A Comparison of Lisinopril with Enalapril by Monitoring Plasma Angiotensin II Levels in Humans

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Abstract—The present study was designed to examine and compare the acute effects of lisinopril (20 mg) and enalapril (10 mg) after a single oral administration on the inhibition of the renin-angiotensin system (RAS) in eight normal subjects. Serum concentration of lisinopril and enalaprilat, an active metabolite of enalapril, reached the respective maximal levels at 6 and 4 hr after administration of the drugs. At 24 hr, the serum concentration of lisinopril was higher than that of enalapril; thus the rate of disappearance of lisinopril was retarded, in comparison to that of enalapril. The reduction of serum angiotensin I converting enzyme (ACE) activity was consistent with the pattern of increase of concentration of the drugs in the serum. However, with these two drugs, the concentration of plasma ANG II was decreased in a similar manner, and it returned to the pretreatment level within 24 hr. Thus, there was no significant difference in ANG II levels throughout the 24 hr study between the lisinopril and enalapril treatment. The results indicate that a single administration of 20 mg lisinopril and 10 mg enalapril show similar potency for lowering the circulating ANG II level, although lisinopril exerts a more sustained inhibition of serum ACE activity. The measurement of ANG II provides useful informations for evaluating the efficacy of ACE inhibitors for the inhibition of circulatory RAS.

Angiotensin I-converting enzyme (ACE) inhibitors have been clinically used as the first choice for treatment of hypertension (1). It is considered that the pharmacodynamic action is mainly due to the inhibition of the renin-angiotensin system (RAS) (2). Although inhibition of ACE activity in the plasma has been conventionally used to estimate the extent of RAS blockade in the circulation, the change of ACE activity does not correlate with the blood lowering effect by ACE inhibitors (3-5). The ACE activity in the plasma provides limited information as a parameter for the activity of circulatory RAS. In the plasma, not only ACE, but also ANG I concentration contributes as a limiting factor for the production of ANG II. Nussberger (6) demonstrated that the concentration of plasma ANG II correlated with that of plasma ANG I under ACE inhibition, supporting the contention that ANG I is one of the determinants of plasma ANG II levels.

Accurate measurement of plasma ANG II levels is difficult because its concentration is very low (7), and the antibody raised against ANG II cross-reacts with ANG I and a variety of ANG II metabolites (8). Recently, the sensitivity and specificity for quantification of ANG II have been improved by using Sep-Pak extraction and HPLC separation (9, 10), and this method has made it possible to estimate accurate ANG II levels.

Lisinopril (10) and enalapril (11) are both long acting drugs and maintain their hypotensive action with oral administration once a day. Lisinopril is a lysine analogue of enalaprilat which is an active metabolite of enalapril (12). Although both drugs have physico-chemical properties (12) and inhibitory kinetics that are similar to ACE in
vitro (13) and in vivo (14), lisinopril differs from enalapril in that it is absorbed more slowly than enalapril, and it requires no bioactivation (15). These differences may affect the time course of plasma ANG II levels after the drug administration. In the present study, the selected dose of lisinopril (20 mg) was twice that of enalapril (10 mg), because the clinically recommended dose of lisinopril for patients with no complications ranges between 20–80 mg/day (16), while enalapril is used in a dose range between 10–40 mg/day (17). The present study was designed to examine and compare the effects of the two drugs on the time course of ANG II and other components of RAS during the 24 hr after a single administration.

Materials and Methods

Eight healthy, normotensive volunteers (age: 32±1 years, body weight: 68±3 kg) participated in the study. The nature of the experiment was explained to each subject, and their written informed consents were obtained. The subjects were maintained on a fixed metabolic diet throughout the study. Meals were given at 08:00, 12:00 and 18:00 hr. Subjects arrived at the Shionogi Biomedical Laboratory by 07:00 hr. Blood was drawn prior to drug administration at 09:00 hr (time 0) and 2, 4, 6, 8, 12, 24 hr later. At each time, the subjects were kept for 30 min in the recumbent position before blood sampling. Capsules containing 20 mg of lisinopril or 10 mg of enalapril were prepared by the manufacturer. A single capsule was administered orally with 1 50 ml of tap water at 09:00 hr. Each subject received both compounds at an interval of 2 months in a single-blind crossover fashion. Plasma concentrations of ANGs I and II were measured with an extraction system that used a Sep-Pak column followed by HPLC and the RIA reported previously (9, 10). A commercial kit was used to assay serum ACE activity (Fujirebio, Ltd., Tokyo) (18). The serum drug concentrations of enalaprilat and lisinopril were measured by the method of least squares. Difference and correlation coefficients were considered statistically significant when P<0.05.

Results

Figure 1 shows the time course changes of drug concentrations of enalaprilat and lisinopril. The enalaprilat reached its peak at the 4th hr and almost disappeared after 24 hr. The concentration change of lisinopril was similar to that of enalaprilat until 4 hr, but reached its peak at 6 hr and remained at 20% of the peak concentration after 24 hr. Table 1 indicated the time course changes of ACE activity, PRA, ANG I, ANG II, and angiotensinogen after administration of lisinopril or enalapril. With lisinopril and enalapril, ACE activity was significantly reduced from the 2nd to 12th hr after the drug administration, and the activity was still inhibited in the lisinopril treated group after 24 hr while the activity returned to the pretreatment value in case of enalapril (table 1). These differences were significant at 8–24 hr (P<0.05), when the lisinopril- and the enalapril-administered groups were compared at the same time points. The maximal inhibitions of ACE activity after lisinopril and enalapril intakes were 94±9% and 84±7% of the pretreatment level, respectively.

By each drug intake, ANG II levels were suppressed, and the concentration of ANG II returned to the pretreatment value after 24 hr.
Table 1. Time course of each parameter after oral administration of lisinopril or enalapril

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug</th>
<th>Time after administration (hr)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>ACE activity (mU/ml)</td>
<td>L</td>
<td>13.2±1.24</td>
<td>5.69±1.8*</td>
<td>1.50±0.29*</td>
<td>0.99±0.14*</td>
<td>1.06±0.16*</td>
<td>1.70±0.34*</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>13.3±1.34</td>
<td>5.06±1.15*</td>
<td>2.15±0.48*</td>
<td>2.55±0.32*</td>
<td>3.78±0.40*</td>
<td>6.85±0.76*</td>
</tr>
<tr>
<td>ANG II (pg/ml)</td>
<td>L</td>
<td>6.76±1.59</td>
<td>3.46±1.06</td>
<td>1.84±0.45*</td>
<td>2.54±0.70*</td>
<td>2.10±0.73*</td>
<td>4.10±1.32</td>
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<tr>
<td></td>
<td>E</td>
<td>7.29±2.13</td>
<td>3.71±0.81</td>
<td>2.89±0.41*</td>
<td>3.79±0.63</td>
<td>2.59±0.45*</td>
<td>5.76±1.28</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>L</td>
<td>1.97±0.39</td>
<td>3.01±0.61</td>
<td>6.26±1.63</td>
<td>10.8±3.0*</td>
<td>8.25±3.02</td>
<td>12.4±3.3*</td>
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<tr>
<td></td>
<td>E</td>
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<td>3.66±0.70</td>
<td>6.13±1.27</td>
<td>9.37±3.10*</td>
<td>4.54±1.01</td>
<td>5.04±0.93</td>
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<tr>
<td>ANG I (pg/ml)</td>
<td>L</td>
<td>30.2±6.81</td>
<td>31.2±7.70</td>
<td>97.2±30.1</td>
<td>161±56.0*</td>
<td>112±48.1</td>
<td>172±46.0*</td>
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<tr>
<td></td>
<td>E</td>
<td>30.2±15.0</td>
<td>41.5±9.18</td>
<td>73.9±14.3</td>
<td>118±30.2*</td>
<td>54.7±14.1</td>
<td>80.8±15.9</td>
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<tr>
<td>Angiotensinogen (pg/ml)</td>
<td>L</td>
<td>1.22±0.13</td>
<td>1.21±0.12</td>
<td>1.19±0.12</td>
<td>1.14±0.12</td>
<td>1.13±0.11</td>
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<tr>
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<td>E</td>
<td>1.38±0.10</td>
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<td>1.27±0.08</td>
<td>1.26±0.09</td>
<td>1.25±0.09</td>
<td>1.20±0.10</td>
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</table>

Asterisks refer to comparisons with the 0 time control value, and Dunnett’s test was used to assess the significance of variables. *P<0.05. L: lisinopril, E: enalapril.
hr. Lisinopril had a tendency to be more potent than enalapril in lowering plasma ANG II levels, although a statistically significant difference was not observed at all time points. The maximal inhibition after lisinopril and enalapril intakes were 78±7% and 64±6% of the pretreatment level, respectively.

Fig. 1. Time course of drug concentrations of lisinopril (●) and enalaprilat (○) after a single oral administration of 20 mg of lisinopril and 10 mg of enalapril, respectively. Enalaprilat is an active metabolite of enalapril. Values represent the means±S.E. of observations made in 8 normal subjects.

Fig. 2. Correlations between the serum levels of drug and the percent inhibition of serum ACE activity following a single oral dose of 20 mg lisinopril (a) and 10 mg enalapril (b). The correlation coefficients were derived from 48 points obtained between 2 and 24 hr. The correlation coefficient was 0.89 between the serum levels of lisinopril and the percent inhibition of serum ACE activity after lisinopril intake. The correlation coefficient was 0.90 between the serum levels of enalaprilat and the percent inhibition of serum ACE activity after enalapril intake. These values were statistically significant (P<0.01).

PRA and ANG I increased by administration of both drugs and the increase by lisinopril was more than that by enalapril (Table 1). After 24 hr the PRA and ANG I values increased to 5 times and 2 times the respective pretreatment values in the lisinopril and enalapril treated groups, respectively. How-
ever, these differences between the two drug administrations were significant only at 12 hr in PRA (P<0.05).

Although the concentration of angiotensinogen was not changed significantly after either drug intake, there was a tendency for the concentration to fall with time.

Figure 2 shows the relationship between drug concentration and ACE activity. Significantly inverse correlations were observed between lisinopril concentration and percent inhibition of ACE activity (r=0.89, P<0.01) and between enalaprilat concentration and percent inhibition of ACE activity (r=0.90, P<0.01).

Figure 3 shows the relationship between PRA and ANG I concentration. Significant correlations were observed in both lisinopril (r=0.93, P<0.01) and enalapril (r=0.80, P<0.01) administration.

**Discussion**

The present study carried out to compare the effects of two ACE inhibitors on circulatory PRS. The inhibition of ACE activity in the serum was more persistent with lisinopril than with enalapril. This result corresponded to that reported by Hodsmam et al. (22). The sustained inhibition of ACE by lisinopril is based on the maintenance of the higher drug concentration after the drug intake as was evident in Fig. 1. Indeed, the ACE activity was inversely correlated with the concentrations of lisinopril and enalaprilat (Fig. 2).

This is consistent with the contention that lisinopril has a more sustained efficacy for RAS blockade than enalapril. However, measurement of ANG II demonstrated that the two ACE inhibitors showed similar patterns of time course change and levels of ANG II at all time points. Thus, lisinopril and enalapril showed a similar potency for inhibition of RAS in the circulation at least with the doses used in the present study. This clearly indicates that when the role of circulating ANG II is evaluated for some pharmacodynamic actions by ACE inhibitors, serum ACE activity can not be an indicator for evaluating the RAS blockade, but measurement of circulating ANG II is essential.

The difference of patterns of ACE inhibition and ANG II concentration is probably due to the fact that plasma II level is determined not only by ACE activity, but ANG I concentration affects the ANG II concentration. The Km (Michaelis-Menten constant) value for ACE is 30 nmol/ml (23), and this value is approximately one thousand times the concentration of plasma ANG I. Therefore, the enhanced concentration of ANG I as a result of
ACE inhibition is also determinant of ANG II production, provided that ACE is not completely inhibited. Indeed, elevated ANG I levels by ACE inhibitors seem to cause the difference in patterns of ACE inhibition and ANG II concentration.

The concentration of ANG I increased linearly with the elevated PRA (Fig. 3). PRA is determined by the concentration of plasma angiotensinogen and enzymatic activity of renin in the plasma. As the angiotensinogen level was maintained at a similar level during 24 hr (Table 1), a change of PRA indicates a change in the enzymatic activity of renin. The increased PRA seems to be attributable to the reduction in ANG II, a potential factor in the feedback mechanism of renin release. Twenty-four hours after lisinopril administration, PRA remained significantly elevated above the basal value, although the ANG II level returned to the basal value. Although we do not know the mechanism for the increase in PRA, it may be explainable by “tissue” RAS (2, 24).

Several investigators (25, 26) reported that when ACE inhibitors are administered, tissue ACE activity is still inhibited although plasma ACE activity returned to the pretreatment level in animal experiments. The ANG II level around the juxta-glomerular cells might have been kept at a low level even when plasma ANG II level returned to the pretreatment level. The low level of ANG II around the juxta-glomerular cells might have stimulated renin release. Further studies are required to elucidate the mechanism, for example, we must determine the locally generated ANG II level.

In conclusion, we indicated that a single administration of 20 mg lisinopril and 10 mg enalapril show similar potency for lowering the circulating ANG II level, although lisinopril exerts a more sustained inhibition of serum ACE activity. The measurement of ANG II provides useful information for evaluating the efficacy of ACE inhibitors for inhibition of circulatory RAS.

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References


