Angiotensin Converting Enzyme Genotype Influences the Response to the Angiotensin II Receptor Antagonist Losartan in Patients with Hypertension

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To examine whether the response to the angiotensin II receptor antagonist losartan varies depending on the angiotensin converting enzyme (ACE) genotype, we prospectively studied the effect of losartan in 42 hypertensive patients (20 men, 22 women; mean age: 60.4 years). After a 4-week observation period, losartan was administered at 50 mg/day and blood pressure was measured every 2 to 4 weeks for 12 weeks. Among the 42 patients, 19, 11, and 12, respectively, had the II, ID, and DD ACE genotypes. The baseline plasma ACE activity in patients with the ID or DD genotype was significantly higher than that in patients with the II genotype (13.8 ± 4.2 vs. 9.6 ± 2.3 IU/l; p = 0.0002). However, age, gender, baseline systolic and diastolic blood pressure (SBP/DBP), and body mass index (BMI) were not different among the groups. After 12 weeks of treatment with losartan alone, DBP in the ID or DD group was significantly higher than that in the II group (85.0 ± 9.0 vs. 77.8 ± 9.6 mmHg, p = 0.018), while the percent reduction in DBP in the ID or DD group was significantly smaller than that in the II group (7.9 ± 8.8 vs. 14.3 ± 10.1%, p = 0.035). Multiple regression analysis showed that the significant predictors of the DBP at 12 weeks were age (p = 0.030), ACE genotype (p = 0.029) and baseline DBP (p = 0.0001). The ACE genotype may be a determinant of the response to losartan in hypertensive patients. (Hypertens Res 2004; 27: 137–140)

Key Words: losartan, angiotensin II receptor antagonist, tailored medicine

Introduction

Despite initial enthusiasm and expectations, recent large-scale studies and meta-analyses of their results have led to the conclusion that angiotensin converting enzyme (ACE) gene polymorphism does not affect blood pressure (BP), although it has been shown to affect plasma ACE activity (1–7). However, ACE gene polymorphism may influence the antihypertensive response when using drugs that act on the renin-angiotensin system. Ohmichi and co-workers showed that the reduction and percent reduction in diastolic blood pressure (DBP) tended to be higher in patients with the II genotype than in those with the ID or DD genotype (8). Furthermore, Katsuya and co-workers reported that the efficacy of antihypertensive drugs in general was less in patients with the ACE DD genotype than in patients with the I allele of the ACE gene (9). Therefore, we prospectively studied whether the response to the angiotensin II receptor antagonist losartan varied depending on the ACE genotype in hypertensive patients.

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Methods

This study was performed at outpatient clinics of the participating hospitals. Inclusion criteria of the study were a systolic blood pressure (SBP) >140 mmHg and/or a DBP >90 mmHg. In addition, all subjects were undergoing their first antihypertensive therapy or had not received antihypertensive medications for at least 1 month. Patients with a DBP >120 mmHg or with major co-morbidities (such as severe hepatic or renal diseases, uncontrollable diabetes, or pregnancy) were excluded from the study.

ACE activity (in IU/l at 37°C) was measured with ACE color (Fujirebio Co., Ltd., Tokyo, Japan), and genomic DNA from peripheral lymphocytes was isolated during the baseline observation period. Genomic DNA was stored until the analysis of ACE I/D genotypes.

After a 4-week baseline observation period, losartan was administered to the patients at 50 mg/day. All of the patients were examined every 2 to 4 weeks for 12 weeks.

Sixty patients who were seen in the participating hospitals from December 1999 to October 2001 were enrolled in this study. Informed consent was obtained from all patients. This study was approved by the Institutional Review Board of Shiga University of Medical Science. Eighteen patients dropped out of the study because they stopped visiting their respective clinics. Thus, 42 patients (20 men, 22 women; mean age: 60.4 years) were analyzed in the present study.

DNA was isolated from peripheral leukocytes and the ACE genotype was determined as previously reported (10). Briefly, the sense primer was 5' CTCAGAGACCACCTCCCAT CTTTCTT-3' and the antisense primer was 5' AGATGTGGCC CATCAATTCGTCAGT-3'. These primers allowed detection of a genomic DNA segment of 490 bp corresponding to the insertion allele (I) as well as a segment of 190 bp corresponding to the deletion allele (D). The amplification profile included an initial denaturation at 94°C for 60 s and 35 cycles of denaturation at 94°C for 60 s, annealing at 58°C for 60 s, and extension at 74°C for 120 s. The polymerase chain reaction (PCR) products were resolved in 1.5% agarose gels and visualized with ethidium bromide staining. The DD genotype of the ACE gene was reconfirmed by a second PCR using Taq extender (Stratagene, La Jolla, USA).

SAS version 6.12 on UNIX was used throughout the study. Since there were too few patients to perform analyses using three groups, the data for the ID and DD genotypes were combined for analyses. Frequencies were compared by a contingency table analysis. Numerical data were analyzed by an unpaired t-test. Multiple regression analysis was performed to investigate the possible influence of the ACE genotype on BP; gender, age, body mass index (BMI), baseline ACE activity, baseline BP and the genotype of the ACE gene (II = 1, ID + DD = 0) were included as independent variables. The data are shown as the mean ± SD.

Results

Among the 42 patients, 19, 11, and 12, respectively, had the II, ID, and DD ACE genotypes. The baseline plasma ACE activity in patients with the ID or DD genotype was significantly higher than that in patients with the II genotype (13.8 ± 4.2 vs. 9.6 ± 2.3 IU/l; p = 0.0002) (Table 1). However, age, gender, baseline heart rate, SBP and DBP, and BMI were not different among the groups (Table 1).

After 12 weeks of treatment with losartan alone, DBP in the ID + DD group was significantly higher than that in the II group (85.0 ± 9.0 vs. 77.8 ± 9.6 mmHg, p = 0.018). Although there was a tendency for a higher SBP at 12 weeks in the ID + DD group than in the II group, it did not reach statistical significance (145.0 ± 12.6 vs. 139.6 ± 16.5 mmHg, p = 0.247) (Fig. 1A). The percent reduction in DBP in the ID + DD group was significantly smaller than that in the II group (7.9 ± 8.8% vs. 14.3 ± 10.1%, p = 0.035) (Fig. 1B). The percent reduction in SBP was not significantly different between the groups (11.0 ± 7.8% in ID + DD vs. 14.7 ± 7.4% in II, p = 0.128) (Fig. 1B).

Multiple regression analysis showed that the significant predictors of DBP at 12 weeks were age (p = 0.030), ACE genotype (p = 0.029) and baseline DBP (p = 0.0001) (Table 2).

Discussion

Previous studies and meta-analyses of these studies have consistently found a strong association between ACE gene polymorphism and plasma ACE activity (1–6). However, most of these studies have reported that there was no association between ACE gene polymorphism and BP (1–4). One possible explanation for this lack of an effect of ACE gene polymorphism on BP may be that high ACE activity alone does not result in elevated BP, since the interplay of multiple factors establishes homeostasis in living systems (11).
The present results show that the response to the angiotensin II receptor antagonist losartan is greater in patients with the ACE II genotype than in those with the ID or DD genotype. Several previous studies on the relations between the ACE genotype and the response to ACE inhibitors have shown similar results. Ohmichi and co-workers reported that the reduction in DBP by the ACE inhibitor imidapril was inversely correlated with plasma ACE activity, and the response tended to be greater in the ACE II genotype (8). Other studies with ACE inhibitors have shown similar results (12, 13). Although it was not their primary focus, there have been three studies that touched on the relation between the ACE genotype and the response to an angiotensin II receptor antagonist (14–16). None of them showed any differences in the BP-lowering effects of angiotensin II receptor antagonist depending on ACE genotype. In one of the studies, the drug was administered at a purposely subhypotensive dose to normotensive subjects. In the other two studies, the main objective was to examine the renoprotective effects of losartan in diabetic nephropathy and its interaction with ACE genotype. Although the difference was statistically insignificant, the reduction in BP was slightly greater in the ACE II genotype group than in ACE DD genotype group in both studies (15, 16).

The finding in the present study that the response to losartan was greater in patients with the ACE II genotype than in those with the ID or DD genotype appears reasonable. Since the receptor antagonist losartan competes with the agonist angiotensin II for binding to the same effector, the action of the agonist will eventually be inhibited, and this inhibition can be overcome by increasing the concentration of agonist. In comparison with the previous study with imidapril, in which there were no statistically significant changes in BP reduction (8), the present study achieved a statistically significant reduction in DBP in a few patients. This may relate to the fact that angiotensin II is generated not only via ACE but also via chymase. With a blockade at the angiotensin II receptor, we might have had more stable results. Tailored medicine is a relatively new idea. It has mostly been discussed in the context of cytochrome P450 gene polymorphisms and drug susceptibility (17–19), or in regard to the effectiveness of chemotherapy and cancer genotypes (20). The present study may lead to the application of tailored medicine in more common disease states such as hypertension.

Table 2. Predictors of DBP at 12-Weeks in Response to Losartan

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.278</td>
<td>0.123</td>
<td>0.030</td>
</tr>
<tr>
<td>Male</td>
<td>-1.548</td>
<td>2.257</td>
<td>0.497</td>
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<td>Baseline ACE activity</td>
<td>0.029</td>
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<td>0.934</td>
</tr>
<tr>
<td>BMI</td>
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<td>0.119</td>
</tr>
<tr>
<td>ACE genotype (II)</td>
<td>-6.144</td>
<td>2.698</td>
<td>0.029</td>
</tr>
<tr>
<td>Baseline DBP</td>
<td>0.757</td>
<td>0.133</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; BMI, body mass index; DBP, diastolic blood pressure.

Fig. 1. Response of blood pressure to losartan according to the ACE genotype. A: Systolic (SBP) and diastolic blood pressure (DBP) at 12 weeks according to the ACE genotype. DBP in the ID + DD group was significantly higher than that in the II group (85.0 ± 9.0 vs. 77.8 ± 9.6 mmHg, p = 0.018). Although there was a tendency for a higher SBP in the ID + DD group than in the II group, the difference did not reach statistical significance. B: The percent reduction in SBP and DBP according to the ACE genotype. The percent reduction in DBP in the ID + DD group was significantly smaller than that in the II group (7.9 ± 8.8 vs. 14.3 ± 10.1%, p = 0.035). The percent reduction in SBP was not significantly different between the groups. SBP12wk, SBP at 12 weeks of treatment; DBP12wk, DBP at 12 weeks of treatment; %dSBP, percent reduction in SBP; %dDBP, percent reduction in DBP.
In this study, the frequency of the D allele (41.7%) was slightly higher than in previous studies in Japan (34.3–39.0%) (21, 22). Furthermore, the distribution of the ACE genotype in this study did not conform to Hardy-Weinberg’s law. One possible reason for the excess DD allele may be chance, since the number of subjects was small. It is highly unlikely that ACE I/D genotyping errors occurred in this study. We confirmed the DD genotype of the ACE gene by a second PCR using Taq extender. Moreover, in the case of equivocal genotypes, we performed a third PCR to verify the genotype of the ACE gene.

In conclusion, the ACE genotype may be a determinant of the response to losartan in hypertensive patients.

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**References**


