Original Article

Long-Term Effects of Olmesartan, an Ang II Receptor Antagonist, on Blood Pressure and the Renin-Angiotensin-Aldosterone System in Hypertensive Patients

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The object of this study is to evaluate the long-term effects of olmesartan on hypertension and the renin-angiotensin-aldosterone system in hypertensive patients. This study evaluated 26 hypertensive male and female outpatients, 36–69 years of age, with a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg. Oral doses of 5 to 40 mg olmesartan were administered once daily. Blood pressure and renin-angiotensin-aldosterone parameters (plasma renin activity and plasma angiotensin I, II, and aldosterone concentrations) were evaluated at 12–16 weeks, 6 months, and 1 year after the start of olmesartan administration. Systolic and diastolic blood pressures were significantly decreased following the administration of olmesartan. The observed decreases in systolic and diastolic blood pressures after 1 year of treatment were 28.8±2.1 mmHg and 15.8±1.3 mmHg, respectively. No change was observed in the pulse rate. The plasma renin activity increased significantly from a baseline premedication mean of 1.26±0.31 ng/ml/h to a mean of 2.58±0.74 ng/ml/h and 2.87±0.72 ng/ml/h after 6 months and 1 year of treatment, respectively. Angiotensin II levels decreased significantly from a baseline of 20.4±3.2 pg/ml to a mean of 8.6±2.1 pg/ml and 6.8±1.8 pg/ml after 6 months and 1 year of treatment, respectively. The plasma aldosterone level also decreased significantly after 6 months of treatment. In hypertensive patients, the long-term administration of olmesartan, a novel AT1 receptor antagonist, decreased both blood pressure and plasma angiotensin II levels. (Hypertens Res 2001; 24: 641–646)

Key Words: Ang II receptor antagonist, olmesartan, renin-angiotensin-aldosterone system

Introduction

Angiotensin (Ang) II is generated from Ang I mainly by angiotensin converting enzyme (ACE). Ang II is one of the most potent vasoconstrictors known. ACE is not only responsible for the conversion of Ang I to Ang II but also degrades bradykinin, which is a strong vasodilator. ACE inhibitors, therefore, exert a vasodilating effect by two different mechanisms; decreasing the production of Ang II and increasing the level of bradykinin. Increased bradykinin levels, however, can lead to well-known adverse reactions, such as cough. Ang II receptor antagonists avoid this problem by specifically acting on the Ang II type 1 (AT1) receptor. Since physiologically this is the last step in its cascade, the bradykinin level should not be affected by this action. Therefore the cough could be avoided and the quality of life improved by the use of AT1 receptor antagonists. At present, several AT1 receptor antagonists are being developed or are already marketed by different companies (1).

Olmesartan is a novel AT1 receptor antagonist synthesized by Sankyo Co., Ltd., Japan (2, 3). After oral administration, it is hydrolyzed to a metabolite in the intestinal tract or liver, and this active metabolite exhibits a continuous antihypertensive effect. The antihypertensive effect of olmesartan in spontaneously hypertensive rats is about 30 times greater than that of losartan potassium, another drug of the same class, and nearly equal to that of candesartan cilexetil. In ad-

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dition, several clinical studies in patients with essential hypertension have previously demonstrated the efficacy and tolerability of this drug when administered once a day (4).

In a previous investigation into the influence of olmesartan on the renin-angiotensin system (RAS), healthy male volunteers were administered Ang I, and the effect of this drug on the pressor response was observed. The pressor response was suppressed, and both plasma renin activity (PRA) and the Ang II concentration were increased. In a study to evaluate the tolerance and efficacy of olmesartan administered to salt-restricted hypertensive patients, the drug was observed to be well tolerated (5). Although these findings suggest the mechanism of action of olmesartan, it is difficult to extrapolate from such information the drug’s clinical efficacy and effects on the RAS.

Several types of AT1 receptor antagonists are already available for treating hypertension, and have shown to increase both PRA and plasma Ang II concentrations in hypertensive patients (6–8). These findings, however, have been obtained only by short-term observations. The long-term effects of AT1 receptor antagonists on the RAS remain to be elucidated.

In the present open-label study, we evaluated the effects of olmesartan on hypertension and the RAS (as measured by PRA and plasma levels of Ang I, II and aldosterone) in hypertensive patients for 1 year.

**Patients and Methods**

Participants enrolled in this study were outpatients with hypertension, aged 30 years or older, who sought treatment at the Cardiovascular Hospital of Central Japan. The hospital’s Institutional Review Board approved the study prior to its start, and all patients gave written informed consent to participate.

Patients already receiving antihypertensive drugs were instructed to discontinue them after consent was obtained. During the approximately 4-week run-in period, a placebo was administered once a day after breakfast. After completion of the run-in period, patients were enrolled in the present study if the mean of two blood pressure measurements was ≥160 mmHg for systolic blood pressure (SBP) and/or ≥95 mmHg for diastolic blood pressure (DBP), and the degree of target organ damage was categorized based on the 1993 WHO/ISH classification.

For safety reasons, patients who met any of the following criteria were excluded from the study: presence of severe hypertension (DBP ≥120 mmHg), secondary or malignant hypertension, a history of myocardial infarction or stroke within 6 months prior to study enrollment, any severe cardiac, hepatic or renal dysfunction, uncontrolled diabetes mellitus (fasting blood glucose ≥200 mg/dl) or on insulin therapy, familial hypercholesterolemia or secondary hyperlipidemia, peptic ulcer, a history of drug allergy, photosensitivity or chronic skin disease, severe anemia or leucopenia, hyperkalemia, or possible bronchial asthma or bronchospasm. Pregnant, breast-feeding, or possibly pregnant women, and those planning to become pregnant during the study period were also excluded.

Olmesartan tablets (5, 10, and 20 mg) were used as the study medication. The treatment was started at 5 mg, and patients were instructed to take the medication orally once a day after breakfast. If it was confirmed that the response was inadequate and the patient was tolerating the treatment, the dose was increased sequentially to 10 mg, 20 mg, or 40 mg according to the schedule shown in Fig. 1 until an adequate effect was observed. An adequate effect was defined as a reduction of ≥20 mmHg in SBP coupled with a reduction of ≥10 mmHg in DBP, a reduction of ≥13 mmHg in mean blood pressure (MBP), or normalization of blood pressure to ≤149/89 mmHg. During the study, concomitant use of other antihypertensive drugs was prohibited. Concomitant use of hypoglycemic and hypolipidemic drugs was allowed if necessary, but the dosage of these drugs could not be changed during the course of the study. In addition, concomitant use of non-steroidal anti-inflammatory drugs, tricyclic antidepressants, H1-blockers, tranquilizers, analgesics, and hypnotics was avoided if possible. There were no salt restrictions placed on the patients’ diets.

On evaluation days, patients were instructed not to eat breakfast and to visit the hospital in the morning after taking the study drug. The sitting blood pressure was measured 3 times in the patient’s right arm, and the mean value of the 3 measurements was used for the analysis data. The blood pressure and the pulse rate were measured every 2–4 weeks at the hospital. The mean of 2 blood pressure measurements was obtained on completion of the run-in period and this value was defined as the baseline blood pressure. The antihy-
pertensive effect was evaluated following 12–16 weeks, 6 months, and 1 year of treatment.

Blood samples were obtained during the hospital visits, 3–4 hours after study medication intake, and after at least 30 min of rest, and the conditions for taking blood samples remained unchanged during the study. PRA and plasma levels of Ang I, Ang II, and aldosterone were determined during the run-in period and following 12–16 weeks, 6 months, and 1 year of treatment. These parameters were measured each time the blood samples were obtained. PRA was measured with commercial radioimmunoassay kits (Dainabot Renin RIA kit II; Dainabot Corp., Tokyo, Japan). PRA was determined by measuring newly synthesized Ang I with phenylmethyl sulfonyl fluoride at a sensitivity of 0.1–20 ng/ml/h (intra-assay CV=3.2–6.3%, inter-assay CV=6.2–10.2%, respectively). Plasma aldosterone level was measured with commercial kits (SPAC-S Aldosterone kit; Dai-ichi Radio-isotope, Tokyo, Japan), with a sensitivity of 25–1,600 pg/ml. The concentrations of Ang I and II were measured by radioimmunoassay using the original methods of SRL, Inc., Tokyo, Japan (9). The sample (50–100 μl) was mixed with assay buffer (Tris buffer) containing 100 μl of tracer [125I-Ang I or Ang II] and 100 μl of the primary antibody to Ang I or Ang II, and incubated for 18–24 h at 2–8°C. Then 100 μl of the secondary antibody and 100 μl of PEG solution were added to the mixture and incubated for 1 h at 2–8°C. After centrifugation at 3,500 rpm for 20 min at 2–8°C, the supernatant was decanted and radioactivity was measured. When Ang I was measured, the coefficient of variation in this method ranged from 1.57 to 5.70% in intra-assay and from 1.02 to 8.80% in inter-assay. On the other hand, when Ang II was measured, the coefficient of variation ranged from 1.48 to 5.08% in intra-assay and from 0.51 to 9.41% in inter-assay.

Statistical Analysis

Values are expressed as the means ± SEM. Dunnett’s test was used to compare values from the baseline run-in period with values obtained during the treatment period. The level of significance was set at p≤0.05 (two-tailed) for all comparisons.

Results

Patient Characteristics and Extent of Exposure

The clinical profile of the patients is shown in Table 1. The age (mean ± SEM) of the patients was 53.2 ± 1.8 (38–69) years. Baseline SBP, DBP, and pulse rate were 163.8 ± 1.4 mmHg, 99.8 ± 1.1 mmHg, and 64.9 ± 1.5 beats/min, respectively.

Table 2 shows the doses of olmesartan after 12–16 weeks, 6 months, and 1 year of administration. The 10 mg dose was administered to the largest number of patients. Only one patient was administered 40 mg of olmesartan.

Blood Pressure, Pulse Pressure and Pulse Rate

Table 3 shows the means and standard errors for blood pressure, pulse pressure, and pulse rate during the run-in period and after 12–16 weeks, 6 months, and 1 year of treatment. Mean SBP and DBP decreased significantly (p<0.001) from baseline to week 12–16, and remained stable thereafter with no further changes during long-term administration. After 1 year of treatment, mean SBP and DBP had decreased to 134.2 ± 2.1 mmHg and 82.9 ± 1.4 mmHg, respectively. Pulse pressure also decreased to 64.0 ± 1.6 mmHg, whereas the pulse rate showed no significant differences from baseline.

The time course of changes in blood pressure is shown in Fig. 2 as the reduction from the baseline. SBP and DBP showed a significant decrease (p<0.001) after 2 weeks of administration. The blood pressure gradually decreased until around week 12, and remained almost unchanged from that
Table 3. Blood Pressure, Pulse Pressure and Pulse Rate at Each Time of Evaluation

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Mean±SEM</th>
<th>MBP (mmHg)</th>
<th>PP (mmHg)</th>
<th>PR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>26</td>
<td>163.8±1.4</td>
<td>99.8±1.1</td>
<td>121.1±1.0</td>
<td>64.0±1.6</td>
<td>64.9±1.5</td>
</tr>
<tr>
<td>12–16 Weeks</td>
<td>25</td>
<td>135.9±2.4***</td>
<td>86.4±1.8***</td>
<td>103.0±1.8***</td>
<td>49.5±1.8***</td>
<td>63.8±1.4</td>
</tr>
<tr>
<td>6 Months</td>
<td>23</td>
<td>131.3±2.8***</td>
<td>83.6±1.5***</td>
<td>99.5±1.8***</td>
<td>47.7±2.1***</td>
<td>63.8±1.1</td>
</tr>
<tr>
<td>1 Year</td>
<td>23</td>
<td>134.2±2.1***</td>
<td>82.9±1.4***</td>
<td>100.0±1.5***</td>
<td>51.3±1.5***</td>
<td>61.9±1.1</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PR, pulse rate. ***p<0.001 (Dunnett's test).

Fig. 2. Time course of changes in blood pressure. The reduction from baseline values (mmHg) is shown for the SBP (open squares) and DBP (closed squares) at each evaluation point. Values are the means±SEM. From the week 2 visit, SBP and DBP were significantly decreased (p<0.001) from baseline.

point to the completion of the study.

Renin-Angiotensin-Adosterone System

Figure 3 shows the time course of PRA and the plasma aldosterone level. After 6 months and 1 year, PRA increased significantly from a baseline of 1.26±0.31 ng/ml/h to means of 2.58±0.74 ng/ml/h and 2.87±0.72 ng/ml/h, respectively (p=0.029 and 0.016). The plasma aldosterone level decreased significantly from a baseline of 11.30±1.09 ng/dl to 7.86±1.53 ng/dl after 6 months (p=0.047). It also decreased after 1 year, but the decrease was not significant compared to baseline (p=0.081).

Figure 4 shows the time course of plasma Ang I and Ang II levels. After 1 year, the Ang I level decreased significantly from a baseline of 145.6±25.3 pg/ml to 61.5±11.3 pg/ml (p=0.017). Ang II also decreased significantly from a baseline of 20.4±3.2 pg/ml to 8.6±2.1 pg/ml and 6.8±1.8 pg/ml after 6 months and 1 year, respectively (p=0.008 and 0.0001).

We also analyzed the data for patients with complete sets of measurements taken at all scheduled evaluation points (19 patients for PRA and 15 patients for plasma Ang I, Ang II and aldosterone levels); the same results were observed for PRA and Ang II. After 1 year, a significant decrease of Ang I was not observed, but a significant decrease of aldosterone was observed in these 15 patients (data not shown).

Correlations among Parameters

Statistical correlations were investigated between the reduction of blood pressure (SBP and DBP) and the percent change of each endocrine parameter (PRA, and the plasma Ang I, Ang II, and aldosterone levels). Correlations were also investigated between the percent changes of each pair of the RAS parameters. None of the pairs of parameters exhibited a clear correlation with each other at any evaluation
that pulse pressure may be a risk factor for cardiovascular 
events in middle-aged and older subjects (10, 11). Although 
the decrease in pulse pressure observed in this study may 
lead to decreased risk for cardiovascular events, these find-
ings require further clarification.

This study also found an increase in PRA and a decrease 
in plasma Ang I, Ang II, and aldosterone levels during the 
long-term administration of olmesartan. The increase of 
PRA and the decrease of the plasma aldosterone level prob-
ably occurred because negative feedback for renin production 
was blocked by the angiotensin receptor antagonistic effect 
of olmesartan.

Although the effects of various angiotensin receptor antag-
ons on the RAS have been investigated previously, the ad-
ministration period in most studies is short and few studies 
have reported data on long-term administration. Ang I and II 
levels are known to increase transiently at the initiation of 
treatment with AT1 receptor antagonists (12–15). However, 
Goldberg et al. (16) report that a transient increase of Ang II 
concentration is followed by a decrease when an AT1 recep-
tor antagonist is administered to hypertensive patients.

In our study, a significant decrease in plasma Ang II was 
observed after 6 months and 1 year of drug treatment, and at 
least two mechanisms may have been responsible for this de-
crease. The first possibility is the depletion of angiotensino-
gen, the substrate for renin. Previous studies have supported 
this hypothesis (17,18). When PRA remains high for a long 
period, production of angiotensinogen is inadequate relative 
to the demand for renin, which results in relative depletion of 
angiotensinogen followed by decreased production of Ang I 
and a consequent decrease of Ang II.

The second possibility is the increased metabolism of Ang 
II. Ang II is metabolized by various peptidases, including 
aminopeptidase, and long-term administration of olmesartan 
may activate this process. Shibasaki et al. (19) reported the 
possible activation of Ang II metabolism, based on the find-
ing that the administration of Ang II receptor antagonists 
quickly decreased the Ang II level without changing the Ang 
IV concentration.

As mentioned above, several studies show a decrease in 
Ang II levels after treatment with angiotensin receptor antag-
ons. Goldberg et al. (16) found that the plasma Ang II lev-
el increased at week 2 and then decreased at week 6, but the 
Ang II level at week 6 was still above baseline. Shibasaki et 
al. (19) also reported increased plasma Ang II levels at day 7 
and decreased levels at days 28 and 56, but the Ang II level 
at day 56 was still above baseline. In the present study, how-
ever, plasma Ang II levels after 6 months and 1 year of treat-
ment were significantly below baseline. This result is quite 
different from those of the previous study, so it is important 
to observe the RAS during long-term treatment with AT1 recep-
tor antagonists.

During treatment with AT1 receptor antagonists, it is be-
lieved that increased Ang II will bind to and stimulate AT1 
receptors. AT1 receptors have unique and largely opposite ef-

**Clinical Safety**

Study treatments were generally well tolerated; however, 
three patients discontinued the study. One patient discon-
tinued because of a serious adverse event. This patient expe-
rienced sudden difficulty in breathing at day 7. The symptoms 
improved immediately, but as there were no predisposing 
factors, a relationship to the study medication was consid-
ered possible. One patient discontinued because of lack of 
efficacy and another withdrew for personal reasons. There 
were no other adverse events related to the study medication.

**Discussion**

In this study, the long-term effects of olmesartan on blood 
pressure and the RAS were investigated in hypertensive pa-
ients. Olmesartan therapy caused the blood pressure to de-
crease significantly compared to baseline after 2 weeks of 
administration, and a stable antihypertensive effect was sub-
sequently observed throughout the treatment period. The 
blood pressure gradually decreased until around week 12 of 
administration, and remained fairly stable thereafter. These 
findings are considered attributable to the dose-titration de-
sign of this study.

Several observational studies show evidence suggesting

**Fig. 4.** Time course of plasma Ang I and Ang II level. N = 
number of patients. Values are mean ± SEM. * p < 0.05,
**p < 0.01 (Dunnett’s test).**
fects such as vasodilation, antiproliferation, and apoptosis in various tissues (20). In this study, Ang II levels decreased gradually during long-term treatment, so there was little possibility that Ang II stimulated AT1 receptors strongly. However, since the effect of AT1 receptor stimulation on various tissues during treatment with AT1 receptor antagonists is still unknown, further investigation will be necessary to determine the nature of these actions.

There was no correlation between the decrease of blood pressure and changes in the RAS. However, an increase in PRA and a decrease in plasma aldosterone concentration were observed in this study; therefore, it is reasonable to conclude that the AT1 receptors were effectively antagonized by olmesartan.

In conclusion, the present study confirmed the favorable antihypertensive effect and tolerability of olmesartan, a novel AT1 receptor antagonist, in hypertensive patients. The study also demonstrated that plasma Ang I and II levels were decreased by long-term treatment with olmesartan. Although further investigation will be necessary to determine the actual effects on the RAS produced by long-term treatment with AT1 receptor antagonists such as olmesartan, the findings in our study improve the understanding of the interaction between AT1 antagonists and the RAS.

References