Comparative Effect of Lercanidipine, Felodipine, and Nifedipine GITS on Blood Pressure and Heart Rate in Patients With Mild to Moderate Arterial Hypertension: The Lercanidipine in Adults (LEAD) Study

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This multicenter, double-blind, parallel-group study compared the effects of three dihydropyridine calcium channel blockers (lercanidipine, felodipine, and nifedipine gastrointestinal therapeutic system) on blood pressure and heart rate in 250 patients with mild to moderate hypertension (diastolic blood pressure ≥95 and ≤109 mm Hg). Patients were randomized to 4 weeks of treatment with once-daily doses of lercanidipine 10 mg, felodipine 10 mg, or nifedipine gastrointestinal therapeutic system 30 mg. After 4 weeks of treatment, the dose was doubled in nonresponding patients. At 8 weeks, no significant differences in blood pressure were observed among the three groups. Increases in heart rate in all three groups induced by stressful conditions before and after treatment were not exacerbated during active treatment. The incidence of adverse drug reactions was lower in the lercanidipine and nifedipine groups than in the felodipine group (p<0.05); in particular, the incidence of edema for lercanidipine was 5.5% vs. 13% for felodipine and 6.6% for nifedipine.
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Calcium channel blockers (CCBs) are widely used for the treatment of systemic arterial hypertension. All the drugs in this class have been found to be effective in lowering blood pressure in hypertensive patients, either as single agents or when combined with other drug classes.[1,2] In particular, dihydropyridine (DHP) CCBs have been shown to improve the prognosis in older patients with isolated systolic hypertension.[3] Additionally, in a randomized, placebo-controlled, crossover study recently published,[4] DHP CCBs were more effective than angiotensin-converting enzyme inhibitors or β blockers in lowering systolic blood pressure (SBP) in patients with hypertension aged 65–86 years (mean age, 77.3 years).

Lercanidipine is a third-generation DHP CCB that is characterized by a gradual onset and long duration of action, as well as vascular selectivity and lack of negative inotropic effects.[5,6] It is effective in different types of arterial hypertension, and its therapeutic efficacy is similar to that of other DHP CCBs.[7] Lercanidipine is well tolerated; the adverse events (AEs) associated with lercanidipine are similar to those commonly observed with other DHP CCBs used as antihypertensive agents.[8] At variance with the other DHPs, no significant changes in heart rate (HR) have been found after the first dose or during long-term treatment with lercanidipine.[9,10] However, lercanidipine has not been directly compared with other DHP CCBs with regard to effects on blood pressure and HR.

The Lercanidipine in Adults (LEAD) study was designed to compare the antihypertensive efficacy of lercanidipine with that of felodipine and nifedipine gastrointestinal therapeutic system (GITS) in adult patients with mild to moderate arterial hypertension. In addition, the study compared the tolerability of the three CCBs and their effects on HR at rest and under stressful conditions.

** A complete list of investigators participating in the study is provided in the appendix.*

METHODS

Study Group

A total of 325 men and women aged 31–74 years with mild to moderate arterial hypertension (diastolic blood pressure [DBP] ≥95 mm Hg and ≤109 mm Hg) were randomized in this multicenter, double-blind, parallel-group trial conducted in Italy and Spain. Close to 80 of the patients had been previously treated, primarily with an angiotensin-converting enzyme inhibitor or a CCB, and were equally distributed in each of three treatment groups. Patients were excluded from the study if their SBP was ≥180 mm Hg or if there was evidence of recent acute myocardial infarction, recent cerebrovascular events, congestive heart failure (New York Heart Association classes III and IV), clinically relevant arrhythmias, liver or renal function impairment (creatinine values >1.5 mg/dL), type 1 diabetes mellitus or decompensated type 2 diabetes, body mass index >30, smoking (more than 10 cigarettes daily), or any other clinical conditions that could have interfered with interpretation of the results.

Study Protocol

After a 1-week wash-out period (in the 80 patients previously receiving antihypertensive treatment) and a 2-week placebo run-in period, patients were randomized to receive once-daily dosages of one of the following treatments: lercanidipine 10 mg (n=109), felodipine 10 mg (n=110), or nifedipine GITS 30 mg (n=106). After 4 weeks of active treatment, the once-daily dosage was doubled in nonresponding patients or in those who were not normalized and was maintained unchanged for an additional 4 weeks. During each study visit, SBP, DBP, and HR at rest were measured in the morning 24±2 hours after swallowing the last tablet. Blood pressure values were recorded as a mean of at least two measurements taken 3 minutes apart after patients were seated for 10 minutes. Caffeine intake and smoking were not allowed for at least 30 minutes before each measurement. No drugs that might have had an influence on HR were allowed during the study. A 12-lead electrocardiogram (ECG) was obtained for all patients at the screening visit (week 3), at the end of the run-in period (week 0), and at the end of the study period (week 8).

Standard laboratory evaluations (complete blood count, complete urinalysis, fasting glucose, blood urea nitrogen, triglycerides, cholesterol, creatinine, total bilirubin, sodium, potassium, alanine aminotransferase, and aspartate aminotransferase) were performed during the washout period and at the end of double-blind treatment. HR was measured using an ECG tracing recorded for 1 minute both in resting and stressful conditions (mental stress as well as isometric stress). Mental stress was induced by using the Stroop Color and Word Test or by asking the patient to count backward. Isometric stress was induced using the handgrip test (30% of maximal voluntary contraction for 3 minutes), which was given 30 minutes after the mental stress test had been completed. To assess the reproducibility, these tests were carried out 2 weeks before randomization and at baseline. The incidence of AEs, whether drug-related or not, was also assessed in the three groups of patients. AEs were either reported by the patients or observed by the investigators.

Following protocol approval by the ethics committee of each investigational center, the study was conducted according to the current principles and norms established by the Declaration of Helsinki and in accordance with the requirements of good clinical practice. Written informed consent was obtained from each patient either before study entry or before any other study-related activity.

Statistical Analysis

The homogeneity of the patient population at baseline was verified by one-way analysis of variance for continuous variables and by the Fisher exact test for categorical variables. Analysis of variance was also used for SBP, DBP, and HR values. Assessment of equivalence between lercanidipine treatment and the two other treatments was carried out using the non-central F distribution. The Fisher exact test was used for analysis of the responder and normalization rates. The number of patients who experienced adverse drug reactions (ADRs), the number of dropouts due to AEs, and the ECG findings in each treatment group were also analyzed by means of the Fisher exact test.

RESULTS

Data from 250 patients—89 in the lercanidipine group, 79 in the felodipine group, and 82 in the nifedipine GITS group—were statistically analyzed for the per protocol analysis. Of the original 325 patients, 43 did not complete the study for different reasons: 32 patients withdrew because of AEs, two withdrew because of protocol violations, eight withdrew their consent, and one was lost to follow-up. Of the remaining 282 patients who completed the study, 32 were not included in the per protocol analysis because of poor compliance or because their measurements were not valid. There was no significant difference in the number of discontinued patients among the three groups, although the highest number was in the felodipine group (20/110, 18.2%) and the lowest was in the lercanidipine group (10/109, 9.2%).

The baseline demographic characteristics of the patients were similar among the three groups (Table I);

no significant differences were observed for any study variable, although the lercanidipine group had the highest number of smokers. The groups were also similar in the frequency of concomitant disorders (the most common being glucose metabolism, lipid metabolism, and arthrosis, equally distributed among the groups) and treatments, although the lercanidipine group had the highest number of patients with diabetes. After 4 weeks of active treatment, the dosage was doubled in 14 patients (15.7%) in the lercanidipine group, in one patient (1.3%) in the felodipine group, and in 11 patients (13.4%) in the nifedipine GITS group.

Effect of Treatment on Blood Pressure

SBP and DBP values significantly decreased in all groups after 4 weeks of treatment (Table II) and further declined at the end of active treatment (Figure 1). Absolute changes in blood pressure evaluated at the end of the trial period were not different among the three groups. The number of responders (defined as patients with a DBP <90 mm Hg at the end of treatment or with a reduction in DBP of at least 10 mm Hg compared with baseline), as well as the number of normalized patients (defined as DBP <90 mm Hg at the end of treatment), was similar among the groups (Figure 2). Identical results were obtained for SBP (responders defined as patients with SBP <140 mm Hg at the end of treatment or with a reduction in SBP of at least 20 mm Hg compared with baseline; normalized patients defined as SBP <140 mm Hg at the end of treatment).

Effect of Treatment on HR at Rest and Under Stress

HR values recorded at rest, before administering treatment, were similar in patients treated with lercanidipine (74.1±10.3 beats/min[bpm]), felodipine (73.8±9.7 bpm), and nifedipine GITS (73.3±9.4 bpm). None of the three treatments significantly changed HR: lercanidipine (74.9±10.0 bpm), felodipine (72.6±9.8 bpm), nifedipine GITS (73.0±9.7 bpm). The superimposable results of both mental and isometric tests carried out 2 weeks before randomization and at baseline demonstrated their reproducibility. Administration of these tests caused a significant increase in HR ($p<0.01$) that was similar in all groups both before and at the end of active treatment (Figure 3). The increase in HR by stress tests was not exacerbated by active treatment in any of the three groups.

Safety

No deaths were reported during the study period. Only two serious AEs occurred during the study—one patient in the lercanidipine group (renal neoplasia) and one in the nifedipine GITS group (mild angina pectoris). In both patients, the events were considered by the investigators to be unrelated to each of the drugs

Table I. Baseline Demographic Characteristics of Patients

	LERCANIDIPINE (N=89)	FELODIPINE (N=79)	NIFEDIPINE GITS (N=82)
Sex (male/female)	41/48	37/42	39/43
Smoker, n (%)	19 (21.4)	9 (11.4)	10 (12.3)
Diabetic (%)	17	7	10
Age (years)*	57.5±9.3	55.6±8.3	58.4±8.6
Height (cm)*	164.1±9.9	166.1±8.2	165.5±9.2
Weight (kg)*	71.8±11.1	74.3±9.6	74.6±9.1
Body mass index*	26.5±2.5	26.9±2.3	27.2±2.0

GITS=gastrointestinal therapeutic system; *all values are means±standard deviation

Table II. Blood Pressure Before and After Active Treatment

	BEFORE TREATMENT	AFTER TREATMENT 4 WEEKS	AFTER TREATMENT 8 WEEKS
SBP (mm Hg)	154.7±11.4	142.4±13.6*	140.5±13.4*
Lercanidipine 10–20 mg (n=89)			
Felodipine 10–20 mg (n=79)	155.1±11.5	139.7±12.7*	138.4±10.3*
Nifedipine GITS 30–60 mg (n=82)	155.1±12.1	143.4±12.4*	141.5±10.4*
DBP (mm Hg)			
Lercanidipine 10–20 mg (n=89)	98.7±3.4	88.0±8.0*	86.5±6.5*
Felodipine 10–20 mg (n=79)	98.7±3.0	85.2±7.2*	85.1±6.6*
Nifedipine GITS 30–60 mg (n=82)	98.6±3.2	88.3±6.4*	85.7±6.9*

All values are means±standard deviation.
SBP=systolic blood pressure; DBP=diastolic blood pressure; GITS=gastrointestinal therapeutic system; *$p<0.01$ within treatment comparison vs. values before treatment

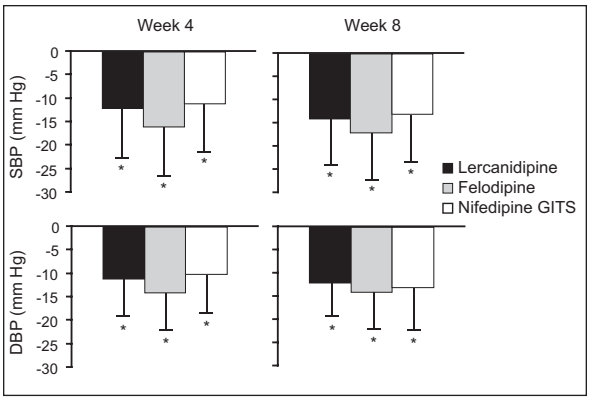

Figure 1. Absolute changes from baseline observed after 4 and 8 weeks of treatment with the three calcium channel blockers. Values are means±standard deviation. SBP/DBP=systolic/diastolic blood pressure; GITS=gastrointestinal therapeutic system; *p<0.01 *within treatment comparison vs. values before treatment*

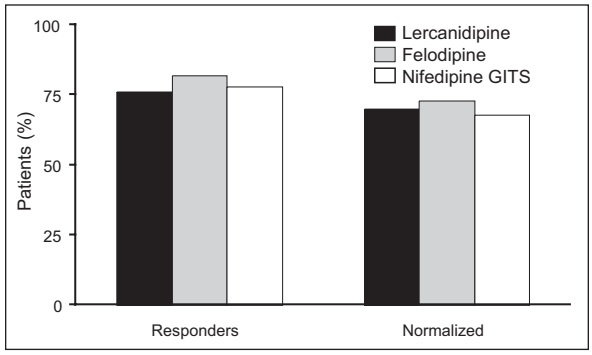

Figure 2. Percentage of patients responding (responders) and normalized (normalized) at the end of each treatment.
GITS=gastrointestinal therapeutic system

under study. AEs related to CCB administration were numerically lower in the lercanidipine group. In particular, headache, edema, dizziness/vertigo, and asthenia/fatigue were less frequent in patients treated with lercanidipine than in those treated with either felodipine or nifedipine GITS. No patients in the lercanidipine group experienced dizziness/vertigo or asthenia/fatigue. Although the study was not powered to show statistical differences among individual AEs, patients treated with lercanidipine had lower rates of edema (5.5% vs. 13.6%), headache (4.6% vs. 13.6%), and palpitations/tachycardia (0.9% vs. 5.5%) than those who received felodipine, while the values were similar to those who received nifedipine (6.6%, 6.6%, and 0.9%, respectively). In particular, the occurrence of edema was always declared at the minimum doses foreseen in the protocol for each drug.

The number of AEs, ADRs, and patients who withdrew from the study because of AEs were lower in the lercanidipine and nifedipine GITS groups than the felodipine group. The differences in the number of ADRs and dropouts because of AEs among the treatment groups were statistically significant (Figure 4). In particular, withdrawals due to edema were lowest in the lercanidipine group (1/109, 0.9%), followed by the nifedipine GITS group (4/106, 3.8%) and the felodipine group (5/110, 4.5%).

During the study, no clinically meaningful changes in the values of the laboratory parameters were noted in any of the treatment groups. Furthermore, no clinically significant ECG abnormalities were observed.

DISCUSSION

The results of the LEAD study demonstrate that three different DHP CCBs—lercanidipine, felodipine, and nifedipine GITS—significantly and equally decreased both SBP and DBP in patients with mild to moderate arterial hypertension. The hypotensive effect was evident after 4 weeks of treatment, and it either persisted unmodified or became more marked after 8 weeks of active treatment suggesting that the antihypertensive efficacy of once-daily doses of lercanidipine 10–20 mg is equivalent to that of felodipine 10–20 mg or nifedipine GITS 30–60 mg. These data confirm the efficacy of each drug in lowering blood pressure in hypertensive patients.[11] This conclusion is also supported by the analysis of responders and normalized patients. At the end of treatment, the large percentage of normalized patients was similar in all groups. However, the effective dose was doubled in a larger number of patients treated with lercanidipine or nifedipine GITS than in those treated with felodipine.

The number of ADRs was significantly lower in the lercanidipine-treated and nifedipine GITS-treated patients than in felodipine-treated patients, while no statistically significant differences were found between lercanidipine and nifedipine. Overall, based on the profile of AEs, the number of ADRs, and the frequency of AEs leading to withdrawal from study medication, lercanidipine had the best tolerability profile, despite the fact that the lercanidipine group contained more diabetic patients and more smokers—two hypertensive populations known to be difficult to treat. As far as the lower incidence of ankle edema during treatment with lercanidipine in comparison with other DHP CCBs is concerned, different hypothetical mechanisms have been suggested: a smaller discrepancy between arteriolar and venular vasodilation due to a lower sympathetic activation and a smaller venoconstriction[12,13]; a smaller effect on vascular permeability with consequent fluid extravasation[13]; the experimental findings that lercanidipine dilates both afferent and efferent glomerular arterioles.[14]

Our results also show that resting HR was not

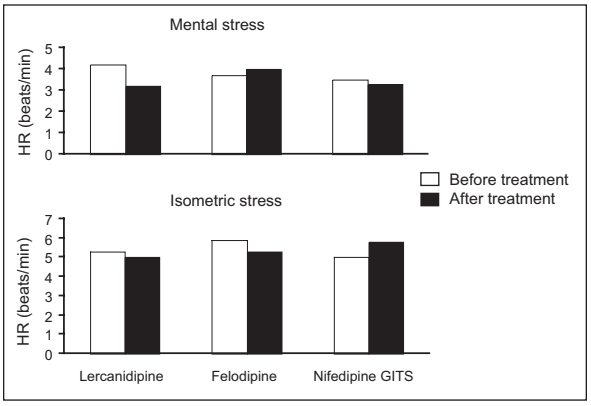

Figure 3. Heart rate (HR) changes during mental and isometric stress
GITS=gastrointestinal therapeutic system

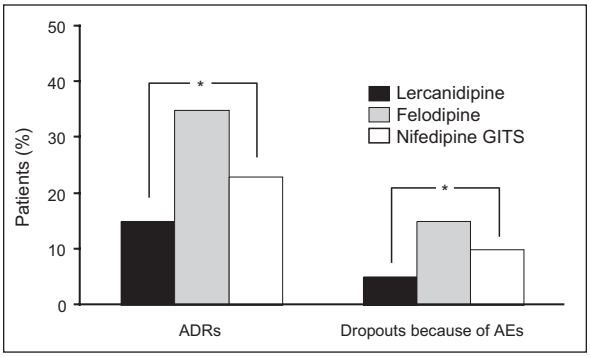

*Figure 4. Percentage of patients who experienced adverse drug reactions (ADRs) or who dropped out because of adverse events (AEs) in the three treatment groups. GITS=gastrointestinal therapeutic system; *p<0.05*

affected during the study by any of the three CCBs. None of the treatments modified the tachycardic response to stressful conditions, indicating that the neurohumoral factors that control cardiovascular homeostasis operate normally.[15] Patients receiving lercanidipine were better protected from the tachycardic stimulus of stress than patients on felodipine or nifedipine GITS, regardless of the provocation.

In conclusion, this study confirmed the antihypertensive efficacy of lercanidipine and demonstrated that the tolerability profile of lercanidipine (in terms of number of ADRs and dropouts because of AEs) is significantly better than that of felodipine and similar to that of nifedipine GITS. Furthermore, our data demonstrate that the cardiovascular parameters are well preserved during antihypertensive treatment with lercanidipine.

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