Comparison of the Effects of an ACE Inhibitor and $\alpha\beta$ Blocker on the Progression of Renal Failure with Left Ventricular Hypertrophy: Preliminary Report

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The aim of this study was to compare the effects of an angiotensin-converting enzyme (ACE) inhibitor and $\alpha\beta$ blocker in combination with a calcium antagonist on the progression of renal function and left ventricular hypertrophy (LVH) in patients with chronic renal insufficiency and hypertension. The 65 subjects in this study were recruited from a cohort of 316 patients. The main criteria for inclusion were echocardiographic diagnosis of LVH (posterior wall thickness $>$12 mm) and serum creatinine of more than 1.5 mg/dl. Antihypertensive treatments were switched to the combination of amlopidine at a dose of 5 mg and benazepril at a dose of 2.5 mg daily or the combination of amlopidine at a dose of 5 mg and arotinolol at a dose of 20 mg daily at random irrespective of whether or not patients had been previously treated. The follow-up period was 2 years. Systolic and diastolic blood pressure were significantly reduced from 150/90±15/11 mmHg to 130/75±11/9 mmHg (ACE) and the levels of serum creatinine were increased significantly from 1.8±0.3 to 2.0±0.4 mg/dl (ACE). In the $\alpha\beta$-blocker group, these two values were similar and no significant changes were found. PWT was decreased from 14.2±0.6 to 12.9±0.3 cm in $\alpha\beta$ blocker but was not significantly decreased in the ACE inhibitor group. In conclusion, combination therapy with a calcium antagonist and $\alpha\beta$ blocker might be effective treatment for hypertensive patients with chronic renal insufficiency and left ventricular hypertrophy. (Hypertens Res 2001; 24: 153-158)

Key Words: renal insufficiency, left ventricular hypertrophy, arotinolol, benazepril

Introduction
Cardiovascular disease is the leading cause of mortality and morbidity in patients in end-stage renal failure (EDRF) in Japan as well as other European countries (1, 2), and hypertension is mainly responsible for this catastrophic event. In renal diseases, hypertension is very common and left ventricular hypertrophy (LVH) is not infrequent (3). Conversely, Devereux and Roman (4) have recently stated that there is a relatively consistent relation between LVH regression and cardiovascular disease, with a favorable change in LV mass corresponding to an apparent reduction of 50% or more in the likelihood of cardiovascular events.

Angiotensin-converting enzyme (ACE) inhibitors are believed to induce regression of LVH and to inhibit the progression of chronic renal insufficiency (5). It is therefore recommended that ACE inhibitors should be used for hypertensive patients with chronic renal insufficiency and LVH. However, the renin-angiotensin system plays both adaptive and maladaptive roles in patients with organ-dysfunction related with hypertension (6). Namely, suppression of angiotensin biosynthesis results not only in release

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of its detrimental vasoconstrictor effects but also in loss of many of the beneficial actions exerted by this hormone in maintaining renal homeostasis. In addition, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (7) has recommended that ACE inhibitors should be used with caution in patients having a creatinine level of 3 mg/dl or greater. Recently, Bakris and Weir (8) proposed that a dose adjustment of ACE inhibitors is needed when the levels of reduction of blood pressure and reservation of autoregulation of the kidney are taken into consideration. Moreover, in hypertensive patients with LVH in whom renal dysfunction is compromised, administration of a full dose of ACE inhibitors is not recommended. For these reasons, it is uncertain whether ACE inhibitors are suitable for hypertensive patients with LVH and renal dysfunction.

Various $\alpha_{\beta}$ adrenoreceptor blockers have been shown to have therapeutic value in patients with congestive heart failure, hypertension, and ischemic heart disease (9). Recently, we have demonstrated that treatment with an $\alpha_{\beta}$ adrenoreceptor blocker, arotinolol, in combination with extended release nifedipine was beneficial for improvement of renal impairment and cardiac damage in patients with accelerated hypertension with severe renal dysfunction (10). Arotinolol, which was developed in Japan, has a structure and action similar to those of carvedilol (11, 12).

In the present study, we compared the effects of arotinolol and benazepril, an ACE inhibitor combined with a long-acting calcium antagonist, amlodipine, on cardiac status and renal function in hypertensive patients with chronic renal insufficiency and LVH.

Patients and Methods

Patients

The 65 subjects in this study were recruited from a cohort of nearly 300 patients treated in our division of the Kidney Disease Center and four affiliated hospitals. The main criteria for inclusion were echocardiographic diagnosis of LVH (posterior wall thickness >12 mm) and serum creatinine of more than 1.5 mg/dl.

Antihypertensive treatments were switched to the combination of amlodipine at a dose of 5 mg and benazepril at a dose of 2.5 mg daily or the combination of amloidipine at a dose of 5 mg and arotinolol at a dose of 20 mg daily at random irrespective of whether patients had received previous treatment. Combination therapies were used because they have previously been reported to be necessary for achieving target blood pressure in numerous large-scale clinical trials (13).

Exclusion Criteria

Exclusion criteria included pregnancy or lactation, significant valvular or coronary heart disease, cardiac arrhythmia or conduction defects, diabetes mellitus, systemic diseases, proteinuria in the nephrotic range of <3.0 g/day, and use of sedative or hypnotic drugs or any other drugs potentially affecting blood pressure during ambulatory monitoring, i.e. corticosteroids. Patients consisted of 37 males and 28 females with a mean age of 52.5 ± 2.5. Underlying causes of renal insufficiency were IgA nephropathy (n=38; 58.4%), hypertensive nephrosclerosis (n=11; 16.9%), polycystic kidney disease (n=4; 6%) and unknown (n=12; 18.4%).

Blood Pressure Measurement

BP was measured in each clinic between 9 and 11 AM using a mercury sphygmomanometer; the first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Two measurements were collected with the patient in the sitting position for 5 and 10 min, respectively, and the average of the 2 values was taken as the BP for inclusion in the study and for the determination of the efficacy of treatment. The following stepped-care regimen was used to try and lower the clinic blood pressure values to less than 130/85 mmHg: 1) dose adjustment of amlodipine up to 20 mg daily; 2) addition of furosemide up to 60 mg daily; and 3) addition of guanabenz at bedtime at a dose of 2 to 6 mg daily. Patients whose blood pressure values remained less than 140/90 mmHg despite these treatments were excluded from the study.

Echocardiography

Left ventricular diameter, septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. Data were averaged over 5 cardiac cycles. Left ventricular mass index was calculated from thickness and diameter values using the Penn convention formula (14). Throughout the study, echocardiography studies were performed before treatment and at the 12th and 24th months after the studied drugs were started.

Laboratory Data

Serum creatinine and electrolyte concentrations, other serum biochemical values (uric acid, glucose, cholesterol, liver enzymes) and complete blood count were measured. Twenty-four-hour urinary excretion of protein was measured every 3 months.

All patients gave their informed consent and the study
Table 1. Baseline Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>ACE inhibitor</th>
<th>aβ Blocker</th>
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<tbody>
<tr>
<td>Age</td>
<td>52.4 ± 2.2</td>
<td>52.5 ± 2.6</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>18/14</td>
<td>19/14</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Blood pressure at the beginning of the study</td>
<td>150/90 ± 9/8</td>
<td>148/92 ± 7/9</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.1 ± 0.4</td>
<td>11.2 ± 0.3</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.9 ± 0.1</td>
<td>4.8 ± 0.1</td>
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was performed in accordance with the Declaration of Helsinki and with local legal requirements.

Statistical Analysis

Values are expressed as the mean ± SEM. The comparisons of benazepril and arotinolol treatments were made with one-way analysis of variance with repeated measurement followed by Bonferroni’s test. A p value less than 0.05 was considered to indicate statistical significance.

Results

Characteristics of the Study Population on Entry

There were no significant differences in age, sex ratio, blood pressure levels, serum creatinine levels, or distribution of renal diseases between the two groups at baseline (Table 1).

Effects of Benazepril and Arotinolol on Blood Pressure

The two combination treatments — i.e., amlodipine and benazepril or amlopridine and arotinolol — resulted in similar reductions in blood pressure. However, both treatments also resulted in a significant decrease in both systolic and diastolic blood pressure compared to baseline (Table 2).

There were no significant changes from the baseline levels in heart rate after 6, 12, or 24 months of treatment in either group (Table 2). In 3 patients in the benazepril and amlopridine group and 2 patients in the arotinolol and amlodipine group, blood pressure values remained above 130/85 mmHg despite the administration of antihypertensive drugs. The data on these 5 patients were excluded from the analysis.

Effects of Combination Therapy on Serum Creatinine

There were no significant differences in the levels of serum creatinine between the two groups throughout the study. At 24 months, the levels of serum creatinine were significantly increased in both groups (p < 0.01) (Fig. 1).

Effects of Combination Therapy on 24 Hour Urinary Excretion of Protein

The average 24 h urinary protein excretion values were 1.01 ± 0.25 g (amlodipine and benazepril) and 0.95 ± 0.66 g (amlodipine and arotinolol) daily at the beginning of the study and were 0.92 ± 0.38 and 1.12 ± 0.48 g daily, respectively, at the end of the study. Throughout the study, there were no significant changes in either group.

Effects of Treatment on Cardiac Structure

LVMi, intraventricular septal thickness and posterior wall thickness were significantly reduced in the group treated with amlodipine and arotinolol but not in that treated with amlodipine and benazepril (Fig. 2 and Table 2) at 1 and 2 years.

Discussion

In this study, we demonstrated that combination therapy with the aβ blocker arotinolol and calcium antagonist amlodipine, or combination therapy with the ACE inhibitor benazepril and amlodipine produced a renoprotective effect in hypertensive patients with chronic renal insufficiency and LVH. Moreover, antihypertensive treatment with arotinolol combined with amlodipine reversed LVH much more than that of benazepril with amlodipine throughout the study.

Several recent large-scale clinical trials (15–17) conducted on hypertensive patients with nondiabetic renal diseases have revealed that the greater the reduction in blood pressure, the greater the preservation of renal function. Based on these results, both the JNC VI (7) and WHO/ISH 1998 (18) guidelines recommended that the target blood pressure is less than 130/85 mmHg in hypertensive patients with chronic renal insufficiency. In the present study, the blood pressure levels were 130/75 ± 2/2 (amlodipine and benazepril group) and 129/72 ± 2/2 (amlodipine and arotinolol group) mmHg, respectively, which corresponded with the target blood pressures recommended in these guidelines. Accordingly, the declines of GFR calculated by the formula of Cockroft and Gault (19) were 3.5 ml/min/year for the amlodipine and benazepril group and 3.2 ml/min/year for the amlodipine and arotinolol group. In studies of both MDRD (16) and REIN (15), hypertensive patients with a nephrotic range of proteinuria received more beneficial effects on
Table 2. Hemodynamic and Echocardiographic Variables at Entry, during Treatment with ACE Inhibitor or αβ Blocker

<table>
<thead>
<tr>
<th></th>
<th>0 month</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
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<tbody>
<tr>
<td></td>
<td>ACE</td>
<td>αβ Blocker</td>
<td>ACE</td>
<td>αβ Blocker</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150±9</td>
<td>148±7</td>
<td>132±3**</td>
<td>129±2**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90±8</td>
<td>92±9</td>
<td>82±2**</td>
<td>70±2**</td>
</tr>
<tr>
<td>Heart rate</td>
<td>74±3</td>
<td>75±3</td>
<td>73±2</td>
<td>71±2</td>
</tr>
<tr>
<td>(beat/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Echocardiographic finding</td>
<td></td>
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<tr>
<td>IVST (mm)</td>
<td>13.0±0.2</td>
<td>12.8±0.1</td>
<td>12.2±0.1*</td>
<td>12.3±0.1*</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>14.6±2.5</td>
<td>14.2±5.1</td>
<td>14.3±2.4</td>
<td>14.0±2.2</td>
</tr>
</tbody>
</table>

Systolic blood pressure; DBP, diastolic blood pressure; IVST, intraventricular septal thickness; PWT, posterior wall thickness. **p<0.01 and *p<0.05: compared to the 0 month. #p<0.05: compared to ACE inhibitor. Values: mean±SEM. Number of patients: ACE inhibitor 29, αβ blocker 31.

Fig. 1. Changes in serum creatinine in hypertensive patients with chronic renal insufficiency and left ventricular hypertrophy. In spite of treatment with amlopidine and ACE inhibitor or αβ blocker, serum creatinine increased significantly at 1 and 2 years. *p<0.05, †p<0.01.

progression of renal function when blood pressure was reduced sufficiently. Moreover, in REIN study (20) both calcium antagonists and ramiplril, an ACE inhibitor, showed a similar ability to reduce proteinuria and markedly reduce blood pressure to less than 120/70 mmHg while preserving renal function. In the present study, we employed a combination therapy with a calcium antagonist and ACE inhibitor or αβ blocker to achieve the target blood pressure of less than 130/85 mmHg. The average reduction of proteinuria was not very remarkable in either group in the present study. The major reasons why the combination therapy with calcium antagonist and αβ blocker or ACE inhibitor did not produce a significant reduction of proteinuria in the present study were 1) the initial proteinuria of the patients enrolled in the current study was not as massive as that of patients in the REIN study (21); 2) the populations in the MDRD (16) and REIN (15) studies were different from that in the present study. In the MDRD study, 25% of patients with non-diabetic renal diseases were patients with ADPKD, and

in the REIN study, 25% were patients with focal glomerular sclerosis (FGS). In our study, more than 50% of enrolled patients had mild proteinuric IgA nephropathy. These kinds of differences might be important, since patients with FGS generally show much more proteinuria than those with IgA nephropathy. Although there was no significant reduction of proteinuria in hypertensive patients in the present study, both treatments inhibited on the progression of renal insufficiency. The percentage reduction in GFR was much greater than in the MDRD or REIN study. In both studies, the average decline of GFR was 6 ml/min/year. Further, in the AIPRI study (17), calcium antagonists were used in approximately 50% of hypertensive patients with nondiabetic renal diseases before the beginning of benazepril administration. This might provide evidence that combination therapy using a calcium antagonist and ACE inhibitor or αβ blocker has a

Fig. 2. Changes in left ventricular mass index in hypertensive patients with chronic renal insufficiency and left ventricular hypertrophy. Treatment with amlopidine and αβ blocker but not ACE inhibitor reduced left ventricular mass index significantly at 1 (*p<0.05) and 2 (†p<0.01) years. Furthermore, there were a significant difference between the two treatments (‡p<0.05).
more beneficial effect on the progression of renal insufficiency.

Atrinolol, an αβ blocker, has a structure and action similar to those of carvedilol (9, 10). In our previous study (10, 22), we provided evidence that combination therapy using slow-release nifedipine, a calcium antagonist, and atrinolol was effective in protecting the heart and kidneys in patients with accelerated hypertension. Shinai et al. (23) demonstrated that atrinolol was able to stabilize the progression of renal function in hypertensive patients with chronic renal insufficiency. The question of whether renin-angiotensin system activity differs between patients with and without chronic renal insufficiency has remained controversial. In several large clinical trials, such as the MDRD, REIN and AIPRI studies, the salt restriction was less than 3 g daily. However, for Japanese people, it is less likely to reduce the daily salt intake less than 7 g daily. This difference of salt intake between Caucasian people and our Japanese people is very important when we discuss the role of the renin-angiotensin system in the reduction in functional nephrons of patients with chronic renal insufficiency. Renin-angiotensin system activity is much more enhanced under condition of reduced salt intake compared to without less salt restriction (24). In the present study, our patients were advised to take less than 7 g of salt daily, and their sodium excretion was found to be approximately 120 mEq/day. This excretion is equivalent to a daily salt intake of 7 g. In the present study, we administered benazepril 2.5 mg daily, which is one half of the usual dose. In spite of the lower dose of benazepril, the delay in progression of chronic renal insufficiency in the present study seemed to be equal to or much greater than the corresponding delays in such foreign clinical trials as the MDRD, REIN etc. These results would seem to rule out the possibility that use of a lower dose of ACE inhibitor results in weakened action against the progression of chronic renal insufficiency.

However, compared to the renoprotective effects of a relatively small dose of ACE inhibitor, the usage of lower dose of ACE inhibitor might reflect the different effects between ACE inhibitor and αβ blocker in combined with calcium antagonist on LVH. This observation is supported by the data of several large-scale clinical trials: for example, the dose of enalapril employed in the CONSENSUS study (25) was 40 mg daily. In the present study, benazepril did not regress LVH compared to atroinolol. In the SOLVD study (26, 27), deterioration of renal function in patients with congestive heart failure was reported. Thus, taking these evidences together, whereas it is clear that ACE inhibitors can delay the progression of chronic renal insufficiency and regression of LVH, ACE inhibitor therapy should be carefully conducted.

In conclusion, the present results suggest that combination therapy using a calcium antagonist and αβ blocker might be safe and beneficial for treatment of hypertensive patients with chronic renal insufficiency and LVH.

References

16. Lazarus J, Bourgoignie J, Kuckalew V, et al, for the


