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Prospective and randomized study of the antihypertensive effect and tolerability of three antihypertensive agents, losartan, amlodipine, and lisinopril, in hypertensive patients

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Abstract We prospectively evaluated the antihypertensive effect and tolerability of three different antihypertensive agents, losartan (angiotensin II receptor blocker), amlodipine (calcium channel blocker), and lisinopril (angiotensin-coverting enzyme inhibitor), in patients with mild-to-moderate hypertension. After a 2-week washout period, 121 patients were randomly allocated to three different groups for 12 weeks. Medications were titrated upward as necessary to achieve the goal office-recorded sitting diastolic blood pressure (SiDBP) (defined as SiDBP $<$90 mmHg or SiDBP $\geqq$900 mmHg but with a $\geqq$10 mmHg drop from baseline). Efficacy and tolerability were assessed after 4, 8, and 12 weeks of therapy with each regimen. At 12 weeks, significant differences in SiDBP compared with data of baseline were noted in all three groups ($P < 0.001$ in all comparisons). Similarly, significant differences in the sitting systolic blood pressure compared with baseline data were also seen for all three groups ($P < 0.001$ in all comparisons). The number of patients reaching goal SiDBP were comparable for the three groups: 25 patients (62.5%) in the losartan group, 27 patients (67.5%) in the amlodipine group, and 22 patients (59.5%) in the lisinopril group (not significant). Amlodipine produced a more pronounced reduction in SiDBP than the other two medications, although without statistical significance. Patients receiving lisinopril showed a high incidence of coughing (31.7%). Low leg edema was noted only in the amlodipine group (7.5%). Compared with the amlodipine and lisinopril groups, the losartan group seemed to have relatively fewer episodes (7.5%), and fewer patients (three cases) experienced adverse effects. In conclusion, this study demonstrates that losartan has the same antihypertensive effect, but has superior tolerability compared with the other two drugs. Coughing was a common side effect of lisinopril therapy in our population.

Key words Angiotensin-converting enzyme inhibitor · Angiotensin receptor antagonist · Calcium channel blocker · Hypertension

Introduction

Previous studies have shown that calcium antagonists[1–3] and angiotensin-converting enzyme inhibitors[4–8] are safe and effective in the control of blood pressure. Losartan is an angiotensin II type 1 receptor antagonist. A single daily dose of losartan appears to lower blood pressure throughout the day.[9] Most comparative studies on the safety and effectiveness of antihypertensive drugs are based on the data of two medications.[10–15] Information of randomized and prospective studies comparing the efficacy of these three different kinds of medications is limited.[16] The purpose of this study was to compare the efficacy and tolerability of three agents, losartan, amlodipine (calcium channel blocker), and lisinopril (angiotensin converting enzyme inhibitor) in patients with mild-to-moderate hypertension.

Methods

Study patients

Patients with mild-to-moderate hypertension (sitting diastolic blood pressure between 95 and 114 mmHg) and no known drug hypersensitivity to the study medications were enrolled. After a 2-week run-in period, each patient was asked to sign an informed consent form. The informed consent forms were approved by the review boards of our

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hospitals. Eligible patients were randomly assigned into three different groups. Patients in the first group began treatment with losartan ($n = 40$) at 50 mg/day, those in the second group began with amlodipine ($n = 40$) at 5 mg/day, and those in the third group began treatment with lisinopril ($n = 41$) at 10 mg/day. If blood pressure remained uncontrolled after 4 weeks, patients had their doses doubled with respect to their original regimens. Efficacy and tolerability were assessed after 4, 8, and 12 weeks of therapy with each regimen.

A complete medical history, physical examination, and laboratory screening including a complete blood count, measurement of serum electrolytes, blood urea nitrogen, creatinine, transaminase, urinalysis, and electrocardiogram, were studied at the time of enrollment. Exclusive criteria included: pregnant or lactating females, secondary hypertension of any etiology, history of malignant hypertension, sitting systolic blood pressure ≧210 mmHg, history of myocardial infarction or angina pectoris, clinically important cardiac arrhythmia, history of unexplained syncope within 2 years, symptomatic heart failure, presence of hemodynamically significant obstructive valvular disease or cardiomyopathy, history of coronary angioplasty or coronary artery bypass surgery within 6 months, clinically important malabsorption syndrome or gastric resection, cirrhosis of the liver, patient with a single functioning kidney, unstable diabetes mellitus (HbA1c $> 7\%$), or another concurrent severe disease which could preclude optimal participation in the study, or which might effect the study measurements (e.g., active neoplasm, active acquired immunodeficiency syndrome, active viral hepatitis B or C). The study protocol was approved by the Review Committee on Ethics of our hospitals.

Study design

If the patient was a virgin case of hypertension with sitting diastolic blood pressure (SiDBP) between 95 and 114 mmHg, he or she might be included directly in the trial (week 0). If a patient had already received medication, the patient was told to stop their current antihypertensive drugs for 2 weeks (visit 1), and return to the clinic 2 weeks later (visit 2, week 0). If the patient met the inclusion criteria and none of the exclusion criteria, he or she was enrolled in the trial at visit 2. Patients were randomly assigned to three different groups: those who received losartan 50 mg, amlodipine 5 mg, or lisinopril 10 mg. One tablet daily in the morning was recommended. Then, the patient was told to come back to the clinic for visit 3 (week 4), and if the SiDBP was ≧90 mmHg, the patient could double the dosage. If the patient could not tolerate the adverse effects after 4 weeks' treatment, (s)he was withdrawn at that time. The patient sat for 10 min to calm down after arriving at the clinic. At each visit, systolic blood pressure, diastolic blood pressure, and pulse rate were measured. The doctor measured blood pressure using a mercury sphygmometer twice, 5 min apart. The resulting diastolic blood pressures were then averaged and recorded as the sitting diastolic blood pressure. The same procedure was applied for recording of the pulse rate and sitting systolic blood pressure (SiSBP). Besides the pulse rate and blood pressure measurement, patients were asked to return to the clinic to document tolerability or to monitor adverse effects and biochemistry after 4, 8, and 12 weeks of therapy.

Statistical analysis

Comparison of the age of three groups was assessed initially using analysis of variance (ANOVA); if the difference was significant, then the Mann-Whitney *U*-test was used to study the intergroup difference. Changes in blood pressure and pulse rate were also analyzed using ANOVA; if the difference was significant, then the Mann-Whitney *U*-test was studied for within-group and inter-group differences. Comparisons were also made using the chi-square test among treatment groups with respect to the number of patients who reached the goal of treatment (SiDBP <90 mmHg or SiDBP ≧90 mmHg, but with a reduction in SiDBP of at least 10 mmHg from the baseline). The difference in sex and adverse effects in the three treatment groups was also compared using the chi-square test.

Results

From January 2001 to December 2002, a total of 129 patients were entered into the study. Eight patients dropped out during the washout period; thus, 121 patients were enrolled in this study. The demographics and characteristics of the patients are summarized in Table 1. There was no statistically significant difference in patient characteristics at baseline among the treatment groups. Twenty-five patients (8 losartan, 8 amlodipine, 9 lisinopril) were found to have moderate hypertension, defined as SiDBP between 105 and 114 mmHg, while the rest had mild hypertension whenever they entered the active treatment phase. Four patients in the lisinopril group had intractable cough and they were excluded after 4 weeks' treatment. The other 117 patients completed 12 weeks of therapy.

Efficacy

The efficacy of antihypertensive treatment was based on the data of 117 patients. At 4 weeks of treatment, significant

Table 1. Demography of study population

	Losartan ($n = 40$)	Amlodipine ($n = 40$)	Lisinopril ($n = 41$)
Age, years			
Male	64.7 ± 13.2	66.0 ± 11.9	63.6 ± 9.2
Female	59.6 ± 9.3	59.0 ± 11.9	60.8 ± 11.0
Sex			
Male	16	18	19
Female	24	22	22

Table 2. Differences in sitting systolic blood pressure (SiSBP) in the three groups

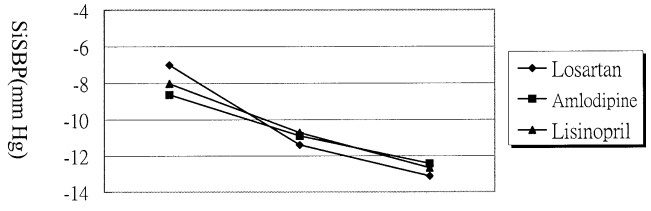
Time	Losartan group	Amlodipine group	Lisinopril group
Baseline	155.1 ± 12.0	153.5 ± 8.9	151.1 ± 9.6
4 weeks	147.6 ± 11.3*	144.8 ± 9.4*	143.1 ± 7.2*
8 weeks	143.2 ± 7.8*	142.6 ± 9.4*	140.4 ± 6.9*
12 weeks	141.5 ± 7.5*	138.5 ± 6.6*	141.0 ± 9.1*

* $P < 0.001$ compared with baseline

Table 3. Differences in sitting diastolic blood pressure (SiDBP) in the three groups

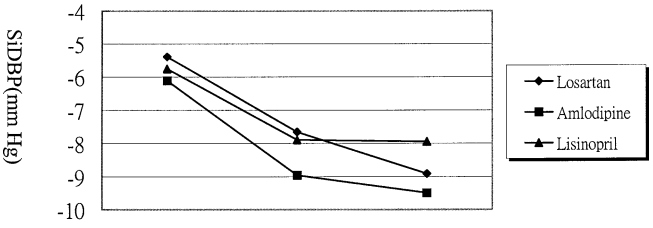
Time	Losartan group	Amlodipine group	Lisinopril group
Baseline	99.8 ± 6.2	99.4 ± 4.2	98.5 ± 4.9
4 weeks	94.3 ± 6.3*	92.7 ± 4.4*	92.8 ± 5.5*
8 weeks	92.0 ± 5.2*	90.6 ± 4.8*	90.3 ± 6.3*
12 weeks	90.7 ± 5.1*	90.3 ± 5.2*	90.1 ± 4.6*

* $P < 0.001$ compared with baseline



	Week 4	Week 8	Week 12
Losartan	-7.0±8.8	-11.4±8.5**	-13.1±9.8**
Amlodipine	-8.6±4.5	-10.9±5.3*	-12.4±4.2**
Lisinopril	-8.0±7.2	-10.7±6.7**	-12.7±7.9**

Fig. 1. Changes in mean (±SD) sitting systolic blood pressure (*SiSBP*) at weeks 4, 8, and 12 in patients receiving losartan, amlodipine, and lisinopril. *$P < 0.01$, **$P < 0.001$ compared with week 4. There were no significant differences in the data between week 8 and week 12 in each group. There were no inter-group differences at different time periods



	Week 4	Week 8	Week 12
Losartan	-5.3±3.6	-7.7±3.7*	-8.9±4.3*†
Amlodipine	-6.1±3.6	-9.0±3.0*	-9.5±2.5*
Lisinopril	-5.8±3.1	-7.9±4.0*	-7.9±2.8*

Fig. 2. Changes in mean (±SD) sitting diastolic blood pressure (*SiDBP*) at weeks 4, 8, and 12 in the different groups. *$P < 0.001$, compared with week 4. There were no significant differences in the data between week 8 and week 12 in each group, except for the losartan group (†$P < 0.05$ compared with week 8). There were no inter-group differences at different time periods

reductions in SiSBP ($P < 0.001$ compared with data of baseline) were noted in all three groups. Similarly, the reductions in SiSBP ($P < 0.001$) compared with the baseline data were also significant at 8 and 12 weeks in all three groups (Table 2). However, there were no differences in the data between week 8 and week 12 in all three groups. There were no inter-group differences at different time periods. Figure 1 demonstrates the change in mean SiSBP at weeks 4, 8, and 12, respectively, in the three groups. At week 8, the reduction in SiSBP was significantly greater for the losartan and lisinopril groups compared with week 4 ($P < 0.001$ in each comparison); there was also a considerable reduction in SiSBP for the amlodipine group compared with week 4 ($P < 0.01$). At week 12, the reduction in SiSBP was significantly greater than that at week 4 ($P < 0.001$) in all three groups. There were no differences in the data between week 8 and week 12 in the three groups.

After 12 weeks of treatment, the distribution of treatment among the patients was as follows. In the losartan group, 18 patients (45%) remained on 50 mg alone and 22 patients (55%) were on 100 mg losartan. In the amlodipine group, 19 patients (47.5%) remained on 5 mg alone, and 21 patients (57.5%) were on 10 mg amlodipine. In the lisinopril group, 21 patients (51.2%) remained on 10 mg alone, and 20 patients (48.8%) were on 20 mg lisinopril.

Table 3 illustrates the reduction in mean SiDBP in each treatment group. The losartan, amlodipine, and lisinopril regimens were comparable in their ability to reduce SiDBP at the end of the 12-week treatment period. Figure 2 shows the changes in mean SiDBP at weeks 4, 8, and 12, respectively, in the three groups. In all three groups the reduction in mean SiDBP at week 8 and week 12 was significantly greater than those at week 4 ($P < 0.001$ in all comparisons). Further reduction of SiDBP at week 12 compared with week 8 in the losartan group was noted ($P < 0.01$). There were no inter-group differences in SiDBP at different time periods among these three drugs. However, it seemed that the amlodipine group showed a more pronounced reduction of the SiDBP among the three groups, although it did not reach statistical significance.

When the response was evaluated based on the percentage of patients who achieved an SiDBP <90 mmHg, 22 patients (55%) in the losartan group were successful, compared with 23 patients (57.5%) in the amlodipine group and 20 patients (54.1%) in the lisinopril group (P not significant). Patients who did not achieve the target of SiDBP <90 mmHg but had a ≧10 mmHg reduction in SiDBP from baseline included 3 patients (7.5%) in the losartan, 4 patients (10%) in the amlodipine and 2 patients (5.4%) in the lisinopril group. Overall, 25 patients (62.5%) in the losartan, 27 patients (67.5%) in the amlodipine, and 22 patients (59.5%) in the lisinopril group reached the goal (P not significant among these three groups). The average pulse rate in the three treatment groups at weeks 4, 8, and 12 were not significantly different from the baseline. Similarly, there were no differences in pulse rate at different time periods (Table 4; P not significant).

Table 4. Pulse rate changes in the three groups

Time	Losartan group	Amlodipine group	Lisinopril group
Baseline	79.6 ± 8.6	79.8 ± 7.8	73.8 ± 9.4
4 weeks	80.6 ± 9.7	81.4 ± 9.0	82.6 ± 9.9
8 weeks	80.2 ± 9.2	82.6 ± 9.9	82.8 ± 9.6
12 weeks	79.9 ± 9.9	79.9 ± 9.9	74.5 ± 9.3

No significant differences in pulse rate among the different groups and time periods were noted

Table 5. Clinical adverse experience (AE) reported by the investigators in patients treated with the three drugs

	Losartan	Amlodipine	Lisinopril
AE patients	3 (7.5%)*	6 (15%)	14 (34.1%)
AE episodes	3 (7.5%)†	10 (25%)	16 (39.0%)
Withdrawal of patient due to AE	0 (0%)	0 (0%)	4 (9.8%)

* $P < 0.05$ compared with lisinopril group; † $P < 0.01$ compared with lisinopril group

Adverse effects

Adverse effects were registered based on the data of the 121 enrolled patients. In the losartan group, 3 patients experienced adverse effects: 1 (2.5%) experienced dizziness, 1 (2.5%) experienced a bad taste, and 1 had a cough (2.5%). In the amlodipine group, 6 patients experienced adverse effects: 3 (7.5%) had low leg edema, 3 (7.5%) developed headaches, and 4 (10%) suffered from dizziness. Four of these patients had more than one adverse effect. In the lisinopril group, 14 patients experienced adverse effects: 2 (4.9%) experienced dizziness, 1 (2.4%) complained of nasal congestion, and 13 (31.7%) had a cough. Two patients had more than one adverse effect. Four patients (9.8%) receiving lisinopril developed all intractable cough and they were subsequently withdrawn from the study. Clinical adverse effects reported according to patient number and episodes are shown in Table 5. Significantly more patients ($P < 0.05$) and more adverse episodes ($P < 0.01$) were experienced in the lisinopril than in the losartan group. Patients receiving lisinopril showed a high incidence of cough (31.7%). Low leg edema was noted only in the amlodipine group (7.5%). Overall, the adverse experiences seemed more prominent in the lisinopril group, followed by the amlodipine group. Losartan seemed to be better tolerated by the study patients.

The biochemistry data, including urea nitrogen, creatinine, transaminase (ALT, AST), glucose, cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, albumin, potassium, sodium, calcium, and uric acid, revealed no significant changes compared with the baseline data in the different treatment regimens.

Discussion

This study demonstrated that all three treatment regimens provided significant blood pressure reduction. Mean SiDBP and SiSBP were significantly reduced from baseline in all treatment groups (Tables 2 and 3). The reduction in blood pressure was not significantly different among the three treatment groups. The goal blood pressure reduction (SiDBP <90 mmHg or reduction of blood pressure ≧10 mmHg from the baseline) was also comparable in the three groups: 52% in the losartan group, 55% in the amlodipine group, and 54% in the lisinopril group.

Losartan, an AT_1 receptor blocker, blocks the actions of angiotensin II on cardiovascular homeostasis; the blockade of these actions by losartan leads to vasodilation, natriuresis, and a reduction in blood pressure.[17,18] Amlodipine (a dihydropyridine antagonist) inhibits the influx of calcium ions into the vascular smooth muscle cells, which causes peripheral arterial vasodilation and a reduction in blood pressure.[19,20] The blockade of the renin-angiotensin-aldosterone system by lisinopril leads to vasodilation, natriuresis, and a reduction in blood pressure.[21] A previous study demonstrated that both losartan and amlodipine were effective in lowering the blood pressure and were tolerated well.[22] Tikkanen et al. found that losartan is an effective antihypertensive drug showing a similar blood pressure-lowering efficacy to that of enalapril.[23] This study also demonstrated that all regimens were effective in controlling blood pressure in patients with both mild and moderate hypertension. However, the report of the Joint National Committee (JNC-6) has not recommended the AT_1 receptor blocker as the choice of initial therapy for hypertensive patients.[24] Besides blood pressure control, losartan appears to offer many other advantages. According to the results of the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial, Dahlöf et al. reported that the reduction in risk for stroke, cardiovascular mortality, and myocardial infarction was 13% greater with losartan than with atenolol.[25] The benefits are beyond what would be expected through blood–pressure reduction alone.[1–3,25,26] They claimed that losartan might be considered as a first-line antihypertensive which may improve the outcome for hypertensive patients with benefits beyond blood pressure reduction. Indeed, a broader application of losartan in hypertensive patients, especially in those with diabetes or proteinuria, might be more beneficial.

The usefulness of antihypertensive drugs depends not only on the degree to which blood pressure is lowered but also on the reduction of complications relative to the adverse effect profile. In our study, the losartan group seemed to have relatively fewer episodes, and fewer patients experienced adverse effects compared with the amlodipine and lisinopril groups. Low leg edema was noted only in the amlodipine group (7.5%). A high incidence of coughing (31.7%) was noted in the lisinopril group. Previous reports stated that the incidence of coughing in patients receiving angiotensin-converting enzyme inhibitors ranged from 0.2% to 25%.[27–32] Several investigators have claimed that the incidence of coughing with angiotensin-converting enzyme inhibitors in the Chinese population is high. Chan et al. documented coughing in 27% of Chinese patients after receiving an angiotensin-converting enzyme inhibitor.[33]

Woo and Chan found that the incidence of coughing was 48% in Chinese patients after the use of lisinopril.[34] A prospective case-controlled study found that the incidence (53%) in Chinese patients receiving angiotensin-converting enzyme inhibitors was much higher than that (18%) in Caucasians, and racial difference was suspected to be the cause.[35] The incidence in our patients was 31.7%, which was close to that reported by Chan et al.,[33] but less than that by Woo et al.[34,35] Nevertheless, the overall influence on the quality of life from each regimen due to the side effects were minimal in this study. Most patients could tolerate the regimens until the end of the study.

In conclusion, this study demonstrates that a high incidence of coughing was noted in the lisinopril-treated group, which suggests that a cough is a common side effect of lisinopril treatment in the Chinese population. Losartan has the same antihypertensive effect but shows superior tolerability compared with the other two drugs. A broader application of losartan in clinical practice is recommended.

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