Lercanidipine and Losartan Effects on Blood Pressure and Fibrinolytic Parameters

Tsung-Hsien Lin, Wen-Chol Voon, Hsueh-Wei Yen, Chih-Hsin Huang, Ho-Ming Su, Wen-Ter Lai, and Sheng-Hsiung Sheu
Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

Antihypertensive agents may modulate fibrinolysis in addition to reducing blood pressure. We conducted a randomized trial to assess the effects of lercanidipine and losartan on blood pressure (BP) lowering and three fibrinolytic parameters: plasminogen activator inhibitor-1 (PAI-1), D-dimer, and fibrinogen. All patients enrolled had essential hypertension and underwent a placebo run-in period of 2 weeks before randomization to either lercanidipine tablets 10–20 mg once daily or losartan tablets 50–100 mg once daily. Twenty-six patients completed this study. After 8 weeks of treatment, both groups of patients had significantly reduced systolic (SBP) and diastolic BP (DBP) (SBP, $p = 0.034$ and 0.050, respectively; DBP, $p = 0.018$ and 0.034 for lercanidipine and losartan, respectively). Both drugs were well tolerated. Only in the group treated with lercanidipine was PAI-1 concentration significantly reduced (57.1 ± 4.7 to 43.1 ± 4.8 ng/mL, $p = 0.047$). No difference was found with D-dimer and fibrinogen in either group. This study shows that both lercanidipine and losartan are effective antihypertensive drugs in patients with essential hypertension. Lercanidipine may provide additional benefit in fibrinolysis.

Key Words: lercanidipine, losartan, fibrinolysis, hypertension, plasminogen activator inhibitor
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Hypertension has long been recognized as one of the principal risk factors for cardiovascular disease. It may be associated with impaired fibrinolysis [1]. Antihypertensive agents that decrease blood pressure (BP) have been shown to be effective in reducing cardiovascular morbidity and mortality [2]. In patients suffering from cardiovascular events, impaired fibrinolysis is known to be a poor prognostic factor [3]. However, agents previously used to treat hypertension, such as diuretics and β-blockers, have adverse effects on lipid, carbohydrate metabolism, and fibrinolysis, perhaps counteracting the beneficial antihypertensive effect [1].

The activity of the renin-angiotensin-aldosterone axis can influence endothelial function and endogenous fibrinolysis. The first angiotensin receptor blocker (ARB) introduced for clinical use was losartan. Some evidence suggests that ARB increases fibrinolysis, but these data are inconsistent [4,5]. Calcium channel blockers (CCBs) are a heterogeneous group of pharmacologic agents commonly prescribed to patients with hypertension and coronary heart disease. Previous studies investigated the impact of CCBs on fibrinolytic activity with conflicting results [6,7]. Later, lercanidipine was introduced as a treatment. It is a vasoselective dihydropyridine CCB that causes systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes [8]. It is a highly lipophilic drug, the action of which has a slower onset and longer duration than other calcium channel antagonists. Furthermore, lercanidipine may have antiatherogenic activity unrelated to its antihypertensive and antioxidant effect [8,9]. However, the effects of lercanidipine on fibrinolysis have not been studied.

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Address correspondence and reprint requests to: Dr. Sheng-Hsiung Sheu, Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Shi-Chuan 1st Road, Kaohsiung 80708, Taiwan.
E-mail: Sheush@kmu.edu.tw

This study investigates the antihypertensive efficacy and safety of lercanidipine and losartan administered orally once daily for 8 weeks to hypertensive Taiwanese patients. We also tested the change of the three fibrinolytic parameters: plasminogen activator inhibitor-1 (PAI-1), D-dimer, and fibrinogen.

Patients and Methods

This was a single-center, randomized, parallel-group study comparing the efficacy and safety of lercanidipine and losartan for the treatment of essential hypertension. The investigators were blinded to the treatment groups. The study was approved by the institutional review committee at Kaohsiung Medical University Hospital. Inclusion criteria included: 1) age older than 18 years; 2) baseline BP over 140/90 mmHg; and 3) willingness to participate in the trial and to sign a written consent. Those who met these criteria were excluded if any of the following was present: 1) secondary hypertension; 2) pregnancy or breast-feeding; 3) history of myocardial infarction, cerebrovascular disease, or congestive heart failure; 4) chronic renal insufficiency (creatinine more than 2 mg/dL); 5) impaired liver function (aspartate transaminase or alanine transaminase greater than twice the upper normal limit); 6) history of CCB or ARB allergy; and 7) other major medical abnormalities (e.g. severe drug allergy, autoimmune disease).

Every visit included a physical examination and BP measurement. All BPs were measured with a mercury sphygmomanometer while sitting. Upon arrival, after a 10-minute rest, the BP was measured twice, with the second reading after a 1- to 2-minute interval. The mean was recorded. Twelve-lead electrocardiography and chest X-ray were taken to exclude significant organic heart disease. Systolic BP (SPB) response rate was defined as the percentage of patients at the end of the study with SBP less than 140 mmHg or a reduction from baseline in SBP by at least 20 mmHg.

Total duration of this trial was 10 weeks (i.e. 2 weeks washout plus 8 weeks of treatment). During the 2-week washout (placebo run-in) period, each subject discontinued all antihypertensive medicines. Eligible patients were then randomized to one of the following parallel treatment groups: lercanidipine 10 mg or losartan 50 mg. The initial 4 weeks served as a titration period, during which we adjusted the dose to achieve the best antihypertensive effect. Patients with a mean SBP greater than 140 mmHg at that time were advanced to the double-strength regimen (lercanidipine 20 mg or losartan 100 mg). At each visit, general open-ended questions were asked to monitor any occurrences of adverse events. During the routine visit at the 6th and 10th weeks, unused medication was counted and recorded to assure dosage compliance.

Laboratory evaluation was done at screening and at the end of the study. Fasting blood samples (8-hour fast) were collected for hematology and biochemistry analysis. Whole blood (10 mL) was collected in sodium citrate tubes and centrifuged for fibrinolytic parameters. Plasma was frozen under –80°C until use. All fibrinolytic parameter analysis was done at the end of the study. PAI-1 was measured using the commercial enzyme-linked immunosorbent assay method (Diagnostica Stago, France). Fibrinogen was measured according to the Clauss clotting method, and D-dimer concentration was measured by the immunoturbidimetric method (Diagnostica Stago).

The primary endpoint of this study was efficacy of BP lowering after 8 weeks with either lercanidipine or losartan treatment. The secondary endpoints were the treatment safety profile and change of fibrinolytic parameters (PAI-1, D-dimer, and fibrinogen).

Statistical analysis

All data were expressed as mean ± standard error of the mean. All tests were two-sided. A p value of less than 0.05 was considered statistically significant. χ^2 test and Wilcoxon rank-sum test were used to compare categorical data and nonparametric data, respectively. The t test was used for analysis between continuous variables. Serial data for repeated measures were analyzed using two-way analysis of variance. The Statistical Package for the Social Sciences (SPSS) 11.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

Baseline data

A total of 35 prospective participants were screened, six were excluded, and 29 (18 in the lercanidipine and 11 in the losartan group) were randomized. Exclusion causes were withdrawal of consent (n = 1) and loss of follow-up after screening (n = 5). The study was terminated early for three participants because of intolerance to adverse effects, and 26 completed the trial (16 lercanidipine, 10 losartan). Effects causing participants to withdraw early on lercanidipine were dermatitis (n = 1) and palpitations (n = 1). The unfavorable losartan side effect was rhinitis (n = 1).

Table 1. Baseline characteristics of study participants

	Lercanidipine (n = 18)	Losartan (n = 11)	p
Age (yr)	51.4 ± 1.5	52.6 ± 2.2	0.740
Sex (male, %)	56	54	1.000
Weight (kg)	66.5 ± 2.5	66.4 ± 3.9	0.805
Fasting blood glucose (mg/dL)	99.7 ± 3.3	99.5 ± 2.3	0.840
Blood urea nitrogen (mg/dL)	13.0 ± 0.7	12.7 ± 0.6	0.822
Creatinine (mg/dL)	0.98 ± 0.05	1.04 ± 0.06	0.380
Cholesterol (mg/dL)	203.0 ± 10.2	191.0 ± 9.2	0.669
Triglyceride (mg/dL)	163.2 ± 19.6	150.1 ± 15.5	0.702
Systolic blood pressure (mmHg)	161.7 ± 3.4	160.0 ± 3.5	0.842
Diastolic blood pressure (mmHg)	99.4 ± 1.4	100.1 ± 1.8	0.912

The baseline characteristics of the 29 participants are given in Table 1. There was no difference between patients taking lercanidipine and losartan with respect to gender, age, body weight, biochemical data, and baseline BP.

Blood pressure

Both treatments significantly reduced BP compared with baseline (Figure 1). The percentage of initial stage 1 and stage 2 hypertension was 22% and 78% in the lercanidipine group, and 36% and 64% in the losartan group (p = 0.408). A total of 11 patients (62%) in the lercanidipine group and 5 (46%) patients in the losartan group were advanced to the double-strength regimen. The average final doses were lercanidipine 16.1 ± 1.2 mg and losartan 72.7 ± 7.9 mg. SBP decreased in patients taking lercanidipine from 161.7 ± 3.4 to 148.4 ± 4.0 mmHg (p = 0.034). Diastolic BP (DBP) dropped from 99.4 ± 1.4 to 93.8 ± 1.9 mmHg (p = 0.018). In the losartan group SBP decreased from 160.0 ± 3.5 to 149.7 ± 5.2 mmHg (p = 0.050) and DBP from 100.1 ± 1.8 to 91.9 ± 4.1 mm Hg (p = 0.034). There was no difference in SBP or DBP reduction between groups (–13.3 ± 5.5 vs –10.3 ± 4.9 mm Hg for SBP reduction, p = 0.712, and –5.6 ± 2.1 vs –8.2 ± 3.3 mm Hg for DBP reduction, p = 0.504).

After 8 weeks of treatment, the response rate was 58.82% in the lercanidipine group (95% confidence interval [CI]: 32.9–81.6%) and 80% in the losartan group (95% CI: 44.4–97.5%, p = 0.451 between the two groups). Mean compliance was satisfactory in both groups: 93.0% in the lercanidipine group and 100% in the losartan group.

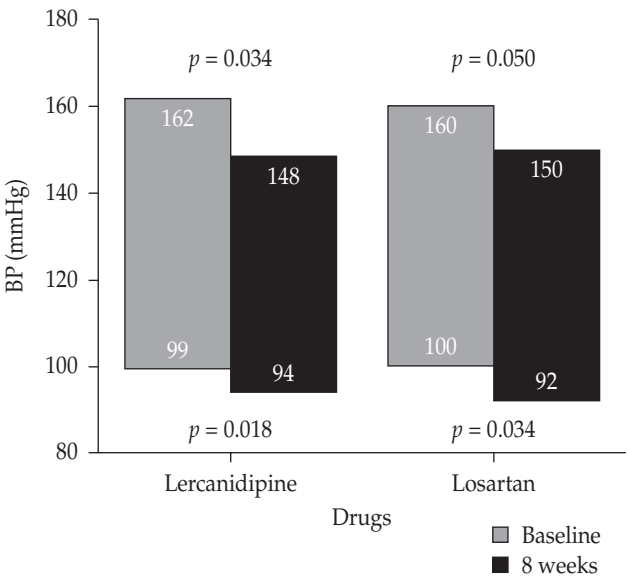

Figure 1. *Systolic and diastolic blood pressure after 8 weeks of treatment with lercanidipine and losartan. Numbers within the bars indicate the blood pressure level in mmHg.*

Safety

Adverse events were defined as treatment-related adverse events (i.e. events that first occurred or worsened after randomization). There was no statistically significant difference in occurrence of adverse events between the two groups (lercanidipine 50.0%; losartan 45.5%; p = 1.000) or in the nature of each adverse event. The most commonly reported treatment-related adverse events were palpitation (lercanidipine 16.7%), dizziness (lercanidipine 5.6%, losartan 18.2%), and rhinitis (lercanidipine 5.6%, losartan 18.2%) (Table 2).

Fibrinolytic parameters

Of the 26 patients who completed the trial, one in the lercanidipine group did not have an adequate amount of blood for fibrinolytic parameter analysis. The remaining 25

Table 2. Reported adverse effects

	Lercanidipine (n = 18)	Lorsartan (n = 11)	p
All adverse events	9 (50.0)	5 (45.5)	1.000
Palpitation	3 (16.7)	0 (0.0)	0.269
Dizziness	1 (5.6)	2 (18.2)	0.539
Rhinitis	1 (5.6)	2 (18.2)	0.539
Sleep problems	2 (11.1)	0 (0.0)	0.512
Chest pain	1 (5.6)	1 (9.1)	1.000
Dyspnea	1 (5.6)	1 (9.1)	1.000
Arthralgia	1 (5.6)	0 (0.0)	1.000
Bronchitis	1 (5.6)	0 (0.0)	1.000
Constipation	1 (5.6)	0 (0.0)	1.000
Dermatitis	1 (5.6)	0 (0.0)	1.000
Cough	0 (0.0)	1 (9.1)	0.379
Headache	0 (0.0)	1 (9.1)	0.379
Neck rigidity	0 (0.0)	1 (9.1)	0.379
Vertigo	0 (0.0)	1 (9.1)	0.379

patients (15 in the lercanidipine group and 10 in the losartan group) had blood collected for fibrinolytic evaluation. PAI-1 was significantly decreased with lercanidipine (57.1 ± 4.3 vs 43.8 ± 4.6 ng/mL, p = 0.047), but not losartan (66.0 ± 6.4 vs 60.5 ± 6.0 ng/mL, p = 0.284). There was no change in either group of D-dimer (0.45 ± 0.08 vs 0.41 ± 0.05 μg/mL, p = 0.724 in the lercanidipine group; 0.45 ± 0.11 vs 0.55 ± 0.24 μg/mL, p = 0.893 in the losartan group) or fibrinogen (2.29 ± 0.14 vs 2.58 ± 0.20 g/L, p = 0.570 in the lercanidipine group; 2.58 ± 0.13 vs 2.55 ± 0.23 g/L, p = 0.959 in the losartan group) (Figures 2 and 3).

Discussion

This study had three findings. First, in Taiwanese patients, essential hypertension treatment with both lercanidipine and losartan were shown to be comparably effective in

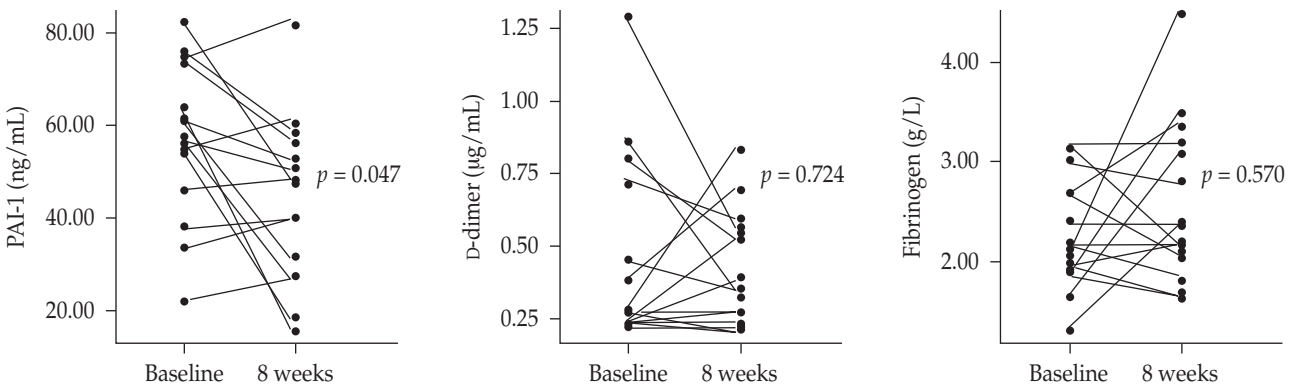

Figure 2. *Fibrinolytic parameters after 8 weeks of treatment with lercanidipine.*

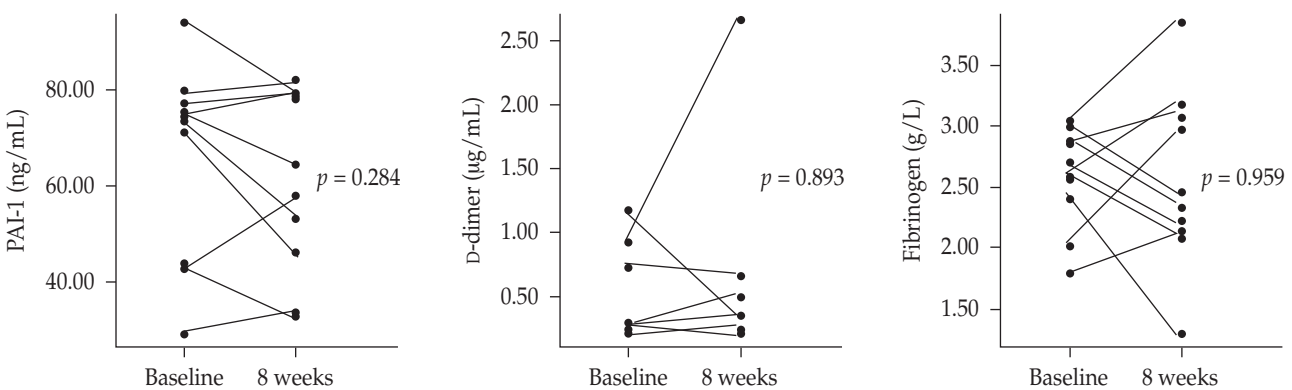

Figure 3. *Fibrinolytic parameters after 8 weeks of treatment with losartan.*

lowering BP. Second, both treatments were well tolerated and had a low withdrawal rate. Third, treatment with lercanidipine may provide additional beneficial effects on fibrinolysis.

CCBs are widely used for the treatment of hypertension and prevention of cardiovascular disease [10]. Some studies suggest that mechanisms in addition to BP control may be important in determining the therapeutic efficacy of CCBs [11]. Many CCBs have been reported to have a potential antiatherogenic effect unrelated to their antihypertensive activity. Lercanidipine has been reported to inhibit arterial smooth muscle cell proliferation and migration [12], to reduce the extent of atherosclerotic lesions [13], to have antioxidant activity and significant reduction of low-density lipoprotein cholesterol oxidation, and to restore endothelial function [9,14]. For the first time, our study shows that lercanidipine may have beneficial effects on fibrinolysis. Impairment of fibrinolysis is instrumental in promoting atherothrombotic events in patients with hypertension. Therefore, several studies have evaluated the impact of CCBs on fibrinolytic activity, but results are conflicting [6,7]. Mechanisms for such an effect are unknown, although a direct action of lercanidipine on vascular endothelium probably plays an important role. Lercanidipine has been suggested to improve endothelial function, mainly by restoring nitric oxide availability and preventing hyperpolarization, an effect probably determined by antioxidant activity [14]. Because PAI-1 is synthesized in the vascular endothelium, and endothelial dysfunction induces an imbalance in fibrinolysis, the improvement of endothelial function might reverse the fibrinolytic imbalance.

Angiotensin II leads to expression of PAI-1 in cell culture by stimulating the tissue factor (TF). This effect is mediated by the angiotensin II type 1 (AT1) receptor [15,16]. Inhibition of angiotensin-converting enzyme activity attenuates the increase in PAI-1 mRNA and plasma activity in diabetic mice with cardiac TF, and AT1 receptor blockade reduces PAI-1 and TF activities in cell culture and animal studies [16,17]. Losartan was the first ARB, having been introduced in the treatment of hypertension in 1995. In 20 patients with moderate hypertension, 4 weeks of treatment with losartan had no effect on PAI-1 antigen, either during basal conditions or during acute hyperinsulinemia induced by oral glucose or insulin infusion [4]. In another larger study, irbesartan and candesartan, but not losartan, significantly lowered plasma levels of PAI-1 antigen [7]. As with the present study, there was no significant change in PAI-1, D-dimer, or fibrinogen after 8 weeks of losartan treatment. Apparently, different ARBs have differing fibrinolysis potency. Therefore, more work is necessary to clarify effects of various ARBs on fibrinolytic parameters.

Extrapolating efficacy and tolerability data from one patient population to another has major limitations, particularly when different ethnic groups are involved [18]. Losartan usage in Chinese populations was previously reported to be well tolerated and to significantly reduce SBP and DBP after 4–8 weeks' treatment [19]. This, however, is the first study to examine the relative efficacy and tolerability of lercanidipine in Chinese hypertensive populations. Lercanidipine was effective and well tolerated. We found that once-daily, 8-week treatment with lercanidipine achieved a significant reduction in SBP and DBP, and was as effective in lowering BP as a once-daily treatment of the same duration with losartan. Patients had satisfactory compliance and response rate.

There were three limitations in our study. First, our investigation involved only a small number of patients. Second, we had no placebo group because of ethical issues. Therefore, we administered lorsartan, which was known to be effective against hypertension but to have a neutral effect on fibrinolysis [4], to the control group. Third, although the change in PAI-1 may have reached statistical significance, it was unclear if this was clinically meaningful.

Conclusions

Both lercanidipine and losartan given once daily are effective and well-tolerated antihypertensive agents in Taiwanese patients with essential hypertension. Eight weeks of treatment with lercanidipine also significantly reduced PAI-1. This effect may provide additional cardiovascular benefit, but it requires confirmation from more extensive clinical data.

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Lercanidipine 與 Losartan 對降血壓及血栓溶解因子的影響

林宗憲　溫文才　顏學偉　黃智興　蘇河名　賴文德　許勝雄

高雄醫學大學附設中和紀念醫院心臟血管內科

降血壓藥物除了可降低血壓外也可能影響血栓溶解。我們進行一隨機分配的研究來探討 lercanidipine 及 losartan 對血壓及血栓溶解因子 (胞漿素原活化抑制因子 -1，D 雙體與纖維原) 的影響。所有的病人皆為原發性高血壓患者且接受 2 週安慰劑後隨機分給每天 lercanidipine 10–20 mg 或 losartan 50–100 mg 的治療。總共有26 位病人完成本研究。在 8 周的治療後兩群病人皆顯著降低收縮壓 (SBP) 與舒張壓 (DBP) (SBP，$p = 0.034$ & 0.050；DBP，$p = 0.018$ & 0.034，分別對 lercanidipine 與 losartan)。兩種降血壓藥物都有良好的耐受性。只有在接受 lercanidipine 治療的病人胞漿素原活化抑制因子 -1 濃度明顯下降 (57.1 ± 4.7 to 43.1 ± 4.8 ng/mL，$p = 0.047$)。D 雙體與纖維原在兩群病人都無顯著變化。本研究顯示 lercanidipine 及 losartan 治療台灣原發性高血壓患者是有效且有好的耐受性。Lercanidipine 治療可能提供額外血栓溶解的好處。

關鍵詞：Lercanidipine，Losartan，血栓溶解，高血壓，胞漿素原活化抑制因子 -1

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通訊作者：許勝雄醫師

高雄醫學大學附設中和紀念醫院心臟血管內科

高雄市三民區十全一路 100 號