Dihydropyridine calcium channel blockers (CCBs) are widely used in subjects with hypertension and coronary artery disease. First generation dihydropyridines (conventional nifedipine, felodipine, isradipine, nicardipine, nitrendipine), characterized by a rapid increase in plasma concentration with consequent rapid onset of vasodilator/antihypertensive effect, have been demonstrated to produce reflex activation of the sympathetic nervous system. This action may be disadvantageous in cardiac patients and may partially explain the disappointing results reported in some observational studies (ie, higher than normal incidence of cardiovascular events among patients with hypertension and acute coronary syndrome treated with short acting dihydropyridines). Second generation dihydropyridines (modified release nifedipine, felodipine, isradipine), characterized by a delayed or modified release mechanism and third generation agents (amlodipine, lercanidipine, lacidipine, and manidipine), which are intrinsically long-acting, due to long plasma or long-receptor half-life, have been shown to minimize fluctuating plasma levels and to cause a lower incidence of unwanted side effects, including lack of activation of heart rate (HR).

Few direct comparisons among the effects of slow-onset, long-acting dihydropyridines on sympathetic nervous activity have been carried out. Therefore, it remains to be clarified whether chronic treatment with these agents produces sympatho-reflex activation and whether differences exist among long-acting dihydropyridines with different pharmacologic characteristics.

With this background, the present study was undertaken to compare the effects of chronic treatment with the slow-release formulation of nifedipine (Bayer, Leverkusen, Germany), nifedipine GITS (Gastro-Intestinal Therapeutic System) and lercanidipine (Recordati, Milan, Italy), a new lipophilic dihydropyridine CCB with a long receptor half-life.
life on blood pressure (BP), HR, and plasma levels of norepinephrine (NE), assessed as a parameter of sympathetic nervous activity.

**Methods**

Male and female outpatients, aged 30 to 65 years, with mild-to-moderate essential hypertension (diastolic BP > 95 and < 110 mm Hg after a 4-week placebo washout period) were considered eligible for the study. Subjects with diabetes mellitus, renal or hepatic insufficiency, myocardial infarction, or stroke within the previous 6 months, clinically relevant cardiovascular disease, smoking habits, history of alcohol abuse, neurologic or psychiatric illnesses, known hypersensitivity to dihydropyridines were excluded from the study. Informed consent was obtained from all subjects. The study protocol was approved by the local ethics committee.

After a 4-week washout period, during which antihypertensive medications, if any, were discontinued and placebo was administered, eligible patients were randomized to receive 10 mg of lercanidipine or 30 mg of nifedipine GITS, both orally, according to a double-blind, parallel group design. After 4 weeks of treatment, if the BP had still not been controlled (diastolic BP > 90 mm Hg) 20 mg of lercanidipine or 60 mg of nifedipine GITS were administered for the next 44 weeks. Patients were checked at the end of the placebo period and after 4, 8, 24, and 48 weeks of active treatment. At each visit BP, HR, and plasma NE levels were evaluated. The BP measurements were taken by using a standard mercury sphygmomanometer (Korotkoff I and V) after the patient had been seated for 10 min. Three consecutive readings were taken and averaged. The HR was measured by pulse palpation for 30 sec, immediately after the BP measurement. Blood samples for the evaluation of plasma NE were taken at specific time intervals: at trough, at peak (3 hours after drug ingestion), and 12 h after drug ingestion. We positioned an intravenous line in the patient’s antecubital vein and after 20 min, a blood sample was taken. Venous blood was drawn into prechilled tubes containing sodium heparin (143 USP/10 mL) and centrifuged immediately at 4°C for 20 min at 3000 rpm. Plasma samples (2 mL) were stored at −80°C until assayed in tubes containing 40 μL preservative solution composed of 95 mg of EDTA and 60 mg of glutathione in 10 mL of water adjusted to pH 7.0. For determination of NE by HPLC, a modification of the method of Remie and Zaagsma, described by Hjemdahl was used. The detection limit was 10 pg/mL, the recovery in plasma was 98%, and the interassay variability was 4%.

**Statistical Analysis**

Data are given as means ± standard deviations. The results were analyzed by analysis of variance. A P value < .05 was taken for statistical significance.

**Results**

Sixty mild-to-moderate hypertensive patients, 28 men and 32 women, aged 30 to 65 years were included in the study and all completed the protocol. The main demographic and clinical characteristics of the patients in each treatment group at baseline are presented in Table 1. The distribution of the patients in the two treatment groups was homogeneous. Of the patients, 33 had to be titrated to the highest dose after 4 weeks of therapy because their diastolic BP was > 90 mm Hg (17 in the lercanidipine group and 16 in the nifedipine GITS group).

Chronic administration of both CCBs similarly reduced BP values (Fig. 1). The mean decrease in systolic and diastolic BP obtained after 48 weeks of treatment was 21.7/15.9 mm Hg with lercanidipine (P < .001 vs placebo) and 20.7/14.6 mm Hg with nifedipine GITS (P < .001 vs placebo). No significant change in HR was observed after chronic treatment with both lercanidipine (−0.1 beats/min; P = not significant) and nifedipine GITS (+0.1 beats/min; P = not significant) (Fig. 1).

Significant increases in NE levels were observed with nifedipine GITS. After 48 weeks, the increases from baseline were maximal at peak (from 239 ± 61 to 295 ± 59 pg/mL, P < .05) but persisted also after 12 h from drug ingestion (from 230 ± 60 to 278 ± 61 pg/mL, P < .05) and at trough (from 227 ± 59 to 286 ± 64 pg/mL, P < .05). Plasma NE concentrations were not significantly affected by chronic treatment with lercanidipine. After 48 weeks NE levels at peak (229 ± 56 pg/mL), at trough (223 ± 55 pg/mL), and 12 h after lercanidipine administration (219 ± 58 pg/mL) were not different from the correspondent levels observed at baseline (248 ± 58 pg/mL at peak, 219 ± 56 at trough, and 227 ± 59 after 12 h).

After 4 weeks of treatment we observed a significant increase in NE concentrations with both nifedipine GITS (from 239 ± 61 to 372 ± 76 pg/mL, P < .001 at peak; from 237 ± 59 to 358 ± 80 pg/mL, P < .001 at trough; and from 230 ± 60 to 365 ± 74 pg/mL, P < .001 after 12 h) and lercanidipine (from 248 ± 58 to 337 ± 60 pg/mL, P < .001).
pg/mL, \( P < .05 \) at peak; from 219 ± 56 to 304 ± 52 pg/mL, \( P < .05 \) at trough; and from 227 ± 59 to 296 ± 56 pg/mL, \( P < .05 \) after 12 h). Such an increase, however, persisted even if to a lesser degree, only during treatment with nifedipine GITS. The NE levels at peak, at trough, and after 12 h were, respectively, 337 ± 75 pg/mL, 336 ± 74 pg/mL, and 325 ± 68 pg/mL, all \( P < .01 \) v baseline, after 8 weeks of treatment, and 306 ± 58 pg/mL, 298 ± 66 pg/mL, and 288 ± 60 pg/mL, all \( P < .05 \) v baseline, after 24 weeks of treatment. In contrast, the increase in NE levels diminished progressively during treatment with lercanidipine, being nonsignificant already at after 8 weeks of therapy, when NE mean values were 271 ± 62 pg/mL at peak, 260 ± 59 pg/mL at trough, and 251 ± 58 pg/mL after 12 h.

**Discussion**

The results of the present study indicate that in chronic treatment of patients with mild-to-moderate hypertension the two long-acting dihydropyridine CCB nifedipine GITS and lercanidipine, despite similar antihypertensive efficacy, displayed different effects on plasma NE levels. In fact, nifedipine GITS produced a significant increase in NE concentrations, which was evident after 4 weeks of treatment and persisted throughout the entire study period. In contrast, lercanidipine caused only a temporary reflex increase in NE levels, which was present after 4 weeks of therapy but disappeared rapidly, being not significant already at 8 weeks of treatment, when NE mean values were 271 ± 62 pg/mL at peak, 260 ± 59 pg/mL at trough, and 251 ± 58 pg/mL after 12 h.

pharmacologic characteristics of the two drugs. In particular, differences in lipophilicity and in membrane partition coefficient may be involved. Unlike nifedipine GITS, lercanidipine is lipophilic, which translates into a long-lasting effect at the receptor and membrane level. This characteristic, besides explaining the slow-onset and the long duration of action of the drug, might also be responsible for different rates of access and removal from the brain, with possible different peripheral manifestations. Dihydropyridine CCB have been demonstrated to reach tissues of the central nervous system and experimental data support the possibility that these drugs directly inhibit sympathetic outflow through central mechanisms. However, further data are needed to confirm such an hypothesis.

Interestingly, chronic treatment with nifedipine GITS, despite the significant increase in NE levels, did not increase HR, which suggests that cardiac sympathetic activation did not occur despite the increase in peripheral sympathetic tone. This finding is in agreement with the results obtained by Wenzel et al by direct measurement of sympathetic nerve activity in the peroneal nerve. With nifedipine GITS, HR remained unchanged whereas muscle sympathetic activity as well as plasma NE levels increased. This suggests that the sympathetic nervous system is not uniformly activated and those cardiac and peripheral sympathetic activities are differently regulated. Possibly the subtle onset of vasodilation with the slow-release preparation of nifedipine is sufficient to selectively increase peripheral nerve activity while leaving HR unchanged, which might be due to the fact that baroreflex sensitivity controlling HR adapts rapidly with nifedipine GITS, whereas peripheral sympathetic activity is still activated. Therefore, caution is needed in extrapolating
from the behavior of HR information to influences on sympathetic cardiovascular function, also because resting HR values depend not only on the sympathetic but also on the parasympathetic nervous system.18

Finally, the reduced sympathetic activation could represent also a possible explanation of the lower potential for edema formation of lercanidipine.19 A lower sympathetic activation could induce less venoconstriction and then less discrepancy between arteriolar dilatation and venular constriction.

One potential limitation of our study is that plasma NE determinations, although widely used in clinical studies to assess sympathetic activity, provide only an indirect measure because only the overflow of the adrenergic neurotransmitter from the synaptic cleft is measured. Furthermore, NE values depend not only on the release of the adrenergic neurotransmitter but also on its tissue clearance and reuptake.18

With all caution due to such limitation, we conclude that the sustained increase in NE levels observed after chronic antihypertensive treatment with nifedipine GITS indicates that sympathetic activation occurs with this drug. In contrast, the lack of NE increase with lercanidipine, possibly related to its pharmacologic properties, suggests that long-term treatment with this drug does not activate the sympathetic nervous system. Although the prognostic significance of this observation remains to be demonstrated, the lack of sympathetic activation with lercanidipine should theoretically be beneficial in treating hypertensive patients.

References