Hemodynamic and Neurohormonal Effects of the Angiotensin II Antagonist Losartan in Patients With Congestive Heart Failure

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**Background.** Losartan is a new specific angiotensin II receptor antagonist with no agonist properties that provides the opportunity to study the consequences of angiotensin II blockade. The objective of the present study was to evaluate the hemodynamic and neurohormonal response to losartan in patients with congestive heart failure.

**Methods and Results.** After baseline hemodynamic measurements using balloon-tipped pulmonary artery and radial arterial catheters, patients were randomized to receive a single dose of placebo or 5, 10, 25, 75, or 150 mg losartan in a double-blind, sequential fashion. Hemodynamic and neurohormonal parameters were then measured periodically for 24 hours. Losartan caused vasodilation in a dose-dependent manner. By the area-under-the-curve method, the reduction in the mean arterial pressure and systemic vascular resistance grew larger up to a dose of 25 mg, but the higher 75- and 150-mg doses did not produce additional vasodilation. In response to losartan, there were compensatory increases in both angiotensin II concentrations and in plasma renin activity, which were greatest at the highest doses. Aldosterone concentrations were significantly lowered with losartan.

**Conclusions.** Blockade of the angiotensin II receptor with the antagonist losartan causes vasodilator and neurohormonal effects in patients with congestive heart failure. The lack of additional vasodilator response with doses of more than 25 mg suggests that neurohormonal activation might limit the efficacy of high doses of losartan. (*Circulation.* 1993;88[part 1]:1602-1609.)

**KEY WORDS** • hemodynamics • heart failure • angiotensin II • losartan

The beneficial hemodynamic effects of angiotensin converting enzyme (ACE) inhibitors are well known and usually ascribed to the prevention of formation of angiotensin II by these agents. However, ACE inhibitors affect other neurohormonal systems as well, including those involved with bradykinin, enkephalins, and substance P,1 and it is unclear to what extent actions not related to angiotensin II have hemodynamic consequences. Evaluation of the hemodynamic effects of blockade of the angiotensin II receptor can help to elucidate the mechanism of the response to ACE inhibition. While the angiotensin II receptor has previously been blocked with peptide compounds such as saralasin, saralasin is not orally active, has a short duration of action, and is a partial agonist.2

Losartan is a new specific angiotensin II receptor antagonist with no agonist properties, and it provides the opportunity to study the consequences of blocking angiotensin II.3 Its hemodynamic effects have never before been evaluated in patients with congestive heart failure. The objective of the present study was to evaluate the hemodynamic and neurohormonal responses to the angiotensin II antagonist losartan, previously known as MK-954 and DuP 753, in patients with congestive heart failure.

**Methods**

**Patient Population**

We studied 66 patients with symptomatic congestive heart failure. There were 55 men and 11 women, aged 34 to 80 years (mean, 61 ± 1 years). All patients had a left ventricular ejection fraction less than 40% by radionuclide angiography (range, 8% to 39%; mean, 24 ± 1%). The cause of heart failure was ischemic heart disease in 36 patients and dilated cardiomyopathy in 30 patients. Twenty-six patients were classified by New York Heart Association criteria as class II, 33 patients were class III, and 7 were class IV. Long-acting ACE inhibitors were not given for at least 14 days prior to the hemodynamic study. Thirty-two patients had received captopril in the month prior to study, and this was withheld for at least 3 days prior to evaluation. Patients had received stable doses of digoxin for 14 days and stable doses of diuretics for 3 days. Previous therapy

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with other vasodilator and antihypertensive agents was withdrawn for at least 72 hours prior to the hemodynamic study. Patients with a systolic blood pressure less than 100 mm Hg and patients with an acute myocardial infarction within 3 months were excluded from the study. This study protocol was approved by the institutional review board or ethical review committee of all participating centers.

**Hemodynamic Measurements**

After written, informed consent was obtained, right heart catheterization and arterial cannulation were performed. On the next morning, after all cardioactive medications were withheld for at least 6 hours, the following hemodynamic variables were measured repeatedly in the fasting state until hemodynamic stability was achieved: mean arterial pressure, heart rate, pulmonary capillary wedge pressure, mean right atrial pressure, and cardiac output by thermodilution. In addition, cardiac index and systemic vascular resistance were calculated from the measured parameters. Hemodynamic measurements were repeated at 20-minute intervals until two consecutive sets of measurements exhibited less than 10% variability.

**Intervention**

Patients were then randomized to receive a single oral dose of placebo or losartan. The study was double blind in that in each panel of approximately 12 patients, one sixth of the patients received placebo and the remainder received active drug. To ensure patient safety, however, the dose of active drug was increased only after the previous dose was safely given to an entire panel. The dose of losartan in the first panel was 5 mg, and this was increased to 10, 25, 75, and 150 mg in subsequent panels. Hemodynamic parameters were then measured after 30 minutes, hourly for 6 hours, and after 10, 12, and 24 hours. Patients were permitted to eat a light meal (with no more than 200 mL of fluid) after the 6- and 12-hour measurements.

**Neurohormonal Assessment**

Neurohormonal concentrations were obtained at baseline and after 0.5, 1, 2, 4, 6, 12, and 24 hours. Blood was obtained for measurement of concentrations of angiotensin II, aldosterone, and norepinephrine and for the assessment of plasma renin activity. Plasma was obtained and frozen within 30 minutes of collection. Neurohormonal concentrations were measured at a central laboratory. Aldosterone and angiotensin II concentrations were assessed by radioimmunoassay, and norepinephrine concentrations were assessed by high-performance liquid chromatography. Plasma renin activity was measured in nanograms of angiotensin I generated per milliliter of plasma per hour of incubation.

**Data Analysis**

Baseline characteristics were compared by Fisher’s Exact Test for categorical variables. An analysis of variance was used to test for treatment group differences for continuous variables.

The hemodynamic and neurohormonal responses to the various doses of losartan were compared by parametric analysis of covariance, using the baseline level as the covariant. Between-group differences for the changes (from baseline) for each variable were evaluated by both an area-under-the-curve analysis and a time point–by–time point analysis. To prevent distortion of the area-under-the-curve analysis by the 24-hour value, this value was not used; area-under-the-curve analysis was performed for the 12-hour postdose interval, with the baseline level as the covariant.

For area-under-the-curve analysis, neurohormonal values are displayed and compared as logarithmic variables. To facilitate understanding other analyses, mean neurohormonal values are displayed as absolute values. Group data are expressed as mean±SEM.

Two patients were not evaluated due to protocol violations. One received 150 mg losartan and developed clinically significant hypotension necessitating intervention. Inclusion of this patient would serve to increase the differences noted. One patient received digoxin in the middle of the study for treatment of atrial fibrillation.

**Results**

There were no significant differences in baseline hemodynamic and neurohormonal parameters among the groups of patients who received each dose of losartan (Table). Furthermore, the analysis of covariance methodology adjusts for any differences.

**Hemodynamic Response**

Losartan caused vasodilation in a dose-dependent manner. The change in each hemodynamic parameter over 12 hours, determined by the area under the curve method, is demonstrated in Fig 1 for each dose of losartan. The mean arterial pressure and systemic vascular resistance progressively decreased up to a dose of 25 mg, but the higher 75- and 150-mg doses did not produce more vasodilation. There were no significant differences among doses regarding changes in right atrial pressure, pulmonary capillary wedge pressure, heart rate, or cardiac index. However, compared with placebo, the right atrial pressure tended to decrease more with losartan, and the cardiac index tended to increase with losartan.

The time course of the hemodynamic changes are demonstrated in Figs 2, 3, and 4. The mean arterial pressure and systemic vascular resistance did not change with placebo but began to fall within 2 hours with the 10-, 25-, and 75-mg doses of losartan. Not only were the decreases in mean arterial pressure significantly different than placebo for many of the time points (indicated by asterisks on Fig 2), but the decreases between 3 and 5 hours were also greater for patients who received 25 mg losartan than for patients who received 5, 10, or 150 mg of the drug. The peak decrease in blood pressure occurred between 4 and 12 hours, with a continued effect still seen at 24 hours after drug administration.

As expected with a vasodilator, the cardiac index (Fig 3) increased after patients received 5 or 25 mg losartan. There were no marked changes in heart rate. The pulmonary capillary wedge pressure and the right atrial pressure both tended to decrease with the drug (Fig 4).

**Neurohormonal Changes**

These hemodynamic actions were accompanied by neurohormonal changes (Fig 5). In response to losar-
Baseline Hemodynamic Parameters for Each Dose of Losartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>25 mg</th>
<th>75 mg</th>
<th>150 mg</th>
</tr>
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<tr>
<td>Cardiac index, L min⁻¹ m⁻²</td>
<td>2.1±0.2</td>
<td>2.0±0.1</td>
<td>2.0±0.2</td>
<td>2.0±0.2</td>
<td>2.3±0.1</td>
<td>1.9±0.2</td>
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<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>22±2</td>
<td>20±3</td>
<td>16±2</td>
<td>19±3</td>
<td>18±2</td>
<td>20±2</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>90±5</td>
<td>86±2</td>
<td>88±5</td>
<td>98±4</td>
<td>87±3</td>
<td>90±4</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>10±2</td>
<td>8±2</td>
<td>9±2</td>
<td>8±2</td>
<td>8±1</td>
<td>8±2</td>
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<tr>
<td>Heart rate, bpm</td>
<td>76±5</td>
<td>76±5</td>
<td>73±2</td>
<td>85±4</td>
<td>76±5</td>
<td>79±5</td>
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<tr>
<td>Systemic vascular resistance, dyne * s⁻¹ * cm⁻⁵</td>
<td>1728±145</td>
<td>1698±110</td>
<td>1919±230</td>
<td>2190±315</td>
<td>1513±91</td>
<td>1898±230</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>650±156</td>
<td>578±85</td>
<td>491±88</td>
<td>610±65</td>
<td>361±60</td>
<td>608±130</td>
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<td>Angiotensin II, pg/mL</td>
<td>55±12</td>
<td>66±38</td>
<td>33±8</td>
<td>50±14</td>
<td>51±15</td>
<td>33±6</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>26±8</td>
<td>23±5</td>
<td>14±3</td>
<td>24±6</td>
<td>11±2</td>
<td>10±3</td>
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<tr>
<td>Plasma renin activity, ng · mL⁻¹ · h⁻¹</td>
<td>8±3</td>
<td>13±10</td>
<td>9±6</td>
<td>7±3</td>
<td>3±1</td>
<td>3±1</td>
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</table>

Aldosterone concentrations were significantly lowered with losartan. Patients who received placebo demonstrated increased plasma norepinephrine concentrations through the day, but norepinephrine concentra-
tions decreased in patients who received 25 or 150 mg losartan.

Response to High Doses of Losartan

There was no greater hemodynamic effect with the highest doses of losartan compared with 25 mg (Figs 1 through 4). Indeed, the patients who received 25 mg appeared to have the greatest vasodilation, with the lowest mean arterial pressure and systemic vascular resistance.

Despite the lack of increased hemodynamic response to the highest doses of losartan, there was evidence of increased stimulation of the renin-angiotensin system in these patients (Figs 5 and 6). Plasma renin activity tended to be greater in the patients who had received 150 mg losartan than in those who received 25 mg. Only patients who had received 75 and 150 mg losartan had increased plasma renin activity (at various times) compared with patients who had received placebo. Six hours after losartan administration, angiotensin II concentrations were greatest in patients who received 150 mg losartan. Aldosterone concentrations tended to decrease more in patients receiving 25 mg losartan than in those receiving the
higher 75- and 150-mg doses. Plasma norepinephrine concentrations also tended to decrease more following 25 mg losartan than following the higher doses.

Discussion
This is the first study to demonstrate that blockade of the angiotensin II receptor with the antagonist losartan causes hemodynamic and neurohormonal effects in patients with congestive heart failure. There was a progressive increase in plasma renin activity and angiotensin II plasma concentrations with ascending doses of losartan and a progressively increasing vasodilator response with ascending doses up to 25 mg. However, the lack of additional vasodilator response with doses of more than 25 mg suggests that neurohormonal activation might limit the efficacy of high doses of losartan.

Hemodynamic Effects
The characteristics of the response to losartan of patients with heart failure are similar to those previ-
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FIG 6. Plots of neurohormonal response to placebo and 25, 75, and 150 mg losartan for 24 hours following drug administration. Asterisk (*) indicates difference (P<.05) compared with placebo. § Indicates difference (P<.05) compared with 25 mg. The higher doses of losartan tended to cause greater neurohormonal activation.

ously reported in other patient populations. In hypertensive individuals, 5 days of losartan administration decreases blood pressure by almost 20 mm Hg, with doses above 50 mg daily providing no additional benefit.4 Twenty-four hours after the last dose, there is still a hypotensive effect. Moreover, doses of losartan (up to 40 mg) prevent a hypertensive response to angiotensin II administration in normal individuals in a dose-dependent manner. This effect lasts at least 25 hours and is accompanied by progressive increases in plasma renin activity and angiotensin II plasma concentrations.5 Our findings in patients with congestive heart failure demonstrate that losartan exerts effects in these patients (with presumed endogenous activation of the renin-angiotensin-aldosterone axis) that are similar to the effects previously noted in normal individuals given exogenous angiotensin II. In the present study, mean arterial pressure and systemic vascular resistance decreased in a dose-dependent manner, and the effects persisted through 24 hours.

It is difficult to compare the extent of vasodilation following administration of losartan with that seen after administration of ACE inhibitors. Variations in doses used, the duration of action of the drugs, and the patient populations evaluated could all affect the findings. It is therefore not surprising that the reported hemodynamic effects of ACE inhibitors vary widely among studies. Teprotide given intravenously in eight patients with heart failure resulted (after 30 minutes) in a decrease of mean arterial pressure of 10 mm Hg, a decrease in left ventricular end-diastolic pressure of 6 mm Hg, and an increase in cardiac index of 0.4 L·min⁻¹·m⁻².6 These findings are very similar to the results of the present study. In contrast, 1.5 hours after administration of high doses of captopril (25 to 150 mg), mean arterial pressure decreased by 17 mm Hg, pulmonary capillary wedge pressure decreased by 10 mm Hg, and cardiac index increased by 0.4 L·min⁻¹·m⁻².7 Thus, it is impossible with the present study to determine whether the effects of the blockade of the angiotensin II receptor with losartan are quantitatively different than the consequences of inhibition of ACE.

**Neurohormonal Response**

In the 24 hours following losartan administration, we noted a compensatory increase in the plasma concentration of angiotensin II and plasma renin activity similar to that previously seen in normal individuals.5 As with the hemodynamic response, the peak inhibitory effect on aldosterone concentrations tended to be with the 25-mg dose. Unlike the hemodynamic response, however, angiotensin II concentrations and plasma renin activity tended to be greater in patients who received more than 25 mg losartan than in those who received a 25-mg dose. That the stimulation of the renin-angiotensin system may have limited the hemodynamic effects of losartan is suggested by the experience with ACE inhibitors. ACE inhibitors prevent the formation of angiotensin II, but doses of ACE inhibitors above a certain threshold do not cause more vasodilation or further decrease angiotensin II concentrations. This is true because plasma angiotensin II concentrations are dependent on both substrate concentration and extent of ACE inhibition.8 Angiotensin II therefore continues to be formed in individuals receiving ACE inhibitors.9 In an analogous fashion, the actions of progressively greater concentrations of angiotensin II may be able to overcome some of the blocking effects of losartan.
Losartan in Heart Failure

The use of an angiotensin II antagonist in heart failure is appealing for many reasons. First, it might be possible to combine an angiotensin II antagonist with an ACE inhibitor to yield a synergistic response. Second, there may be clinically important differences between angiotensin II antagonists and ACE inhibitors that might produce different side effects. ACE inhibitors have many actions in addition to the inhibition of angiotensin II production. Angiotensin converting enzyme cleaves (among other substances) angiotensin I, bradykinin, enkephalins, and substance P. However, the extent to which each of these effects produces the beneficial and deleterious consequences of ACE inhibitors in heart failure is unknown.

Differences in the actions of losartan and ACE inhibitors have been particularly noted regarding renal function. There are indications that the improved renal blood flow caused by ACE inhibitors is not merely secondary to decreased angiotensin II concentrations. In rabbits, B2 bradykinin receptor antagonist must be administered with losartan to exert the same renal vasodilatory effects noted with an ACE inhibitor, suggesting that bradykinin exerts important renal vasodilatory effects. There are also differences between losartan and captopril regarding sodium and water excretion, glomerular filtration rate, and distribution of blood flow within the kidney. Similarly, many of the side effects of ACE inhibitors may be related to factors other than their effects on angiotensin II. For example, the cough frequently seen with ACE inhibitors appears to be related to prostaglandins.

Despite the multiple effects of ACE inhibitors, some studies suggest that their antihypertensive effect is only related to their effects on angiotensin II. In experimental high renin hypertension, losartan and an ACE inhibitor exert the same vasodilatory effects (although the heart rate increases only with losartan). The effects seen in the present study suggest that losartan is an active drug that produces vasodilation by its antagonism of the angiotensin II receptor. If the beneficial effects of ACE inhibitors on symptoms and survival in patients with heart failure are caused by the inhibition of angiotensin II formation, an angiotensin II antagonist could conceivably produce similar beneficial effects with fewer side effects.

Study Limitations

The present study was an acute single-dose study, and the chronic effects of losartan need to be evaluated. While 25 mg losartan appears to be the optimal dose in this study, it is possible that with repeated dosing a lower dose would yield similar optimal concentrations. In heart failure patients especially, abnormal hepatic and renal function often mandate smaller doses of a drug. Of course, chronic use of losartan might also lead to receptor concentration changes and decreased efficacy of this dose. Just as β-receptor concentration and activity changes with β-blockers, angiotensin II receptor concentration or activity may be altered by an antagonist. Further chronic studies of losartan in patients with heart failure will answer these questions.

Ideally, evaluation of an angiotensin II antagonist should be performed in patients not previously exposed to ACE inhibitors. We attempted to minimize the effects of ACE inhibitors by evaluating only patients who had not received ACE inhibitors long enough to eliminate plasma concentrations of these agents. Nevertheless, the prolonged effects of ACE inhibitors consequent to the long tissue half-life of ACE inhibitors may have decreased the acute effects observed in the present study.

This study evaluated 12 or fewer patients in each panel, and the power of the study was not strong enough to rule out any greater hemodynamic effects with the highest doses. However, the consistency of this and previous studies suggests that, at higher doses, the extent of the increase in neurohormonal activation is greater than any increase in vasodilator response. While this does not prove that neurohormones limit the hemodynamic response to high doses of losartan, such actions are important following administration of other vasodilators.

As with ACE inhibitors, an acute dose of losartan is a vasodilator in patients with congestive heart failure. Also analogous to ACE inhibitors, administration of doses above a certain threshold demonstrate very little additional effect. Only further studies will show whether these similar hemodynamic characteristics will translate into similar clinical utility.

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References


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