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Comparative effects of lercanidipine, lacidipine, and nifedipine gastrointestinal therapeutic system on blood pressure and heart rate in elderly hypertensive patients: the ELderly and LErcanidipine (ELLE) study

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Abstract

This study was conducted to compare the antihypertensive efficacy and safety of lercanidipine with those of lacidipine and nifedipine gastrointestinal therapeutic systems in patients aged 65 years or above with mild-to-moderate hypertension. Patients were randomized to receive lercanidipine 5 mg, lacidipine 2 mg, or nifedipine 30 mg for 24 weeks. After 2 weeks, the dose was doubled in non-responding patients. At 24 weeks, blood pressure was significantly reduced in the three treatment groups. The decrease in systolic blood pressure was similar in all three groups. The decrease in diastolic blood pressure in the lercanidipine group (−18.3 mmHg) was comparable to that in the nifedipine group (−17.7 mmHg), but exceeded that in the lacidipine group (−16.6 mmHg). The incidence of adverse drug reactions (ADRs) was lowest in the lercanidipine group (19.4%) compared with the nifedipine group

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(28.4%) and the lacidipine group (27.1%). In particular, edema was least frequent in the lercanidipine group (2.8%) compared with the lacidipine group (7.5%) and the nifedipine group (10.1%). These data demonstrate that lercanidipine is effective in lowering blood pressure in older adult hypertensive patients while maintaining a superior tolerability and safety profile.

Keywords: Antihypertensive agents; Hypertension; Calcium channel blocker; Lercanidipine; Lacidipine; Nifedipine

1. Introduction

Examination of the latest National Health and Nutrition Examination Survey (Franklin et al., 2001) has revealed that of the approximately 42 million adult Americans with hypertension, three quarters are aged 50 years or above. Of those aged 65 years or above, more than half have hypertension, defined by the sixth report of the US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure as a systolic blood pressure (SBP) and a diastolic blood pressure (DBP) $\geq$140/90 mmHg (JNC, 1997). Additionally, a substantial percentage of those aged 65 years or above have isolated systolic hypertension (ISH), defined as an SBP $\geq$140 mmHg with a DBP of $<$90 mmHg. Although all measures of blood pressure—SBP, DBP, and pulse pressure—are strongly and directly related to the risk of coronary and cerebrovascular events, SBP is the single best predictor of cardiovascular events in older adults (Psaty et al., 2001).

Reports from the JNC (1997) and from international expert panels (Guidelines Subcommittee, 1999) have given equal weight to SBP and DBP in the classification of hypertension. The need to treat hypertension in older adults is no longer questioned, based on the known risks of hypertension as well as the results of clinical trials showing that treatment of ISH and elevated DBP in patients aged 60 years or above consistently reduces cardiovascular morbidity and total and cardiovascular mortality (Hansson, 1996; Mulrow et al., 2000; Staessen et al., 2000). A meta-analysis of 8 studies in which more than 15 000 older hypertensives with moderate ISH ($\geq$160 mmHg) were enrolled has shown substantial benefits of antihypertensive drug treatment (Staessen et al., 2000). A recent study comparing the efficacy of treatment using a dihydropyridine calcium antagonist with that of placebo has shown that drug treatment of stage 1 ISH (SBP 140–159 mmHg/DBP $<$90 mmHg) is effective, safe, well tolerated, and associated with beneficial effects on left ventricular hypertrophy and quality of life (Black et al., 2001).

Despite the strength of these intervention studies, only approximately 25% of hypertensive patients are being treated to goal (Burt et al., 1995). In patients aged 50 years or above, ISH is predominant, with 82% having SBP in excess of the target goal versus 17% with DBP in excess of the target goal. Both hypertension, in general, and ISH, in particular, are strongly age dependent; SBP progressively increases with age in untreated individuals, while DBP increases until age 50 and declines from the

sixth decade onward (Burt et al., 1995). The pathophysiology of hypertension is different in older than in younger adults. The aging process is characterized by changes in vascular structure and function, as well as in neurohumoral mechanisms involved in cardiovascular control (Zannad, 2000). A great number of older hypertensives have diabetes mellitus and other comorbid conditions, and a blood pressure even lower than 140/90 to $<130/80$ mmHg should be the goal for all diabetic patients (American Diabetes Association, 2002).

Due to age-related differences, it is likely that some classes of antihypertensive drugs would be more suitable for use in older patients. Indeed, it has been suggested that calcium antagonists and thiazides are more effective and well tolerated in patients aged 65 years or above (Brown, 2001; Morgan et al., 2001). This hypothesis is supported by the results of a recent clinical trial that demonstrated a striking 42% decreased risk of stroke and a 26% reduced risk of fatal and nonfatal cardiac end points in the group of patients treated with a dihydropyridine calcium antagonist (Staessen et al., 1997). In particular, attention has focused on the newer, intrinsically long-acting calcium antagonists that are less likely to induce significant reflex tachycardia or sympathetic activation by virtue of their gradual onset and prolonged duration of activity (Epstein, 2000).

Lercanidipine is a novel, lipophilic dihydropyridine calcium antagonist with high vascular selectivity and a long duration of antihypertensive effect attributed to its unique pharmacologic and pharmacokinetic activity (Meredith, 1999). Clinical studies have shown that lercanidipine at daily doses of 10–20 mg results in a greater antihypertensive effect than that of placebo and an antihypertensive effect comparable to that of other antihypertensive drugs, including other dihydropyridine calcium antagonists (Leonetti, 1999; Blair and McKlellan, 2000). We therefore conducted a study to compare the efficacy and tolerability of lercanidipine with those of lacidipine and nifedipine gastrointestinal therapeutic systems (GITS) in patients aged 65 years or above with mild-to-moderate arterial hypertension.

2. Subjects and methods

A total of 324 patients were randomized to the three treatment groups. The per-protocol efficacy population consisted of 261 patients (176 women and 85 men) aged 65 years or above (mean age, 73 years) with mild-to-moderate essential systolic and diastolic hypertension, defined as a sitting SBP of 140–180 mmHg, and a sitting DBP of 90–109 mmHg. The protocol was approved by the local Ethical Committee and conducted according to the rules of Good Clinical Practice. Written informed consent was obtained from each patient before entering the study.

This multicenter, double-blind, randomized, parallel group study had a 7-day washout period for patients already receiving antihypertensive treatment. After a 2-week placebo run-in period, patients were randomized to receive once-daily doses of lercanidipine 5 mg, lacidipine 2 mg, or nifedipine GITS 30 mg for 24 weeks of treatment.

Patients were classified as normalized if DBP was reduced to <90 mmHg at the end of active treatment and as responders if DBP was reduced by ≥ 10 mmHg versus

baseline or was <90 mmHg at the end of active treatment. After 2 weeks of treatment, the dose was doubled in patients who were not responding to treatment, and this dose was maintained unchanged for the remainder of the study.

Baseline blood pressure and heart rate were recorded at the end of the placebo run-in period and after 2, 8, 16, and 24 weeks of active treatment. Twenty-four hours after the dose of studied drug, with the patient in the sitting position, blood pressure was measured twice at 3-min intervals using the auscultatory method. Karotkoff phases I and V were used to identify SBP and DBP, respectively.

All patients underwent a 12-lead electrocardiogram (ECG) at baseline and after 8 and 24 weeks of treatment. Standard laboratory evaluations were performed before treatment and at week 24. Any clinically significant laboratory changes observed at week 24 were reported as ADRs. All other adverse effects (AEs) detected by the investigator or reported spontaneously by the patient were recorded at each visit, and the relationship to study drug treatment was determined by the investigator. Patients were excluded from the study, if they had severe or malignant essential hypertension or secondary hypertension, orthostatic hypotension, evidence of recent myocardial infarction or stroke, congestive heart failure (NYHA class III–IV) or other major cardiovascular event, renal insufficiency (creatinine ≥ 1.5 mg/dl), obesity (body mass index, BMI > 30), clinically relevant arrhythmias, a gastrointestinal system disorder, or liver disease.

2.1. Statistical analysis

The primary analysis was planned to show an equivalent decrease in DBP between lercanidipine and lacidipine and between lercanidipine and nifedipine GITS after 24 weeks of treatment. The comparisons were made using the noncentral F-test (Wellek and Michaelis, 1991). Covariance analysis of DBP, SBP, and heart rate (HR) changes, using the baseline as a covariable, was carried out to test the difference between treatments and the differences versus baseline within each treatment group. Either the χ^2-test or Fisher's exact test was used for the analysis of the percent of responding or normalized patients. The number of patients with AEs, as well as the number of patients with ECG findings at each visit, were also analyzed by means of the χ^2-test or Fisher's exact test.

The results are reported as means $\pm$ S.D. for continuous variables and as frequency and percent for categorical variables. Differences that resulted in $P < 0.05$ are referred to as statistically significant.

3. Results

A total of 324 patients were randomized into the study: 108 patients in the lercanidipine group, 107 in the lacidipine group, and 109 in the nifedipine group. Thirty-two patients withdrew from the study (12, 8, and 12 from each group, respectively), and the number of randomized patients who completed the study was 96 in the lercanidipine group, 99 in the lacidipine group, and 97 in the nifedipine

group. Of these, 31 were protocol violators and therefore were excluded from the per-protocol efficacy analysis.

Baseline demographic and clinical characteristics of patients included in the per-protocol efficacy population were similar in the three groups (Table 1). As shown in Fig. 1, baseline SBP, DBP, and HR values were similar in the three treatment groups. After 2 weeks of active treatment, 14% of patients in the lercanidipine group required dose increases compared with 19% of patients in the lacidipine group and 11% of patients in the nifedipine group; these differences were not statistically significant. Both SBP and DBP significantly decreased at week 2 and continued to decrease after 8 and 16 weeks of active treatment in all three groups.

At the end of the treatment period, both SBP and DBP were significantly and markedly reduced in each of the three active treatments. SBP was reduced by 26.8 ± 13.1 mmHg in the lercanidipine group, 25.8 ± 15.0 mmHg in the lacidipine group, and 28.6 ± 11.2 mmHg in the nifedipine group. DBP was reduced by 18.3 ± 7.6 mmHg in the lercanidipine group, 16.6 ± 8.1 mmHg in the lacidipine group, and 17.7 ± 6.3 mmHg in the nifedipine group. The difference in DBP between the lercanidipine and nifedipine groups met the pre-specified criterion for equivalence; however, testing of equivalence between lercanidipine and lacidipine was not confirmed because of a treatment effect that favored lercanidipine. Heart rate did not change significantly during the study in any of the three groups (Fig. 1).

As shown in Fig. 2, at the end of the treatment period, the percent of responding and normalized patients in the three treatment groups was significantly different between groups ($P < 0.001$). The percent of either responding or normalized patients in both the lercanidipine and nifedipine groups was higher than in the lacidipine group.

3.1. Safety

AEs, whether or not considered related to the study drugs, were reported in 52 (48.2%) lercanidipine patients, 56 (52.3%) lacidipine patients, and 66 (60.6%) nifedipine patients. Twelve patients discontinued the study because of AEs: two in the lercanidipine group, two in the lacidipine group, and eight in the nifedipine

Table 1
Demographic and clinical characteristics at baseline

	Lercanidipine ($n = 84$)	Lacidipine ($n = 93$)	Nifedipine ($n = 84$)
Sex (m/f)	30/54	34/59	21/63
Age (years)	74 ± 8	74 ± 7	72 ± 6
Height (cm)	162 ± 8	163 ± 7	162 ± 7
Weight (kg)	66 ± 10	66 ± 11	66 ± 10
BMI (kg/m^2)	25 ± 3	25 ± 3	25 ± 3
SBP (mmHg)	166.6 ± 11.2	167.8 ± 11.6	167.3 ± 11.1
DBP (mmHg)	97.6 ± 4.6	97.7 ± 4.4	97.2 ± 4.2
HR (beats/min)	74.4 ± 7.4	74.3 ± 8.7	75.7 ± 8.5

Note: Data are mean ± S.D.

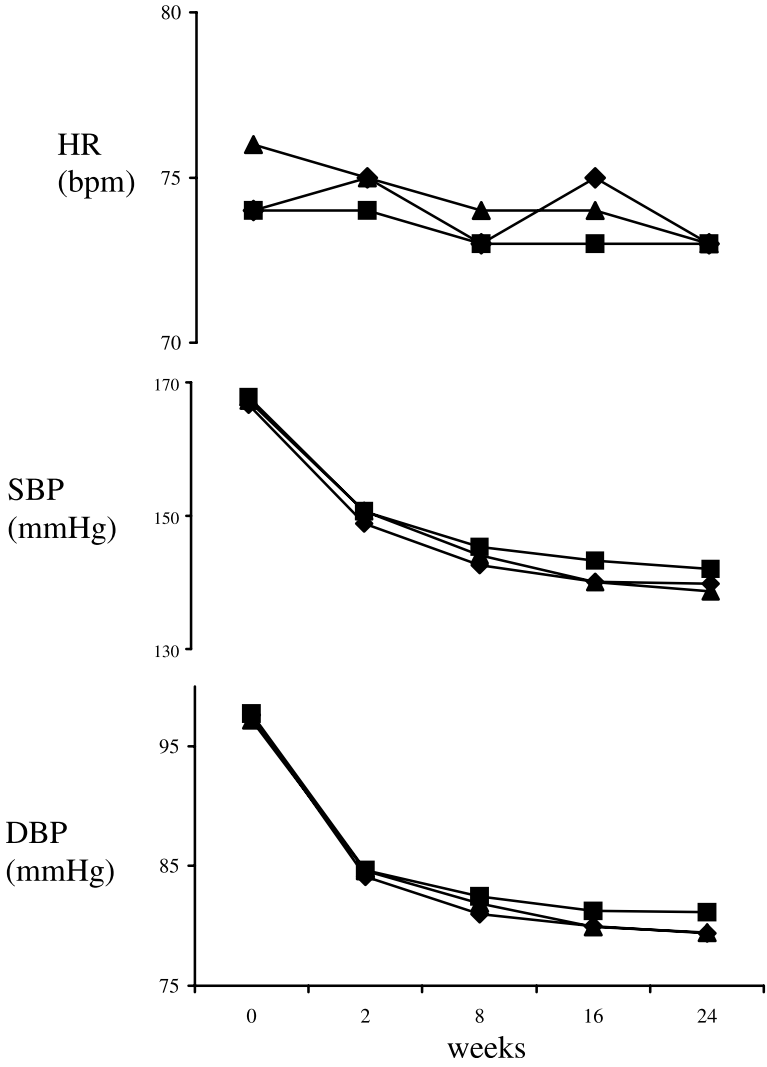

Fig. 1. The effects of once-daily administration of lercanidipine 5 or 10 mg (◆), lacidipine 2 or 4 mg (■), and nifedipine 30 or 60 mg (▲) on systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at baseline (0) and after 2, 8, 16, and 24 weeks of treatment. The change in blood pressure was statistically significant in each treatment group compared with baseline ($P < 0.01$, ANCOVA). There was no significant effect on HR.

group. Three of these AEs were considered serious; two patients in the nifedipine group died, one patient of sudden death and the other of pneumonia; neither cause was considered related to the study drug by the investigator. One patient randomized to the lacidipine group was hospitalized for a hypertensive crisis that occurred 2 days after the initiation of active treatment; the investigator attributed this event to an insufficient therapeutic effect. The remaining nine patients discontinued the study

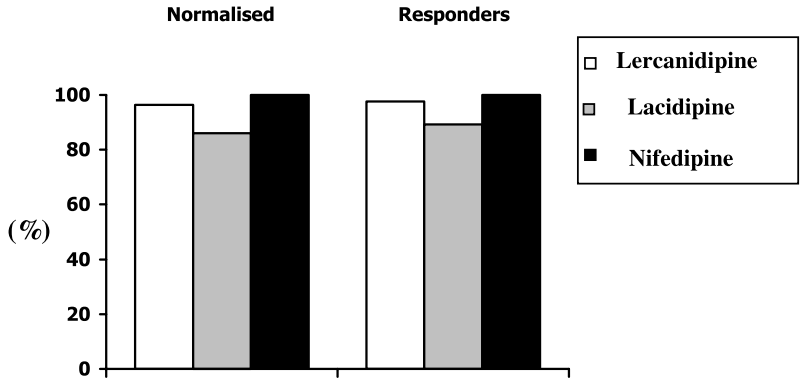

Fig. 2. Percent of normalized patients (left, $P < 0.001$ between groups) and responding patients (right, $P < 0.001$ between groups) at the end of 24 weeks of treatment with once-daily doses of lercanidipine 5 or 10 mg, lacidipine 2 or 4 mg, and nifedipine 30 or 60 mg.

due to ADRs: depression (nifedipine group), hypotension (nifedipine group: two patients), dyspepsia (lercanidipine group: two patients), asthenia (lacidipine group), renal hypertension (nifedipine group) and edema (nifedipine group: two patients).

The incidence of ADRs was 19.4% in the lercanidipine group, 27.1% in the lacidipine group, and 28.4% in the nifedipine group. The most common ADRs, in order of frequency, were ankle edema, increased liver enzymes, headache, and flushing (Fig. 3). The incidence of all of these ADRs, with the exception of headache, was highest in the nifedipine group, while the incidence of edema was lowest in the lercanidipine group. The difference among groups in the incidence of edema showed a trend in favor of lercanidipine ($P < 0.10$). Fig. 4 summarizes the overall incidence of AEs, ADRs, and dropouts due to AEs among the three treatment groups.

Fifty-one patients had clinically significant laboratory changes at the end of the study, 20 of which were considered ADRs. The incidence of treatment-related adverse laboratory changes was slightly higher in the nifedipine group (7.3%)

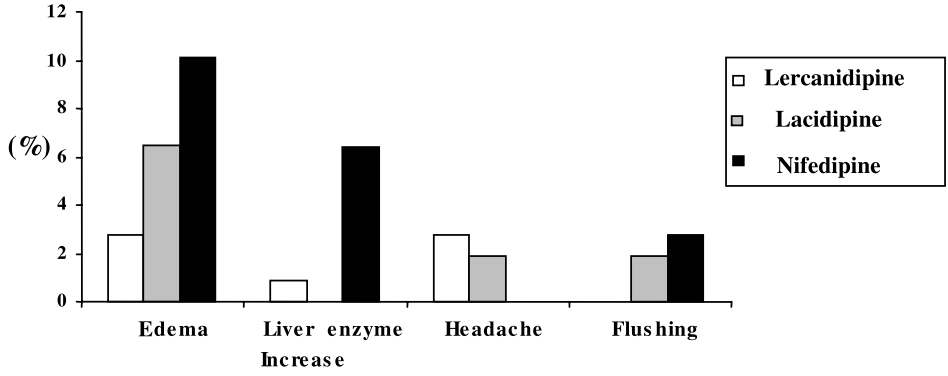

Fig. 3. Incidence (%) of the most frequently reported adverse drug reactions during 24 weeks of treatment with once-daily doses of lercanidipine 5 or 10 mg, lacidipine 2 or 4 mg, and nifedipine 30 or 60 mg.

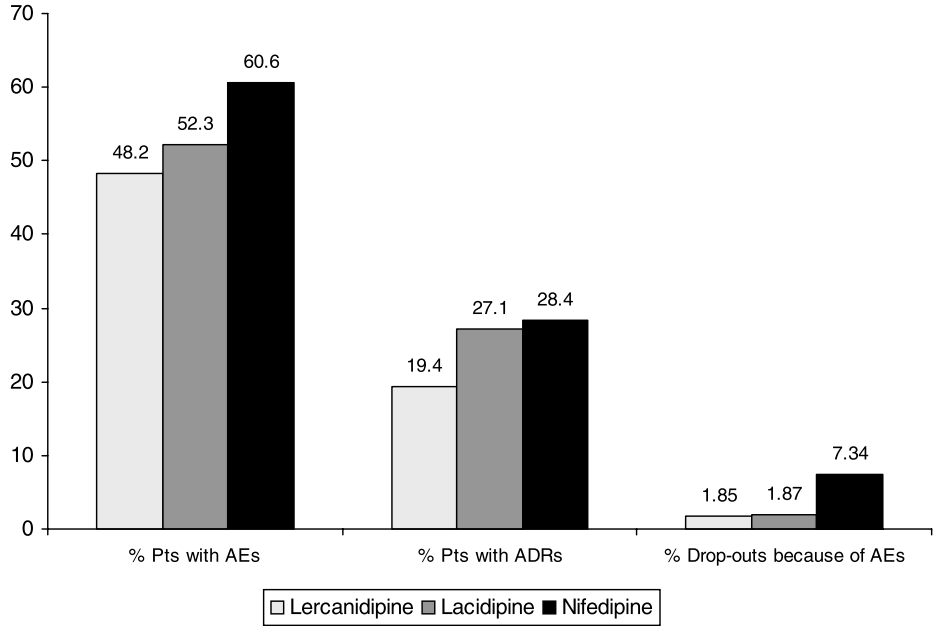

Fig. 4. Incidence (%) of adverse events, adverse drug reactions, and discontinuations due to adverse events during 24 weeks of treatment with once-daily doses of lercanidipine 5 or 10 mg, lacidipine 2 or 4 mg, and nifedipine 30 or 60 mg.

compared with the lacidipine group (6.5%), and it was lowest in the lercanidipine group (4.6%). No significant changes in ECG parameters were observed in any group during the study.

4. Discussion

The results of this study demonstrate that the calcium antagonists lercanidipine, lacidipine, and nifedipine, each administered once daily, significantly and markedly decrease both SBP and DBP in patients aged 65 years or above with mild-to-moderate arterial hypertension. A significant antihypertensive effect was evident after 2 weeks of treatment at the lowest dose of each study drug in the majority of patients (86% in the lercanidipine group, 81% in the lacidipine group, and 89% in the nifedipine group). The antihypertensive effect of lercanidipine was comparable to that of nifedipine and better than that of lacidipine in lowering DBP.

Despite a marked, consistent antihypertensive effect, none of the drugs significantly changed HR, indicating a lack of reflex activation of the sympathetic nervous system. The most commonly reported ADRs associated with dihydropyridine calcium antagonist therapy are headache and peripheral edema (mainly of the lower legs and ankles) (Ostergren et al., 1998; Schaefer et al., 1998; Morgan et al., 2001). The incidence of ADRs was lowest in the lercanidipine group (19.4% versus either

the lacidipine group at 27.1% or the nifedipine group at 28.4%), primarily due to the markedly lower incidence of edema in patients receiving lercanidipine. The superior tolerability profile of lercanidipine has been attributed to the lipophilic nature of the drug and its unique membrane-controlled kinetics, which imparts a gradual onset and long duration of antihypertensive effect (Herbette et al., 1998). The incidence of ADRs with lercanidipine was similar to that observed in previous clinical trials with younger hypertensive patients (Leonetti, 1999), suggesting that lercanidipine is also well tolerated in patients aged 65 years or above.

In conclusion, the results of this study demonstrate that the antihypertensive effect of lercanidipine was comparable to that of nifedipine and was associated with a lower incidence of edema. The antihypertensive effect of lercanidipine was better than that of lacidipine. Of the three drugs studied, lercanidipine had the lowest incidence of ADRs, including ankle edema. These data are consistent with previous findings obtained in younger adult hypertensive patients and demonstrate that lercanidipine is effective in lowering blood pressure in older adult hypertensive patients while maintaining a superior tolerability and safety profile.

Appendix A: List of participating investigators

U. Senin (Main Investigator)	Perugia
G. Abate	Chieti
R. Antonelli Incalzi	Taranto
L. Bartorelli	Roma
D. Cucinotta	Bologna
A. Di Stefano	Catania
F. Fabris	Torino
E. Feraco	Cosenza
E. Ferrari	Pavia
S. Forconi	Siena
E. Laguzzi	Alessandria
G. Masotti	Florence
D. Mastrangelo	Castellana Grotte
L. Motta	Catania
E. Paciaroni	Ancona
V. Pedone	Forlì
M. Santonastaso	Vittorio Veneto

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