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Improved Tolerability of the Dihydropyridine Calcium-Channel Antagonist Lercanidipine: The Lercanidipine Challenge Trial

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The objective of this 8-week open-label study was to compare the tolerability of lercanidipine, a dihydropyridine calcium-channel antagonist (CA), with that of other CAs in the treatment of hypertension. Subjects already taking amlodipine, felodipine, nifedipine gastrointestinal therapeutic system (GITS), or nitrendipine and experiencing CA-specific adverse effects (AEs) were switched to lercanidipine for 4 weeks and then rechallenged with their initial treatment for 4 weeks. Results showed that at comparable levels of BP, lercanidipine was associated with a significantly lower incidence of ankle edema, flushing, rash, headache and dizziness compared with other CAs ($p < 0.001$). After 4 weeks of lercanidipine, mean systolic blood pressure (SBP)/diastolic blood pressure (DBP) was 142.1/86.7 mmHg. After rechallenge with other CAs for 4 weeks, mean SBP/DBP was 141.1/86.7 mmHg. In this open-label study, lercanidipine compared with other CA seems to provide a significant improvement in tolerability with comparable antihypertensive effect. *Key words: calcium-channel antagonist, dihydropyridine, hypertension, lercanidipine.*

INTRODUCTION

The beneficial effects of calcium-channel antagonists (CAs) in the management of hypertension relate to their ability to induce systemic vasodilation. Long-acting dihydropyridine (DHP) CAs – for example, amlodipine, felodipine, nifedipine gastrointestinal therapeutic system (GITS), and nitrendipine – are widely used in the treatment of hypertension because of their efficacy, metabolic neutrality and low incidence of adverse effects (AEs) [1, 2]. CAs are particularly effective and well tolerated when used in combination with other agents, and clinical trials support the safety and efficacy of CAs for a wide range of hypertensive patients, including the elderly and those with uncomplicated mild-to-moderate hypertension, diabetes or isolated systolic hypertension [2–4].

Unfortunately, like other antihypertensive agents, CAs display characteristic classwide AEs, including dizziness, flushing, rash and headache, mainly due to the rapid onset of vasodilatory effects. Peripheral edema – leg and ankle swelling – is another distressing AE associated with use of CAs [2, 5, 6]. Calcium-channel blocker (CCB)-associated peripheral edema occurs in the absence of sodium retention and is not related to cardiac failure. While edema is believed to be a local phenomenon associated with relative differences in venous and arteriolar dilatation, the exact cause of this troublesome AE remains unclear [7, 8].

In a recent study [6] of 1067 men and 933 women with essential hypertension who received monotherapy with a CA, the AEs that were reported most frequently in both men and women were edema ($n = 272$; 13.6%), headache ($n = 115$; 5.8%), flushing ($n = 78$; 3.9%) and rash ($n = 39$; 2.0%). Overall, more women than men reported AEs (35.3% vs 22.7%; $p < 0.001$) and discontinued therapy due to AEs (18.5% vs 11.5%; $p = 0.04$). In addition, the incidences of headache (7.0% vs 4.7%; $p = 0.03$) and flushing (5.6% vs 2.4%; $p = 0.003$) were significantly higher in women. Edema was reported in more women than in men (15.6% vs 11.8%), although the difference was not statistically significant. Edema and other AEs associated with the use of CAs led to discontinuation from treatment in 14.6% of the study population [6].

Lercanidipine hydrochloride is an effective DHP CA used to treat hypertension that is associated with a low rate of AEs, including a low rate of peripheral edema and no significant effect on heart rate (HR) [9–12]. Lercanidipine has been available in several countries worldwide since 1997. Lercanidipine provides 24-h sustained blood pressure (BP) reduction with once-daily dosing [11, 12].

The present study was undertaken to determine whether hypertensive patients experiencing AEs while

* See the appendix for a list of centers participating in the study.

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taking the CAs amlodipine, felodipine, nifedipine GITS or nitrendipine – alone or in combination with other antihypertensive drugs – would experience a lower incidence of AEs when switched to lercanidipine. Our purpose was to test the hypothesis that lercanidipine would have an improved AE profile compared with other CAs.

METHODS

A total of 125 men and women with mild-to-moderate essential hypertension were enrolled in the study. Mild-to-moderate hypertension was defined as systolic BP (SBP) $\geq$ 140 mmHg and $\leq$180 mmHg and diastolic BP (DBP) $\geq$ 90 mmHg and $\leq$115 mmHg. Subjects were enrolled from 11 clinical hypertension units with long-standing experience in the outpatient management of hypertension; these units were directly connected with the clinical coordinating center of the study, located at the Department of Medicine of the S. Orsola University Hospital in Bologna. The study protocol was approved by the Ethical Committee of the University of Bologna and by other local committees (e.g. Hospital of Cesena, Hospital of Cento) when required. Written informed consent was obtained from each subject.

Subjects were included in the study if they had been treated with a DHP CA alone or in combination with other antihypertensive drugs for at least 3 months and if they reported at least one of the following index AEs typically associated with the use of DHP CAs: ankle edema, flushing, headache, rash or dizziness. Only those subjects whose AEs were confirmed at two different occasions 5–7 days apart were enrolled in the study.

Subjects with malignant or secondary hypertension, primary headache or migraine, severe venous insufficiency, or unstable angina were excluded from the study, as were those who had experienced an acute myocardial infarction or stroke; those who had renal failure (serum creatinine $>$2.00 mg/dl), liver disease, or systemic or neoplastic disease; and those who did not give informed consent. Subjects were also excluded if, in the judgment of the investigator, they were unable to cooperate with any aspect of the study or to fill out the questionnaire.

Study protocol

This was a multicenter, open-label study with 8 weeks of active treatment. Supine and standing BP and HR (the average of three measurements made in the same position 1 min apart) and the occurrence of AEs were determined at baseline, at the start of the study (week 0), and at study visits at weeks 2, 4 and 8. Subjects reported AEs they experienced by completing a questionnaire, on which was randomly listed the AEs commonly associated with the use of various antihypertensive drugs, with no emphasis given to particular AEs. A physician blinded to the study protocol and to the treatment assignments assessed the occurrence of AEs, which were graded on the questionnaire as mild, moderate or severe, throughout the study. In particular, the occurrence of ankle edema was directly assessed by the blinded physician who has to confirm the patient's report in terms of presence/absence of the edema. According to this conservative approach, patients with only a reduction in the amount of ankle edema during lercanidipine treatment do not contribute to the overall beneficial effects of the drug in terms of reduction of primary end point.

After a 5–7-day run-in period, during which subjects took their prestudy therapeutic regimen, they were then switched to lercanidipine 10 mg/day for 2 weeks. At the week 2 visit, the dosage was increased to 20 mg/day for nonresponders (SBP $>$ 140 mmHg, DBP $>$ 90 mmHg or both). Treatment with lercanidipine was maintained for a total of 4 weeks. At the week 4 visit, subjects were switched back to their initial CA (at the same dosage as was previously taken) for another 4 weeks.

Study endpoints

The primary study endpoint was to determine whether switching to treatment with lercanidipine would significantly reduce the incidence of index AEs in subjects who had been receiving long-term treatment with amlodipine, felodipine, nifedipine GITS or nitrendipine, alone or in combination with other antihypertensive drugs. In addition, the incidence of AEs not specifically attributable to CAs was evaluated, including impotence and fatigue, the occurrence of which was considered a suitable index of spontaneous fluctuations in individual drug tolerability. The study treatment was adjusted to achieve the same BP control during the two treatment phases to exclude any interaction between the extent of BP control and the rate of AEs.

Statistical analysis and sample size

The study sample size was calculated according to an assumed incidence of index AEs at enrollment of 100.0% and a reduction during lercanidipine treatment by 25%, with an alpha-error of 0.05 and a power of the study of 80%. Values are expressed as mean $\pm$ standard deviation, and p-values $>$0.05 were rejected. The crude sample size was adjusted for a dropout rate of 5% in 8 weeks, thus reaching a final sample size of 120 patients.

The proportion of subjects with one or more AEs is reported as a percentage of the subjects enrolled in the trial. The comparison between the BP and HR values measured during the two study periods was carried out by an analysis of variance for repeated measurements. The incidence of index AEs as well as that of nonspecific AEs

Table I. *Demographic and clinical characteristics of subjects at week 0*

Demographic and clinical characteristics	Men ($n = 68$)	Women ($n = 57$)
Mean age (years)	61.4 ± 10	64.3 ± 11
Range (years)	49–73	51–75
Mean SBP (mmHg)		
Supine	143.9 ± 12	145.6 ± 14
Standing	139.4 ± 13	142.7 ± 14
Mean DBP (mmHg)		
Supine	87.5 ± 6	86.8 ± 8
Standing	87.0 ± 6	87.0 ± 8
Mean HR (beats/min)		
Supine	74.0 ± 10	76.9 ± 10
Standing	73.2 ± 10	79.5 ± 10

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
Values (except the range of ages of subjects) are mean ± standard deviation.

occurring during treatment with either lercanidipine or other CAs was compared with the χ^2 test or the Fisher exact test when appropriate.

To avoid any influence of age or menopause on the assessment of the primary endpoint, a predefined subgroup analysis was carried out in the elderly (aged >60 years) and in postmenopausal women. A further subgroup analysis was performed in subjects according to their initial drug treatment to exclude the possibility that the extent of the potential benefit of lercanidipine could be related to the prevention of the negative effect of one specific drug.

RESULTS

Demographic and clinical characteristics of the 125 subjects at week 0 are presented in Table I. The mean age of the study group was 62.9 ± 11 years. There were no clinically meaningful differences between men and women in supine and standing SBP, DBP or HR.

The different CAs and their corresponding mean daily doses are shown in Table II. At study entry, 64 subjects (51.2%) were taking amlodipine, 28 subjects (22.4%) were taking nifedipine GITS, 21 subjects (16.8%) were taking felodipine and 12 subjects (9.6%) were taking nitrendipine; 45.6% (57/125 subjects) were receiving monotherapy. The antihypertensive drugs most commonly used in combination therapy, and which were continued when subjects were switched to lercanidipine, were angiotensin-converting enzyme (ACE) inhibitors, diuretics and beta-blockers. Almost 70% of subjects treated with two or more drugs received ACE inhibitors or diuretics, whereas approximately 25% of subjects received beta-blockers. Table III shows the incidence of index AEs at week 0. Ankle edema was the most prevalent, present in approximately 90% of subjects. Flushing and headache were present in approximately 40% of subjects, followed by rash and dizziness, which were present in approximately one-fourth of subjects.

Mean supine and standing SBP and DBP and HR in men and women throughout the 8-week study are shown in Table IV. These indices were maintained at or below baseline levels throughout the course of the study. At week 2, the dosage of lercanidipine was increased to 20 mg/day in six subjects formerly receiving another CA (two amlodipine, two nifedipine GITS, one felodipine and one nitrendipine). At week 4, the average dose of lercanidipine was 10.48 mg.

Reduction of index AEs

As shown in Fig. 1, the treatment with lercanidipine for 4 weeks was associated with significant reductions in the incidence of index AEs compared with other CAs.

Table II. *Calcium antagonists (mean daily dose) at week 0*

Regimen and dose variable	Amlodipine ($n = 64$)	Felodipine ($n = 21$)	Nifedipine GITS ($n = 28$)	Nitrendipine ($n = 12$)
Monotherapy [no. (%)]	29 (45.3)	8 (38.0)	15 (53.5)	5 (41.6)
Dose ± SD (mg)	8.9 ± 2.0	9.5 ± 1.1	38.2 ± 13.0	15.0 ± 7.0
Minimum dose (mg)	5	5	30	10
Maximum dose (mg)	10	10	60	20

GITS, gastrointestinal therapeutic system; SD, standard deviation.

Table III. *Adverse effects in 125 hypertensive subjects at week 0*

Adverse effect	Total ($n = 125$) [no. (%)]	Amlodipine ($n = 64$) [no. (%)]	Nifedipine GITS ($n = 28$) [no. (%)]	Felodipine ($n = 21$) [no. (%)]	Nitrendipine ($n = 12$) [no. (%)]
Ankle edema	113 (90.4)	56 (88.0)	25 (89.3)	21 (100)	11 (91.7)
Flushing	47 (37.6)	20 (31.2)	15 (53.6)	7 (33.3)	5 (41.7)
Headache	47 (37.6)	20 (31.2)	9 (32.1)	13 (61.9)	5 (41.7)
Rash	29 (23.2)	13 (20.3)	9 (32.1)	4 (19.0)	3 (25.0)
Dizziness	36 (28.8)	18 (28.1)	6 (21.4)	5 (23.8)	4 (33.3)

Overall, the incidence of edema with lercanidipine was reduced by 46% ($p < 0.001$), flushing was reduced by 51% ($p < 0.001$), headache and rash were both reduced by 53% ($p < 0.001$), and dizziness was reduced by 26% ($p < 0.05$) vs other CCBs. Upon rechallenge to initial treatment with CAs, the incidence of ankle edema, rash and headache returned to baseline or near-baseline levels. A separate evaluation of data according to baseline CCB treatment, showed that the incidence of index AEs experienced by subjects was evenly reduced by lercanidipine in patients receiving baseline therapy with amlodipine, nifedipine GITS and felodipine, whereas no specific results can be reported for nitrendipine due to the small number of subjects.

Incidence of AEs by age and sex

The incidence of ankle edema was similar in subjects younger than and subjects older than 60 years of age, and in men and women. Compared with other CAs, lercanidipine was associated with a significantly lower incidence of ankle edema in both subjects younger than and subjects older than 60 years of age ($p < 0.001$). At the initial visit, the incidence of flushing was higher in women than in men (55% vs 25%, respectively). Treatment with lercanidipine was associated with significantly lower incidences of flushing than treatment with other CA s – by 40% in men ($p < 0.05$) and by 45% in women ($p < 0.001$).

Table IV. *Blood pressure and heart rate in 125 hypertensive subjects*

Variable	Therapy with CCBs at study entry (week 0)	Lercanidipine 10 mg/day (week 2)	Lercanidipine 10 or 20 mg/day (week 4)	Rechallenge with CAs (week 8)
BP (mmHg)				
Men				
Supine SBP	143.9 ± 12	145.7 ± 13	143.9 ± 12	141.8 ± 11
Supine DBP	87.5 ± 6	89.1 ± 10	87.5 ± 7	86.6 ± 6
Standing SBP	139.4 ± 13	143.2 ± 14	140.3 ± 12	139.0 ± 11
Standing DBP	87.0 ± 6	89.3 ± 10	86.7 ± 7	86.6 ± 6
Women				
Supine SBP	145.6 ± 14	142.2 ± 13	140.3 ± 10	140.4 ± 11
Supine DBP	86.8 ± 8	86.7 ± 7	84.6 ± 6	84.9 ± 5
Standing SBP	142.7 ± 14	139.3 ± 14	138.8 ± 9	137.9 ± 11
Standing DBP	87.0 ± 8	86.8 ± 7	85.2 ± 6	85.5 ± 6
HR (beats/min)				
Men				
Supine	74.0 ± 10	73.2 ± 9	72.7 ± 8	71.8 ± 9
Standing	73.2 ± 10	75.5 ± 9	75.5 ± 8	74.4 ± 9
Women				
Supine	76.9 ± 10	74.0 ± 9	76.2 ± 8	75.5 ± 9
Standing	79.5 ± 10	74.0 ± 9	77.8 ± 8	77.7 ± 9

CCBs, calcium-channel blockers; CAs, calcium-channel antagonists; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Values are expressed as mean ± standard deviation.

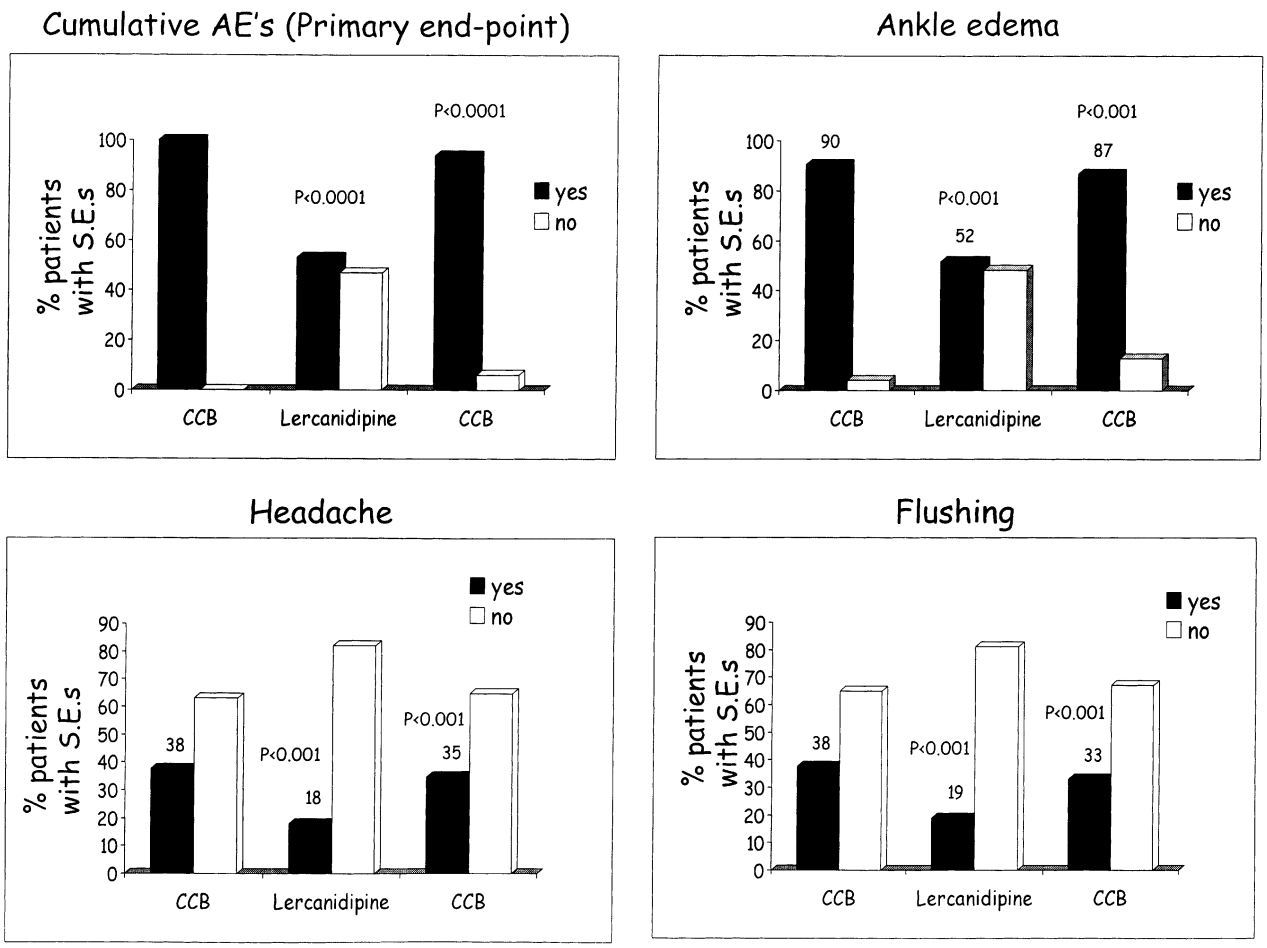

Fig. 1. Cumulative and separate incidence of index adverse effects (AEs) (e.g. ankle edema, flushing, headache, dizziness, rash) in hypertensive subjects treated with different CCBs for ≥3 months, following switch to lercanidipine for 4 weeks, and following rechallenge with baseline CCBs for an additional 4 weeks. * $p < 0.001$ and † $p < 0.05$ vs CCB.

Incidence of nonspecific AEs

Nonspecific AEs reported by subjects included impotence, fatigue, muscle pain, depression, cough, fluid retention, dry mouth, heartburn and gastrointestinal disorders. The overall incidence of nonspecific AEs did not differ significantly: 24% with other CAs at week 0, 19% with lercanidipine at week 4 and 17% with rechallenge at week 8 (Fig. 2). While the incidence of impotence was not significantly different (18% at week 0, 17% at week 4 and 16% at week 8), the incidence of decreased libido was significantly lower in subjects treated with lercanidipine at week 4 (18% vs 8%; $p < 0.05$, vs week 0).

Tolerability and dropouts

As shown in Table IV, lercanidipine did not significantly change HR from week 0 to week 4 of the study. Two subjects dropped out after 4 weeks of lercanidipine treatment since they refused to return to their initial treatment, which was amlodipine 10 mg/day. There were no dropouts due to AEs.

DISCUSSION

The results of this open-label study clearly suggests that the treatment with lercanidipine is associated with a significantly lower incidence of index AEs compared with other long-acting DHP CAs at comparable levels of BP control and with no significant effect on HR. In particular, when compared with incidence rates on other long-acting CAs at baseline, the cumulative and separate incidences of dizziness, ankle edema, flushing, rash and headache were significantly reduced (by 26% to 53%) during treatment with lercanidipine. This support the possibility that lercanidipine might provide a significant improvement in tolerability profile in patients who deserve a treatment with CCBs at comparable levels of BP.

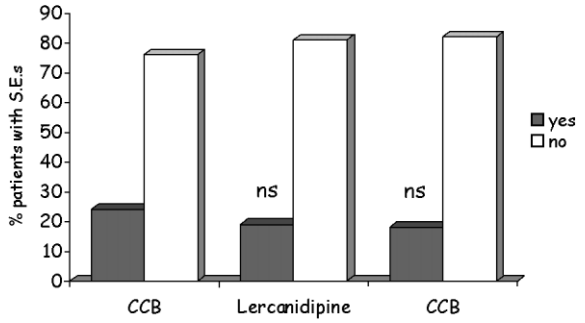

Fig. 2. Cumulative rate on non-CCB specific AEs in hypertensive subjects treated with different CCBs for $\geq$3 months, following switch to lercanidipine for 4 weeks, and following rechallenge with baseline CCBs for an additional 4 weeks.

The present study was basically undertaken to investigate the clinical benefit from a switch to lercanidipine therapy and its results are applicable to the "real world" of patient care, where patients who experience intolerable AEs are often switched from a CA to another class of drugs. Despite some methodological limitations, the data suggest the possibility of treating patients who effectively respond to a CCB by simply switching from one compound to another of the same class but with a better tolerability profile. This would prevent physicians to select CAs for antihypertensive therapy based on their efficacy profile while they have to switch therapy when patients experience intolerable AEs.

As with all studies, the present study has some limitations. Since the study design involved a population of subjects who experienced AEs on a CA, they were made aware that they would receive a different drug. The study was designed to ask the patients to discriminate between two different CAs, and thus was based on self-report. As in any study or clinical situation, a placebo response cannot be ruled out.

However, the nature of any potential benefit or detriment that could be experienced during the study was not described to the patients, and the same blinded physician assessed the occurrence of AEs throughout the study. The results of the study showed that the improved tolerability was not observed across the entire spectrum of AEs reported by subjects, but was limited only to the index AEs, thus suggesting an offset to any negative effect of the study design on the primary endpoint. It is, however, likely that the considerable degree of difference in tolerability seen with lercanidipine compared with the other CAs is the result of a significant clinical effect, and in addition, the study closely parallels the routine practice of switching patients from one CA to another CA based solely on AEs.

The reason for an apparently better tolerability profile of lercanidipine is probably related to its pharmacological profile. Lercanidipine is structurally related to the class of 1,4-DHP CAs but it is clearly different from other DHPs. The pharmacological activity of lercanidipine is not controlled by the plasma compartment but rather by the arterial tissue wall compartment, where it may be stored over a long period and from which it can gradually interact with calcium channels in arterial smooth muscle cells [13, 14]. Lercanidipine has a greater solubility within the arterial cellular membrane bilayer and prolonged residence time in the smooth muscle membrane compared with other long-acting CAs. This results in a relatively short plasma half-life whereas a lipophilic membrane anchor to the tissue wall compartment is responsible for a long duration of action [13]. Rapid removal from plasma may be the reason behind the favorable tolerability profile of lercanidipine, although further studies are warranted.

In a double-blind, randomized study of the comparative effect of lercanidipine and nifedipine GITS, both CAs produced similar reductions in SBP and DBP, but lercanidipine was associated with significantly less pronounced edema compared with nifedipine GITS [15]. Two objective measurements were used to determine the extent of drug-induced ankle edema: Archimedes' principle of water displacement (ankle–foot volume [AFV]) and measurement of pretibial subcutaneous tissue pressure (PSTP) by direct manometry. Compared with nifedipine GITS, lercanidipine produced a significantly ($p < 0.001$) less pronounced increase in AFV (143.6 vs 284.2 ml) and PSTP (0.9 vs 1.8 cmH_2O) [15]. The authors concluded that the pharmacokinetic and pharmacodynamic properties of lercanidipine might contribute to its lower potential to cause edema.

More recently, Pedrinelli and colleagues [16] compared the potential for edema with amlodipine with that of lercanidipine in 22 men (mean age: 48 ± 5 years) with untreated mild-to-moderate hypertension. The water displacement method was used to measure leg weight and provided an objective measure of edema. Study drugs were administered once daily at the recommended dosages of amlodipine 10 mg and lercanidipine 20 mg to achieve comparable decreases in BP. The crossover, sequence-randomized study included 2 weeks of active treatment preceded and followed by 2-week washout periods to allow the recovery of study variables to baseline. Both study drugs induced similar, significant decreases in BP from baseline. Amlodipine induced an increase in leg weight from baseline that was twice as great as that seen with lercanidipine (amlodipine, 80 ± 91 g vs lercanidipine, 37 ± 74 g; $p < 0.03$).

The results obtained in the present study are confirmed by the results of a recently completed multicenter double-blind study in which the efficacy and tolerability of

lercanidipine were compared with that of amlodipine and lacidipine in 828 elderly patients (mean age, 70 years) with moderate hypertension (SB$P > 160$ mmHg or DBP > 95 mmHg) [17]. Data from the first 6 months of the study showed that at comparable BP lowering, lercanidipine was associated with a greater than 50% reduced incidence of edema and 75% fewer early study dropouts due to edema, compared with amlodipine.

Finally, the results of the ELYPSE study (Eficacia de Lercanidipino y su Perfil de Seguridad) [18], a multicenter, open, prospective surveillance study, confirm the efficacy and tolerability of lercanidipine in essential hypertension in daily clinical practice. The study included 9059 patients with grade 1 or 2 essential hypertension; the overall incidence of AEs was 6.5%, and the most frequent were headache (2.9%), ankle edema (1.2%), flushing (1.1%) and palpitations (0.6%).

The lower incidence of AEs observed in patients treated with lercanidipine could have some important clinical implications since it could improve to rather unsatisfactory compliance to treatment that characterizes the hypertensive population. Patient compliance with antihypertensive therapy is particularly poor because mild-to-moderate hypertension is a condition requiring lifelong treatment, and many patients feel worse on therapy than they do when untreated [19–24]. The development of better-tolerated antihypertensive drugs might significantly improve the effectiveness of treatment and its impact in term of cardiovascular prevention and reduce the proportion of patients who do not achieve benefit from an effective treatment strategy.

CONCLUSION

The present study included patients reporting AEs when previously treated with CAs and supported the possibility that they could experience a considerable improvement in tolerability when switched to lercanidipine. The results of the present study, which must be confirmed in the future by a randomized study design, provide the first demonstration that in patients who complain AE's from treatment, there is the possibility of switching to better tolerated drug of the same family thereby increasing the potential impact of CCB treatment in patients with hypertension.

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