Journal of Cardiovascular Pharmacology™
40:133–139 © 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Lercanidipine in Type II Diabetic Patients With Mild to Moderate Arterial Hypertension

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Summary: This study evaluates the effects of lercanidipine antihypertensive treatment on glucose homeostasis in patients with type II diabetes mellitus with mild to moderate hypertension. Forty patients were enrolled. After a 2-week wash-out period, they were randomly allocated to receive in double-blind manner either 10 mg or 20 mg in single daily administration for 8 weeks. Nonresponding patients after the initial 4 weeks, were titrated up to 20 mg and 30 mg lercanidipine, respectively. At the end of the double-blind treatment, all patients entered in single-blind 4 weeks placebo follow-up. Systolic and diastolic blood pressure significantly decreased in both groups of patients after 4 weeks of treatment, and decreased further during the following 4 weeks. In both groups, progressive and significant decrease in fasting blood glucose, glycosylated hemoglobin and area under the curve of the oral glucose tolerance test were detected during lercanidipine treatment. Similarly, a decrease in serum fructosamine values were also observed. All variables returned to towards baseline values during the placebo follow-up period. Adverse events (headache and mild asthenia) were limited to two patients and resolved spontaneously. These data indicate that lercanidipine is effective in lowering high blood pressure in hypertensive patients with type II diabetes mellitus and does not exert negative effects on glucose homeostasis. **Key Words:** Calcium-antagonists—Essential hypertension—Glucose homeostasis—Lercanidipine—Type II diabetes mellitus.

Diabetes mellitus, an important cardiovascular risk factor, is often associated with arterial hypertension (1). It has been shown that the coexistence of the two clinical conditions greatly increase the incidence of cardiovascular events and accelerate the development of diabetic nephropathy and retinopathy (1). Both the elevated blood pressure and the complex metabolic abnormalities should be corrected effectively in these patients to prevent vascular and renal damage. When the therapeutic goals are not achieved by non-pharmacological therapy, treatment with antihypertensive drugs is recommended, especially in patients with other concomitant risk factors for cardiovascular disease such as diabetes mellitus (1, 2,3). It is however important that the antihypertensive treatment may improve, or at least it does not impair, glucose tolerance. Calcium antagonists potentially may

Received May 29, 2001; accepted January 28, 2002.

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This study was supported by a research grant from Recordati Industria Chimica e Farmaceutica S.p.A., Italy.

DOI: 10.1097/01.FJC.0000016321.50950.78

influence glucose metabolism since it has been shown in vitro that the release of insulin is inhibited by calcium channel blocking drugs (4,5); however, their short-term effects on glucose blood levels in diabetic hypertensives are not very clear (6,7,8). Although the majority of controlled clinical studies have not shown any adverse effects on glucose metabolism (9,10), diabetogenic effects occasionally have been reported with both calcium antagonists and diuretics, even if they usually are attributable to the high dosages (11,12). Therefore, the role of calcium antagonists in diabetes mellitus has not yet been established clearly.

Lercanidipine, a new dihydropyridine calcium antagonist, has been shown to exhibit a good therapeutic efficacy and tolerability profile in patients with mild to severe arterial hypertension (13,14), or in patients with resistant essential hypertension (15). In particular, because of its selective and long-acting vasodilator activity with a slow onset of action, lercanidipine is devoid of any effects on cardiac contractility or heart rate (HR) (13,16–19), thus presenting an improved cardiovascular safety in comparison to older agents of the same class.

The present study was done in type II diabetic patients with mild to moderate arterial hypertension to evaluate the influence of lercanidipine treatment, at effective antihypertensive dosages, on glucose metabolism.

METHODS

A total of 40 patients of both sexes, aged 18–70 years, with type II diabetes mellitus and mild to moderate arterial hypertension were enrolled in this study. Patients, treated with diet or with oral hypoglycemic agents, were under stable metabolic control for at least 2 years. Mild to moderate hypertension was defined as a supine diastolic blood pressure (DBP) between 95 and 115 mm Hg inclusive, confirmed at the end of the wash-out period. Severe hypertensives (systolic blood pressure [SBP] >220 mm Hg or DBP >115 mm Hg) were excluded from the trial; other exclusion criteria were any conditions contraindicating the use of calcium antagonists or those interfering with the evaluation of the results, such as cardiac and renal diseases, obesity, insulin treatment, diabetic neuropathy or glycosylated hemoglobin (HbA1) > 8%. Once approved by the local Ethics Committee, the study was conducted according to the Good Clinical Practice standards, and all patients gave their written informed consent before enrolment.

Protocol

The study was conducted using a double-blind dosing schedule randomized to two parallel groups, each treated with different initial dosages of lercanidipine administered once daily by the oral route.

After 2 weeks of antihypertensive drug wash-out, one group of patients (n = 20) was treated with 10 mg lercanidipine (L 10) and the other group (n = 20) with 20 mg lercanidipine (L 20) for 4 weeks. At the end of this period, responding patients (defined as DBP <90 mm Hg, or DBP decrease from baseline of at least 10 mm Hg) were kept at the same drug dosage, while nonresponding patients were titrated up to 20 mg (group 1) and 30 mg lercanidipine (group 2), respectively. All patients were treated for another 4 weeks; after 8 weeks of active treatment, all patients underwent a period of follow-up with placebo for 4 weeks.

The SBP, DBP, HR, fasting blood glucose were measured before the wash-out period, every 2 weeks during the whole study and at the end of placebo follow-up; oral glucose tolerance test (OGTT), HbA1, and plasma fructosamine were measured before treatment, after 4 and 8 weeks of active treatment with lercanidipine, and at the end of the placebo follow-up period. All the measurements were taken at trough, 24 ± 2 hours from the last drug administration, in fasting conditions.

The dose of anti-diabetic drugs for those patients treated with oral hypoglycemics and the diet were not modified during the study period.

Efficacy was evaluated in each group by comparing the baseline blood pressure values with the values measured after the active treatment and after 4 weeks of placebo follow-up.

TABLE 1.
Patient characteristics in two groups initially treated with lercanidipine daily

		Lercanidipine		
		10 mg/day (n = 19)	20 mg/day (n = 19)	p
Sex (male:female)	18:20	10:9	8:11	0.516
Age (y)	59.4 ± 6.4	61.7 ± 5.6	57.1 ± 6.5	0.026
Height (cm)	165.7 ± 9.3	167.0 ± 8.9	164.5 ± 9.7	0.408
Weight (kg)	71.7 ± 10.2	72.5 ± 10.8	70.9 ± 9.9	0.611
Diabetes duration (y)	6.8 ± 3.7	8.0 ± 4.3	5.4 ± 2.5	0.038
Oral antidiabetics	n = 16	n = 9	n = 7	0.600
SBP (mm Hg)	156.8 ± 6.1	156.7 ± 6.5	156.8 ± 5.8	0.948
DBP (mm Hg)	101.8 ± 3.4	101.3 ± 3.7	102.4 ± 3.1	0.343
HR (bpm)	73.8 ± 4.7	73.8 ± 5.4	73.8 ± 4.0	0.973

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

n = 38 patients total.

Values are shown as mean ± standard deviation for L10 (lercanidipine 10 mg/day; n = 19) and L20 (lercanidipine 20 mg/day; n = 19).

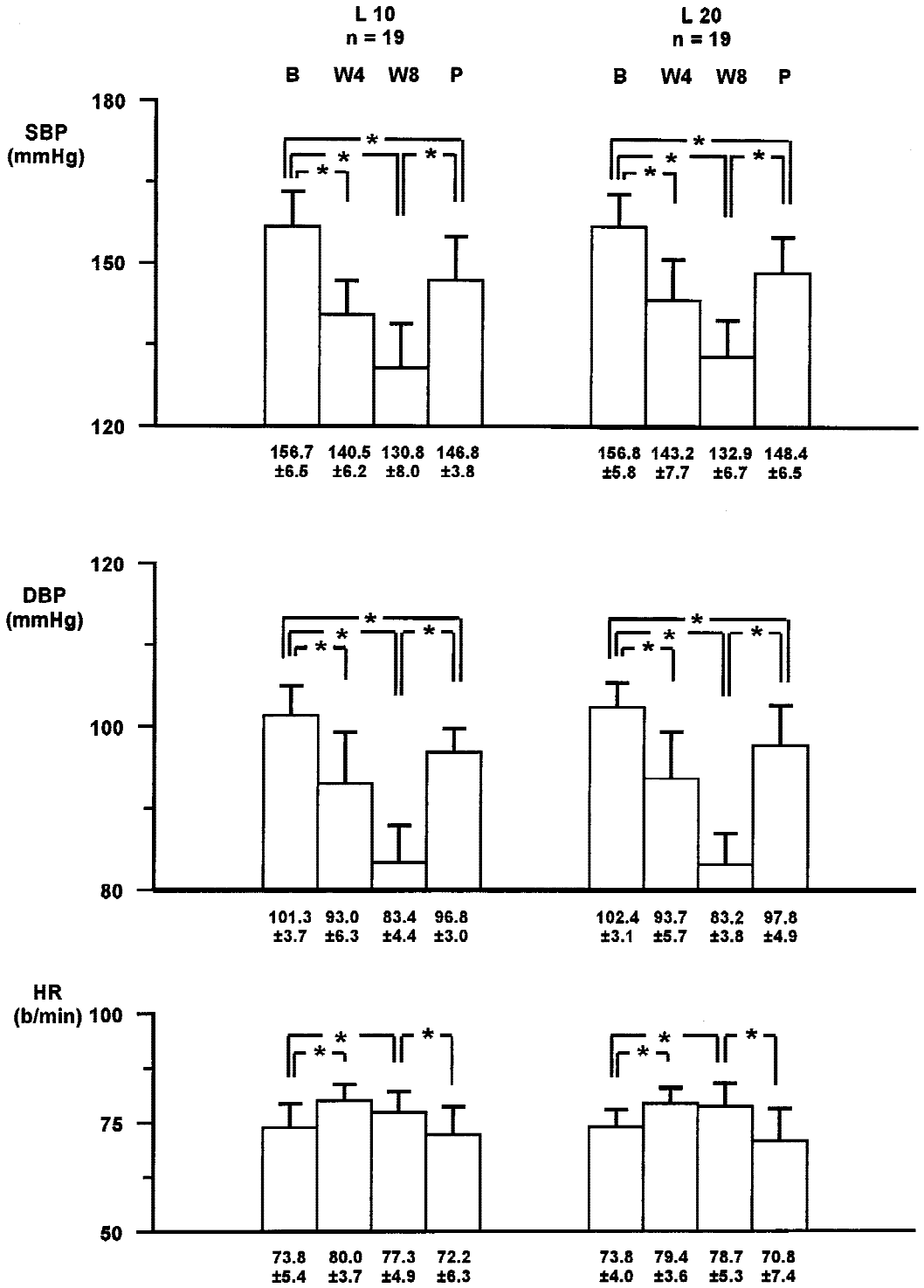

FIG. 1. Effects of lercanidipine on systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in hypertensive type II diabetic patients. Histograms and bars are means ± SD of values measured before treatment (B), after 4 (w 4) and 8 weeks (w 8) of lercanidipine treatment either with 10–20 mg lercanidipine o.d. (L 10) or with 20–30 mg lercanidipine o.d. (L 20), and 4 weeks after the reintroduction of placebo (P). Actual values are displayed below each histogram. *$p < 0.001$ (difference between the values).

The percentage of responding patients, as defined before, and normalized patients (DBP <90 mm Hg) was evaluated in each group after 4 and 8 weeks of lercanidipine treatment. Blood pressure was measured in the supine position (mean value of at least two measurements taken 3 min apart) and after 2 min of upright posture, according to the WHO recommendation (2).

Statistical Analysis

Values are expressed as mean ± SD. The calculated area under the curve (AUC) was used as an index of the OGTT.

Comparison of the initial characteristics of the two groups of patients was done by Student *t* test for age, height, weight and duration of diabetes, and by χ^2 test for gender and hypoglycemic treatment.

The analysis of variance (split-plot model) was applied to SBP, DBP, HR, AUC, HbA1, fasting blood glucose and fructosamine. The frequencies of responding and normalized patients were analyzed using the χ^2 test.

RESULTS

Patients

The characteristics of the two groups of patients initially treated once a day with 10 mg or 20 mg lercanidipine are summarized in Table 1, together with their clinical characteristics.

No statistically significant differences were detected between the two groups for sex distribution, height, weight, SBP, DBP, HR and the number of patients treated with hypoglycemic agents. The mean age and the duration of diabetes were higher in the patients treated with 10 mg lercanidipine. Such a difference, however, was not considered relevant from a clinical point of view, since both groups of patients resulted in a mean age class typical for type II diabetes and hypertension, and the difference in the duration of diabetes was negligible in terms of difference in disease complications.

Efficacy

As shown in Figure 1, SBP and DBP significantly decreased in both groups of patients after 4 weeks of treatment with 10 or 20 mg lercanidipine, reaching a further small but significant ($p < 0.001$) decrease of BP in both group after 8 weeks of treatment.

At the end of the follow-up period when patients were treated with placebo, SBP and DBP were higher than 8 weeks values even if they did not reach the baseline values.

During the whole study, no significant differences in BP were observed between the L 10 mg and L 20 mg groups. This was confirmed also by the percentage of patients responding to or normalized by 4 week treatment with 10 mg lercanidipine (55%) as compared with those receiving 20 mg lercanidipine (50%). After further 4 weeks, titration to 20 mg in the lower dose group produced a BP control in 95% of the sample, while all patients in the upper dose group normalized, including non responding patients titrated to 30 mg. No statistically significant difference were detected between the two groups at any time.

Before treatment, the values of fasting blood glucose, HbA1 and fructosamine were similar in the two groups of patients (Table 2).

During lercanidipine treatment, blood glucose, HbA1 and fructosamine progressively and significantly decreased in both groups of patients.

TABLE 2.

Effects of lercanidipine treatment on glucose homeostasis parameters in hypertensive patients with type II diabetes

	Before	Week 4	Week 8	Placebo follow-up
Fasting Blood Glucose (mg/dl)				
L10	153 ± 25	141 ± 18*	133 ± 19*	147 ± 17*
L20	149 ± 19	138 ± 23*	134 ± 17*	148 ± 17*
Glycosylated hemoglobin (HbA1%)				
L10	5.8 ± 0.9	5.6 ± 0.9*	5.5 ± 0.9*	5.6 ± 1.0*
L20	5.7 ± 1.1	5.6 ± 1.1*	5.4 ± 1.1*	5.6 ± 1.1*
Fructosamine (mg/dl)				
L10	280 ± 48	256 ± 47*	230 ± 45*	261 ± 39*
L20	266 ± 44	240 ± 45*	216 ± 38*	246 ± 43*

Values are shown as mean ± standard deviation for L10 (lercanidipine 10–20 mg/day; n = 19) and L20 (lercanidipine 20–30 mg/day; n = 19). Placebo follow-up was 4 weeks after the end of the treatment period.

*$p < 0.001$ versus baseline. No statistically significant differences were observed between treatment groups (analysis of variance test).

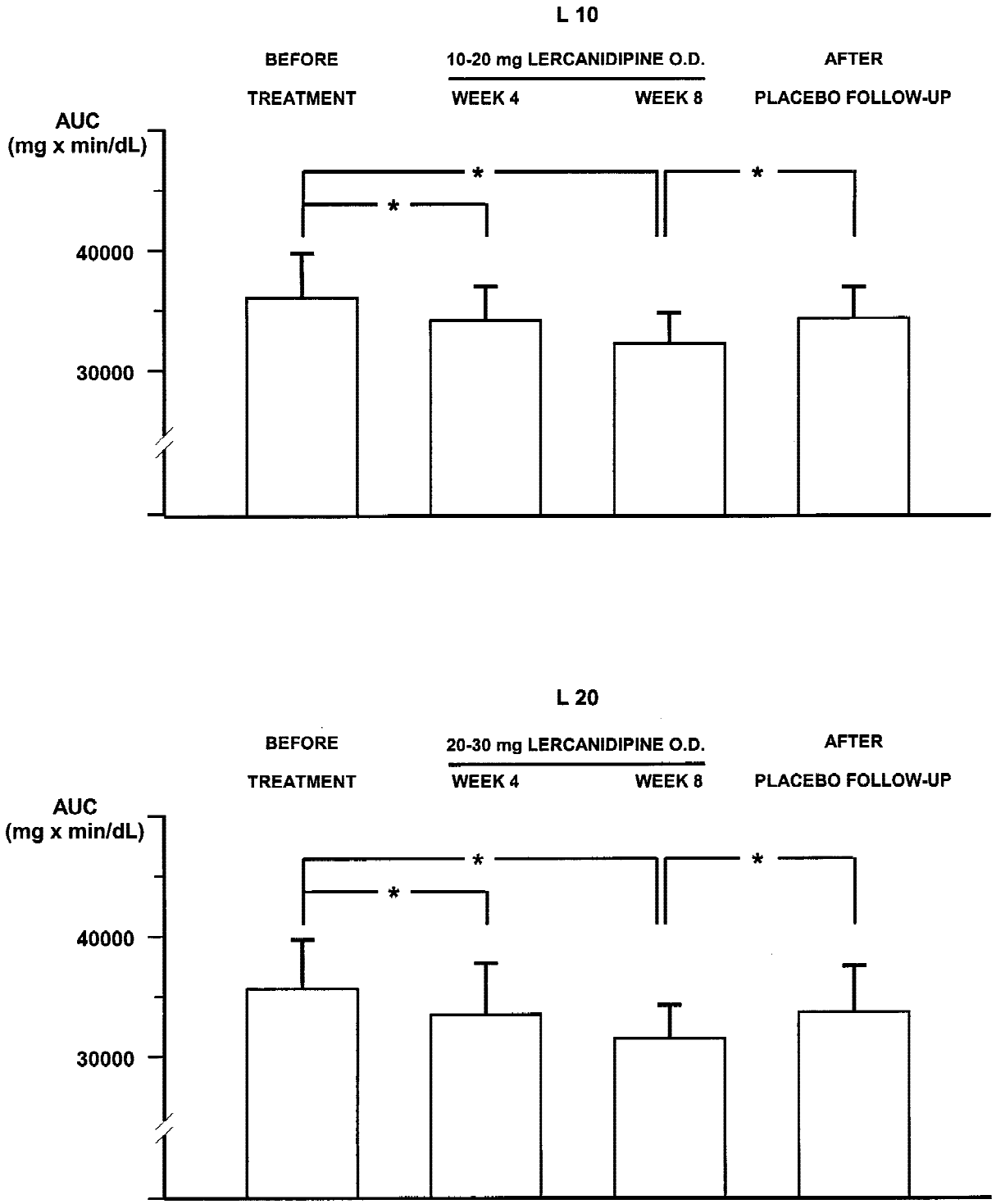

FIG. 2. Effects of lercanidipine on oral glucose tolerance test in hypertensive type II diabetic patients. Histograms and bars are means ± SD of values of the area under the curve (AUC) obtained by oral glucose administration (75 g in 200 ml of water to be drunk in 5 min.) in patients treated with 10–20 mg lercanidipine (L 10, N = 19) or with 20–30 mg lercanidipine (L 20, N = 19). *$p < 0.001$ (difference between the two values).

Similarly, the AUC obtained during the OGTT progressively and significantly decreased during the active treatment with lercanidipine in both groups (Fig. 2). All these variables returned to baseline values at the end of the follow-up period when patients were on placebo treatment (Table 2, Fig. 2).

Tolerability

As compared with baseline values, the HR significantly was higher after 4 and 8 weeks of treatment (each $p < 0.001$). The HR returned to baseline values during the placebo follow-up period. No major adverse events related to the drug were observed during the study; only two patients (one on 10 and one 20 mg lercanidipine) complained upon questioning of mild headache and asthenia, respectively. These side effects spontaneously resolved without having to stop the antihypertensive treatment.

One patient in each group dropped out during the placebo follow-up period for personal reasons.

DISCUSSION

The results of this study demonstrate that antihypertensive treatment with lercanidipine, which is effective in lowering blood pressure in patients with type II diabetes mellitus, did not alter glucose metabolism. If any, a slight but significant improvement in all the metabolic parameters was observed. The slight changes in HbA1 and fructosamine values during this short observation period may have been incidental because it has been seen that both these parameters may change very slowly over time (20,21). Nevertheless, decrease in HbA1 was found consistently in all patients.

These findings might suggest that the antihypertensive treatment with lercanidipine exerts a favorable effect on glucose metabolism. This interpretation is further supported by the observation that all metabolic parameters returned to the baseline values during the last period of placebo treatment.

The slight improvement in glucose metabolism can be ascribed to the overall better compliance of the patients since they were being treated under more controlled clinical conditions.

These data also indicate that the effect of lercanidipine treatment on glucose homeostasis is independent of the dosage because no differences were observed between the two treatment groups.

In addition, the present results confirm the efficacy and good tolerability of antihypertensive treatment with lercanidipine as described previously (13,15).

Arterial hypertension in diabetic patients represents an increase in cardiovascular risk and a more rapid development of atherosclerotic lesion (22). In these patients, the antihypertensive effect should be achieved without any deterioration of the glucose homeostasis. Antihypertensive drugs such as beta-blockers and diuretics are known to exert a negative influence on glucose metabolism (23,24). Current evidence suggests that calcium antagonists do not seem to affect glucose homeostasis in both short and long-term studies (25).

LIMITATIONS AND CONCLUSION

The results of this study indicate that lercanidipine, when used at therapeutic doses (10, 20 mg once a day), appears to improve the glucose profile in hypertensive patients with type II diabetes mellitus with an adequate antihypertensive effect and a good tolerability profile. However, the 30 mg once a day dose of lercanidipine used in the setting of a clinical trial is an "experimental" one: this dose was used to obtain a "normalization" of the blood pressure values in those patients refractory to dosages usually used (10, 20 mg) and who would have also required low dosages of other classes of antihypertensive drugs to control the BP: in fact, the primary end point of this study was to verify the real effect only of lercanidipine on glucose metabolism.

The slight HR changes in both groups of patients, even if statistically significant, likely are attributable to the physiological variability of the subjects.

Finally, our study, although short term, has shown that lercanidipine can be used safely and effectively in diabetic patients with mild to moderate arterial hypertension; therefore, this finding should be confirmed by controlled long-term studies in diabetic patients.

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