Effects of Losartan on Blood Pressure, Plasma Renin Activity, and Angiotensin II in Volunteers

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Losartan is an orally active, nonpeptide angiotensin II (Ang II) (site-1) receptor antagonist. We conducted a multiple-dose study in healthy male volunteers to investigate the tolerability, blood pressure effects, and changes in plasma renin activity (PRA) and plasma Ang II concentration associated with once-daily administration of 100 mg losartan for a week. Subjects were studied on a standardized sodium diet (24-hour urinary sodium excretion, 98±37 [SD] mEq per 24 hours on the placebo run-in day). Measurements of blood pressure, heart rate, PRA, Ang II, and aldosterone were taken during a placebo run-in day and after single and multiple (7 days) daily doses of losartan (100 mg, n=10) or placebo (n=4). Ang II was measured specifically by high performance liquid chromatography coupled with radioimmunoassay. In subjects given losartan, respective decreases (systolic/diastolic) from run-in in supine blood pressure 6 hours after dosing were (mean±SD), compared with the placebo run-in day, first dose: -8.8±9.6/-6.8±5.0, last dose: -11.6±8.9/-7.0±4.8 mm Hg (p<0.05 for all changes). At this 6-hour time point, corresponding increases from run-in in PRA were from 1.2±0.6 to 12.0±6.3 (first dose) and 9.6±4.9 (last dose) ng angiotensin I per milliliter per hour and in Ang II were from 4.3±1.7 to 72.4±33.1 and 45.7±14.1 pg/mL. All changes in PRA and Ang II were statistically significant within the losartan-treated group, and the biochemical changes were significantly greater than those in the placebo-treated group. The increment in Ang II was less after the last dose than after the first (p<0.05). The drug was well tolerated by all subjects. These data indicate that, under the conditions of this study, losartan administration (100 mg/day for eight doses over 9 days) results in treatment-related decreases in blood pressure and increases in PRA and Ang II octapeptide. (Hypertension 1993;21:704-713)

KEY WORDS • losartan • DuP 753 • angiotensin II • plasma renin activity • receptors, angiotensin

Losartan (Figure 1) is a potent, orally active nonpeptide angiotensin II (Ang II) antagonist.1-4 The drug is being investigated as therapy for hypertension and heart failure and is anticipated to be a more specific mechanism for inhibiting the renin-angiotensin system than angiotensin converting enzyme inhibitors. Early clinical investigation of losartan has shown single and multiple doses up to 40 mg to be well tolerated and pharmacologically active, with doses of 10 mg or greater blocking pressor responses to exogenous angiotensin I (Ang I) and Ang II.5,6 Also, through blockade of Ang II receptors in the juxtaglomerular apparatus, which inhibits renin release, losartan administration results in dose-related increases in plasma renin activity (PRA) and immunoreactive Ang II.5,6 Studies have also been completed that demonstrate the tolerability of single doses up to 300 mg and more than 90% blockade of responses to exogenous Ang II by oral doses of 80-120 mg (unpublished data, Du Pont Merck Pharmaceutical Corp. and Merck Research Laboratories). In these studies, effects of losartan on resting blood pressure and heart rate in healthy subjects have not been readily apparent. In addition, pharmacokinetic analyses have indicated that, although losartan has a relatively short half-life (unpublished data, Du Pont Merck Pharmaceutical Corp. and Merck Research Laboratories), the predominant circulating form of the drug is a carboxylic acid metabolite (E-3174, Figure 1) that is more potent and has a longer half-life than losartan.2,3 In fact, the time course of increases in PRA and plasma Ang II concentration and blockade of responses to exogenous angiotensin is better correlated to levels of the metabolite than to levels of parent drug (see Reference 5 and unpublished data, Du Pont Merck Pharmaceutical Corp. and Merck Research Laboratories).

The general objective of the present study was to further investigate the effects of single and multiple doses of losartan in healthy male volunteers. Of interest were the following specific objectives: 1) confirming the tolerability and absence of hemodynamic effects in healthy subjects and 2) assessing changes in PRA and Ang II concentrations after single and multiple doses, during standardized sodium intake, using a highly specific radioimmunoassay (RIA) for Ang II coupled with high performance liquid chromatography (HPLC).
Methods

Study Design

This was a double-blind, placebo-controlled, parallel study that was divided into three clinical phases: run-in, first-dose, and multiple-dose (Figure 2). In each phase, subjects were carefully studied during an inpatient testing day when blood pressure and heart rate were carefully monitored and blood was collected at defined intervals for measurement of PRA, plasma Ang II concentration, and plasma aldosterone concentration. The first phase was a single-blind placebo run-in day (first testing day). The second phase (next day) was a double-blind single-dose day (second testing day) during which subjects received either a single oral 100-mg dose of losartan \( (n=10) \) or a single dose of placebo \( (n=4) \), with treatment assignment according to an unbalanced, random-allocation schedule. Forty-eight hours later, subjects entered the third, double-blind multiple-dose phase, during which those previously allocated to receive losartan continued to take the drug, 100 mg once daily for 7 consecutive days (a total of eight doses over 9 days), and those allocated to placebo continued to receive placebo. The third testing day coincided with the 24-hour period after administration of the eighth (and last) dose of the double-blind study drug.

For each of the three testing days, subjects were sequestered at the clinical research unit the evening before dosing and fasted from midnight that night until 3 hours after the dose. Subjects were fed 3 and 6.5 hours after dosing on the testing days. Subjects remained in the unit the night after each testing day. On other study days, all doses of the study drug were administered under direct observation, at the same time (±30 minutes) each day, with 250 mL water and 30 minutes before a meal. Beginning 3 days before the run-in day and continuing through the third testing day (a total of 13 days), subjects were provided a diet estimated to contain 135–165 mEq sodium and 70–90 mEq potassium per 24 hours. The purpose of the diet was to standardize sodium intake to aid in interpretation of changes in PRA, Ang II concentration, and blood pressure. However, we did not attempt to assure that subjects were truly in "balance" on the diet before testing. To monitor the diet, we made 24-hour urine collections during the run-in day and after the first and last dose of losartan. Respectively, on each of these collections, urinary sodium excretion (mean±SD) in subjects given losartan/placebo were 98±37/93±8, 66±16/46±11, and 85±21/75±23 mEq per 24 hours. Based on these sodium excretion rates, the subjects appear to have been moderately sodium restricted, as indicated by the 0.7±0.6 ng Ang I per milliliter per hour \( (p<0.01) \) increase in predose PRA from run-in to first-dose days in the losartan group (Table 2).

Fourteen male subjects were enrolled, aged 18–31 (mean, 24.4) years and weighing 161±22 lb (within ±20% of ideal body weight). Subjects were in general good health, without excessive intake of caffeine (≤4 cups of coffee per day) or tobacco (≤10 cigarettes per day) and with sitting blood pressure ≤135/85 mm Hg. Before the study was begun, the protocol and consent form were reviewed and approved by the Institutional Review Board of Thomas Jefferson University. All
subjects provided written, informed consent before enrollment into the study. Subjects were studied in two groups of seven subjects each.

**Study Procedures and Assay Methods**

**Blood pressure and heart rate measurements.** On each testing day, supine (average of two measurements after 5 minutes in a supine position) and standing (single measurement after 2 minutes of standing) blood pressure and heart rate were measured at defined intervals after dosing using a Dinamap (Critikon, Tampa, Fla.) automated sphygmomanometer. In evaluating blood pressure changes after losartan or placebo, the first 8 hours of each testing day were analyzed statistically.

**Plasma renin activity and aldosterone assays.** For measurement of PRA and aldosterone, samples were collected in precooled syringes containing ethylenediaminetetraacetate (EDTA, 1.5 mg/mL whole blood) and quickly centrifuged at 4°C. Plasma was frozen in 1-mL aliquots at −20°C until time of assay. Plasma aldosterone levels were measured by solid-phase RIA (Coat-a-count, Diagnostic Products, Los Angeles, Calif.). Briefly, 0.2 mL plasma was pipetted into antibody-impregnated tubes, followed by addition of 1 mL 3H-aldosterone. The tubes were incubated at 37°C for 3 hours and decanted, and bound radioactivity was measured by gamma radiation counting. Sample values were calculated from comparison with log-logit calibration curves created using increasing amounts of standards (0−1,200 pg/mL). The sensitivity of the assay was approximately 16 pg/mL.

PRA was determined by a modification of the method described by Kodish and Katz. Plasma aliquots (300 μL) were added to two separate ice-cold tubes containing 200 μL of 0.12 M maleate buffer, pH 6.0, which contained the protease inhibitors phenylmethylsulfonyl fluoride (0.1 mM), soybean trypsin inhibitor (4 mg/mL), and benzamidine (1 mM). One assay tube remained in an ice bath, and the other was placed in a 37°C bath for 2 hours. At the end of this period, 200-μL aliquots from each tube were transferred for RIA of renin.

Specific renin activity was determined by subtracting the values obtained in the cooled assay tube from those at 37°C. The sensitivity for the assay was approximately 10 pg Ang I, and values are reported as nanograms Ang I per milliliter per hour.

**Angiotensin II assay.** Ang II concentration in plasma was measured by modification of published methodology that couples RIA with a relatively specific antibody for Ang II with HPLC separation of angiotensin peptides. For these measurements, blood was placed into a prechilled tube containing (final concentrations) enalaprilat (3.6 μM), 1,10-phenanthroline (2.5 mM), and K₂EDTA (1.5 mg/mL), cooled thoroughly, centrifuged at 4°C, and plasma stored frozen at −20°C until analysis. Thawed samples (2.0 mL) were spiked with 125I-Ang II as internal standard and chromatographed on hexane-prewashed, preconditioned 500-μg C8 disposableBond Elute columns (Analytech International, Harbor City, Calif.). Angiotensin peptides were eluted with 2×1-mL 50% acetonitrile/50% water, containing 0.1% trifluoroacetic acid, and were dried, resuspended in 300 μL 20% acetonitrile/0.1% trifluoroacetic acid, and filtered.

The filtered samples were chromatographed on a 4.6×150 mm Dynamax C8 reversed-phase HPLC column (Rainin Instrument Co., Woburn, Mass.) using a flow rate of 1 mL/min at 45°C. Angiotensin peptides were separated with a 20-minute linear gradient from 20% to 35% acetonitrile containing 0.1% trifluoroacetic acid adjusted to pH 4.0 with NH₄OH. Retention times (minutes) for various angiotensin peptides were: Ang I, 16.5; [Des-Asp]Ang I, 17.4; Ang II, 11.9; angiotensin III ([Des-Asp]Ang II), 13.2; Ang II-(3–8) hexapeptide, 13.5; Ang II-(4–8) pentapeptide, 10.8; and 125I-Ang II, 16. HPLC fractions (0.5 mL) were dried, reconstituted with 200 μL buffer containing 10 mM potassium phosphate, 1 mM EDTA, 0.25 mM thimerosal, and 0.1% (wt/vol) gelatin, pH 7.3, and an aliquot was counted for determination of overall recovery. Ang II was quantitatively measured by competitive binding RIA using a commercially available Ang II antisera (Amersham No. RPN1771). The RIA reaction mixture was incubated overnight at room temperature and treated with dextran-coated charcoal to separate bound and unbound Ang II. The supernatant was counted, and the Ang II values were read off a standard curve made from solutions of known (0–96 pg per tube) Ang II concentration. Day-to-day precision for plasma control material yielded coefficient of variation values of 16% at 18.3 pg/mL (n=15) and 13% at 5.1 pg/mL (n=12). Cross-reactivity of Ang II antisera with angiotensin peptides was: Ang II, 100%; angiotensin III, 53%; Ang I, 0.1%; Ang II-(3–8), 11%; and Ang II-(4–8), 15%.

**Clinical tolerability assessment.** The tolerability of losartan in each subject was monitored by periodic assessment of complete blood counts, chemistry panels, urinalyses, and electrocardiograms. On each testing day, 24-hour urine was collected for measurement of electrolyte, protein, and creatinine excretion.

**Data Analysis**

In planning this study, published data on variability of PRA and Ang II in healthy volunteers given enalapril dose were used to determine sample size. For the purposes of comparing multiple-dosing results with single-dosing results, the study had 80% power (a=0.05, two-tailed) to detect respective increments in PRA and Ang II concentration of 4.5 ng Ang I per milliliter per hour and 4.3 fmol Ang II per milliliter (approximately 4.3 pg/mL).

The general approach to the statistical analysis was to compare measurements collected after the first and last dose of losartan with measurements at the corresponding times after dosing on the placebo run-in day. Multiple-dosing results were then compared with single-dose results. For measurements of PRA, Ang I, and aldosterone, all time points were analyzed. For blood pressure and heart rate, measurements during the first 8 hours after dosing on each day were analyzed, with baseline for supine measurements on each day defined as the average of measurements made at the time of dosing and 15 minutes before dosing. A single measurement of standing blood pressure and heart rate, immediately before dose, was baseline for changes in standing blood pressure and heart rate. For the purposes of reporting the results, run-in refers to the single-blind placebo run-in day; first dose is the period after the first...
Statistical analysis between the two groups showed some statistically significant (or nearly significant) differences between treatments at the times of apparent maximal effect: hours 3 ($p<0.05$ for last dose), 5 ($p<0.01$ for first dose, $p=0.07$ for last dose), and 6 ($p<0.05$ for first and last dose) for supine systolic blood pressure, and hour 5 ($p<0.01$ for first and last dose) for supine systolic blood pressure. During the 8-hour observation period, particularly after the first dose, supine heart rate (Figure 4) tended to increase more in the losartan than placebo group. It was noted that, during the run-in day, supine heart rate was stable in both groups but significantly higher in the placebo group at 1, 2, 4, and 6 hours after single-blind placebo. Together, these data suggest a modest blood pressure-lowering effect of losartan, under the conditions of this study.

Similar trends to those seen for supine blood pressure were apparent for mean standing blood pressure measurements (not shown). For example, the change in standing blood pressure 6 hours after dosing was $-14\pm12/-7\pm12$ and $-10\pm10/-6\pm9$ mm Hg for first and last dose, respectively, in the losartan group, and $0.3\pm10/-1\pm7$ and $-10\pm10/-1\pm10$ mm Hg at corresponding times in the placebo group. These effects are generally similar to the changes in supine blood pressure summarized in Table 1. On the average, standing heart rate changes within groups, relative to the placebo day, tended to be greater in the losartan group than in the placebo group (Figure 4), with effects most apparent after the first dose of losartan. These results are consistent with the supine hemodynamic changes described above (Table 1).

### Renin-Angiotensin II-Aldosterone System Responses

Earlier reports at lower doses\(^6\) indicated that losartan administration is associated with sustained, dose-
related increases in PRA and Ang II. However, Ang II was measured by RIA without separation of peptides to confirm that observed increments were in the Ang II octapeptide. It was therefore of interest to determine the level of stimulation of PRA after single- and multiple-dose administration of losartan using HPLC to separate the Ang II octapeptide from Ang I and smaller peptide fragments. Table 2 summarizes the renin-angiotensin-aldosterone system measurements during the single-blind run-in placebo day and the changes from these measurements before (-1 hour) and after (6, 6.5, and 24 hours) dosing with the first and last doses of double-blind losartan or placebo. As with the analysis of blood pressure and heart rate, mean change is shown in measurements on the “dosing” days from the run-in day. Also included in the table are the differences between first and last doses. Figure 5 depicts the changes in supine measurements of PRA and Ang II. With respect to both supine and standing measurements of PRA and Ang II, clinically meaningful and statistically significant increases from run-in were noted within the losartan group and between the losartan and placebo groups. Of note, the significant increase in predose PRA and Ang II from run-in to first dose in the losartan group was not different from the similar increases in the placebo group. Presumably, as indicated above, this increment is secondary to modest sodium restriction resulting from the diet provided to the volunteers. Plasma aldosterone levels did not change appreciably during the study.

Several other observations are relevant to these data. As indicated in Table 2, the 6.5-hour renin-angiotensin-aldosterone system measurements were made in samples collected after 30 minutes of ambulation. With respect to PRA, during the run-in day, there was the expected increase in mean activity of 1–2 ng Ang I per milliliter per hour (approximately doubling) from supine to standing positions. As indicated by the changes from run-in to treatment days, this absolute postural increment in PRA was maintained during the double-blind portion of the study. A similar postural increment in Ang II was noted during the run-in day and after the last dose of losartan. Six to 6.5 hours after the first dose of losartan, the postural increment in mean Ang II concentration was not apparent.

Six hours after dosing, PRA did not change significantly from first to last dose (-2.5±6.4 ng Ang I per milliliter per hour, p=NS). In contrast, the mean change in Ang II concentration was significantly less after the last dose compared with the first dose (−26.7±35.2 pg/mL, p<0.05), suggesting some attenuation of this aspect of the response to losartan after several days of administration.

To investigate the relation between PRA and Ang II during the study, we initially constructed a scatterplot of supine Ang II concentration versus supine PRA 6 and 24 hours after single-blind placebo and after the first and last dose of each double-blind treatment (Figure 6). In general, this plot suggested a relation between Ang II
FIGURE 4. Line graphs show mean changes in supine (top panels) and standing (bottom panels) heart rates after first (––O) and last (––●) dose of placebo (right panels) and losartan (left panels), 100 mg once daily for eight doses over 9 days. Shown are changes (numbers in parentheses indicate reductions) from the corresponding time after dosing during the placebo run-in day (see Table 1 for statistical analysis of supine measurements). *p<0.05 for within-group change, losartan-treated subjects only; arrows on placebo graphs indicate where the change after losartan was significantly different (p<0.05) from that after placebo, after the first dose (filled arrow) or last dose (open arrow). bpm, Beats per minute.

and PRA. It is apparent from this plot that Ang II levels relative to PRA in four subjects at 6 hours after the first dose are elevated from the other points, suggesting greater increments in Ang II for each unit of PRA. To explore this further, we calculated the ratio of Ang II to PRA for each of these points. The geometric mean ratios of Ang II to PRA are summarized in Figure 7. A statistical analysis of the change in these ratios shows significant increases within the losartan group 6 (p<0.05) and 24 (p<0.01) hours after the first dose of losartan. In one extreme, one subject had ratios of 2.9 6 hours after placebo, 16.1 after his first dose, and 10.2 6 hours after his last dose of losartan. By the last dose of losartan, on the average, ratios of Ang II to PRA had returned toward baseline, being significantly less 6 hours after the last dose than 6 hours after the first dose (p<0.05).

Tolerability

As in any early study of a new drug, it was also important to carefully evaluate subjects for untoward consequences of study drug administration. Subject tolerability was monitored by regular assessment of clinical laboratory tests (complete blood count, chemistry panel, and urinalysis), by electrocardiogram, and by observation and questioning for clinical adverse events. Analysis of serum chemistry panels showed no significant (p≤0.05) within-group or between-group changes in any of the measured analyses during the study (the chemistry panel consisted of measurements of urea nitrogen, creatinine, total bilirubin, alanine and aspartate aminotransferases, alkaline phosphatase, lactate dehydrogenase, glucose, total protein, sodium, potassium, chloride, bicarbonate, calcium, and inorganic phosphorous). Approximately 600 mL blood was collected during the entire 10-day study. Presumably as a result of this blood loss, at the time of the poststudy evaluation, hemoglobin had decreased approximately 2 g/dL and hematocrit had decreased approximately six percentage points in subjects given either losartan (p≤0.01 within this group) or placebo. Urinalysis results showed no remarkable changes. No clinically significant changes in electrocardiographic intervals or interpretation were noted in any subject.

Clinical adverse events were mild and nonspecific, including one episode of loose bowel movements in one subject, epigastric discomfort in another individual, and several occurrences (four subjects) in which blood pressure decreases from supine to standing position were noteworthy but asymptomatic (e.g., supine: blood pressure, 102/46 mm Hg; heart rate, 50 beats per minute; 2 minutes standing: blood pressure, 70/50 mm Hg; heart rate, 70 beats per minute). One subject reported superficial peeling of his palms beginning during the first several days of losartan administration. No local symptoms (such as burning, itching, or exudate) were associated with these findings, which resolved over several weeks. However, this subject also had evidence of
Table 2. Renin-Angiotensin-Aldosterone Responses to Losartan and Placebo

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<th>Day</th>
<th>Treatment</th>
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<th>Hour 6</th>
<th>Mean measurement (±SD)</th>
<th>Hour 6.5</th>
<th>Mean measurement (±SD)</th>
<th>Hour 24</th>
<th>Mean change (±SD)</th>
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<td>10.1±49.1</td>
<td>36.1±78.3</td>
<td>82.9±44.2*</td>
<td></td>
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<tr>
<td>first dose</td>
<td>Losartan</td>
<td>82.9±53.0</td>
<td>52.6±62.0</td>
<td>132.2±61.8</td>
<td>103.8±84.4</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>23.2±68.7</td>
<td>-10.5±15.0‡</td>
<td>-14.7±67.0</td>
<td>52.6±78.7‡</td>
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<td></td>
<td>Run-in to</td>
<td>32.8±21.7</td>
<td>-4.7±28.3</td>
<td>-3.7±41.7</td>
<td>-34.4±75.8</td>
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<tr>
<td>last dose</td>
<td>Losartan</td>
<td>-1.2±51.2</td>
<td>-20.6±53.2</td>
<td>-50.9±112.1</td>
<td>-30.3±64.6</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>-50.1±52.4</td>
<td>-57.3±65.1</td>
<td>-135.8±63.1</td>
<td>-138.2±151.0</td>
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</table>

Ang I, angiotensin I. Values are mean±SD measurements on the run-in day and changes from run-in to first dose (day 1) and last dose (day 9) and from first to last dose at corresponding times after dosing. n=10 for losartan (100 mg); n=4 for placebo. Measurements at Hour 6.5 were taken after 30 minutes ambulation.

*p≤0.01, mean changes from run-in or first to last dose.

fp≤0.01, losartan vs. placebo.

4.05<p≤0.10, 6p≤0.05, mean changes from run-in or first to last dose.

hemolysis (schistocytes, crenated red blood cells) on his peripheral smear during the treatment period without decreases in haptoglobin, hemoglobinuria, increases in lactate dehydrogenase, or decreases in hemoglobin or hematocrit (other than as expected in such a study). These events were judged to be of uncertain relation to administration of losartan.

Discussion

In summary, losartan was found to be sufficiently well tolerated at 100 mg once daily to permit use of this dose in future studies. Modest decreases of blood pressure were noted during losartan administration, which indicate that, in healthy men, Ang II can play a role in the maintenance of resting blood pressure. However, these observations were made under conditions of modest sodium restriction (based on 24-hour urinary sodium excretion and small increases in PRA before administration of double-blind losartan or placebo). The extent to which this study condition influenced our results cannot be determined from this exploratory study. Blockade of endogenous Ang II was indicated by clearly defined increases in PRA and concomitant increases in plasma Ang II concentration.

Effects on aldosterone concentration in blood were not apparent, presumably because of the complex mechanisms known to control aldosterone release.16,17 Based on prior data5-6 and the known capacity of endogenous Ang II to act on a feedback receptor on the juxtaglomerular apparatus,18-20 it was anticipated that losartan administration would result in an increase in PRA and concomitant increases in plasma Ang II concentration.
and last 100-mg dose of losartan. The methodology used specifically measures Ang II octapeptide, indicating that observed increments reflect changes in the concentration of the most biologically active peptide. The magnitude of the change was greater 6 hours after dosing, compared with 24 hours. The data also indicate that the level of stimulation of PRA and Ang II is slightly less after the last than the first dose, consistent with the hypothesis that the magnitude of the initial response is related to discharge of stored renin from the juxtaglomerular apparatus, as has been shown in animals given angiotensin converting enzyme inhibitors. This differs somewhat from prior observations. However, study conditions (i.e., sodium balance), losartan dose, and methodology for measurement of Ang II also differed between the studies.

The implications of these increases in PRA and Ang II cannot be determined from this study in healthy volunteers. Studies in hypertensive patients are required to determine whether similar increases are noted

![Figure 5](image-url)

**Figure 5.** Bar graphs show mean change from the corresponding time after dosing on the run-in day of plasma renin activity (top panels) and plasma angiotensin II concentration (bottom panels) in subjects allocated to receive losartan 100 mg daily (left panels) and placebo (right panels) for eight doses over 9 days. In each panel, changes after the first and last dose of double-blind therapy are shown. Solid bars indicate changes from 1 hour predose on the run-in day to 1 hour before the first and last dose. Shaded bars indicate corresponding changes 6 hours after dosing. Open bars indicate changes 24 hours after dosing. *p≤0.01 vs. change in placebo group. AI, angiotensin I.

![Figure 6](image-url)

**Figure 6.** Scatterplot shows supine plasma angiotensin II and plasma renin activity measurements in subjects given losartan and placebo (inset).
in this target population. Furthermore, losartan is a selective antagonist of only a single Ang II binding site,"22-25 which mediates all known physiological effects of angiotensin. It is not known whether unblocked effects of increased Ang II at other binding sites are of any clinical consequence to the safety profile and hemodynamic effects of losartan. In the absence of long-lasting Ang II blockade, increases in plasma Ang II concentration of the magnitude demonstrated would be expected to have hemodynamic activity.14,15

In general, a relation between PRA and Ang II could be defined; the ratio of Ang II concentration to PRA was assumed to be an index of this relation. It was of interest that this ratio was higher after the first dose of losartan, when the greatest increases in Ang II were noted, than during the run-in day and after the last dose of losartan. The implication is that more Ang II is produced per unit of PRA at this time than at other times. An explanation for this observation is not readily apparent from the data collected in this study. It is possible that these differences are a result of greater in vitro generation of Ang II associated with initial stimulation of renin release.10 Alternatively, several physiological hypotheses are possible, including changes in Ang II clearance, which seem unlikely, and changes in Ang II generation.26 One explanation is that angiotensin converting enzyme is somehow downregulated, resulting in less-efficient conversion of Ang I to Ang II. This seems unlikely in view of the ubiquity of the enzyme.26 Another potential control point in the system that could be rate limiting is the amount of circulating angiotensin. It is not known whether unblocked effects of increased Ang II at other binding sites are of any clinical consequence to the safety profile and hemodynamic effects of losartan. In the absence of long-lasting Ang II blockade, increases in plasma Ang II concentration of the magnitude demonstrated would be expected to have hemodynamic activity.14,15

A modest, sustained, and persistent effect of losartan to reduce blood pressure was noted in this study. These changes did not result in apparent clinical symptoms. Also noted were statistically significant increases in standing heart rate, particularly after the first dose of losartan, but without postural hypotension. Together, these data suggest that, under the conditions of this study (overnight supine rest, moderate sodium depletion, limited environmental stimulation), the blood pressure of healthy male volunteers is somewhat dependent on endogenous Ang II.

Acknowledgment
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References


Effects of losartan on blood pressure, plasma renin activity, and angiotensin II in volunteers.
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