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Comparison of losartan and amlodipine in renally impaired hypertensive patients

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Comparison of losartan and amlodipine in renally impaired hypertensive patients. Effects of losartan and amlodipine on blood pressure and albuminuria were compared in a randomized, double-blind, parallel trial involving 48 patients with essential hypertension (sitting diastolic blood pressure between 95 to 115 mm Hg) and impaired renal function (creatinine clearance of 30 to 60 ml/min/1.73 m^2). After four weeks of placebo administration, patients were stratified according to baseline albuminuria ($<$ or $\geq$ 300 μg/min) and randomized to once-daily treatment with losartan 50 mg ($N = 24$) or amlodipine 5 mg ($N = 24$) for 12 weeks. Titration to losartan 50 mg/hydrochlorothiazide (HCTZ) 12.5 mg or amlodipine 10 mg was possible at weeks 3 or 6 for patients having an inadequate blood pressure response. After 12 weeks of treatment, the mean decreases in sitting diastolic and systolic blood pressures were significantly larger in the losartan group (-18.1 ± 7.2 and -27.7 ± 15.2 mm Hg) than in the amlodipine group (-12.4 ± 7.5 and -16.3 ± 12.1 mm Hg; $P = 0.009$ and $P = 0.008$, respectively). The greater antihypertensive response to losartan was not influenced by the initial degree of albuminuria. The losartan and amlodipine regimens were well-tolerated. Baseline levels of albuminuria were reduced after 12 weeks of losartan treatment (median change of -29.5 μg/min), while amlodipine therapy was associated with a median increase (48.4 μg/min) in this renal marker at week 12. The treatment difference was statistically significant ($P = 0.021$). These results indicate that losartan 50 mg, administered alone or in combination with HCTZ 12.5 mg, is more effective than amlodipine 5/10 mg in lowering blood pressure and albuminuria in patients with essential hypertension complicated by impaired renal function.

High blood pressure, even modest elevations, has been shown to be a strong, independent risk factor for end-stage renal disease [1]. Losartan potassium (losartan; COZAAR™) is a potent and selective blocker of the AT_1 subtype of angiotensin II receptors. In patients with essential hypertension, once daily administration of losartan administered alone at doses of 50 and 100 mg or in combination with hydrochlorothiazide (HCTZ) 12.5 mg has been shown to be well-tolerated and efficacious in lowering blood pressure throughout the 24-hour dosing interval [2, 3]. In human kidneys, angiotensin II receptors are predominantly of the AT_1 subtype [4], and losartan treatment has been shown to reduce albuminuria among individuals with renal disease at least as effectively as the angiotensin converting enzyme (ACE) inhibitor, enalapril [5].

The present 12 week trial was designed to compare the effects of losartan on blood pressure and metabolic parameters indicative of renal function with those of amlodipine, a widely used and effective antihypertensive agent belonging to the dihydropyridine class of calcium antagonists.

Key words: essential hypertension, albuminuria, blood pressure, end-stage renal disease, hydrochlorothiazide.

METHODS

Study design

The study consisted of a pre-placebo period of at least one week duration, a four-week placebo baseline period and a 12-week active treatment period in which eligible patients were randomized to once daily treatment with losartan 50 mg or amlodipine 5 mg. Randomization was performed in a stratified manner within each investigational site according to baseline albuminuria ($<$ 300 or $\geq$ 300 μg/min). Titration to losartan 50 mg plus hydrochlorothiazide (HCTZ) 12.5 mg or amlodipine 10 mg was indicated for patients whose sitting diastolic blood pressure (SiDBP) remained at or above 106 mm Hg at week 3 or at or above 90 mm Hg at week 6. All trial medications were administered once daily in the morning.

Patient population

Forty-eight male or female patients with essential hypertension and impaired renal function, defined as a creatinine clearance between 30 and 60 ml/min/1.73 m^2, were recruited at seven investigational sites in Italy, Norway,

Portugal and Spain. Informed consent was obtained from each patient prior to study participation, as was ethical committee approval. All patients provided informed consent. All patients were at least 18 years of age, and had no concurrent medical conditions or therapy that might affect blood pressure. In particular, no patient had a diagnosis of acute renal failure, known renal arterial stenosis, uncontrolled diabetes mellitus or a clinically significant serum potassium, AST or ALT abnormality. Prior to single-blind treatment with placebo, all current antihypertensive medication was discontinued for at least seven days (4 weeks for ACE inhibitor drugs). Only patients whose trough SiDBP (that is, 22 to 26 hr after the preceding morning dose) was between 95 and 115 mm Hg after two and four weeks of placebo therapy qualified for randomization to double-blind therapy.

Table 1. Demographics and baseline characteristics

Characteristic	Losartan	Amlodipine
Patients *N*	24	24
Male	12	19
Female	12	5
Age *years*		
Mean (SD)	55.7 (12.2)	54.9 (12.1)
Race		
Caucasian	24	24
Coexistence of diabetes	9	11
SiDBP *mm Hg*		
Mean (SD)	101.4 (6.0)	101.2 (6.5)
Albuminuria *μg/min*		
Median	359.2[a]	396.7
< 300 μg/min	10	10
≥ 300 μg/min	12	14

[a] For two patients the baseline albuminuria was not recorded

Study variables

Trough blood pressure, heart rate and body wt were measured at three week intervals during the active treatment period. Blood was sampled, and a fresh morning urine sample was provided after one week of placebo administration and after 6 and 12 weeks of active treatment for routine fasting hematology, blood chemistry and urinalysis evaluations. Twenty-four-hour urine collections were performed at weeks -4 and -3 of the placebo period and twice at week 12, separated by a two to three day interval, for determination of urine volume and excretion of albumin and creatinine. All laboratory tests, except for tests used to evaluate initial eligibility and monitor patient safety, were performed by a central laboratory.

Statistical analysis

All patients who had a baseline and at least one post-randomization measurement were included in the analyses of blood pressure and laboratory variables. The last double-blind measurements of withdrawn patients were carried forward to subsequent time points.

Changes from baseline in trough sitting diastolic (SiDBP) and systolic (SiSBP) blood pressures at week 12 were analyzed for comparative efficacy between treatment groups using a least squares analysis of the means based upon an analysis of variance (ANOVA) that included treatment, center and stratum (baseline microalbuminuria) as main effects and terms for treatment-by-center and treatment-by-stratum interactions. Within group comparisons were assessed by means of a one-sample *t*-test. Due to the non-normality of the 24-hour urine data, changes from baseline to week 12 were analyzed using the Wilcoxon signed-ranked test.

The antihypertensive response to treatment was categorized as: SiDBP < 90 mm Hg; SiDBP ≥ 90 mm Hg and a decrease from baseline of ≥ 10 mm Hg; and SiDBP ≥ 90 mm Hg and a decrease from baseline of < 10 mm Hg. The responses were compared between the treatment groups using MuCullagh's method for ordered categorical data including treatment and stratum as main effects.

Statistical significance was defined as a P value ≤ 0.05, two-sided.

RESULTS

Patient characteristics

Of the 48 patients enrolled, 12 men and 12 women were randomized to the losartan group and 19 men and 5 women were randomized to the amlodipine group. The two groups were similar with respect to age, race, coexistence of diabetes, severity of hypertension, SiDBP at baseline and median albuminuria at baseline (Table 1). All patients in the losartan group completed the 12 weeks of active treatment. A total of five patients in the amlodipine group discontinued prematurely; two were withdrawn for clinical adverse experiences, one discontinued for insufficient response and two were withdrawn for major protocol violations.

Antihypertensive efficacy

Except for one patient in the amlodipine group who did not have post-randomization blood pressure measurements, data from all randomized patients were included in the efficacy analyses. While statistically significant reductions from baseline in trough SiDBP and SiSBP at week 12 were observed in both treatment groups, the magnitude of the reductions were significantly larger following losartan therapy compared to treatment with amlodipine ($P = 0.009$ for SiDBP and $P = 0.008$ for SiSBP; Table 2). No significant interactions between study center or albuminuria stratum could be established for either blood pressure variable. Figure 1 displays the mean change from baseline in SiDBP and SiSBP at week 12 as a function of baseline albuminuria (< 300 or ≥ 300 μg/min). For both subgroups, the blood pressure lowering response was consistently greater in the losartan group.

Half ($N = 12$) of the patients randomized to losartan

Table 2. Mean change in trough sitting diastolic and systolic blood pressures at week 12

Parameter	Losartan ($N = 24$)	Amlodipine ($N = 23$)
SiDBP		
Baseline mean (SD)	101.4 (6.0)	100.8 (6.4)
Week 12 mean (SD)	83.3 (7.0)	88.5 (8.5)
Change from baseline: mean (SD)	−18.1 (7.2)[b]	−12.4 (7.5)[b]
Treatment difference		
Least square mean (95% CI)	−5.8 (−10.1%, −1.5%)	
P value[a]	0.009	
SiSBP		
Baseline mean (SD)	165.2 (15.2)	161.3 (16.8)
Week 12 mean (SD)	137.5 (18.8)	145.0 (16.1)
Change from baseline: mean (SD)	−27.7 (15.2)[b]	−16.3 (12.1)[b]
Treatment difference		
Least square mean (95% CI)	−11.3 (−19.5%, −3.1%)	
P value[a]	0.008	

Abbreviations are: SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure.

[a] P value for pairwise comparison; ANOVA

[b] Significant change from baseline, $P < 0.001$; within treatment comparison (t-test)

required the addition of HCTZ 12.5 mg after three ($N = 4$) or six weeks ($N = 8$). In the amlodipine group, nine patients were titrated to 10 mg after three ($N = 1$) or six weeks ($N = 8$) because they did not reach the desired goal of trough SiDBP < 90 mm Hg. After 12 weeks of treatment, 96% of losartan-treated patients and 87% of amlodipine-treated patients had a SiDBP < 90 mm Hg or a decrease in SiDBP from baseline of least 10 mm Hg (between-group difference, $P > 0.10$).

Effects on renal parameters

Table 3 summarizes the mean baseline and median and mean changes from baseline in albuminuria and creatinine clearance at week 12 for the losartan and amlodipine groups. Losartan therapy was associated with a reduction in albuminuria after 12 weeks, while amlodipine therapy was associated with median increase in this marker of renal function. The between treatment difference was statistically significant ($P = 0.021$). The change in creatinine clearance after 12 weeks of treatment did not differ significantly between the groups.

Safety and tolerability

Seven patients (29%) in the losartan group and five (21%) in the amlodipine group reported at least one clinical adverse experience during the 12-week active treatment period. Dizziness and headache (one report each) were the only adverse experiences considered at least possibly related to active treatment in the losartan group. None of the adverse experiences in the losartan group were considered serious, and no patient withdrew prematurely from losartan therapy because of an adverse experience. In the amlodipine group, there were three reports of edema, and one report each of tachycardia, cerebral edema and headache considered at least possibly drug-related. There was one serious adverse experience in the amlodipine group (myocardial infarction). This patient, and an additional patient who experienced tachycardia, headache and cerebral edema two days after beginning amlodipine therapy, discontinued the study prematurely due to their adverse experiences.

There were no serious adverse laboratory experiences. Mean changes in serum potassium levels or serum lipid profiles (total cholesterol, HDL-cholesterol and triglycerides) after 12 weeks of active treatment were small and did not differ significantly between the losartan and amlodipine groups.

DISCUSSION

Patients with high blood pressure and renal disease are a high-risk population since elevated blood pressure is associated with a more rapid progression of renal failure [6]. Several interventional studies have demonstrated that this progression can be attenuated by effective control of blood pressure with antihypertensive medication [7, 8]. According to the recent report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, patients with renal insufficiency (that is, those with a high degree of proteinuria) should be treated to a lower blood pressure goal [9]. In the present study of patients with impaired renal function complicated by mild to moderate hypertension, the angiotensin II blocker losartan produced clinically meaningful reductions in sitting diastolic and systolic blood pressure that averaged 18 and 28 mm Hg, respectively, after 12 weeks. The blood pressure response to losartan was comparable across the two stratum of albuminuria (< 300 or ≥ 300 μg/min). Moreover, the reductions seen following once daily treatment with losartan 50 mg or losartan 50 mg/HCTZ 12.5 mg were statistically superior to those observed following once daily treatment with amlodipine 5 to 10 mg.

Albuminuria is a strong predictor for the development of overt renal and cardiovascular events. Reduction of albuminuria has been considered as a subrogate marker for renal protection [10, 11]. Although the reduction in proteinuria can be related to lowering blood pressure, it appears that drugs blocking the renin-angiotensin-aldosterone system have an effect that is beyond their antihypertensive effect. This has been clearly demonstrated with ACEIs [12, 13]. An adjustment by blood pressure was not made in this study, however, results of the present trial confirm the ability of losartan to reduce albuminuria. For example, losartan was previously shown to be comparable to enalapril in decreasing albuminuria and lowering blood pressure in patients with renal disease and hypertension [14]. Furthermore, results of the present trial demonstrated that losartan was significantly more effective than amlodipine in reducing the urinary excretion of albumin. These findings are in agreement with those reported by Holdass

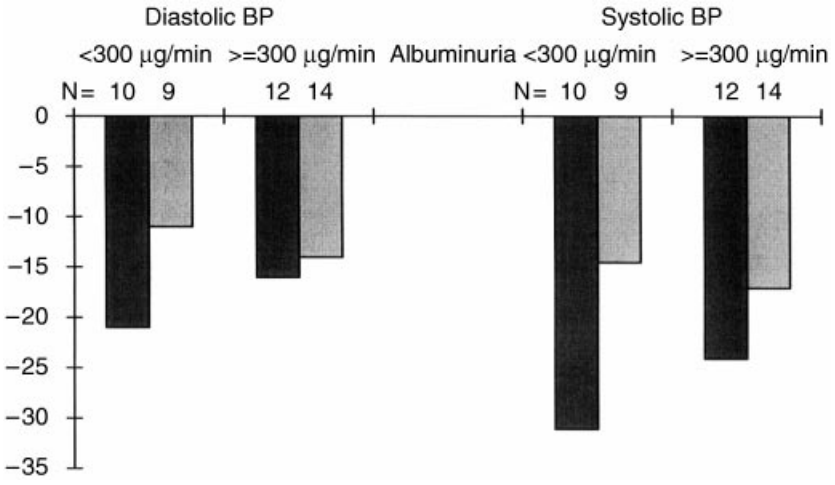

Fig. 1. Mean change from baseline in sitting diastolic and systolic blood pressures at week 12 as a function of treatment group and baseline albuminuria stratum (treatment-by-stratum interaction not significant; $P = 0.128$ for SiDBP and $P = 0.209$ for SiSBP). Symbols are (■) losartan; (▨) amlodipine.

Table 3. Mean and median changes in 24-hour urine measurements at week 12

Parameter	Losartan		Amlodipine
Albuminuria *μg/min*			
No. evaluated	22		22
Baseline mean (SD)	510.0 (707)		842.7 (1052)
Change from baseline			
Median (Q1-Q3)	−29.5 (−229, 13.3)		48.4 (−131, 606.9)
Mean (SD)	−94.7 (580)		268.5 (615)
P value[a]		0.021	
Creatinine clearance *ml/min*			
No. evaluated	23		17
Baseline mean (SD)	44.8 (12.7)		46.1 (12.9)
Change from baseline			
Median (Q1-Q3)	0.8 (−5.0, 8.5)		−2.0 (−8.1, 4.1)
Mean (SD)	0.0 (11.3)		−2.3 (13.7)
P value[a]		0.447	

[a] Between-treatment comparison, Wilcoxon signed-rank test

and colleagues [15], who showed that urinary albumin excretion was significantly decreased in patients with non-diabetic renal disease following four weeks of treatment with losartan but was increased a comparable course of amlodipine treatment. Results of animal and clinical studies on the ability of calcium channel blockers to retard progression to renal failure have been variable and generally less striking than those with ACE inhibitors [16, 17].

Losartan alone or with the addition of a low dose of hydrochlorothiazide did not significantly alter creatinine clearance in this study. The present results, coupled with those from a previous investigation showing that losartan does not adversely alter renal hemodynamics [18], suggest a nephroprotective effect for losartan in patients with essential hypertension.

No differences in tolerability between losartan and amlodipine were found in the present study. The favorable safety profile of losartan observed in this study is consistent with the overall safety profile seen in studies of hypertensive patients [19]. Across this large cohort involving over 2990 patients, dizziness was the only side effect reported as drug-related that occurred in patients receiving losartan at an incidence greater than placebo of at least 1%. In particular, cough and angioedema, adverse experiences noted with ACE inhibitors and thought to be related to bradykinin potentiation, are infrequently reported during losartan therapy.

In summary, once daily administration of losartan 50 mg, administered alone or in combination with HCTZ 12.5 mg, was more effective than amlodipine 5/10 mg in lowering blood pressure and albuminuria in patients with essential hypertension complicated by impaired renal function.

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