Effect of Losartan on Nocturnal Blood Pressure in Patients With Stroke: Comparison With Angiotensin Converting Enzyme Inhibitor

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Background: Treatment of nocturnal hypertension has been reported to be beneficial for primary and secondary prevention of stroke. We compared the effects of angiotensin II antagonist (losartan) and angiotensin converting enzyme inhibitor (quinapril) on nocturnal blood pressure (BP) and sympathetic nervous activity in patients with hypertension and stroke.

Methods: According to a prospective, randomized, cross-over design, 30 hypertensive patients with a previous history of stroke (25 hemorrhage, 5 infarction) were assigned randomly to receive losartan (50 mg) or quinapril (10 mg) once daily for 4 weeks. The patients were switched to the alternative regimen for an additional 4-week period. In the last week of each treatment, 24-h ambulatory BP monitoring was performed every 30 min, and 24-h urine was collected for the measurement of catecholamine.

Results: Neither systolic nor diastolic BP during daytime differed between losartan and quinapril treatments, but those during nighttime were lower with losartan treatment than with quinapril treatment. The nocturnal decreases in systolic and diastolic BP were both greater with losartan treatment than with quinapril treatment (systolic BP: 6.1% ± 5.9% v 2.5% ± 6.9%, diastolic BP: 6.4% ± 6.5% v 3.3% ± 7.8%, both P < .05). The nocturnal decrease in urinary norepinephrine excretion was greater with losartan treatment than with quinapril treatment (52.8% ± 9.7% v 42.8% ± 17.2%, P < .05).

Conclusions: Losartan enhances the nocturnal decrease in ambulatory BP compared with that of quinapril in patients with a previous history of stroke presumably by way of the suppression of nocturnal sympathetic nervous activity.

Key Words: Angiotensin II antagonist, angiotensin converting enzyme inhibitor, stroke, nocturnal blood pressure, sympathetic nervous activity.

A strong association between the level of blood pressure (BP) and the risk of the first stroke episode has been established by prospective observational studies.1,2 The UK Transient Ischemic Attack Aspirin trial has shown a similar association between BP and the risk of stroke among individuals with a history of transient ischemic attack or stroke.3 The other trials in patients with a history of cerebrovascular disease4,5 suggest that the reduction rate of stroke risk may be similar in patients with and without cerebrovascular disease. Taken together, for both first and recurrent stroke, the relationship between BP and stroke risk is steep and continuous, and no lower level below which the risk of stroke does not continue to decline is identified.

Angiotensin converting enzyme (ACE) inhibitors are the standard treatment for hypertensive patients with a history of stroke. Despite the established benefits of ACE inhibitor treatment, these agents are not prescribed to all patients because of concerns related to adverse effects. The benefit of ACE inhibition has been attributed largely to blockade of the production of angiotensin II, but also to bradykinin accumulation.6 Bradykinin accumulation, however, has been implicated as a contributor to the adverse effects associated with ACE inhibitor treatment. In particular, bradykinin enhances norepinephrine release by a presynaptic mechanism,7,8 and would result in the lack of nocturnal decrease of BP. Angiotensin II antagonists, such as losartan, directly block angiotensin II at the AT1 receptor with no accumulation of bradykinin. Therefore, angiotensin II antagonists would provide similar benefits.
to ACE inhibitors with fewer adverse effects.6,9 In addition, angiotensin II antagonists would restore the diurnal pattern of BP by no accumulation of bradykinin. The present study was designed to compare the effects of losartan on the nocturnal decrease in BP and sympathetic nervous activities with those of ACE inhibitor in hypertensive patients with a previous history of stroke.

Methods

Subjects

Thirty patients (16 men and 14 women; mean age, 61 years, range, 42 to 77 years) with a previous history of stroke and essential hypertension were investigated during admission to Reimeikyo Rehabilitation Hospital. All patients gave informed consent before the study. The patients had mild-to-moderate hypertension with casual clinic systolic BP between 140 and 180 mm Hg and diastolic BP between 90 and 110 mm Hg. On admission, all of them had mild hypertension with either casual systolic BP higher than 140 mm Hg or diastolic BP higher than 90 mm Hg. The diagnosis of stroke was made according to the World Health Organization criteria: rapidly developing clinical signs of focal or global loss of cerebral function with symptoms lasting more than 24 h, with no apparent cause other than vascular origin. All patients underwent computed tomographic scanning and magnetic resonance imaging to define the type and site of stroke. Twenty-five patients had cerebral hemorrhage (11 at putamen, 13 at thalamus, and 1 at brain stem), whereas 5 patients had cerebral infarction (2 at thalamus, 1 at cortex, and 2 at brain stem). Patients with secondary hypertension were excluded by physical examination, urinalysis, adrenal computed tomographic scan, and hormonal examinations including plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma catecholamine concentrations, and 24-h urinary excretions of 17-hydroxycorticosteroids and 17-ketosteroids. There was no evidence of heart failure, liver damage, or renal dysfunction in any of the patients. In the 24 patients, a long-acting calcium antagonist (5 mg of amlodipine) had been already administered, and was continued during the study.

Protocol

The study was performed with a prospective, randomized, cross-over design. The patients were allocated randomly to receive either losartan (50 mg once daily) or quinapril (10 mg once daily), in the morning for a 4-week period. These agents have similar pharmacodynamic and pharmacokinetic properties, and the doses prescribed have been shown to have similar efficacy. 10,11 Time to achieve peak plasma concentration is about 1 h after oral administration for losartan and 3 to 4 h for its active metabolite EXP3174. Elimination half-life of losartan is about 2 h and that of EXP3174 is 6 to 9 h. Quinapril is a nonsulfhydryl ACE inhibitor that is deesterified to its active metabolite quinaprilat. Time to achieve peak plasma concentration is about 1 h after administration for quinapril and 2 h for quinaprilat. Elimination half-life of quinaprilat is about 20 h. The trough/peak ratios of losartan and quinapril are both about 0.5. The patients were switched to the alternative agent for an additional 4 weeks. Thirty subjects maintained a constant activity pattern, which was composed of getting up at 6 AM and going to bed at 9 PM, and were subjected to specific diets arranged by the amount of salt (7 g of salt/day). Compliance to the prescribed diet was assessed by measurements of 24-h urinary sodium excretion. On the second day of admission, BP was measured at 6 AM in a recumbent position and blood was drawn from all subjects for the determination of serum creatinine, sodium and potassium, PRA, PAC, plasma norepinephrine concentration, and plasma epinephrine concentration.

On the last days of losartan and quinapril treatments, every 30-min noninvasive ambulatory BP and heart rate monitoring were performed for 24 h using the TM-2421 (A and D Co., Tokyo, Japan). The ambulatory data were calculated by the oscillometric method. All subjects were asked to record the time of daily activities including waking up and going to bed. In the present study, all subjects manifested no disturbance of sleep by the noise of the monitor. Fifteen hours from 6 AM to 9 PM were defined as daytime and 9 h from 9 PM to 6 AM as nighttime. On the last days of losartan and quinapril treatments, 24-h urine was collected for the measurements of urinary norepinephrine, epinephrine, and dopamine (DOPA). The nocturnal decreases in ambulatory BP and urinary catecholamines were calculated as (Daytime − Nighttime)/Daytime × 100%.

Laboratory Procedures

Plasma was separated by centrifugation at 4°C for 10 min, and stored at −80°C until the measurement of various items. Serum sodium and potassium ion concentrations were measured with a flame photometer. Serum creatinine level was measured by an autoanalyzer method. Norepinephrine, epinephrine, and DOPA concentrations were measured by high performance liquid chromatography. The PRA and PAC were measured by radioimmunoassay.

Statistical Analysis

All values were shown as mean ± one standard error (SEM). Differences in means were assessed by unpaired or paired Student t test for comparison of two variables. Differences between groups were analyzed by two-way ANOVA. A P value < .05 was evaluated as a statistically significant value.

Results

Ambulatory BP

As shown in Fig. 1A and Table 1, ambulatory systolic BP with losartan treatment was higher during daytime and
lower during nighttime. This circadian pattern of BP was also maintained with quinapril treatment, and there was no significant difference in the average of 24-h ambulatory diastolic BP between losartan (76.0 ± 2.5 mm Hg) and quinapril (78.0 ± 2.8 mm Hg) treatments (paired t test and two-way ANOVA). However, ambulatory diastolic BP with losartan treatment was significantly lower than that with quinapril treatment during nighttime, although there was no significant difference in the average of ambulatory diastolic BP during daytime. As a result, the nocturnal decrease in ambulatory diastolic BP was significantly greater with losartan treatment than with quinapril treatment as systolic BP (Table 1).

**Ambulatory Heart Rate**

The effects of losartan and quinapril treatments on ambulatory heart rate are shown in Fig. 1C and Table 1. The circadian pattern of heart rate was similar to that of ambulatory BP, and the average of 24-h ambulatory heart rate did not differ between losartan (67.8 ± 2.8 beats/min) and quinapril (66.8 ± 2.8 beats/min) treatments. There was no significant difference in ambulatory heart rate during daytime and nighttime and its nocturnal decrease rate between losartan and quinapril treatments.

**Urinary Norepinephrine, Epinephrine, and DOPA Excretions**

Urinary norepinephrine, epinephrine, and DOPA excretions during daytime were higher than those during nighttime. There was no significant difference in urinary norepinephrine, epinephrine, and DOPA excretions during daytime and nighttime between losartan and quinapril treatments. Table 1 shows the comparison of the nocturnal decrease rates in urinary norepinephrine, epinephrine, and DOPA excretions between losartan and quinapril treatments. The nocturnal decrease rate in urinary norepinephrine excretion was slightly but significantly greater with losartan treatment than with quinapril treatment. In contrast, there was no significant difference in the nocturnal decrease rates in urinary epinephrine and DOPA excretions between losartan and quinapril treatments.

**Discussion**

**Effect of Losartan and Quinapril on Ambulatory BP**

In the patients with essential hypertension, both losartan and ACE inhibitors have been shown to decrease BP throughout the day without changing the circadian rhythm of BP. In the patients with stroke, however, antihypertensive agents may exacerbate dysfunction of focal central nervous system when used at the acute phase. At the chronic phase of stroke, losartan and ACE inhibitors are the standard treatment for hypertension, and these drugs appear to provide similar benefits by blocking the
effects of angiotensin II and have the similar efficacy in lowering BP. In this study, we showed that in the patients with a previous history of stroke, the nocturnal decrease in BP was greater with losartan treatment than with quinapril treatment, despite no difference in ambulatory BP during daytime. One possible explanation for this finding is that the pressure decreasing effect of quinapril and its duration were lower and shorter than those of losartan. The averages of ambulatory systolic BP during 24 h and daytime were both lower by 6 and 4 mm Hg, respectively, with losartan treatment than with quinapril treatment. However, there was no statistically significant difference in the averages of ambulatory BP. These agents have similar pharmacodynamic and pharmacokinetic properties. Furthermore, the doses of these agents prescribed have been shown to have similar trough/peak ratios.10,11 These indicate that the diurnal pattern of BP is different between losartan and quinapril treatments in the patients with a history of stroke.

The nocturnal decrease in BP may cause intermittent global or focal central nervous system dysfunction in the elderly and in patients with cerebral artery stenosis. However, ACE inhibitors and angiotensin II antagonists were shown to shift the upper and lower limits of autoregulation of cerebral blood flow to the lower level of BP.14,15 Therefore, these agents seem to maintain focal cerebral blood flow even during the sleeping period. On the other hand, the level of nocturnal BP was associated with the development of organ damage. A lack of a nocturnal decrease in BP,16 defined as nondippers, was reported to progress organ damage more rapidly than in dippers.17 Thus, as shown in this study, the angiotensin II antagonist losartan seems to provide benefits not only in keeping focal cerebral blood flow but in recovering the normal circadian pattern of BP. The interaction between the treatment effects with losartan or quinapril and with a long-acting calcium antagonist may have to be considered when assessing the present results, as most patients (80%) were already taking a calcium antagonist before the study.

### Table 1. Daytime and nighttime averages and percent nocturnal decrease in parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daytime Average</th>
<th>Nighttime Average</th>
<th>Percent Nocturnal Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Losartan</td>
<td>Quinapril</td>
<td>Losartan</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130.9 ± 2.6</td>
<td>135.1 ± 2.6</td>
<td>122.6 ± 2.6†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80.0 ± 1.5</td>
<td>81.0 ± 1.6</td>
<td>74.7 ± 1.4†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.8 ± 1.4</td>
<td>68.5 ± 1.3</td>
<td>59.9 ± 1.3</td>
</tr>
<tr>
<td>Urinary NE (µg)</td>
<td>66.3 ± 7.2</td>
<td>64.9 ± 12.9</td>
<td>31.9 ± 3.8</td>
</tr>
<tr>
<td>Urinary E (µg)</td>
<td>9.0 ± 1.2</td>
<td>7.0 ± 0.8</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>Urinary DOPA (µg)</td>
<td>368.5 ± 39.6</td>
<td>479.7 ± 119.3</td>
<td>196.4 ± 25.6</td>
</tr>
</tbody>
</table>

BP = blood pressure; NE = norepinephrine; DOPA = dopamine; E = epinephrine.
* P < .01 vs quinapril; † P < .05.

### Effect on Sympathetic Nervous Activity

By measuring urinary norepinephrine excretion, we demonstrated indirectly that the nocturnal suppression of sympathetic nervous activity was not much but significantly different between losartan and quinapril treatments. Losartan and ACE inhibitors have different effects on local formation of angiotensin II and bradykinin. Losartan inhibits the effects of angiotensin II generated through both ACE-dependent and ACE-independent pathways at the site of AT1 receptor,6,17 whereas ACE inhibitors suppress the generation of angiotensin II only through ACE-dependent pathways and additionally accumulate bradykinin. Because both angiotensin II and bradykinin enhance norepinephrine release by a presynaptic mechanism,7,8 it is feasible that tissue concentrations of norepinephrine at the neuroeffector junction may be higher during ACE inhibitor treatment than during losartan treatment. The difference in the diurnal pattern of BP between losartan and ACE inhibitor treatments may be related to the difference in sympathetic nervous activity.

It still remains unclear whether a nocturnal decrease in BP in the patients with hypertension and a history of stroke may provide benefits in the secondary prevention of stroke. An angiotensin II antagonist seems to be a useful alternative agent to block the renin-angiotensin-aldosterone system in the patients in whom ACE inhibitors are not tolerated. It should be clarified whether angiotensin II antagonists are a fully effective substitute for ACE inhibitors in the patients with stroke.

### References


