Efficacy and Tolerability of Losartan in Hypertensive Patients With Renal Impairment

Robert Toto, Pamela Shultz, Leopoldo Raji, Helen Mitchell, Wayne Shaw, Denise Ramjits, Jenny Toh, Shahnaz Shahinfar, for the Collaborative Group*

Abstract—We evaluated the blood pressure–lowering activity, tolerability, and safety of losartan in 112 hypertensive (sitting diastolic blood pressure, 90 to 115 mm Hg) patients with chronic renal insufficiency including mild renal insufficiency (30 to 60 mL/min per 1.73 m²; n=51), moderate to severe renal insufficiency (10 to 29 mL/min per 1.73 m²; n=33), or on hemodialysis (n=28). After a 3-week placebo period, once-daily losartan was administered for 12 weeks. The daily dose of 50 mg was increased to 100 mg after 4 weeks in patients whose sitting diastolic blood pressure remained ≥90 mm Hg or was reduced by <5 mm Hg. A second, non–angiotensin-converting enzyme inhibitor, antihypertensive drug was added after 8 weeks as needed. Twenty-four–hour creatinine clearance was determined and renal clearance studies of inulin and para-aminohippurate were done in a subset of 11 patients. Trough sitting blood pressures were reduced at the end of the first week in all groups. At weeks 4, 8, and 12, the reductions in systolic blood pressure/diastolic blood pressure averaged −11.9/−8.7, −10.8/−9.4, and −14.7/−12.1 mm Hg in patients with mild renal insufficiency; −7.7/−6.3, −13.1/−11.8, and −14.1/−10.6 mm Hg, in moderate to severe renal insufficiency; −17.0/−12.7, −19.1/−14.4, and −22.7/−18.0 mm Hg in hemodialysis. Creatinine clearance, glomerular filtration rate, and effective renal plasma flow were stable. Losartan was withdrawn in only 6 patients because of a clinical or laboratory adverse experience. Hyperkalemia (>6 mEq/L) requiring discontinuation of losartan occurred in only one (group 2) patient. We conclude that once-daily losartan, given as monotherapy at doses of 50 or 100 mg or in combination with other antihypertensive drugs, was effective in reducing blood pressure in hypertensive patients with chronic renal disease and that losartan regimens were well tolerated in all groups, including those on hemodialysis. (Hypertension. 1998;31:684-691.)

Key Words: losartan ■ angiotensin II ■ renal insufficiency ■ hemodialysis ■ renin-angiotensin-aldosterone system

Hypertension is a major contributor to the progression of chronic renal diseases1–4 and is present in most patients with progressive renal disease and in all individuals with hypertensive nephrosclerosis. Together, diabetic nephropathy and hypertensive nephrosclerosis account for nearly two thirds of the new cases of end-stage renal disease in the United States.5 Moreover, hypertension is an important contributing factor to morbidity and mortality among hemodialysis patients.5–7 Clinical studies in these patient populations indicate that BP control plays a critical role in slowing the progression of disease and may even prevent progression in some patients with hypertensive nephrosclerosis.3–5

The mechanisms of hypertension in such populations are complex; however, the RAAS is thought to be an important contributor to the pathogenesis of hypertension and renal disease in renal failure. Several studies have shown that treatment with ACE inhibitors lowers BP, reduces proteinuria, and slows the rate of progression of renal disease.6,7 Recently, a new class of drugs that selectively inhibit the RAAS by specifically targeting the angiotensin II AT1 receptor have been developed for the treatment of hypertension. Losartan, the first of this new class of antihypertensive agents, is an orally active, highly specific competitive antagonist that blocks the binding of angiotensin II to the AT1 receptor subtype.10 In patients with essential hypertension, once-daily doses of 50 or 100 mg losartan have been shown to effectively lower BP throughout the 24-hour dosing interval and to be well tolerated.11–16

Losartan is rapidly absorbed after oral administration and undergoes carboxylation, forming an active metabolite, E-3174, and several inactive metabolites.17 Both losartan and its active metabolite are highly protein bound and neither are removed by hemodialysis.18 Losartan clearance is primarily nonrenal, whereas clearance of E-3174 occurs through both renal and nonrenal routes. Plasma concentrations of E-3174, however, are not significantly altered in patients with renal impairment or in patients undergoing hemodialysis.18

The present study was designed to evaluate the antihypertensive effectiveness, safety, and tolerability of losartan, administered alone in once-daily doses of 50 or 100 mg or in combination with a non–ACE inhibitor antihypertensive...
agent, in patients with varying degrees of chronic renal insufficiency, including end-stage renal disease.

**Methods**

This multicenter, open-label study was conducted at 18 clinical centers in the United States. Institutional Review Board approval was obtained from each center and all patients gave their informed consent. All procedures performed in this study were conducted in accordance with institutional guidelines.

**Patient Selection**

Adult (age ≥21 years) male and female outpatients with a diagnosis of hypertension associated with impaired renal function were screened for enrollment. Patients with known or suspected renal artery stenosis were excluded from participation. If eligible, all current antihypertensive medications were withdrawn and patients underwent a complete physical examination including medical history, chest radiograph, ECG, and laboratory safety testing. Patients were given 3 weeks of placebo treatment. Those with a trough SBP between 90 and 115 mm Hg at the end of the placebo baseline period and whose CLcr, after 3 weeks of placebo therapy was ≤60 mL/min per 1.73 m² were eligible to receive treatment with losartan. Patients were classified into three groups on the basis of their baseline CLcr: group 1 (mild renal insufficiency: CLcr of 30 to 60 mL/min per 1.73 m²); group 2 (moderate renal insufficiency: CLcr of 10 to 29 mL/min per 1.73 m²); and group 3 (end-stage renal disease).

**Study Design**

The study consisted of a 3-week placebo baseline period followed by a 12-week, open-label active treatment period in which patients received losartan once daily in the morning administered at a starting dose of 50 mg. Hemodialysis patients who underwent morning or early afternoon dialysis received losartan after dialysis on these days and at approximately that same time on all other days. After 4 weeks of losartan therapy, patients whose trough SBP remained at ≥90 mm Hg or whose trough DBP was <90 mm Hg but did not experience ≥5 mm Hg decrease from baseline had an additional antihypertensive agent added to their daily losartan regimen. The choice of the second antihypertensive drug was left to the investigator’s discretion with the stipulation that ACE inhibitors were not to be used; dosage adjustments of the second drug were permitted to optimize BP control after 2 weeks.

**Efficacy Variables**

BP measurements were obtained with the use of a mercury sphygmanometer. The protocol provided specific, standardized steps for all centers to follow in performing all sitting and standing BP measurements for both trough and peak throughout the study. Trough measurements were taken 22 to 26 hours after the prior day’s dose; and peak measurements were taken 5 to 8 hours after the day’s dose. Analyses were not performed or predefined in the protocol to assess precision, reproducibility, and variation of BP measurements within a center and among centers.

Measurements of trough BP were made immediately before the morning dose at each visit, and peak BP measurements were made 5 to 8 hours after dose at baseline, on the first day of losartan treatment, and at weeks 1, 4, 8, and 12 of active treatment. Twenty-four-hour urine collections were obtained in nonhemodialysis patients during the baseline and active treatment periods for determination of creatinine clearance and protein excretion. Laboratory evaluations, including hematology, chemistry, and urinalysis, were performed during the baseline period and after 4, 8, and 12 weeks of active treatment. Tolerability of study treatment was assessed by monitoring of spontaneous reports of adverse experiences at each visit.

**Renal Clearance Studies**

A subset of 11 nondialysis patients, enrolled from 3 centers, underwent renal clearance studies at the end of the placebo baseline period and after 8 weeks of treatment with losartan alone. Clearance of inulin and PAH were performed to measure GFR and ERPF, respectively.79 (One patient did not undergo the ERPF measurement at week 8.) Patients presented fasting on the morning of the study, after having taken their placebo or losartan dose. They were water-loaded orally and with DSW intravenously to 20 mL/kg or until a urine specific gravity of ≤1.010 was achieved. Priming doses of inulin and PAH were given in an intravenous bolus, followed by continuous infusions.

The infusion rate was adjusted for the patient’s estimated GFR, as assessed by creatinine clearance in order to maintain an approximate plasma concentration of 40 μmol/L (20 mg/dL) inulin and 92.5 μmol/L (2 mg/dL) PAH. After a 60-minute equilibration period, four 30-minute urine collections were obtained with plasma samples taken at the midpoint of each collection. Urine losses were replaced with water (mL/min) orally. Plasma and urine samples for PAH were determined by AutoAnalyzer (Technicon); inulin samples were assayed according to the method of Walser et al.77 The values obtained from each collection period were averaged, and GFR and ERPF were calculated as [(urine concentration of inulin or PAH)/plasma concentration of inulin or PAH]×urine flow rate (mL/min)]. Each were corrected for 1.73 m² body surface area. Results during the baseline period were compared with results after 8 weeks of losartan therapy by paired t test.

**Statistical Analysis**

Changes from baseline in trough and peak SBP and DBP were evaluated. Mean changes from baseline within each renal impairment group were analyzed with a paired t test. All patients with at least one active treatment period BP measurement were included in the efficacy analyses; the last measurement of withdrawn patients was carried forward to subsequent time points. Additionally, changes from baseline in trough SBP at week 12 were analyzed in demographic subgroups stratified according to age (≥65/<65 years), sex, race (black/nonblack), or baseline hypertensive category (<105/≥105 mm Hg).

The incidence of adverse experiences across the three renal impairment groups was analyzed with Fisher’s exact test. Within-group changes from baseline for selected laboratory parameters of clinical importance (ie, serum urea nitrogen, serum creatinine, and protein excretion, and creatinine clearance) were evaluated with the Wilcoxon signed rank test. Statistical significance was defined as a value of P≤0.05 (two-sided).

**Results**

**Patient Characteristics**

Of the 112 patients enrolled in this study, 51 had mild renal insufficiency (CLcr: 30 to 60 mL/min per 1.73 m²), 33 had moderate renal insufficiency (CLcr: 10 to 29 mL/min per 1.73 m²), and 28 had end-stage renal disease requiring hemodialysis. Table 1 presents the baseline and demographic characteristics of patients in each group as well as for the entire patient population.
Of the 112 patients who were enrolled, 93 completed the study. Only 6 patients were discontinued because of clinical or laboratory adverse experiences, 2 patients were withdrawn for uncontrolled hypertension, and the remainder of those who did not complete the study were discontinued for administrative reasons or protocol violations.

Losartan Dosage and Concomitant Antihypertensive Therapy
Among the 93 patients who completed 12 weeks of active treatment, BP was controlled in 47 (50%) patients while on losartan monotherapy. Among these patients, 26 (28%) were maintained on losartan 50 mg. BP was controlled in the remaining 46 (50%) patients with losartan and another antihypertensive agent(s). There were no significant differences among the three renal insufficiency groups in the distribution of patients who were maintained on losartan monotherapy or were given concomitant therapy involving a second antihypertensive drug (Table 2). The most frequently used second antihypertensive agents were diuretics (n=24, 52%), of which furosemide was the most commonly prescribed, and calcium channel blockers (n=12, 26%), of which nifedipine (regular or sustained release formulations) was the most frequently given.

Blood Pressure Reductions
Eight patients were not included in the analyses of trough BP because of missing valid baseline or posttreatment values. Data from the remaining 104 patients who received therapy, excluding 1 patient in group 2 who initially received treatment with losartan 100 mg rather than 50 mg, were included in the analyses of trough BP changes. The mean (±SD) baseline SiSBP/SiDBP in groups 1, 2, and 3 were 159.0±20.6/98.2±7.0, 160.7±23.2/100.4±7.3, and 163.7±19.3/103.3±6.9 mm Hg, respectively. Significant decreases from baseline in trough SiDBP and SiSBP were observed in all groups beginning at week 1 and continuing throughout therapy (P<.05). Fig 1 and 2 illustrate mean trough SiDBP and SiSBP measurements at baseline and weeks 1, 4, 8, and 12 of active treatment for the three groups. Mean changes in standing BP were similar to changes observed in sitting BP. Twenty-four–hour urine sodium excretion rate in group 1 averaged 166 mEq at baseline and did not change significantly during the study (4 weeks, 164 mEq; 8 weeks, 173 mEq; and 12 weeks, 160 mEq). Similarly, in group 2 patients, urine sodium at baseline was 115 mEq and was not significantly different during the study (4 weeks, 128 mEq; 8 weeks, 135 mEq; and 12 weeks, 126 mEq). Therefore, the hypotensive

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild (n=51)</th>
<th>Moderate to Severe (n=33)</th>
<th>Hemodialysis (n=28)</th>
<th>All Patients (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Clcr, mL/min per 1.73 m²</td>
<td>45.2±9.87</td>
<td>20.48±5.43</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>14 (27%)</td>
<td>9 (27%)</td>
<td>9 (32%)</td>
<td>32 (29%)</td>
</tr>
<tr>
<td>Male</td>
<td>37 (73%)</td>
<td>24 (73%)</td>
<td>19 (68%)</td>
<td>80 (71%)</td>
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<tr>
<td>Age</td>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58.5±14.0</td>
<td>57.4±14.0</td>
<td>44.1±14.4</td>
<td>54.6±15.3</td>
</tr>
<tr>
<td>Range</td>
<td>28-82</td>
<td>28-78</td>
<td>21-77</td>
<td>21-82</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>30 (59%)</td>
<td>16 (48%)</td>
<td>9 (32%)</td>
<td>55 (49%)</td>
</tr>
<tr>
<td>Black</td>
<td>15 (25%)</td>
<td>12 (36%)</td>
<td>12 (43%)</td>
<td>39 (35%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (16%)</td>
<td>5 (16%)</td>
<td>7 (25%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>12 (24%)</td>
<td>12 (36%)</td>
<td>5 (18%)</td>
<td>29 (26%)</td>
</tr>
</tbody>
</table>

Mild indicates Clcr 30 to 60 mL/min per 1.73 m²; Moderate to Severe, Clcr 10 to 29 mL/min per 1.73 m².

Blood Pressure Reductions
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porting these adverse experiences compared to patients with renal impairment as significantly more hemodialysis patients reported related experiences reported under “All Patients” does not represent the total of patients in any one renal insufficiency group are mild, averaging only 4.4 mm Hg in all patients.

Safety and Tolerability
Twenty-seven percent (n=30) of the total population reported clinical adverse experiences that were considered by the investigator to be possibly or probably related to study treatment. Those adverse experiences that were reported by ≥4% of patients in any one renal insufficiency group are presented in Table 3 (the number of clinical adverse experiences reported under “All Patients” does not represent the total of the three groups). The occurrence of hypotension, nausea, and cough appeared to be associated with the degree of renal impairment as significantly more hemodialysis patients reported these adverse experiences compared to patients with mild renal insufficiency (P<.05). It is unlikely that the three reports of cough among hemodialysis patients are treatment related because there was a higher incidence of respiratory complaints (ie, dyspnea, allergic rhinitis, chronic obstructive pulmonary disease) at study entry among patients in this group. Two patients with moderate renal impairment reported flank pain during the study; neither of these episodes were considered related to study treatment and neither was associated with hematuria or increases in uric acid excretion, serum creatinine, or BUN. Hypotension prompted the early withdrawal of one patient each in groups 2 and 3, and two additional patients in group 3 were discontinued because of skin rash and dizziness, respectively.

Effects on Renal Function and Proteinuria
Mean creatinine clearances in groups 1 and 2 were not significantly changed from the respective baseline values of 45.3 and 20.5 mL/min per 1.73 m² after 12 weeks of therapy (Table 4). There was, however, large variability in the individual responses during treatment, and two patients in group 2 experienced reductions in creatinine clearance that were reported as adverse experiences. In both of these patients, creatinine clearances returned toward baseline values during continued losartan treatment.

Of the subset of 11 patients in whom clearance studies for GFR and ERPF were performed, 5 were in the mild renal insufficiency group and 6 were in the moderate to severe renal insufficiency group. The mean age was 65.3±4.0 years; 9 were males, 3 were black, and 2 were diabetic. Two patients were on losartan 50 mg and 9 patients were on losartan 100 mg at the time of the second set of clearance studies. Mean GFR was 34.1±3.6 mL/min per 1.73 m² (mean±SE) at baseline and 33.8±6.1 mL/min per 1.73 m² after 8 weeks of losartan treatment (P=NS). ERPF (n=10) was also not significantly changed from baseline to 8 weeks of losartan treatment, with mean values of 128.4±23.6 and 136.7±26.5 mL/min per 1.73 m², respectively (P=NS). As noted previously, the ERPF determination was not performed on 1 patient at week 8.

There was a statistically significant reduction of ~23% in 24-hour urine protein excretion relative to baseline after 12 weeks of treatment in both the mild (2991 to 2307 mg/24 hours; mean decrease of ~684 mg/24 hours) and moderate to severe (3692 to 2795 mg/24 hours; mean decrease of ~897 mg/24 hours) renal insufficiency groups (P=0.05). The time course of changes in the urine protein excretion rate are shown in Fig 3 for both groups.

Overall, there were no clinically meaningful changes in the mean values of laboratory parameters indicative of renal function (ie, creatinine, BUN) during the course of the study. There were fluctuations of 0.03 to 0.22 mmol/L (0.3 to 2.5 mg/dL) in serum creatinine throughout the study. Sustained increases in serum creatinine ranging from 0.04 to 0.18 mmol/L (0.5 to 2.0 mg/dL) were apparent in 10 patients; however, no corresponding changes in creatinine clearance were observed in these patients. Furthermore, no patients were discontinued due to increases in serum creatinine. One patient with type 1 diabetes progressed to end-stage renal failure requiring dialysis and experienced a gradual increase in serum creatinine of 0.38 mmol/L (4.3 mg/dL) by the end of the

![Figure 1. Mean reduction from baseline in trough sitting diastolic blood pressure after 1, 4, 8, and 12 weeks of losartan therapy. CrCl indicates creatinine clearance. *P=.05.](image1)

![Figure 2. Mean reduction from baseline in trough sitting systolic blood pressure after 1, 4, 8, and 12 weeks of losartan therapy. CrCl indicates creatinine clearance. *P=.05.](image2)
This patient entered the study with a baseline creatinine clearance of 12 mL/min per 1.73 m², a serum creatinine of 0.68 mmol/L (7.7 mg/dL), and a urine protein excretion rate of 14 g/24 hours. This event was not considered related to losartan treatment and was considered a natural progression of the patient’s underlying disease process.

**Other Laboratory Measurements**

In the total population, laboratory abnormalities that were considered drug related by the investigator were reported in 18 patients (16.5%). However, only 2 patients were discontinued because of laboratory adverse experiences; a patient in group 2 was discontinued because of hyperkalemia and a patient in group 3 because of increased liver enzymes. Laboratory parameters of specific interest in this study were the magnitude of

<table>
<thead>
<tr>
<th>Adverse Experience</th>
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<tbody>
<tr>
<td><strong>Mild (n=51)</strong></td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Edema/swelling</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Impotence</td>
</tr>
<tr>
<td>Infection, upper respiratory</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Occlusion, vascular graft</td>
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<tr>
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<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
</tbody>
</table>

Mild indicates \( CL_{cr} > 30 \) to 60 mL/min per 1.73 m²; Moderate to Severe, \( CL_{cr} \) 10 to 29 mL/min per 1.73 m².

*<4% of patients in each group.

Table 3. Clinical Adverse Experiences Reported by at Least 4% of Patients in Any One Group

**TABLE 4. Mean Changes From Baseline to Week 12 in Creatinine Clearance**

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>n</th>
<th>Baseline Mean±SD</th>
<th>Week 12 Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 60 mL/min per 1.73 m²</td>
<td>46</td>
<td>45.3±9.9</td>
<td>44.9±13.8</td>
</tr>
<tr>
<td>10 to 29 mL/min per 1.73 m²</td>
<td>23</td>
<td>20.5±5.4</td>
<td>19.1±10.3</td>
</tr>
<tr>
<td>All patients</td>
<td>69</td>
<td>37.0±14.6</td>
<td>36.3±17.6</td>
</tr>
</tbody>
</table>

**Figure 3.** Mean changes from baseline in 24-hour urine protein excretion rate after 1, 4, 8, and 12 weeks of losartan therapy. Clcr indicates creatinine clearance.
changes in serum concentrations of potassium, uric acid, hemoglobin, and hematocrit. In each renal insufficiency group, only small changes in mean serum potassium (−0.024 to 0.113 mmol/L; P=NS) were observed. The proportion of patients exhibiting a decrease in serum potassium of >0.5 mmol/L from baseline to the final study visit ranged from 8% to 18%; the proportion of patients having >0.5 mmol/L increase in serum potassium likewise ranged from 15% to 23%. As mentioned previously, one patient in group 2 was discontinued because of hyperkalemia.

Mean changes in serum uric acid concentrations of −0.068 to 0.013 mmol/L (−1.153 to 0.211 mg/dL) were observed after 12 weeks of treatment. Less than 10% of patients in any of the three renal insufficiency groups experienced an increase from baseline to the final study visit in serum uric acid of >0.12 mmol/L (2.0 mg/dL); 32% of patients in group 3 had a decrease in serum uric acid of >0.12 mmol/L (2.0 mg/dL) (P≤.05).

Only minor decreases were seen in hemoglobin (mean changes in three groups ranged from 0.012 to 0.065 mmol/L [0.077 to 0.419 g/dL]) and hematocrit (−0.0043 to −0.015 [−0.432 to −1.470%]) at the final study visit in each group. There were no reports of anemia, and no patients were discontinued due to decreased hematocrit.

Discussion

The results of this study demonstrate that the angiotensin II receptor antagonist losartan, administered once daily at doses of 50 or 100 mg, is effective in lowering BP in hypertensive patients with varying degrees of chronic renal insufficiency. Significant reductions in trough SiDBP and SiSBP were apparent as early as the first week of treatment with losartan 50 mg in patients with mild to severe renal insufficiency and in patients requiring hemodialysis. The significant reductions in BP were achieved with one half of the study population remaining on monotherapy with losartan 50 or 100 mg throughout the 12-week treatment period. The remaining 50% of patients were treated with losartan 100 mg and other antihypertensive agents during the last 4 weeks of the study; in the majority of these patients the second antihypertensive drug was a diuretic. Although the present study was not designed to answer the question of whether 100 mg per day of losartan was more effective than 50 mg per day, we found that 21 of 67 patients exhibiting a decrease in serum uric acid of >0.12 mmol/L (2.0 mg/dL) (P≤.05).

Losartan was generally well tolerated in this study, with only four patients withdrawing because of a clinical adverse experience. Headache was the most common adverse experience in the overall study population and was reported with a similar incidence in all three renal groups. Despite effectively reducing BP by the end of the first week of treatment, losartan did not induce first-dose hypotension, even among hemodialysis patients. The decreases in SiSBP and SiDBP 5 to 8 hours after the initial dose were mild, averaging only −4 to −5 mm Hg.
in the mild renal insufficiency group, −5 to −7 mm Hg in the moderate renal insufficiency group, and −4 mm Hg in the hemodialysis group. Although hypotension prompted withdrawal of two patients who were receiving therapy with losartan 50 mg, neither episode was considered severe and neither required treatment. There were no reports of first-dose hypotension or angioedema.

Only minor changes in serum potassium were apparent at weeks 4, 8, and 12 in hemodialysis and nonhemodialysis patients. Eighteen percent of the total study population experienced an increase in serum potassium levels of >0.5 mmol/L by the end of the study, and only one patient had an elevation in serum potassium that resulted in premature withdrawal. However, the majority of these patients experienced fluctuations in serum potassium during the treatment period that were well within the normal range. It is expected that compounds that block the RAAS can potentially increase serum potassium. Additionally, hyperkalemia is not uncommon among patients with compromised renal function, and patients with severe renal dysfunction have been reported to be more susceptible to potassium retention brought on by changes in dietary potassium intake or endogenous factors, as well as blockade of the RAAS.

Minor decreases in serum uric acid were noted during the treatment period, which is consistent with the modest hypouricemic effect of losartan that has been previously observed in clinical studies with hypertensive patients treated with losartan.

Anemia is a well recognized complication of advanced renal disease because of a diminution of the production of erythropoietin. It has been suggested that angiotensin II plays an important role in erythropoietin production and that RAAS blockade in patients with compromised production of erythropoietin, such as those with renal insufficiency, can result in further reductions in hemoglobin and hematocrit. Only minor decreases were observed in hemoglobin and hematocrit with losartan treatment in this study, and there were no adverse experiences or premature withdrawals as a result of anemia.

The purpose of the present study was to gain experience with the new angiotensin II receptor antagonist losartan in patients with different degrees of renal impairment. A limitation of the study is the absence of a comparative placebo-treated group. This study was not designed with a placebo control arm, in that withholding antihypertensive treatment from hypertensive patients with moderate to severe renal impairment and those patients on hemodialysis would not be considered ethical, since adequate BP control is essential.

In summary, the results of this 12-week study suggest that losartan, administered at an initial dose of 50 mg once daily and subsequently titrated to 100 mg, is highly effective in lowering BP and is generally well tolerated in a hypertensive population with mild to severe chronic renal insufficiency. In some patients, its efficacy is enhanced by addition of a diuretic and/or other antihypertensive agents. In addition, the BP-lowering effect of losartan is accompanied by a significant reduction in proteinuria in patients with chronic renal insufficiency. Losartan may play an important role in the management of hypertension in patients with various degrees of renal impairment due to its efficacy and favorable tolerability profile.

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References


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