (19.4)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>ARBs, n (%)</td>
<td>18 (58.1)</td>
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<td>Direct renin inhibitor, n (%)</td>
<td>2 (6.5)</td>
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<td>Diuretics, n (%)</td>
<td>5 (16.1)</td>
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<tr>
<td>β blockers, n (%)</td>
<td>7 (22.6)</td>
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<td>Statins, n (%)</td>
<td>20 (64.5)</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Amlodipine, n (%)</td>
<td>24 (77.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nifedipine CR, n (%)</td>
<td>7 (22.6)</td>
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<td>-</td>
</tr>
<tr>
<td>Laboratory profile</td>
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<tr>
<td>TC (mg/dL)</td>
<td>190 ± 28</td>
<td>188 ± 29</td>
<td>0.486</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>103 ± 19</td>
<td>103 ± 23</td>
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<tr>
<td>HDL-C (mg/dL)</td>
<td>57 ± 14</td>
<td>56 ± 13</td>
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<tr>
<td>TG (mg/dL)</td>
<td>148 ± 91</td>
<td>144 ± 91</td>
<td>0.753</td>
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<td>ALT (mg/dL)</td>
<td>22 ± 10</td>
<td>25 ± 16</td>
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<tr>
<td>AST (mg/dL)</td>
<td>25 ± 8</td>
<td>26 ± 8</td>
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<tr>
<td>HbA1c (%) NGSP</td>
<td>6.2 ± 0.8</td>
<td>6.0 ± 0.6</td>
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<tr>
<td>FBS (mg/dL)</td>
<td>112 ± 22</td>
<td>113 ± 18</td>
<td>0.795</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.82 ± 0.21</td>
<td>0.82 ± 0.21</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.4 ± 1.2</td>
<td>5.6 ± 1.2</td>
<td>0.120</td>
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<tr>
<td>eGFR (ml/minute/1.73m²)</td>
<td>70 ± 16</td>
<td>70 ± 15</td>
<td>0.876</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartic aminotransferase; Hb, hemoglobin; NGSP, National Glycohaemoglobin Standardisation Programme; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; and eGFR, estimated glomerular filtration rate.
Effect of blood pressure and eGFR: Changes in BP are shown in Figure 1. Compared to the baseline, there was no significant change in systolic and diastolic BP at 2, 4, and 6 months after switching to benidipine. Moreover, throughout the study period, all patients maintained the target BP of JSH 2009. The eGFR was 70.3 ± 15.7 mL/minute/1.73 m² at baseline and 70.2 ± 15.2 mL/minute/1.73 m² 6 months after switching to benidipine (Table).

Effect of UACR: A significant reduction in UACR was noted (median change -36.9%, IR -59.1 to 6.1), from 33.5 mg/g•Cr (IR 13.9 to 90.6) at baseline to 19.6 mg/g•Cr (IR 10.6 to 43.5) at 6 months after switching ($P = 0.001$) (Figure 2). We analyzed the changes in UACR according to the daily doses of benidipine. A significant reduction in UACR in patient groups who switched to 4 mg per day of benidipine was found (median change -33.4%, IR -46.1 to 8.3), from 21.7 mg/g•Cr (IR 15.4 to 42.4) at baseline to 17.3 mg/g•Cr (IR 10.3 to 30.7) at 6 months after switching ($P = 0.030$). Moreover, in patients who switched to 8 mg per day of benidipine, there was a significant decrease in UACR (median change -40.2%, IR -61.7 to 3.7), from 43.0 mg/g•Cr (IR 13.1 to 186.5) at baseline to 20.3 mg/g•Cr (IR 10.7 to 76.3) at 6 months after switching ($P = 0.011$).

Effect of PRA and PAC: The PRA was reduced from 2.3 ng/mL/hour (IR 0.8 to 6.1) at baseline to 1.6 ng/mL/hour (IR 1.2 to 2.7) at 6 months after switching. The difference was not statistically significant ($P = 0.063$). A significant reduction in PAC was noted (median change -11.8%, IR -29.8 to 1.1), from 104.7 ± 46.8 pg/mL in all patients at baseline to 86.7 ± 33.3 pg/mL at 6 months after switching ($P = 0.002$) (Figure 3). When stratified by the daily dose of benidipine after switching, the PAC in patient groups who switched to 4 mg per day of benidipine decreased from 88.5 pg/mL (IR 64.6 to 112.0) at baseline to 72.8 pg/mL (IR 59.9-99.3) at 6 months after switching, but it did not reach statistical significance ($P = 0.096$). However, in patients who switched to 8 mg per day of benidipine, there was a significant decrease in PAC (median change -13.2%, IR -29.7 to 2.3), from 100.0 pg/mL (IR 79.8 to 133.8) at baseline to 87.2 pg/mL (IR 72.0 to 106.5) at 6 months after switching ($P = 0.017$) (Figure 4).
Correlation between baseline values (UACR, PRA, and PAC) and changes in their values: We examined the relationships between UACR, PRA, and PAC at baseline (prior to switching from L-type CCBs to benidipine) and their rates of change. All baseline values showed a negative relationship with their rates of change (Figure 5). These results suggest that a higher baseline parameter value results in a greater reduction.

Safety and tolerability: After switching to benidipine, no serious side effects or cardiovascular accidents occurred.

**DISCUSSION**

This study demonstrated that in patients with essential hypertension who achieved the target BP indicated by the Treatment Guidelines of the JSH 2009, switching from an L-type CCB to the equivalent strength of the T/L-type CCB benidipine reduced the UACR independent of the antihypertensive effect. In addition, the product of aldosterone was inhibited in the group that received high doses of benidipine. Furthermore, switching to benidipine showed a greater effect on reduction in the patients with higher values of UACR, PRA and PAC, and these findings may suggest the efficacy of benidipine in patients with a high risk of cardiovascular diseases.

L-type CCBs mainly dilate the afferent arteriole of the glomerulus of the kidney and do not impact the efferent arterioles, thereby increasing the intraglomerular pressure. T/L-type CCBs and N/L-type CCBs also dilate the efferent arterioles and reduce the intraglomerular pressure. As a result, it was reported that urinary excretion of albumin is reduced. Furthermore, it was also reported that aldosterone itself impairs basement membrane functions of the glomerular capillary, which is responsible for urinary excretion of protein. Accordingly, the current study results suggest that in addition to the dilatation of the efferent arterioles by benidipine, the inhibition of the production of aldosterone led to a reduction of the uri-
The mechanism of action of the inhibition of the production of aldosterone by a T/L-type CCB is as follows: The T/L-type CCB inactivates the T-type Ca channels present in the adrenal cortex, resulting in inhibition of the influx of Ca into the T-type Ca channels. As a result, the expression of aldosterone synthase enzyme at the adrenal cortex is inhibited.

Akizuki, et al conducted an in vitro study using human adrenal cortex cells (NCI-H295R cells) and 10 minutes after the addition of various CCBs, 10 mM KCl was added to induce the production of aldosterone, and the aldosterone concentration in the culture media was measured 24 hours later. Consequently, the L-type CCB nifedipine did not inhibit the secretion of aldosterone while benidipine inhibited aldosterone secretion in a dose-dependent manner. Our results also demonstrated a dose-dependent reduction of the PAC by benidipine, which strongly supports our hypothesis.

Abe, et al randomly administered amlodipine and benidipine to patients with moderate renal impairment who were being treated by angiotensin receptor blockers and investigated the urinary excretion of albumin and the PAC. They reported that benidipine resulted in reductions of the plasma concentration of aldosterone and the urinary excretion of albumin. The present results demonstrate that switching from L-type CCBs to the T/L-type CCB benidipine led to a reduction in the UACR and the PAC. This study was not designed to demonstrate the superiority of benidipine versus L-type CCBs. However, for patients with essential hypertension who manifest micro-albuminuria and increased PAC during treatment for hypertension, which are potential cardiovascular risks, the current study results may be applicable as guidance in the selection of CCBs in clinical practice.

Evidence from studies shows that inhibition of the renin-angiotensin system (RAS) or reduction in urine protein is effective for preventing cardiovascular disease (CVD)/chronic kidney disease (CKD) with or without over activity of the RAS or severity of the CKD. It should be noted however that high levels of PRA, PAC and albuminuria include important prognosis factors predicting a poor outcome for CVD/CKD. Alderman, et al reported in a longitudinal study in hypertensive patients at risk of coronary artery disease that those with higher baseline PRA values were at a greater risk of myocardial infarction. Other studies also demonstrated that higher baseline PAC values led to lower survival rates in patients with ST-elevation myocardial infarction or heart failure.

A 4-year follow-up study of 1688 non-hypertensive participants conducted by Vasan, et al showed that increased PAC at baseline predisposed persons to the development of hypertension or an elevation of BP. Other studies revealed that there are positive correlations between the PAC and left ventricular mass index and apnea hypopnea index as risk markers for CVD. The Chronic Kidney Disease Prognosis Consortium reported that a high level of albuminuria was associated with increased relative risks for all-cause and cardiovascular mortality in a meta-analysis of a general population (approximately 100,000 participants).

In this study, we demonstrated that switching from an L-type CCB to benidipine in patients with higher levels of PRA, PAC and albuminuria, ie, patients with a higher potential risk for poor outcomes for CVD/CKD as described above, is more efficacious for reducing the risk for their poor CVD/CKD outcomes. This finding indicates that patients with over activity of
the RAS and increased albuminuria may be at high risk for poor outcomes of CVD/CKD. As a result, they could greatly benefit from the effects of the medical intervention.

Moreover, it has been demonstrated that an increased pre-treatment PRA level correlates with a decrease in BP response due to telmisartan and reduced albuminuria due to eplerenone.\textsuperscript{28-30} Bianchi, et al evaluated the effect of spironolactone in patients with CKD already treated with RAS inhibitors. In their study, high levels of PAC before treatment were associated with an increase of the reduction in proteinuria 2 weeks after treating with spironolactone.\textsuperscript{30} Other studies also showed that inhibition of the RAS is more markedly effective for treating patients with a decline in renal function.\textsuperscript{31,32} These findings support that RAS inhibitors exert a clear effect in patients at high risk for CVD/CKD; however, further studies are necessary in order to definitively ascertain the mechanism of the therapeutic action based on the results of this study.

RAS inhibitors can be selected as a first-line treatment in hypertensive patients with concomitant CKD. As a second-line treatment in patients at high risk of CVD, a long-acting CCB must be considered. As a second-line therapeutic action based on the results of this study.

**Clinical implications:** In this study, while renal function was still relatively maintained, benidipine reduced the degree of albuminuria and inhibited the secretion of aldosterone, a potent factor that exacerbates cardiovascular disease or an independent risk factor for cardiovascular disease. Accordingly, the early use of benidipine may be beneficial for the protection of cardio-renal functions in the future. Furthermore, when co-administered with L-type CCBs and renin-angiotensin inhibitors, it may be useful for the management of a breakthrough reduction in aldosterone.\textsuperscript{30} Recently, Unger clearly stated in a review paper concerning the renin-angiotensin-aldosterone system that T/L-type CCBs are similar to RAS inhibitory medication, a treatment option to achieve the inhibition of aldosterone. Thus, its effectiveness is broadly recognized.\textsuperscript{30} Benidipine has been shown to be effective in CKD and coronary spastic angina as well as essential hypertension.\textsuperscript{35-38} From now on, it seems important to select drugs by considering the class effects of CCB on the inhibition of cardiovascular accidents.

**Study limitations:** First, it should be remembered that the current study adopted a switchover design and did not carefully investigate potential differences between different drugs (L-type CCBs, T-type CCB). Second, the study evaluated the effects of benidipine not dependent on BP. In patients who experienced an increase in BP after switching to benidipine and whose treatment regimen was accordingly changed, such as an increased dose of benidipine, we did not evaluate the urinary excretion of albumin or the plasma concentration of aldosterone. Third, due to the relatively small number of patients in this study, stratified analysis of the study results, such as by L-type CCB (nifedipine CR, amlodipine) or concomitant medications, could not be performed. Finally, the urinary excretion of sodium and potassium, which are affected by the secretion of aldosterone, should have been measured.

**Conclusion:** In patients who maintained BP control even after the switch from an L-type CCB to the T/L-type CCB be-nidipine, benidipine reduced the urinary excretion of albumin and the PAC, especially in the group that received high doses of benidipine. The results suggest that the treatment of hypertension by benidipine with its high selectivity to the T-type Ca channel may confer cardio-renal protection.

**ACKNOWLEDGMENT**

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**Disclosure**

All authors declare that they have no competing interests.

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