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Therapeutic Profile of Manidipine and Lercanidipine in Hypertensive Patients

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ABSTRACT

Manidipine and lercanidipine are considered effective and safe in the treatment of chronic arterial hypertension and are equipotent in reducing blood pressure (BP) levels. Their main side effect is ankle-foot edema. After a 2-week placebo run-in period, these 2 drugs were compared in a controlled parallel-group study lasting 3 months, involving 53 patients with mild-to-moderate essential hypertension (26 assigned to manidipine and 27 to lercanidipine). At the end of the active treatment period, BP was significantly reduced in comparison with the end of the placebo phase in both the manidipine and the lercanidipine groups, without significant differences between the 2 drugs. Daytime BP was significantly reduced by 5.5%/5.6% with manidipine and by 3.8%/6.6% with lercanidipine, while smaller reductions were seen at nighttime. The smoothness index was the same with both drugs. Unlike lercanidipine, manidipine significantly reduced both basal (–30%) and minimal vascular resistance (–39%), qualifying it as a potent vasodilator. Despite vasodilation, heart rate was not increased but was even slightly reduced by treatment. Ankle-foot edema was observed with both drugs but was less pronounced with manidipine, probably because of greater postcapillary dilatation. In conclusion, manidipine and lercanidipine are both effective and safe

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in mild-to-moderate essential hypertension, although the former seems to have a more favorable tolerability profile than the latter.

Keywords: manidipine; lercanidipine; clinical trial; hypertension; plethysmography; circulation; vasodilator

INTRODUCTION

Dihydropyridine calcium channel blockers (DCCBs) are among the drugs of choice for the treatment of hypertension because of their efficacy[1] and potential beneficial effects, such as protecting against end-organ damage,[2] renal protection,[3,4] and natriuretic,[5] antiplatelet,[6] anti-ischemic,[7] and antiatherogenic[2,8] activities. These benefits are reflected in the latest editions of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines on hypertension management.

Several new DCCBs have been introduced in clinical practice in recent years. The advantages of third-generation DCCBs, such as manidipine, lercanidipine, and lacidipine, include high vasoselectivity,[9] little or no cardiodepressant activity, and improved receptor and kinetic profiles.[9,10] These newer compounds have, in comparison with the older DCCBs, a greater chance of smoothly reducing blood pressure (BP) over 24 hours. Also, because of their intrinsically long receptor$_{T1/2}$,[10] they seem to activate the sympathetic drive to a lesser extent.[11] Ankle-foot edema, probably the only important side effect of DCCBs, seems to be less pronounced[12] and less frequent[13] with third-generation long-receptor$_{T1/2}$ compounds.

Manidipine has been tested in multicenter trials and found to be safe, well tolerated, and effective in reducing BP over 24 hours at doses of 5 to 40 mg daily. It has been able to increase renal blood flow and glomerular filtration rate and to improve quality of life, according to the General Well-Being Schedule.[3,10,14]

Lercanidipine has an unique chemical structure that contributes to greater solubility within the arterial cellular membrane bilayer and consequently has a particularly high tropism for vascular smooth muscle cells[15] and a long duration of action. In large studies, it has been found to be safe and effective at a daily dose of 10 to 20 mg.[15-18]

Although these two drugs are innovative and widely used, they have never been compared in a controlled clinical trial. A particular concern is ankle-foot edema,[18] an adverse event that has lead to drug discontinuation.[13] It has been suggested that this clinical problem is less evident with newer compounds than with older ones,[1] but uncertainties remain about the mechanism by which edema is produced.

The purpose of this study was to investigate the incidence of ankle-foot edema with 2 new-generation DCCBs and to define the hemodynamic changes that may cause it.

PATIENTS AND METHODS

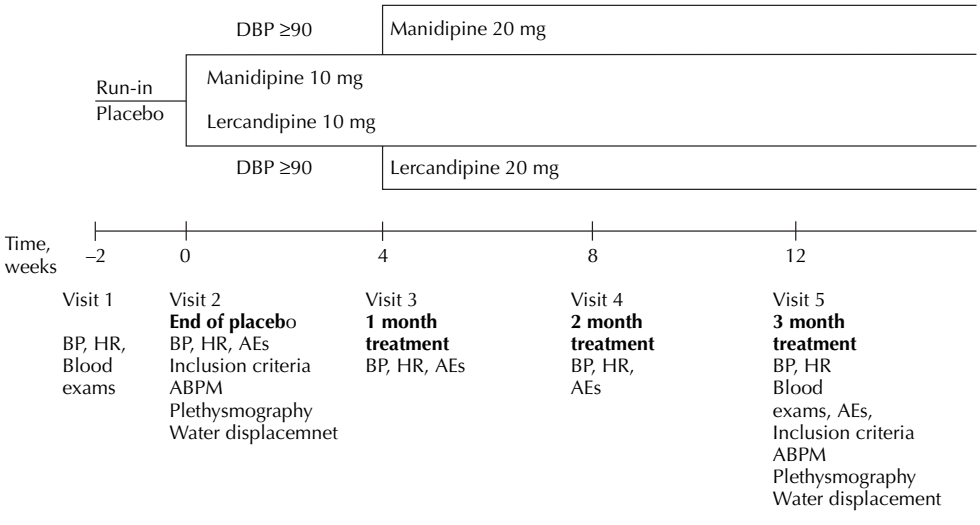
The study was a controlled, randomized, parallel-group blind trial conducted in a single center in Italy.

Patients aged 18 to 75 years with mild-to-moderate essential hypertension (defined as a supine diastolic BP within the range of 90 to 109 mm Hg and a supine systolic BP <180 mm Hg) were eligible for the study. They had to be untreated for hypertension (or to be under current therapy not providing adequate control or producing unacceptable side effects) and have electrocardiogram findings of nothing more serious than left ventricular hypertrophy, first-degree atrioventricular block, or nonischemic ST-T changes. Pregnant women and those who might become pregnant during the study where not eligible.

Caffeine-containing beverages and foods, as well as tobacco products, were not allowed for a period of 4 hours before each visit. Patients maintained a normal diet prior to and during the study. They were instructed not to add salt to their food during the study or eat foods having a high salt content. Any other medication able to affect BP was not allowed.

The plan of the study is shown in Figure 1. During a 2-week run-in period, all subjects received placebo tablets indistinguishable from active treatment. At the end of this period, those who had diastolic BP ≥90 mm Hg and <110 mm Hg were randomized to either manidipine (10 mg/day) or lercanidipine (10 mg/day) once a day in the morning. The dose was doubled for those having diastolic BP ≥90 mm Hg after 1 month of therapy (nonresponders).

Fig 1. Study design.



DBP=diastolic blood pressure; HR=heart rate; AEs=adverse events; ABPM=ambulatory BP monitoring

Office BP was detected at each visit with the patient in the sitting position using a well-calibrated mercury sphygmomanometer and an inflatable cuff. To minimize the alert reaction, BP was measured after at least a 5-minute rest period in triplicate at 1-minute intervals, and the average of the last 2 readings was used. Pulse heart rate was taken at each BP measurement and averaged. Office BP was always taken on the same arm in each subject at approximately the same time (7 AM to 10 AM), that is, 22 to 24 hours after the last drug intake. Diastolic BP corresponded to Korotkoff's phase 5.

Ambulatory BP monitoring (ABPM) was performed for 24 hours at visits 2 and 5 using a 2430 device (TM2430, Takeda, Japan[19]), with a microphone placed on the left brachial artery. Each ABPM recording was started after the administration of the morning dose and lasted 24 hours. The correct positioning of the monitor was checked using a standard mercury sphygmomanometer; the difference between manual and automated readings had to be ≤5 mm Hg. While measurements were taken, the subject's arm had to be extended and still. To be considered valid, ABPM recordings had to have a success rate of 80% or more, with at least one valid daytime recording per hour and at least one valid nighttime recording every 2 hours. If valid recordings were not obtained, the ABPM had to be repeated. If the ABPM was repeated at visit 5, another tablet had to be taken for an additional 24-hour period. The ABPM was programmed to record every 20 minutes from 7 AM to 10 PM and every 30 minutes from 10 PM to 7 AM. Daytime and nighttime were defined as 2 time periods extending from 10 AM to 8 PM and from midnight to 6 AM, respectively.

Arterial rest flow was detected in the leg by means of an indium-gallium-in-silicone strain-gauge plethysmograph (Angioflow, Microlab, Padova, Italy[20]), providing automatic measurement of rest flow ($mL \times min \times dL_{tissue}$); for this purpose, venous occlusion over venous pressure and under diastolic arterial pressure (50 mm Hg)[21] was repeatedly applied for 20 seconds, and flow was extrapolated from the slope of the electrical conductivity curve versus time. The average of 5 consecutive measurements was taken into account. The strain-gauge, fit to the leg circumference of each subject, was placed at the middle of the calf. Rest peripheral resistance was calculated ($mm\ Hg \times min \times dL_{tissue} \times mL^{-1}$) from the ratio between mean arterial BP and arterial rest flow.

Postischemic arterial peak flow ($mL \times min^{-1} \times dL^{-1}_{tissue}$) was detected with the same device after 10 minutes of arterial occlusion (cuff pressure 300 mm Hg) coupled with active foot flexions (1 flexion/3 sec).[22] After the cuff was inflated for 5 minutes, the occlusion pressure was suddenly released and digit volume pulses were followed for the next several minutes. In such conditions of extreme vasodilation (vasoparalysis), the minimal arterial resistance calculated in $mm\ Hg \times min \times dL_{tissue} \times mL^{-1}$ from the mean arterial pressure/postischemic flow ratio reflects the diameter of the small arteries and therefore gives an indirect indication of the artery wall thickness.[23]

Leg venous compliance was evaluated at visits 2 and 5 with strain-gauge plethysmography by occluding venous outflow with a cuff inflated at 70 mm Hg until volume plateau was reached.

Peripheral edema was measured at the calf at visits 1 and 5 by means of a water-displacement plethysmograph.[24] The left foot and calf were carefully placed into a perspex water bath (provided by Microlab, Padova, Italy), with the subject seated on a hospital bed. The water temperature was 30°C. The device was provided with an overflow tube set at 35 cm above the foot sole. The water overflow that resulted

from the water rise due to ankle-plus-foot volume was spilled and repeatedly weighed on an electronic scale (1 g=1 mL). The average of 3 measurements was considered to be leg volume. The difference between the two volumes determined at visits 1 and 5 was taken as a measure of drug-induced edema.[24] This method is considered the most direct, accurate,[24-26] and reproducible[13] way to measure ankle and foot volumes.

The number of supplies assigned to a patient participating in the study and returned by that patient at the following visit was used as a measure of treatment compliance. At the end of the trial or during a monitoring visit, all returned drugs were checked against a supplies accountability form, and any discrepancy was explained.

An adverse event was defined as any untoward medical occurrence that did not have a causal relationship with treatment; adverse reaction was defined as a noxious and unintended response to a drug. Adverse events and reactions, as reported spontaneously by each subject, were recorded at each visit. Physical examination was also performed at each visit. The body weight of each patient dressed in lightweight indoor clothing, without shoes, was measured at visits 1 and 5.

Quantitative reduction of systolic and diastolic BP was estimated at each visit and compared with the BP at visit 2. Comparison between the efficacies of the 2 treatments was investigated at the end of the active treatment period by means of analysis of covariance using BP at visit 2 as covariate; the assumption of validity of covariance was previously checked.

Frequency of adverse effects was expressed as percent rate and compared with the χ^2 test. Laboratory data were treated as continuous variables and compared with analysis of covariance after adjustment for age and sex.

The Ethics Committee of the Unità Locale Socio-Sanitaria No 4 of the Veneto Region approved the study. All the investigators agreed to conduct the trial according to the principles of the Declaration of Helsinki 1964, revised in Italy in 1983, and all other applicable laws and regulations on the use of therapeutic agents.

A valid written consent was given by each patient participating in this study prior to any procedures. Adequate information was given about the aims, methods, anticipated benefits, and potential hazards of study treatment, as well as the freedom of the patient to refuse to enter into the study or to withdraw from it at any time.

Statistical Analysis

Reduction of peripheral resistance was used for determining sample size. Expecting a difference of 8 mm Hg×min×dL_{tissue}×mL^{-1} reduction of resistance between manidipine and lercanidipine at visit 5, a standard deviation of 10 mm Hg×min×dL_{tissue}×mL^{-1} was assumed from a previous study of the same group.[23] Statistical tests were two-tailed with α=.05 and power (1–β)=.80.

Continuous items were averaged and expressed as mean ± standard deviation, categorical items as percent frequency; 95% confidence intervals were provided when necessary. Group comparability was assessed by means of analysis of variance for continuous variables and by means of χ^2 test (or Fisher exact test when necessary) for discrete variables. Because of a mild difference in gender distribution, results were adjusted for gender when appropriate.

Variables derived from ABPM were averaged hourly, and 24-hour curves were established. The trend within each curve and differences between curves were evaluated with repeated-measures analysis of variance. Daytime and nighttime periods were analyzed separately. Smoothness index was also calculated for each subject. For this purpose, the average BP values for each hour of the 24-hour monitoring period were first calculated, at both visits 1 and 5. From these, all hourly BP changes induced by treatment were obtained, and the average of these hourly values was computed together with its standard deviation, which represents the dispersion of the antihypertensive effect over the 24-hour values. Finally, the standard deviation was normalized by dividing its value for the mean (coefficient of variation), and the inverse of this ratio, indicating the degree of smoothness, was defined as the smoothness index.[27]

RESULTS

Fifty-four patients were randomized (27 to manidipine and 27 to lercanidipine). One patient in the manidipine group withdrew his consent and dropped out after 4 weeks and was not considered in the final analysis.

The two groups differed only in male–female ratio (65%:35% in the manidipine group and 48%:52% in the lercanidipine group, $P<.05$), while age (65.8±10.0 vs 68.1±6.8 years), body mass index (28.4±4.2 vs 29.1±4.1 $kg \cdot m^{-2}$), smoking habits (7.7% vs 11.1%), blood lipids, blood glucose, and historical items were not significantly different.

At the end of the placebo period, sitting BP was 156±14/94±3 mm Hg in the manidipine group and 159±11/95.5±5 mm Hg in the lercanidipine group (no significant difference).

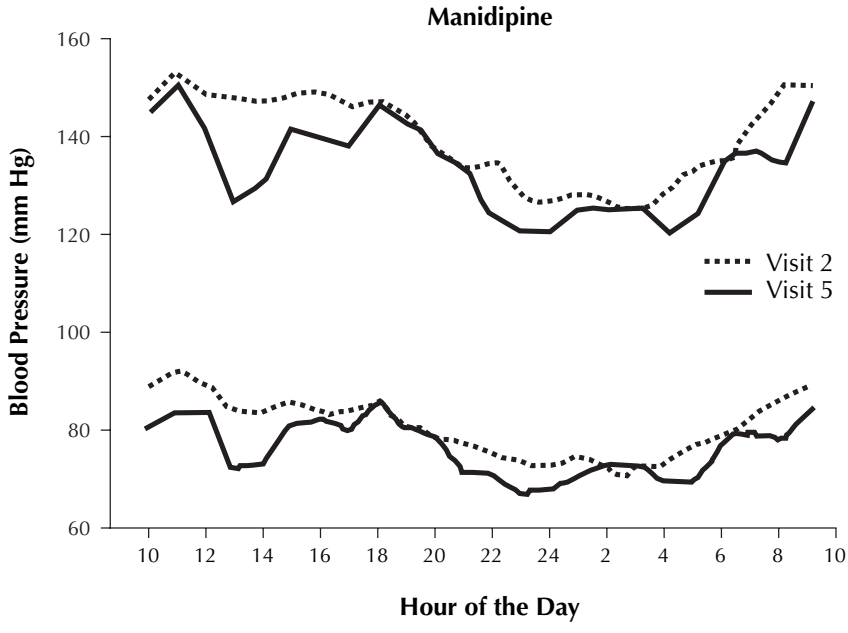
Because of dosing variations during treatment, at the end of the third month, 18 patients (72%) in the manidipine group were treated with 10 mg/day and 7 (28%) with 20 mg/day. In the lercanidipine group, 21 patients (77.8 %) were treated with 10 mg/day and 6 patients (22.2 %) with 20 mg/day (no significant difference between drugs).

Repeated-measures analysis of covariance applied to the effect of treatment (Fig 2) did not show any significant difference between manidipine and lercanidipine.

The daytime and nighttime BP values recorded at the end of the placebo phase and at the end of active treatment are shown in Table 1. A significant reduction of systolic/diastolic daytime BP versus baseline was observed both with manidipine (–5.5%/–5.6 %) and with lercanidipine (–3.8%/–6.6 %) and was comparable for both drugs, while only a shift reduction was observed during nighttime. The 24-hour BP profiles before and after both active treatments are plotted in Figure 3. With manidipine, the 24-hour smoothness index was 0.30±0.65 for systolic and 0.30±0.46 for diastolic BP, with lercanidipine 0.23±1.01 and 0.24±0.76, respectively.

Pulse heart rate recorded at visits 3, 4, and 5 showed a mild reduction in comparison with placebo for both drugs (–2%, –2%, and –6.4% with manidipine; –.1%, –3.3%, and –4.9% with lercanidipine. Visit 5 results for both treatment groups versus baseline were significant ($P<.01$).

Fig 2. 24-hour blood pressure profile.



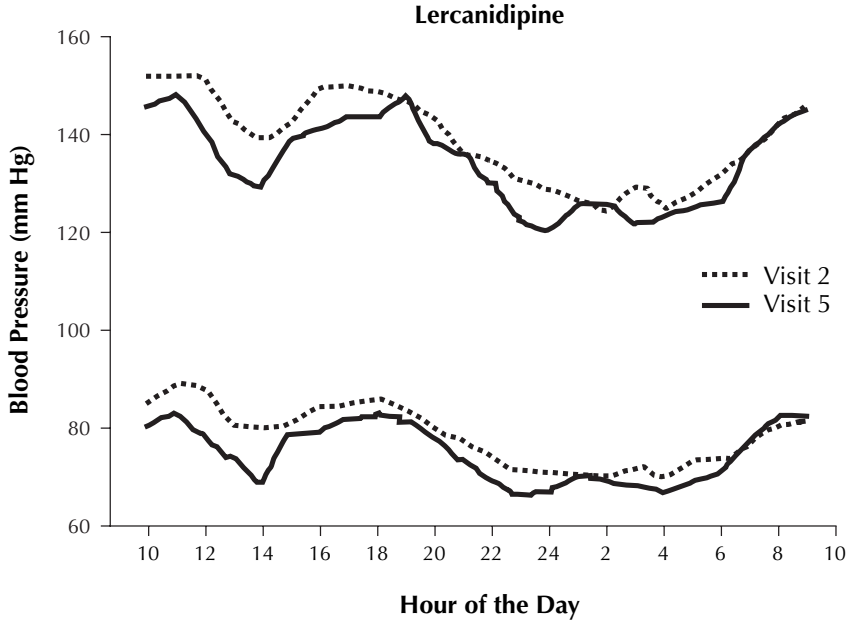


Table 1. Ambulatory Blood Pressure Monitoring

	Manidipine (n=26)		Lercanidipine (n=27)	
	Visit 2 End of Placebo Phase	Visit 5 End of Active Treatment	Visit 2 End of Placebo Phase	Visit 5 End of Active Treatment
24-hour SBP (mm Hg)	140.6±12.8 (135.2–146.0)	134.5±12.7* (129.2–139.9)	139.3±11.3 (134.8–143.8)	135.6±11.8 (130.9–140.2)
24-hour DBP (mm Hg)	81.2±5.6 (78.8–83.6)	77.1±7.1* (74.1–80.1)	78.7±7.9 (75.6–81.9)	75.4±5.6* (73.2–77.7)
Daytime SBP (mm Hg)	147.5±14.4 (141.4–153.6)	139.4±16.3* (132.5–146.3)	147.1±11.8 (142.5–151.8)	141.5±12.2* (136.7–146.4)
Daytime DBP (mm Hg)	85.3±7.3 (82.3–88.4)	80.5±10.1* (76.3–84.8)	84.7±9.2 (81.0–88.3)	79.1±6.9* (76.4–81.8)
Nighttime SBP (mm Hg)	129.4±14.5 (123.2–135.5)	126.2±13.1 (120.6–131.7)	127.6±13.7 (122.2–133.0)	124.7±14.3 (119.1–130.4)
Nighttime DBP (mm Hg)	74.3±6.9 (71.4–77.2)	72.4±7.6 (69.2–75.6)	71.0±8.1 (67.8–74.2)	69.2±7.6 (66.2–72.2)

Mean±standard deviation (95% confidence intervals).
*P<.001 vs visit 2 (end of placebo phase). Two cases excluded because of incomplete data.

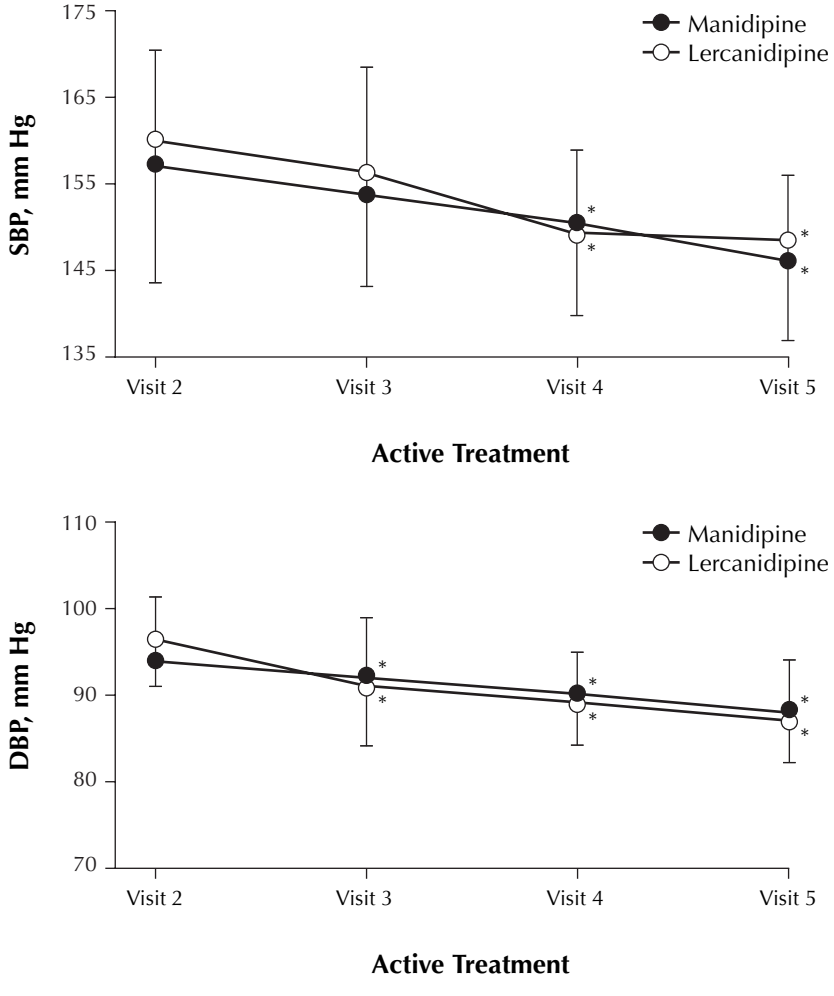
Leg resistance decreased with manidipine (–30%, P<.005) but not with lercanidipine (Table 2). Minimal resistance decreased significantly with manidipine (–39%, P<.005).

With manidipine, there was a trend toward an increase in leg venous compliance (+8.2%), while with lercanidipine it remained unchanged (Table 2).

Eleven subjects (42.3%) had mild-to-moderate adverse events with manidipine and 13 (48.1%) with lercanidipine (nonsignificant difference). In the manidipine group, only 6 adverse effects were judged as probably correlated to the drug (2 cases of headache, 4 of edema, 1 of vertigo), 2 as possibly correlated (1 case of asthenia and 1 of vertigo), and 7 as noncorrelated. In the lercanidipine group, 6 adverse events were judged as probably correlated (1 case of headache, 3 of edema, 2 of vertigo), 6 as possibly correlated (2 cases of headache, 1 of palpitation, 1 of diarrhea, 1 of edema, 1 of vertigo), 12 as noncorrelated, and 1 (tinnitus) as doubtfully correlated. No patients discontinued the study because of adverse effects, and no reactions were judged severe by the investigator.

After 3 months of treatment with lercanidipine, ankle-plus-foot volume significantly increased by 6.6% (9.5 % if the analysis included the 21 patients who had an increase in leg volume). With manidipine, volume increase was of a lesser extent (4.4%; Fig 4) and not significant.

Fig 3. SBP and DBP during active treatment phase.



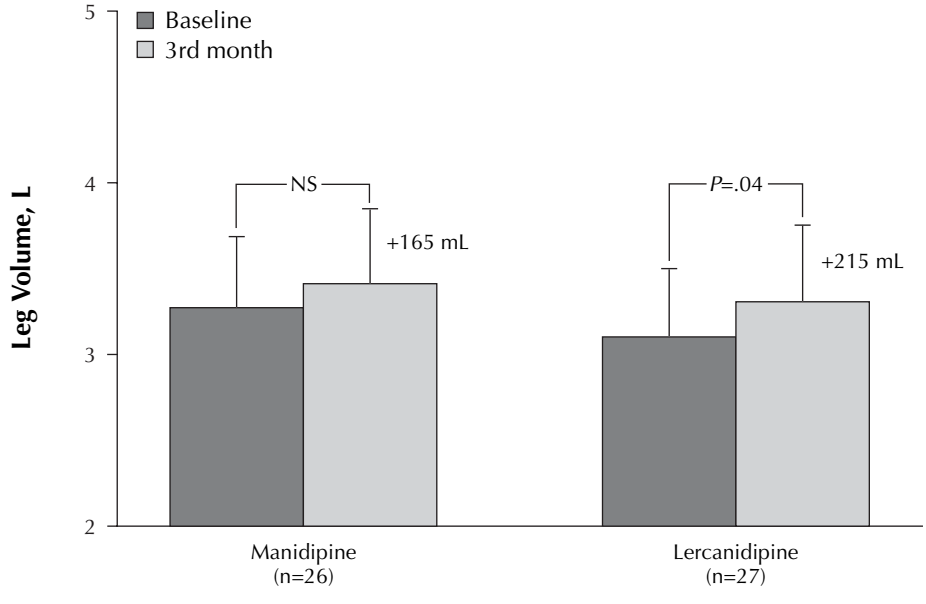
*P<.01 vs visit 2

Table 2. Arterial and Venous Parameters

	Manidipine (n=26)		Lercanidipine (n=27)	
	Visit 2 End of Placebo Phase	Visit 5 End of Active Treatment	Visit 2 End of Placebo Phase	Visit 5 End of Active Treatment
Rest flow ($mL \times min \times dL_{tissue}$)	3.4±1.8 (2.7–4.2)	4.4±2.6* (3.3–5.6)	3.9±1.5 (3.3–4.6)	3.8±1.6 (3.2–4.5)
Peak flow ($mL \times min \times dL_{tissue}$)	16.6±13.4 (10.8–22.4)	20.8±12.6 (15.6–26.0)	12.3±8.6 (8.8–15.7)	17.2±11.5 (12.3–21.7)
Rest resistance ($mm\ Hg \times min \times dL_{tissue} \times mL^{-1}$)	42.3±18.5 (34.9–49.8)	29.6±15.0* (23.4–35.8)	35.5±15.0 (29.6–41.5)	32.5±15.5 (26.4–38.6)
Minimal resistance ($mm\ Hg \times min \times dL_{tissue} \times mL^{-1}$)	11.6±8.0 (8.4–14.8)	7.1±4.3* (5.3–8.9)	13.6±6.6 (10.7–15.9)	8.6±4.7 (6.8–10.5)
Venous capacitance ($mL \times dL_{tissue}^{-1}$)	4.9±2.3 (3.9–5.8)	5.3±2.3 (4.4–6.3)	4.0±1.4 (3.4–4.5)	4.0±1.5 (3.4–4.6)

Mean±standard deviation (95% confidence intervals).
*P<.005 vs visit 2 (end of placebo phase).

Fig 4. Leg (ankle-foot) volume at baseline and the end of study.



NS=nonsignificant

DISCUSSION

Because of the comparable effectiveness of antihypertensive drugs, the choice of a class of drugs or of a drug within a specific class is influenced by factors such as prolonged duration of action, low incidence of side effects, metabolic neutrality, safety for target organs, and, last but not least, the acceptance of patients in controlled clinical trials and in phase-4 surveillance. In other words, it is not enough that an antihypertensive drug is able to reduce blood pressure; it must also have favorable ancillary properties and an optimal pharmacodynamic and pharmacokinetic profile. In affluent countries with a high cultural level, hypertensive patients are increasingly aware of their disease and cardiovascular risk. In such situations, the physician's or specialist's direct control of patients tends to subside, visits become less frequent, and patients tend to be entrusted with the daily management of long-term antihypertensive treatment. To avoid compliance reduction, tolerability, acceptability, and reliability of a drug are therefore as important as efficacy. It is also necessary to be reassured about the absence of silent side effects, which can counter the favorable effects of blood pressure reduction.

In the present controlled trial, manidipine and lercanidipine showed a comparable effect on BP, both measured conventionally and by 24-hour ABPM. This is not surprising, since in previous comparison studies other DCCBs always proved equally effective as antihypertensive agents.[13] The BP reduction compared with baseline (up to 7.4% for systolic and 9.6% for diastolic) was that expected in medium-term monotherapy. ABPM demonstrated that, with both drugs, the BP reduction was due to a homogeneous fall, especially during the daytime. Finally, the smoothness index[27] was also comparable with both drugs.

Although they exhibited a small difference in antihypertensive efficacy, the 2 drugs showed a different effect on peripheral hemodynamics. A clinically important and statistically significant arterial vasodilation was observed with manidipine, but not with lercanidipine. In fact, peripheral resistance at rest decreased by 30% and arterial flow increased by 29% in patients treated with manidipine, while they remained unchanged in patients treated with lercanidipine.

During the 3 months of treatment, vasodilation was accompanied not by an increase in heart rate but by a mild decrease. This should not come as a surprise since it has been recently observed that the adrenergic stimulation caused by DCCBs is transient and rapidly returns to baseline,[28] particularly if long-lasting DCCBs are employed.[29] In particular, Fogari et al have recently shown that plasma norepinephrine, an index of sympathetic activation, does not increase with manidipine.[11] This is of extreme interest from a clinical point of view as reflex tachycardia is an absolutely unwanted side effect, one that can increase the cardiovascular risk particularly in elderly patients with coronary heart disease. Modern clinical pharmacology tends to prevent this effect by combining DCCBs with drugs that decrease the sympathetic discharge and by preferring molecules, like those described here, that appear to be intrinsically free from this problem.

As indirectly demonstrated by the reduction of postischemic peripheral resistance, manidipine also appeared to be able to reduce vascular hypertrophy.[23] If confirmed in longer lasting clinical trials and in a greater number of patients, this finding could tip the scales in favor of manidipine, since myocardial hypertrophy is one of the main components of coronary risk.

Both manidipine and lercanidipine were safe and well tolerated and did not modify unfavorably the metabolic profile of hypertensive patients. Ankle-foot edema was

the most relevant side effect. Ankle-foot edema affects 1.2% to 19% of patients treated with DCCBs,[16] a frequency that rises to 50% if simple leg heaviness is considered,[13] and compels discontinuation in 2.0% to 8.5 % of cases.[13] In the present trial, edema was observed mainly in the lercanidipine group (+215 mL on average), while it was much less prominent (+165 mL) in the manidipine group. The theory is that edema may be related to an arteriolar dilatation that, as a consequence of reflex sympathetic activation, is not accompanied by adequate postcapillary dilatation.[9,12] This appears to lead to increased intracapillary pressure, promoting fluid exudation from the intravascular space to the interstitium.[9,20,30] In the current study, a trend toward an increase of venous compliance was observed after manidipine treatment but not after lercanidipine treatment, possibly indicating a reduced tone at the venous capillary side with the former. This finding coincides with the observation that, compared with other DCCBs, manidipine reduces postglomerular capillary resistance.[3,9] Another explanation could be that the proportion of men was greater in the manidipine group than in the lercanidipine group. In fact, it has been shown that edema is more common in women than in men.[13] Lund-Johansen et al[12] recently described with water displacement volumetry a degree of edema with lercanidipine in women comparable with that observed in the present study and significantly lower than that found with amlodipine. This confirms the clinical impression that the edemigenous potential is different for different DCCBs,[9,11] suggesting that trials with a crossover design aimed at directly comparing DCCBs with different vascular selectivity[10] and pharmacokinetic properties may be advisable.[9,13,29]

In conclusion, both manidipine and lercanidipine were well tolerated and effective in reducing BP. However, the rate of normalization with manidipine was double that associated with lercanidipine, probably because of the lower baseline BP values. Manidipine acted as a more potent vasodilator than lercanidipine, without increasing heart rate. It was also able to reduce arteriolar wall thickness, as shown by reduced maximal arterial resistance. Vasodilatory edema occurred with both drugs, although less frequently with manidipine than with lercanidipine.

REFERENCES

1. Borghi C, Prandin MG, Dormi A, Ambrosini E. Improved tolerability of the dihydropyridine calcium-channel antagonist lercanidipine: the lercanidipine challenge trial. *Blood Pressure.* 2003; 12(suppl 1):14-21.
2. McClellan KJ, Jarvis B. Lercanidipine: a review of its use in hypertension. *Drugs.* 2000;60:1123-1140.
3. Arima S, Ito S, Omata K, Tsunoda K, Yaoita H, Abe K. Diverse effects of calcium antagonists on glomerular haemodynamics. *Kidney Int.* 1996;55(suppl):S132-S134.
4. Sabbatini M, Leonardi A, Testa R, Vitaioli L, Amenta F. Effect of calcium antagonists on glomerular arterioles in spontaneously hypertensive rats. *Hypertension.* 2000;35:775-779.
5. Campo C, Garcia-Vallejo O, Barrios V, et al. The natriuretic effect of nifedipine gastrointestinal therapeutic system remains despite the presence of mild-to-moderate renal failure. *J Hypertens.* 1997;15(12 pt 2):1803-1808.
6. Chou TC, Li CY, Yen MH, Ding YA. Antiplatelet effect of amlodipine: a possible mechanism through a nitric oxide-mediated process. *Biochem Pharmacol.* 1999;58:1657-1663.
7. Buhler FR. Cardiovascular care with the new T-type calcium channel antagonist: possible role of attendant sympathetic nervous system inhibition. *J Hypertens Suppl.* 1997;15:S3-S7.
8. Simon A, Levenson J. Effects of calcium channel blockers on atherosclerosis: new insights. *Acta Cardiol.* 2002;57:249-255.
9. Angelico P, Guarnieri N, Leonardi A, Testa R. Vascular-selective effect of lercanidipine and other 1,4-dihydropyridines in isolated rabbit tissues. *J Pharm Pharmacol.* 1999;51:709-714.

10. Messerli FH. Calcium antagonists in hypertension: from hemodynamics to outcomes. *Am J Hypertens.* 2002;15(7 pt 2):94S-97S.
11. Fogari R, Malamani GD, Zoppi A, et al. Comparative effect of lercanidipine and nifedipine gastrointestinal therapeutic system on ankle volume and subcutaneous interstitial pressure in hypertensive patients: a double-blind, randomized, parallel-group study. *Curr Ther Res Clin Exp.* 2000;61:850-862.
12. Lund-Johansen P, Stranden E, Helberg S, et al. Quantification of leg oedema in post-menopausal hypertensive patients treated with lercanidipine or amlodipine. *J Hypertens.* 2003;21:1003-1010.
13. Leonetti G. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *Am J Hypertens.* 2002;15:932-940.
14. Cheer SM, McClellan K: Manidipine: a review of its use in hypertension. *Drugs.* 2001;61:1777-1799.
15. Epstein M. Lercanidipine: a novel dihydropyridine calcium-channel blocker. *Heart Dis.* 2001;3: 398-407.
16. Barrios V, Navarro A, Esteras A, et al. Antihypertensive efficacy and tolerability of lercanidipine in daily clinical practice. The ELYSPE study. Eficacia de Lercanidipino y su Perfil de Seguridad. *Blood Press.* 2002;11:95-100.
17. Specchia G, Saccaggi SP, Chezzi C. Cardiovascular safety of lercanidipine in patients with angina pectoris: a review of six randomized clinical trials. *Curr Ther Res Clin Exp.* 2001;62:3-15.
18. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. *Curr Cardiol Rep.* 2002;4:479-482.
19. Palatini P, Frigo G, Bertolo O, Roman E, Da Corta R, Winniki M. Validation of the A&D TM-2430 device for ambulatory blood pressure monitoring and evaluation of performance according to subjects' characteristics. *Blood Press Monit.* 1998;3:255-260.
20. Casiglia E, Petucco S, Pessina AC. Antihypertensive efficacy of amlodipine and enalapril and effects on peripheral blood flow in patients with essential hypertension and intermittent claudication. *Clin Drug Invest.* 1995;11(suppl):97-101.
21. Sakaguchi S, Ishitobi K, Kameda T. Functional segmental plethysmography with mercury strain gauge. *Angiology.* 1972;23:127-135.
22. Eichna LW, Wilkins RW. Blood flow to the forearm and calf. Reactive hyperemia: factors influencing the blood flow during vasodilation following ischemia. *Bull Johns Hopkins Hosp.* 1941;68:450-456.
23. Muiesan ML, Rizzoni D, Zulli R, et al. Cardiovascular characteristics in normotensive subjects with or without family history of hypertension. *Clin Exp Hypertens.* 1996;18:901-920.
24. Brjiker F, Hejidra YF, Van Den Eishout FJ, Bosch FH, Folgering HT. Volumetric measurements of peripheral oedema in clinical conditions. *Clin Physiol.* 2000;20:56-61.
25. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper-extremity volume estimates: comparison of calculated volume derived from girth measurements and water displacement volume. *Phys Ther.* 2003;83:134-145.
26. Weir MR, Rosenberger C, Fink JC. Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. *Am J Hypertens.* 2001;14:963-968.
27. Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. *J Hypertens*. 1998;16:1685-1691.
28. Grassi G, Serravalle G, Turri C, Bolla G, Mancia G. Short- versus long-term effects of different dihydropyridines on sympathetic and baroreflex function in hypertension. *Hypertension.* 2003; 41:558-562.
29. Messerli FH, Grossman E. Pedal edema-not all dihydropyridine calcium antagonists are created equal. *Am J Hypertens.* 2002;15:1019-1020.
30. Salmasi AM, Belcaro G, Nicolaides AN. Impaired venoarteriolar reflex as a possible cause for nifedipine-induced ankle oedema. *Int J Cardiol.* 1991;30:303-307.