Combination of Half Doses of Angiotensin Type 1 Receptor Antagonist and Angiotensin-Converting Enzyme Inhibitor in Diabetic Nephropathy

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Background: To investigate the renoprotective effect of combination therapy with an angiotensin I converting enzyme inhibitor and an angiotensin type I receptor blocker (ARB) on diabetic kidney disease, half doses of each monotherapy were given to type 2 diabetic patients with albuminuria.

Methods: Urinary albumin index (UAI) and blood pressure (BP) were measured in a total of 27 outpatients with type 2 diabetes mellitus receiving 10 mg imidapril or 8 mg candesartan per day. Either agent was then substituted with a combination of 5 mg imidapril and 4 mg candesartan. After 3 months of combination therapy, UAI and BP were measured. Changes in the parameters were assessed by paired t-test.

Results: Although BP was not significantly different prior to and at the end of combination therapy, log-transformed UAI was significantly reduced (P = 0.003) from an initial UAI (mean log-transformed UAI ± SD) of 79.4 (27.4–231) mg/g Cre to 52.5 (17.1–161) mg/g Cre at the end of combination therapy. The reduction was not associated with the initial UAI, initial BP, decrease in BP, pretreatment medication or other concomitant antihypertensive agents.

Conclusions: In patients with type 2 diabetes and nephropathy, dual blockade of the renin system with an angiotensin-converting enzyme inhibitor and angiotensin receptor blocker significantly reduces albuminuria and, thus, may be renoprotective even when the doses of the agents are reduced by one half. Am J Hypertens 2005; 18:13–17 © 2005 American Journal of Hypertension, Ltd.

Key Words: Angiotensin-converting enzyme, renin–angiotensin system.

There is an increasing number of patients with diabetes mellitus in many countries. Diabetic kidney disease, one of its microvascular complications, is also markedly increasing and has become a major cause of end-stage renal disease worldwide. Intervention for preventing and delaying the development and progression of diabetic kidney disease is not only a medical concern but also a social issue. Despite extensive efforts, however, medical interventions thus far are not effective enough to prevent the progression of the disease and the development of end-stage renal disease.

Among several mechanisms involved in the development and progression of diabetic kidney disease, renal hemodynamic factors have been shown to play an important role in its pathogenesis; among these, high intraglomerular pressure is particularly problematic. Intraglomerular pressure is affected by the renin–angiotensin (RA) system. Angiotensin II, the physiologically active component of the RA system, increases the vascular tonus of postglomerular efferent arterioles more strongly than of preglomerular afferent arterioles, leading to intraglomerular hypertension. Suppression of the RA system, therefore, lessens intraglomerular pressure, which is protective against glomerular damage and thus beneficial for delaying the development of diabetic kidney disease. In fact, the renoprotective effects of two classes of pharmacologic agents on the RA system, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin type 1 receptor blockers (ARB), have been established in diabetic


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kidney disease, and recent guidelines propose the use of these classes of agents as first-line agents in the treatment of this disease.

Recently, several studies have revealed some differences in the renoprotective effects of these two classes of agents, in addition to a common major effect on the RA system: an ACEI acts on the kalikrein–kinin system affecting vasoconstriction, whereas an ARB blocks the biological effect of angiotensin II generated via ACE-independent pathways. Given the complementary nature of these two classes of agents, it is therefore possible that a combination of these two has the potential for better renoprotection than either agent alone. To date, several clinical studies have pointed to a beneficial effect of combination therapy with these two agents for diabetic kidney disease as well as for non-diabetic kidney diseases. In these studies, however, one agent was superimposed on the other class of agent without alteration of the former dose, thus allowing investigation of the additional effect of the other class of agent. It is still to be elucidated whether the combination per se is superior to each monotherapy for treatment of diabetic kidney disease.

To address this issue, in the present study, an ACEI or ARB was substituted with a combination of one half the dose of each monotherapy, and urinary albumin level and blood pressure (BP) was measured in type 2 diabetic patients with microalbuminuria or macroalbuminuria. The results indicated a beneficial effect of the combination therapy on diabetic kidney disease, even with one half the dose of each monotherapy.

Methods

The study subjects were 27 Japanese patients (15 male and 12 female) with type 2 diabetes mellitus who were attending Osaka University Hospital (Osaka, Japan) or its affiliated hospitals. The mean (± SD) age of the subjects was 62.4 ± 8.5 years. Diabetes mellitus was diagnosed according to the guidelines of the American Diabetes Association. All patients had been treated with either 8 mg candesartan cilexetil or 10 mg imidapril for 3 months. Patients with other known kidney diseases, inflammatory or infectious disease, hepatic cirrhosis, severe lung disease, or malignant disease were excluded.

Before the replacement of each monotherapy, BP and urinary albumin index (UAI) in a spot urine test were measured. The mean BP was calculated as diastolic pressure plus one third of pulse pressure. The mean duration of diabetes was estimated from the time of the first symptom attributable to the disease or, if symptoms were absent, from the time of the first detection of glycosuria. Blood pressure was measured in the supine position, and mean BP was calculated as diastolic pressure plus one third of pulse pressure.

To assess urinary albumin excretion, urinary concentrations of creatinine and albumin were measured by creatinase–creatinase–SOD–FADH method and a turbidimetric immunoassay method, respectively. The HbA1c was measured by HPLC and the normal range in the hospital was 3.8% to 5.8%. Serum creatinine was also measured. Subjective symptoms were monitored for adverse effects such as cough.

Statistical Analysis

Data are given as mean ± SD. Because the distribution of UAI was highly skewed, logarithmic transformation was performed. The mean ± SD of the log-transformed UAE were then calculated and expressed as the corresponding UAI. A paired t test was adopted to analyze differences in clinical parameters, including log-transformed UAE, between values before and after combination therapy. The difference and 95% confidence interval of log-transformed UAI were calculated. An unpaired t test was used to analyze differences in measurements between subgroups. A univariate linear regression model was used, and the amount of variance explained by the measurements was indicated by $r^2$. A P value < .05 was considered to be statistically significant.

Results

In the patients studied, mean ± SD body mass index was 24.3 ± 2.7 kg/m² and mean duration of diabetes was 14.0 ± 6.9 years. With regard to diabetes treatment in these patients, two patients were on insulin, one was treated with nateglinide, and two were not receiving antidiabetic medication. All of the remaining patients were receiving sulfonylureas without other antidiabetic medication (n = 10) or in combination with biguanides (n = 4), α-glucosidase inhibitors (n = 5), or both (n = 3). In nine of the 27 patients 8 mg candesartan cilexetil was substituted, and in the remaining 18 patients 10 mg imidapril was substituted. The reason why subjects treated with imidapril monotherapy were twice as many as those treated with candesartan was possibly because of the fact that ACEI had been more commonly used than ARB in Japan. These patients had been treated with either agent for 8 ± 5 months (range 3–19 months). Of the 27 subjects, 13 (48%) were treated with either candesartan or imidapril alone and 14 (52%) with other antihypertensive agents. All of these patients was begun. After 3 months of treatment with the combination therapy, BP and UAI were measured in the same way.

Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Duration of diabetes was estimated from the time of the first symptoms attributable to the disease or, if symptoms were absent, from the time of the first detection of glycosuria. Blood pressure was measured in the supine position, and mean BP was calculated as diastolic pressure plus one third of pulse pressure.
receiving other antihypertensive agents were taking calcium blockers; two patients were also treated with β blockers and a third patient was given a diuretic.

Table 1 summarizes the clinical data of the diabetic patients before and at the end of 3 months of combined therapy. There were no significant differences between values before and after combination therapy for glycated hemoglobin and serum creatinine or for systolic and diastolic BP. However, UAI significantly decreased (P = .003) from the level before (geometric mean of 79.4 mg/g Cre) to that after (52.5 mg/g Cre) combination therapy, with a mean reduction of 34% (95% confidence interval, 14% to 49%) (Fig. 1).

The ratio of UAI after/before combination therapy was not associated with the initial log-transformed UAI level \( r^2 = 0.08 \) or initial mBP \( r^2 = 0.08 \), indicating that the combination therapy was clinically effective irrespective of the degree of albuminuria or BP. This reduction ratio was not correlated with change in mBP level \( r^2 = 0.07 \), indicating that amelioration of albuminuria was not explained by a decrease in BP. When UAE was separately assessed according to pretreatment medication, geometric means of UAE before and after the combination therapy in patients who had been pretreated with imidapril were 54.6 and 39.0 mg/g Cre, whereas those in patients with candesartan pretreatment were 96.0 and 60.9 mg/g Cre. There was no significant difference \( (P = .37) \) in the ratio of UAI after/before combination therapy between the imidapril and candesartan pretreatment groups.

It is possible that the initial UAI in the patients receiving additional antihypertensive treatment could have been substantially different from that in the patients who did not. The initial UAE, however, was not statistically significantly different between patients with and without other medications \( (P = .8) \), geometric mean of 80.0 and 79.0 mg/g Cre, respectively). Similarly, there were no significant differences in initial systolic BP \( (P = .4) \), 142 ± 8 and 139 ± 14 mm Hg, respectively) and diastolic BP \( (P = .6) \), 86 ± 8 and 84 ± 10 mm Hg, respectively) between patients with and without antihypertensive treatment. To assess the effect of concurrent antihypertensive agents other than ACEI or ARB, the UAI ratio was compared between patients with and without concurrent therapy. The ratio was not significantly \( (P = .11) \) different between those with and without other antihypertensive agents (0.98 ± 0.69 and 0.65 ± 0.34, respectively), indicating that the renoprotective effect was independent of concurrent antihypertensive therapy.

**Table 1.** Clinical parameters before and after combination therapy with imidapril and candesartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.7 ± 1.5</td>
<td>7.8 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>140 ± 11</td>
<td>142 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>84 ± 9</td>
<td>85 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Cre (mg/dL)</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>UAI (mg/g Cre)</td>
<td>79.4 (27.4–230)</td>
<td>52.5 (17.1–161)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Cre = creatinine; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; NS = not significant \( (P > .05) \); SBP = systolic blood pressure; UAI = urinary albumin index.

Data are mean ± SD or geometric mean (mean log-transformed UAI) and range (mean log-transformed UAI ± SD).

**FIG. 1** Urinary albumin index (UAI) before and after combination therapy in patients with type 2 diabetes mellitus. Geometric UAI (mean log-transformed UAI ± SD) is shown on a logarithmic scale. Squares and lines indicate subjects pretreated with imidapril. Circles and dotted lines indicate subjects pretreated with candesartan. *Significant difference in UAI before and after combination therapy \( (P = .003, \text{paired } t \text{ test}) \).

**Discussion**

In this study of patients with type 2 diabetes mellitus, UAE was significantly decreased by combination therapy with half doses of ACEI and ARB, compared to each monotherapy, indicating a superior renoprotective effect of the combination of ACE and ARB, even with half doses, on diabetic nephropathy. The present results extended the findings of previously reported renoprotection of combination therapy, in which one agent was added to another, and further support the clinical benefit of combination therapy in the management of diabetic kidney disease.

As for the renoprotective effect of combination therapy on diabetic nephropathy, there have been several reports showing a better outcome than with monotherapy,\(^8\)–\(^12\) with a mean reduction in albuminuria of 16% to 43% compared with each monotherapy, except in one pilot study that included seven patients with type 2 diabetes.\(^16\)
which did not demonstrate beneficial effects. The study design of these reports with addition of an ARB to an ACEI, however, did not properly address the issue of whether the renoprotective effect was due to a possible benefit of the combination per se or simply to stronger blockade of the RA system. Combination therapy resulted in decreased BP in these studies with one, suggesting the latter possibility. The present study with half doses of each monotherapy demonstrated potential benefits of combination therapy itself for diabetic kidney disease.

There are several possible mechanisms explaining the superior renoprotection of combination therapy. First, an ARB can overcome an escape phenomenon under chronic ACEI treatment, in which plasma angiotensin II and aldosterone levels increase, after an initial decrease, to the pretreatment levels. Second, chronic administration of an ACEI in a human study was demonstrated to upregulate vascular expression of AT1R, the activation of which is effectively suppressed by an ARB. Third, an ARB inhibits the biological effect of angiotensin II generated by enzymes other than ACE, which was reported to comprise more than 40% of angiotensin II within the human kidney. Thus, ARB administration in combination with an ACEI is considered to be effective through multiple mechanisms. On the other hand, an ACEI causes vasodilation in an RA-independent manner through its effect on the kallikrein–kinin system, as well as its inhibitory effects on coagulation, which is not observed with an ARB. Therefore, an ACEI may exert its renoprotective effect by mechanisms that are not achieved by an ARB. Thus, the combination of ACEI and ARB is considered to protect against renal damage in a complementary manner. In fact, the combination of ACEI and ARB has been shown to be associated with a decrease in renal angiotensin II level and urinary level of transforming growth factor–β, and with an increase in renal intestinal fluid levels of bradykinin and cyclic guanosine 3′, 5′-monophosphate (cGMP). Taking these findings together, it is likely that the combination of an ACEI and an ARB might be more beneficial for protection against renal damage by potentiating each other rather than by simply acting in an additive manner.

In this study, the combination of half doses of ACEI and ARB was effective in reducing albuminuria compared with either dose alone, despite no significant alteration of BP, suggesting that its local effect on glomeruli is more profound than its systemic effect on vascular tone. This may not be solely explained by the predominant RA system within the kidneys, where all the components of the RA system are present, with a 1000-fold higher concentration of angiotensin than that in plasma. Rather, the complementary actions of the two agents within the kidney may have a more profound renoprotective effect. Accumulating lines of evidence support that inhibition of the RA system is particularly effective in reducing intraglomerular pressure. Thus, it is speculated that potentially more effective inhibition of the RA system by the combination has a predominantly vasodilatory effect on efferent arterioles, leading to a reduction in intraglomerular pressure and thus to renoprotection.

The observed effects of RA dual blockade on albuminuria were not different between subjects with and without concurrent antihypertensive therapy. It is shown that a considerable proportion of diabetic individuals do not reach the optimal BP goal (<130/80 mm Hg), as in the case of the present study subjects. It is to be elucidated whether the combination would still be better, even if BP was controlled below the goal by either monotherapy or combination therapy. Provided that many diabetic patients need multiple antihypertensive agents to attain the BP goal, the beneficial renoprotective effect of combination therapy irrespective of concurrent antihypertensive therapy further supports the clinical implication of the combination in many diabetic individuals.

In the present study, albeit statistically not significant, the reduction in UAI tended to be smaller in diabetic subjects receiving other antihypertensive medication than in subjects not receiving this medication. It is possible that there was a substantial difference in the initial UAE between those with other antihypertensive treatment and those without, which could have affected the results regarding renoprotection. The initial UAE, however, was comparable in patients with and without other medication. In addition, actual BP per se was similar in the two groups. Therefore, although the statistical power may not be strong enough because of the relatively small sample size, it is unlikely that the difference between the two groups in UAI or BP at baseline per se affected the results. It remains unclear whether combination therapy with an ACEI and ARB is more effective in subjects without other antihypertensive medication. To address this issue, a larger study might be necessary.

In conclusion, the present study in inpatients with type 2 diabetes indicated that the combination of half doses of ACEI and ARB was associated with decreased UAI compared with each monotherapy, indicating a beneficial renoprotective effect of RA dual blockade in diabetic kidney disease, even with half doses of the two agents. The clinical effectiveness of combination therapy that we report here further warrants its application to diabetic kidney disease and may contribute to amelioration of the prognosis of the disease.

References