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Lercanidipine (Rec 15/2375): A Novel 1,4-Dihydropyridine Calcium Antagonist for Hypertension

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INTRODUCTION

Hypertension is one of the major risk factors for coronary heart disease and the most important risk factor for cerebrovascular diseases (1). In most countries, almost 20% of the population has high blood pressure levels; two-thirds of those have mild hypertension and the remaining have a more severe disease (2). It is clear, therefore, that the treatment of hypertension is a primary public health care objective. Both mortality and morbidity appear to be directly related to the degree of hypertension, even if substantial differences can be detected in relation to the severity of the disease. In fact, each year 3% to 5% of the elderly hypertensive patients with a history of cardiovascular disease develop a serious cardiovascular accident and one out of 1000 young hypertensive patients without any other risk factor will also develop a serious event every year. Furthermore, it has been clearly demonstrated that antihypertensive treatment decreases the risk in both groups (2).

Although significant progress has been made in the prevention and treatment of hypertension, the problem is still far from being completely clarified and solved. During the last 20 years there has been a substantial effort to develop effective pharmacological agents for the treatment of hypertension (1,2). Over the past 10 years, the calcium channel blockers have gained a primary role because they have a powerful effect and are easy to use (32,57). Most of the calcium channel antagonists currently approved for clinical use belong to three distinct chemical classes (23): the phenylalkylamines (e.g., verapamil), the dihydropyridines (1,4-DHPs; e.g., nifedipine), and the benzothiazepines (e.g., diltiazem). Receptors specific for each of these three major classes have been identified in the L-type (long-lasting, large-capacitance) voltage-dependent calcium channel. At the cardiovascular level, this class of drugs provides effective therapy for hypertension and angina (32,57). Their efficacy reflects the ability to reduce peripheral and coronary arterial resistance, secondary to an inhibition of calcium ion influx through specific calcium channels in the vascular smooth muscle. The best known and most widely used 1,4-DHP

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calcium antagonist nifedipine is not an ideal agent because of its short duration of action and poor functional selectivity, which may lead to inotropic impairment whenever a diseased myocardium is involved or when an association with β-blockers is desirable (47,51,63–65).

In recent years the need for further research with calcium antagonists based mainly on structural modification of the potent and vasoselective dihydropyridines, has been recognized. The two most important requirements for a new calcium antagonist and for a new antihypertensive drug, in general, are: 1) tissue selectivity to reduce the likelihood of undesirable side effects, and 2) a gradual onset and long duration of action to improve compliance and reduce neuroendocrine activation. The second-generation agents in the 1,4-DHP class have, in fact, greater vascular selectivity than nifedipine at the regional or systemic level, which may translate into a therapeutic advantage (20,40–42,46–48,51). A disadvantage of most of the available second-generation 1,4-DHPs is, however, their short duration of action that requires two or three daily doses.

A research program was started at Recordati, aiming at the synthesis of new dihydropyridines with greater vascular selectivity and longer-lasting activity than the available standard calcium antagonists. One compound (lercanidipine, formerly Rec 15/2375; trademarks: ZANIDIP^{R}, ZANEDIP^{R}; methyl 1,1-dimethyl-2-[N-(3,3-diphenylpropyl)-N-methylamino]ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate), was selected for development among many derivatives synthetized.

CHEMISTRY

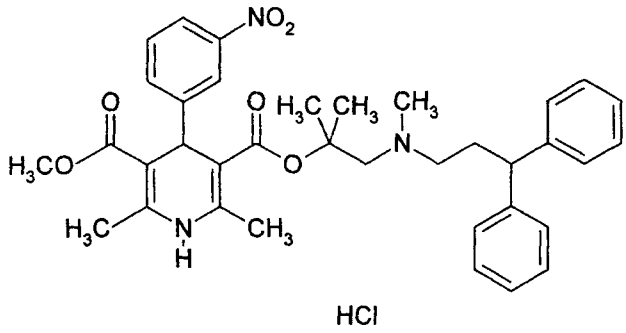
Lercanidipine was selected from a series of new 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids dialkyl esters, bearing different bulky and lipophilic aminoalkyl moieties in one of the two ester groups, synthesized as part of research on molecular hybrids, based on the preparation of new compounds containing the active moieties of different drugs having similar pharmacological effects (36,45). In order to improve the duration of action by increasing the overall lipophilicity of the new compounds of this series, structural variations at the aryl group at position 4 of the 1,4-DHP and at the non-basic alkyl ester were introduced, as well as in the length and branching of the alkyl group linking the bulky amino group to the dihydropyridine nucleus. Because of its high potency in *in vitro* and *in vivo* assays and to the long duration of its antihypertensive effect, lercanidipine was selected for development.

The chemical structure and physico-chemical characteristics of this drug are shown in Fig. 1. The presence of the 3,3-diphenylpropylmethylamino-2-methyl-2-propyl chain confers to lercanidipine a unique structure, characterized by high flexibility and very high lipophilicity in the presence of an ionizable amino group.

PHARMACOLOGY

The animal pharmacology reported in this review demonstrates that lercanidipine fulfills the requirements for a new antihypertensive drug, namely gradual onset and long duration of action with no neuroendocrine activation, tissue selectivity, and lack of myocardial contractility impairment.

Its *in vitro* calcium antagonistic activity is clearly related to a gradual block of calcium entry in smooth muscle cells via L-type calcium channels. The antihypertensive effect was



$C_{36}H_{41}N_3O_6$. HCl M.W. 648.205

PHYSICO - CHEMICAL CHARACTERISTICS

Appearance:	citrine-yellow crystalline powder	
Melting point:	185-188 °C	
Solubility (20-25 °C):	water:	9.3 mg/100 ml
	ethanol 95%:	4.7 g/100 ml
	ethanol 99%:	4.7 g/100 ml
	dimethylformamide:	>100 g/100 ml
Partition Coefficient (log P):	6.1	(calculated from log D in 2-octanol/acidic buffer)
Apparent Dissociation Constant (pKa):	6.8	(about 20% in the dissociated form at pH = 7.4)

Note: the doses and concentrations of lercanidipine reported in this paper actually refer to the hydrochloride salt (10 mg = 9.4 mg of the base).

FIG. 1. Chemical structure and physio-chemical characteristics of lercanidipine.

tested in several different experimental models, such as the spontaneously hypertensive rat (SHR), which closely resembles primary hypertension in humans (22), the two-kidney, two-clip model of renovascular hypertension in dogs (73), and normal, non-hypertensive animal species. The results demonstrate that lercanidipine is a potent antihypertensive agent whose effects arise gradually and persist several hours. Its selectivity for vascular

tissue was demonstrated in several *in vitro* and *in vivo* models. At *in vitro* concentrations similar to those achieved in plasma by therapeutic doses in humans, there was no negative inotropic effect. No alteration of the sympathetic and vagal balance of cardiovascular control, and an interesting antiischemic activity were also observed.

Calcium Antagonistic Activity

In displacement binding studies on different membrane preparations labeled by [^{3}H]PN200-110 or [^{3}H]nitrendipine (26,37), lercanidipine was as potent as nitrendipine, nicardipine, or niguldipine, and more potent than nifedipine or amlodipine (Table 1). The affinity of lercanidipine for the L-type of calcium channel labeled by the tritiated ligands translates into a functional calcium antagonistic activity.

The simultaneous evaluation of the effects of lercanidipine on K^+-induced contraction and intracellular calcium levels ($[Ca^{2+}]_i$) of guinea pig ileal longitudinal smooth muscle (37), showed that lercanidipine markedly inhibited the K^+-induced increase both in tone and in $[Ca^{2+}]_i$ (Fig. 2). The lack of inhibition of epinephrine-induced contraction of rat aorta shows that lercanidipine selectively inhibits the influx of extracellular calcium into smooth muscle through voltage-dependent channels, without effects on the receptor-operated calcium channels (26). Lercanidipine inhibition of the extracellular influx of calcium into rat aorta smooth muscle is potential-dependent, since its potency increased more than 100-fold in parallel to the increase of $[K^+]$ in incubation bath (26), in agreement with findings from electrophysiological studies. These studies (12), in fact, showed that lercanidipine did not affect the commonly investigated parameters in tissues or cells kept at a normally polarized membrane potential (−80 mV). A blocking activity on the calcium current (I_{Ca}) by lercanidipine was apparent, however, when the cells were kept at a depolarized holding potential (−40 mV). I_{Ca} blockade and recovery from block developed slowly, being markedly slower than that observed with nimodipine under the same experimental conditions (Fig. 3).

The smooth onset of lercanidipine calcium antagonistic activity is supported also by the data shown in Table 2. The potency of this drug in inhibiting the K^+-induced contraction of rat aortic strips (26,37) is shown to increase gradually over a 3-h incubation period, more slowly than with the other investigated 1,4-DHPs.

TABLE 1. *Inhibition of specific [^{3}H]PN200-110 or [^{3}H]nitrendipine ([^{3}H]NIT) binding in different animal tissue homogenates by lercanidipine and reference compounds*

	Rat Brain		Rat Heart	Rabbit Heart
Compound	[^{3}H]PN200-110	[^{3}H]NIT	[^{3}H]NIT	[^{3}H]PN200-110
Lercanidipine	0.24	0.30	0.22	0.07
Nifedipine	1.90	1.60	2.02	0.77
Nicardipine	0.18	0.10	0.16	n.t.
Nitrendipine	0.16	0.12	n.t.	0.13
Amlodipine	5.44	n.t.	n.t.	n.t.
Niguldipine	n.t.	n.t.	n.t.	0.24

Data represent the mean K_i values (nM).
n.t. = not tested

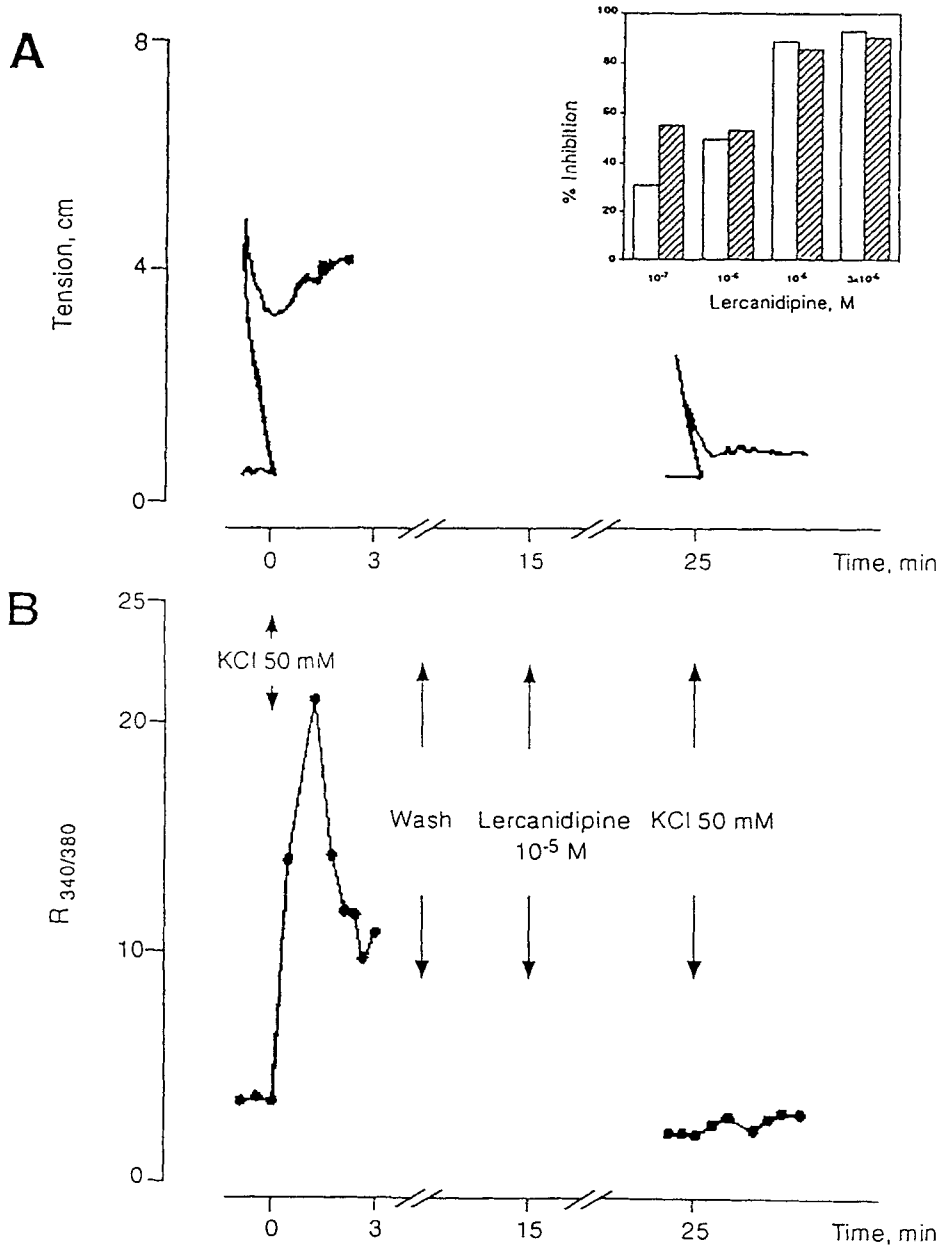


FIG. 2. A) Representative tracing of the simultaneous recording of 50 mM KCl-induced variations in force development and B) ratio of fluorescence at 340 and 380 nm (index of $[Ca^{2+}]_i$ levels) in the absence and presence of 10^{-5} M lercanidipine, tested on the same strip of guinea pig ileal longitudinal smooth muscle. The inset represents the inhibition of the same parameters by increasing concentrations of lercanidipine, evaluated 3 min after K^+ challenge. Mean values from n = 3 at 10^{-5} M and n = 2 at 10^{-7} M, 10^{-6} M, and 3×10^{-5} M lercanidipine. Open bars = tension; dashed bars = ratio 340/380 nm.

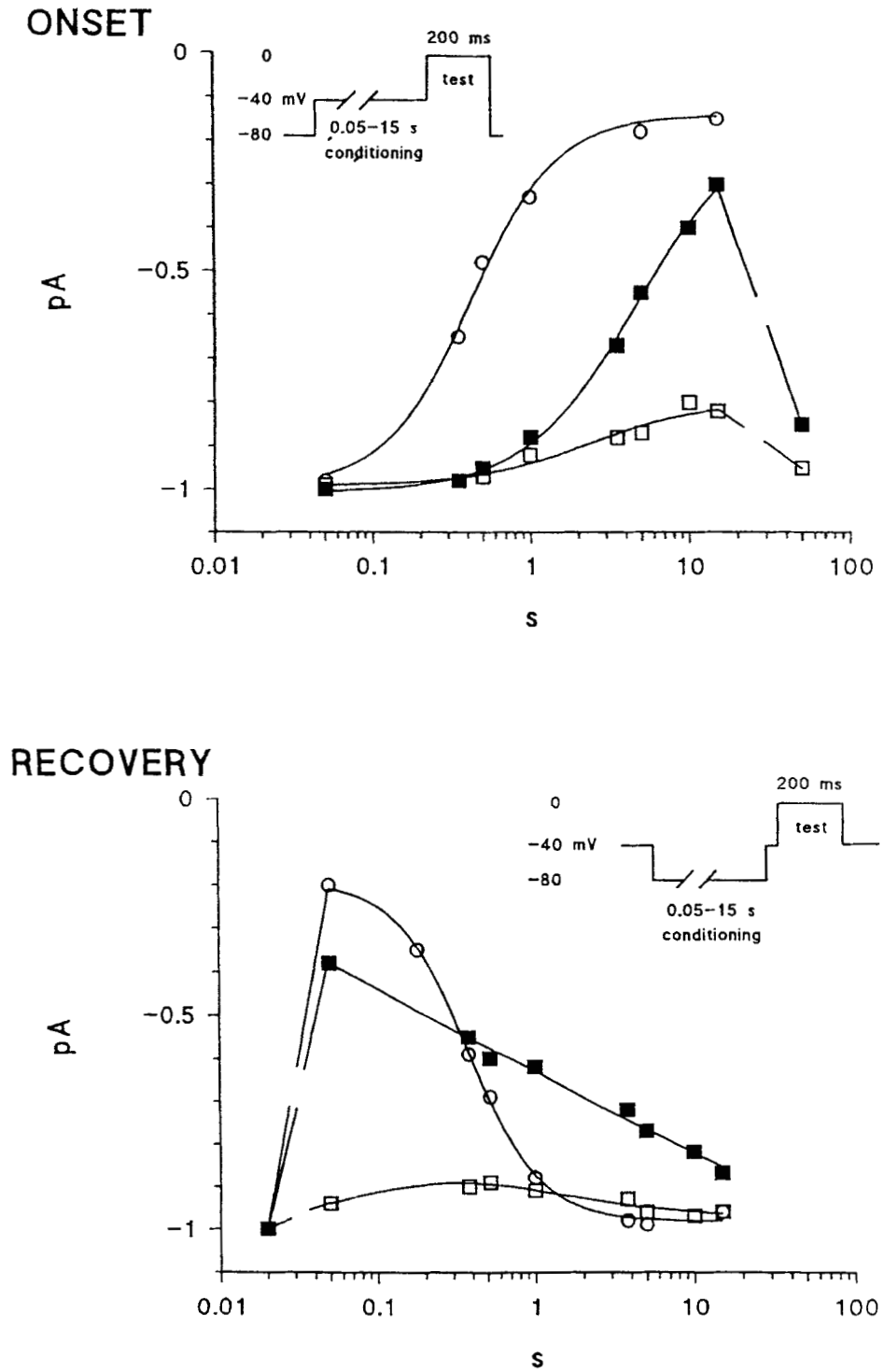


FIG. 3. Onset of the voltage-dependent effect of lercanidipine (filled squares; 1 μM) on calcium current, and its recovery from the voltage-dependent block in isolated guinea pig cardiac myocytes. Graphs show normalized plot of current measured during the test pulse in the absence (control; open squares) and presence of the compound, after a prepulse (conditioning) to −40 mV (onset) or −80 mV (recovery) of increasing duration (0.05 to 15 s); the normalized current is plotted against conditioning pulse duration. The effect of nimodipine (open circles; 0.5 μM) is shown for comparison. Inset: voltage protocol.

TABLE 2. *Functional calcium-antagonistic activity in rat aortic strips of lercanidipine and reference compounds*

	(IC_{50}, M)				
Compound	0.5 h	1.0 h	1.5 h	2.0 h	3.0 h
Lercandipine	7.0×10^{-9}	3.1×10^{-9}	1.0×10^{-9}	3.2×10^{-10}	1.3×10^{-10}
Nifedipine	3.7×10^{-9}	n.t.	4.3×10^{-9}	n.t.	n.t.
Nitrendipine	1.2×10^{-9}	1.8×10^{-9}	1.3×10^{-9}	1.2×10^{-9}	8.5×10^{-10}
Felodipine	n.t.	6.6×10^{-10}	n.t.	3.2×10^{-10}	2.3×10^{-10}

Data represent the IC_{50s} (concentrations producing 50% of inhibition of 80 mM K^+-induced contractions) determined after different incubation time.
n.t. = not tested

Antihypertensive Activity

Potency

In SHR (60,62), lercanidipine reduced arterial blood pressure in dose-dependent manner. After intravenous (i.v.) administration, lercanidipine was equipotent to felodipine in reducing diastolic blood pressure (DBP); it proved relatively more potent than nicardipine or nitrendipine and markedly more potent than nifedipine or amlodipine. A similar rank of potency was detected after oral (p.o.) administration of lercanidipine to catheterized hypertensive rats or to intact, non catheterized animals (Table 3). In chronically catheterized dogs subjected to renovascular hypertension (60), lercanidipine or nitrendipine decreased DBP in a dose-dependent manner and were equipotent (ED_{25} = 0.9 and 0.7 mg/kg p.o., respectively). After repeated oral administration in these models (2.5 and 1 mg/kg once-a-day for 21 and 15 d in rats and dogs, respectively), the magnitude of DBP reduction induced by lercanidipine remained constant during the period of treatment, indicating no tolerance of the antihypertensive effect (60).

The hypotensive effect of lercanidipine was also studied in chronically catheterized normotensive rats and dogs. Its potency in reducing DBP after intravenous and oral administration was similar to that obtained in hypertensive animals (60,62).

TABLE 3. *Antihypertensive effects of lercanidipine and reference compounds in SHRs after intravenous or oral administration*

	ED_{25}		
	for DBP		for SBP
Compound	μg/kg i.v.	mg/kg p.o.	mg/kg p.o.
Lercanidipine	15.5 (11.0–23.0)	1.0 (0.8–1.3)	2.3 (1.9–2.8)
Felodipine	10.9 (9.0–13.0)	1.6 (1.2–2.2)	6.2 (5.1–7.7)
Nicardipine	39.4 (33.0–47.0)	3.0 (2.7–3.3)	7.1 (5.2–9.6)
Nitrendipine	51.9 (40.0–67.0)	4.7 (3.7–6.1)	n.t.
Nifedipine	118.0 (75.0–186.0)	n.t.	6.2 (5.0–7.6)
Amlodipine	436.6 (246.0–873.0)	n.t	n.t.

Data represent the ED_{25} values (dose inducing 25% decrease of diastolic [DBP] or systolic [SBP] blood pressure) recorded by chronic catheter implantation (DBP), or by the tail cuff method (SBP), and 95% confidence limits.
n.t. = not tested

Gradual Onset and Long-Lasting Action

Although the antihypertensive effect of lercanidipine in animals was not substantially different, with respect to potency, from that of the other reference 1,4-DHPs studied, its activity is characterized by a peculiar gradual onset and long-lasting duration of action.

In vivo studies (60,62) showed that, in chronically catheterized animals, the time to the maximum effect of lercanidipine was significantly longer than for nicardipine, felodipine, nifedipine or nitrendipine (Table 4). The antihypertensive effects persisted up to 6 h after intravenous administration of 100 μg/kg of the drug, and up to 9 h after oral administration at 3 mg/kg. The analysis of the overall antihypertensive activity combining potency and duration of action shows that, after intravenous administration, a reduction by 20% of DBP over a period of 3 h was achieved with lercanidipine or felodipine, but not with nicardipine or nitrendipine (Table 4).

In anesthetized open-chest dogs (61) after intravenous administration, lercanidipine and nitrendipine induced peripheral and coronary vasodilation with the same potency, but the peak effects of lercanidipine occurred about 30 min after the administration, whereas those of nitrendipine were present after 1 to 3 min, with a rapid return to baseline values (Fig. 4). Similar results were obtained after intravenous administration of lercanidipine or nitrendipine in conscious dogs (68). These *in vivo* findings parallel the different *in vitro* kinetic behavior of lercanidipine, in comparison with other reference DHPs (26,37).

In addition to long incubation time needed to reach the greatest functional calcium antagonistic activity of lercanidipine (Table 2), the recovery of isolated rat aorta contractile response to 80 mM K^+ after incubation with lercanidipine was null, also at 6 h after removal of the drug from the bath (Fig. 5). On the contrary, nifedipine or nitrendipine reached maximal activity after an 0.5 h incubation (Table 2) and the recovery was always almost complete after a 1 to 2 h washout period (Fig. 5). After incubation with amlodipine, contractility of the tissue was still impaired after a 1 h washout, but showed a clear trend to recover starting at 3 h after washout.

The gradual onset and long-lasting effect of lercanidipine can be explained by its lipophilicity that favours its concentration in tissues, as described for other 1,4-DHPs (28,31). As suggested for other lipophilic DHP Ca^{2+} antagonists (28,72), the drug receptor binding mechanism may involve also drug partitioning into the lipid bilayer matrix of the cell membrane, followed by lateral diffusion to its specific receptor site. The prolonged

TABLE 4. *Duration of the antihypertensive effects of lercanidipine and reference compounds in SHRs after intravenous administration*

Compound	Time of Peak Effect min ± $S_{\bar{x}}$	$AOC_{0\text{-}3h}$ $ED_{20\text{-}h}$ μg/kg i.v.
Lercanidipine	9.1 ± 1.0	33 (22–50)
Felodipine	4.4 ± 0.9	23 (11–47)
Nicardipine	4.0 ± 0.5	n.d.
Nitrendipine	3.8 ± 2.0	n.d.
Nifedipine	3.8 ± 0.3	n.d.
Amlodipine	49.3 ± 4.0	559 (349–896)

Data represent the mean time (± $S\bar{x}$) of peak effect, and AOC (area over the percent decrease in DBP vs. time and 95% confidence limits).
n.d. = not determinable

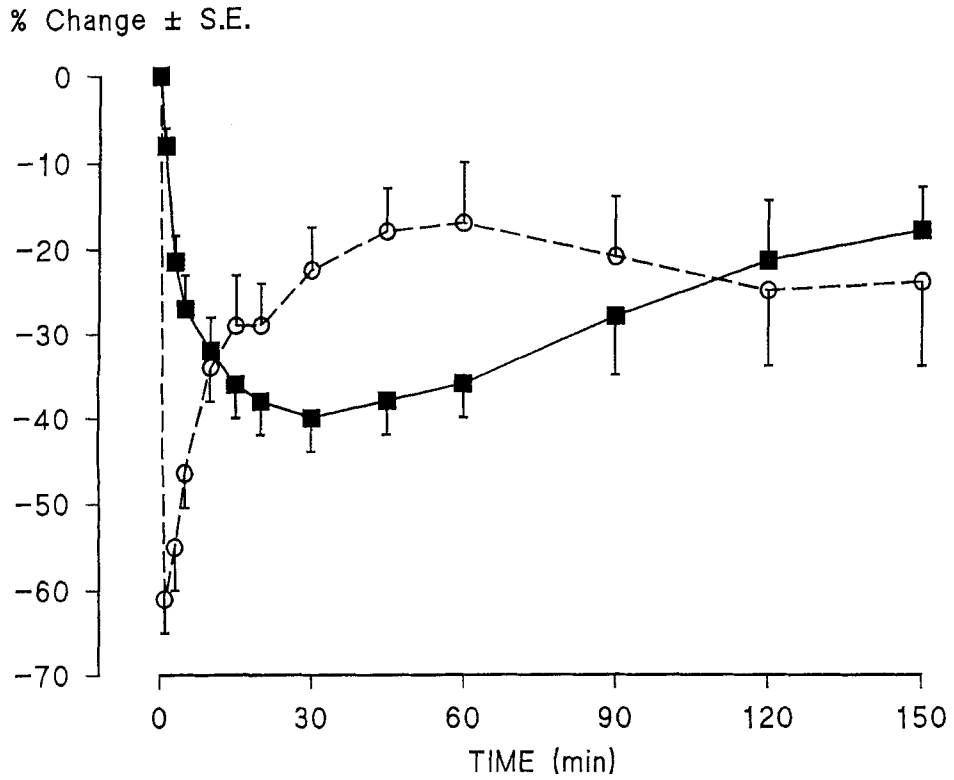


FIG. 4. Time-course of the effect of lercanidipine (filled squares; 5 μg/kg i.v.) and nitrendipine (open circles; 5 μg/kg i.v.) on coronary resistance in anesthetized open-chest dogs.

storage in membrane compartments could contribute to the long duration of action. Confirmation of this hypothesis was obtained by studying the partitioning of lercanidipine between an aqueous buffer and phosphatidylcholine vesicles, mimicking the cell membrane bilayer. These data show that lercanidipine is endowed with one of the highest membrane partition coefficients among the 1,4-DHPs so far investigated. In addition, release from the vesicle membrane is very slow, ensuring long permanence in the phospholipidic bilayer (29).

Selectivity

Receptor binding studies demonstrated negligible or no affinity of lercanidipine for several neurotransmitter receptors (including α_1- and α_2-adrenergic) and ion channel binding sites in comparison with its very high affinity for the L-type calcium channels (26). An *in vivo* confirmation of these findings was obtained in pithed rats (8), where lercanidipine proved to be a potent peripheral vasodilator when tested against angiotensin II-induced vasoconstriction (mediated by calcium influx), and, on the contrary, was poorly active against the vasoconstriction induced by α_1 or α_2 stimulation.

The functional calcium antagonistic activity of lercanidipine was measured in parallel to that of nitrendipine in isolated rat aorta, bladder, and colon preparations as relaxing potency against tonic contractions induced by preincubation with K^+ (26,27). Lercani-

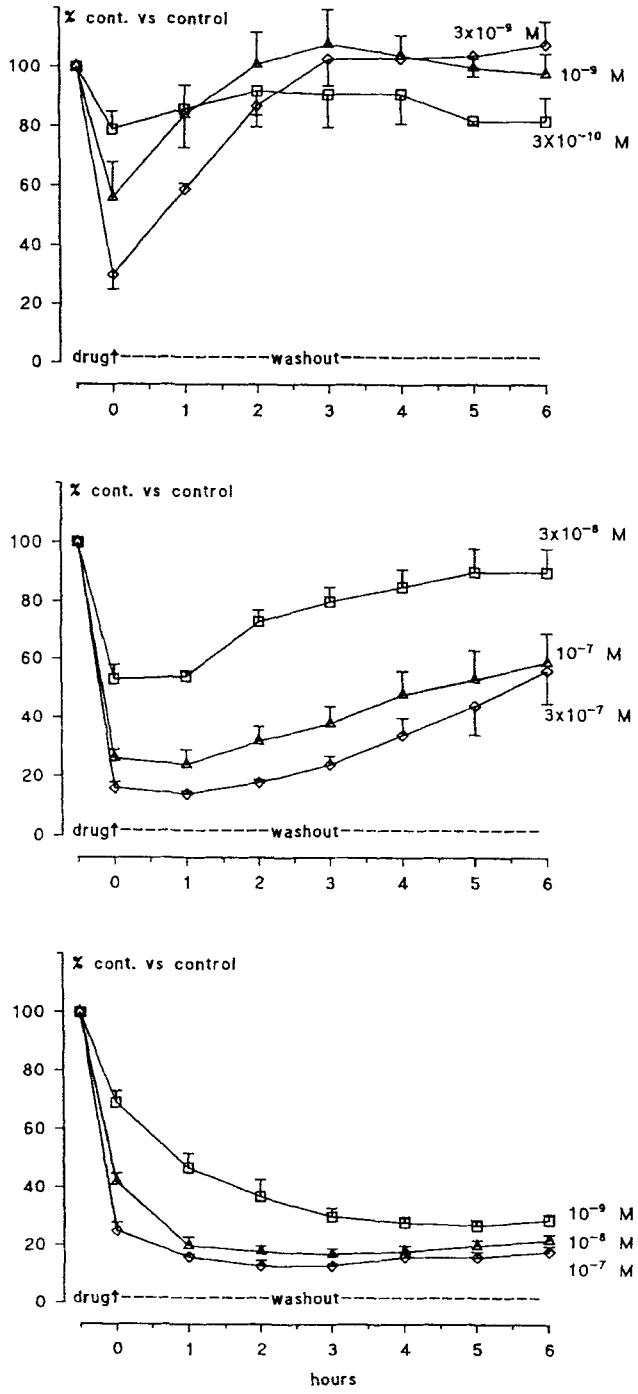


FIG. 5. Recovery of rat aorta contractile response to 80 mM K^+ following washout of different concentrations of nitrendipine (upper panel), amlodipine (middle panel) and lercanidipine (lower panel) incubated for 0.5 h. Data represent the mean ($\pm S_{\bar{x}}$) percent of K^+-induced contraction of 3 to 5 different aortic preparations/ concentration in comparison to the control response.

dipine produced a concentration-dependent relaxation of these tissues (IC_{50} values after 3 h incubations were 0.13, 23, and 1.1 nM, respectively), showing potency ratios of 177 for bladder vs. aorta, and 8.5 for colon vs. aorta, indicating a remarkable vascular selectivity of the compound. In contrast, nitrendipine showed nearly the same potency in the three tested tissues (potency ratio of 0.2 and 0.8 for bladder/aorta and colon/aorta, respectively).

In electrically driven rabbit right ventricular strips (26,27), lercanidipine showed a very weak negative inotropic activity (IC_{50} value after 3 h incubation was 12 μM), being 857- and 667-fold less potent than felodipine or nitrendipine, respectively. The action on vascular smooth muscle in comparison to cardiac muscle (vasoselectivity) of second generation 1,4-DHPs is more pronounced than for nifedipine (20,40–42,46–48,51). A comparison between the *in vitro* vascular and cardiac effects of a single concentration of lercanidipine, as well as nitrendipine and felodipine, is shown in Fig. 6. All tested compounds, exerted similar calcium antagonistic effects on vascular tissue at lower concentrations than on cardiac tissue. This difference in active concentrations is markedly greater with lercanidipine than with the reference compounds, indicating better vasoselectivity.

Several factors determine the relative vascular selectivity between the structurally heterogeneous family of 1,4-DHPs (24,69). One important factor is the role of membrane potential. It is well known that calcium channels exist in different forms depending on the membrane potential of the cells. At a resting potential of −80 mV, virtually all channels are in the low-affinity resting state, which is only weakly susceptible to 1,4-DHP inactivation. On the contrary, 1,4-DHPs bind very tightly to the inactivated state of calcium channels, which predominates at depolarized potentials of −10 to 0 mV (5). As reported by several authors (43,48,74) vascular muscle has higher depolarized resting potential (−50 to −60 mV) than cardiac muscle (−80 to −95 mV). The potential dependence of the calcium antagonistic activity of lercanidipine on blood vessels is similar to that of some other 1,4-DHPs (26), its time dependence is, however, very different (see Fig. 3), and this difference could explain the greater vascular selectivity exerted by this compound in comparison to the other 1,4-DHPs tested. As a consequence, in all the *in vivo* models studied, lercanidipine did not show any negative inotropic effect, in contrast with the standards tested.

In conscious chronically catheterized rabbits (9), lercanidipine caused a potent and long-lasting vasodilation with no negative inotropism. These studies were carried out in rabbits with autonomically intact (AI) heart function control, or suppressed (AS) by cholinergic and β-adrenergic blockade. The reference compound was nifedipine. Both drugs comparably reduced mean arterial blood pressure in both experimental conditions, and caused a reflex tachycardia in AI rabbits. Cardiac contractility, on the other hand, was differently affected by the two drugs. Lercanidipine caused a mild but significant increase in cardiac contractility, measured as the first derivative of left ventricular pressure (dP/dt_{max}). This increase in inotropism was insensitive to autonomic suppression. Nifedipine, on the contrary, caused a dose-dependent reduction of dP/dt_{max}, parallel to the reduction in mean blood pressure in both protocols (Fig. 7). In anesthetized dogs (27), at doses producing the same degree of vasodilation, lercanidipine increased the cardiac contractility index much more than either nitrendipine or nifedipine (Fig. 8). Similar results were obtained in conscious instrumented dogs, in comparison with nitrendipine (68). The time relaxation constant τ, an index of global ventricular diastolic function, was not modified

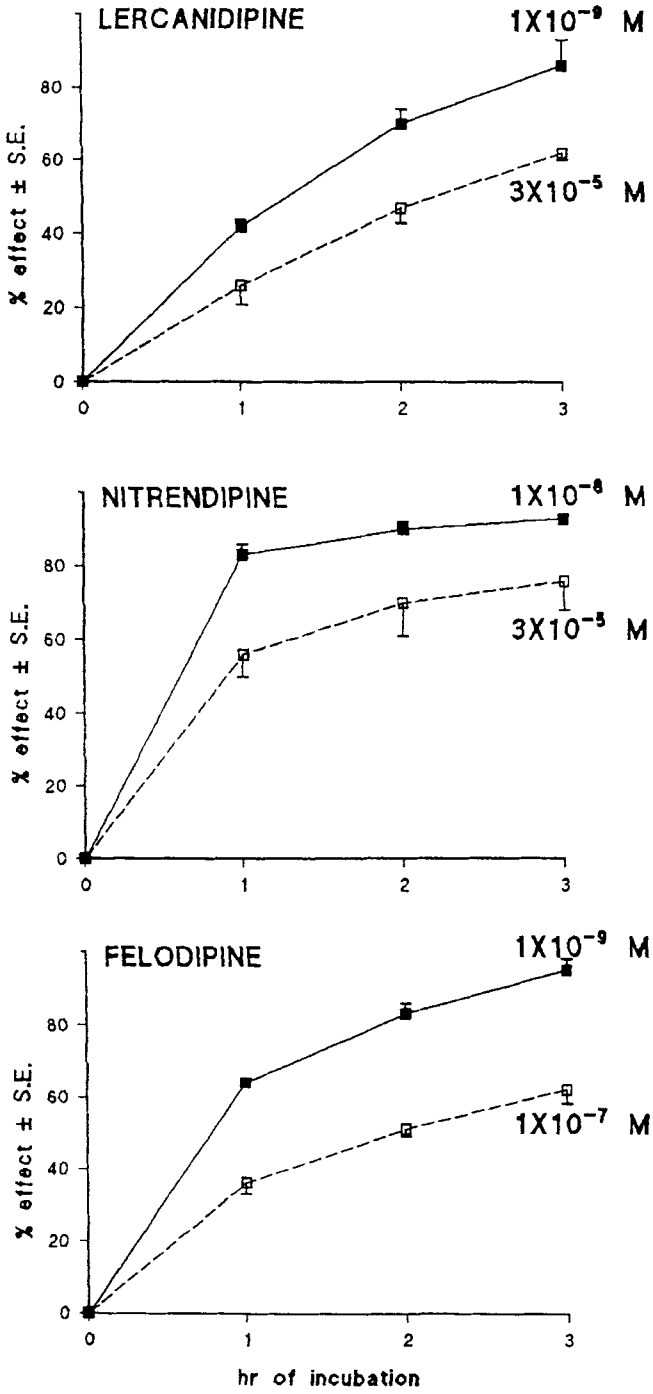


FIG. 6. Time course of the effects of lercanidipine, nitrendipine, and felodipine on vascular smooth muscle (filled squares) or cardiac muscle (open squares). Data represent the percent of relaxation of rat aorta pre-contracted by KCl 80 mM, or the percent reduction in basal contractile force of electrically driven rabbit heart ventricular strips.

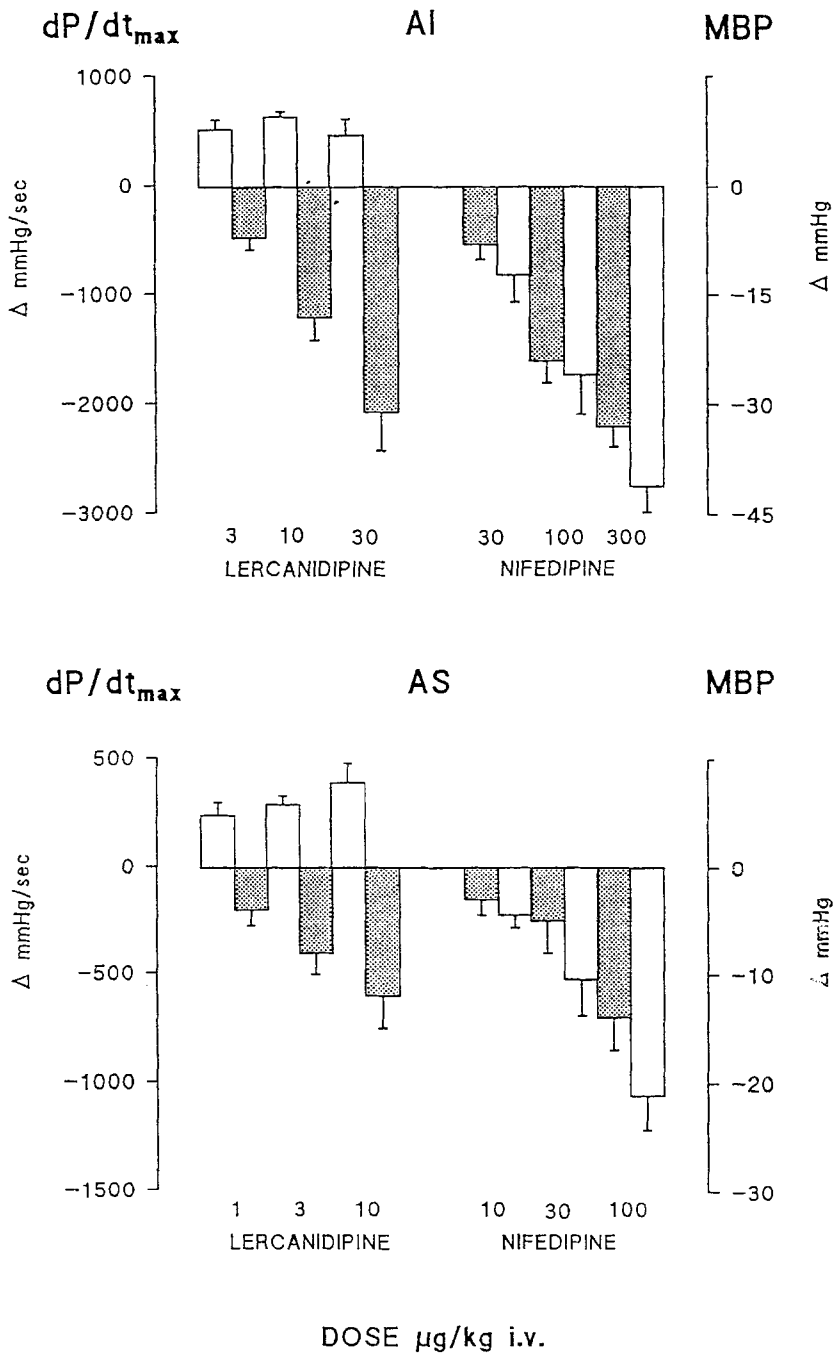


FIG. 7. Effects of i.v. administration of lercanidipine and nifedipine on blood pressure (MBP = mean blood pressure; filled bars) and cardiac contractility ($\Delta dP/dt_{max}$; open bars) in conscious rabbits during autonomically intact (AI) or suppressed (AS) heart function control.

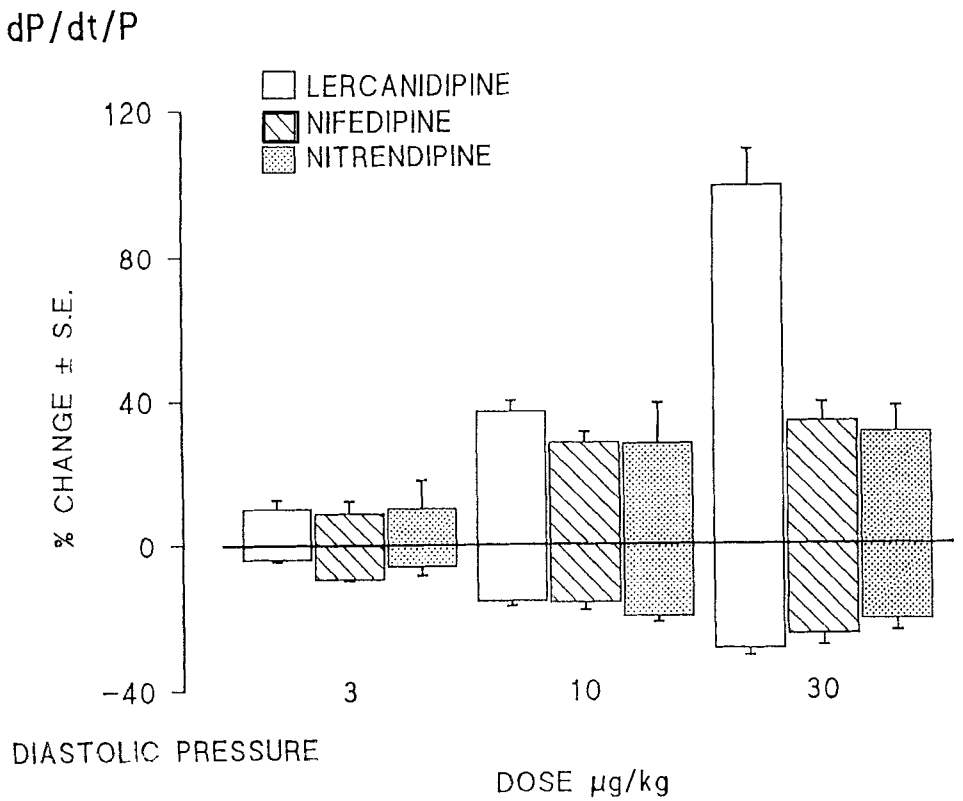


FIG. 8. Effects of cumulative i.v. injection of lercanidipine, nitrendipine and nifedipine, on diastolic blood pressure (DBP) and cardiac contractility index (dP/dt/P) in anesthetized dogs.

by lercanidipine either before or during β-adrenergic blockade. This confirms that lercanidipine does not modify ventricular diastolic function and exerts its calcium entry blocking action on peripheral vascular smooth muscle. Furthermore, in this animal species the effect of lercanidipine on cardiovascular neural regulation was explored by means of power spectral analysis (68). Even at a dose inducing marked reduction of peripheral resistance and coronary blood flow, lercanidipine did not induce a significant modification of the spectral indices, indicating lack of significant sympathetic activation.

Antiischemic Activity

The antiischemic effect of DHP calcium antagonists is predominantly related to hemodynamic unloading of the left ventricle resulting from reduction of peripheral resistance, and to an improvement in coronary flow due to the reduction in coronary resistance. These two effects reduce oxygen consumption and improve its delivery, thus favouring the myocardial oxygen delivery/uptake ratio, which, when altered, is the cause of angina in humans. The antiischemic activity of lercanidipine has been confirmed in several different experimental models, such as *in vitro* preparations, anesthetized rats after methacholine administration to produce a Prinzmetal's-like angina, and hemodynamic studies in anes-

thetized and conscious dogs. The cardioprotective effect of lercanidipine was similar to that exerted by the other 1,4-DHPs. Lercanidipine differs from other 1,4-DHPs, however, as it possesses an additional capacity of cardiac protection: it reduces oxidative stress occurring during ischemia and reperfusion as result of oxygen free radical attack at concentrations markedly lower than those of other 1,4-DHPs.

Using a perfused rabbit heart preparation, Rossoni et al. (55) demonstrated the ability of lercanidipine to antagonize the coronary contraction induced by endothelin-1. Moreover, lercanidipine abolished the increase of coronary perfusion pressure caused by the inhibitor of nitric oxide (NO) biosynthesis L-NMMA (N^G-monomethyl-L-arginine), and markedly diminished the increased responsiveness of coronary vasculature to endothelin induced by blockade of NO biosynthesis.

The antianginal effect of lercanidipine was studied in normotensive anesthetized rats after a bolus of methacholine, which causes constriction of the coronary arteries, manifested by ST segment elevation in the ECG (59). Lercanidipine inhibited the methacholine-induced ST segment elevation in a dose-dependent manner. This effect of lercanidipine lasted longer and was more pronounced than that of nifedipine, nicardipine, or verapamil.

The hemodynamic studies performed in anesthetized and conscious dogs (61,68) showed that lercanidipine induces a dose-related, long-lasting reduction in coronary vascular resistance with concomitant increase in coronary blood flow.

In isolated and perfused rabbit hearts, lercanidipine, infused before ischemia, prevented in a concentration-related manner the increase in stiffness without interfering with the generation of 6-keto-PGF_{1a} by the perfused heart, both during the preischemic and the reperfusion periods (55). In time course studies (10,55), lercanidipine reduced the rise in diastolic pressure during ischemia and improved recovery on reperfusion when given before or at the onset of ischemia. The mechanism of cardiac protection with lercanidipine was studied in depth in this model by evaluating several biochemical parameters (12). Lercanidipine reduced myocardial damage, normalizing several parameters such as CPK release, oxygen consumption, ATP-generating capacity, mitochondrial and tissue calcium overload, and release of oxidized glutathione. In isolated mitochondria incubated with ferrous ions, lercanidipine exerts an antioxidant activity, preventing the lipid peroxidation and improving the capacity of mitochondria to utilize oxygen for oxidative phosphorylation and to transport calcium (7). Such action has been described for other calcium antagonists, particularly for 1,4-DHPs (33,71), at much higher concentrations than those found to be effective with lercanidipine.

Effects of Enantiomers

In common with other calcium antagonists of the same pharmacological class such as nicardipine or amlodipine, the molecule of lercanidipine has a chiral centre at position 4 of the DHP ring. The compound is obtained as a balanced racemate. Several *in vitro* and *in vivo* studies have been performed with the enantiomers of lercanidipine (12,13,15,27, 37,62,68).

On the whole, the calcium antagonistic activity of lercanidipine is related to the S-enantiomer, in agreement with other examples in this class of drugs (Table 5). Binding and functional studies demonstrated that the activity of the R-enantiomer is two orders of

TABLE 5. *Results of the main pharmacological studies performed with lercanidipine's enantiomers*

Model	lercanidipine	S-lercanidipine	R-lercanidipine
[^{3}H]nitrendipine binding:			
rat brain, K_i nM	0.30	0.11	37.80
[^{3}H]nitredipine binding:			
rat heart, K_i nM	0.22	0.10	44.68
[^{3}H]PN200-110 binding:			
rat brain, K_i nM	0.24	0.16	14.63
K^+-induced contraction:			
rat aorta IC_{50} nM	1.30	0.43	16.00
SH rats: DBP ED_{25} μg/kg i.v.	15.5	5.0	2450.0
SH rats: DBP ED_{25} mg/kg p.o.	1.0	0.7	>>10
Normotensive rats:			
DBP ED_{25} μg/kg i.v.	16.3	3.6	277.0
RH dogs: DBP ED_{25} mg/kg p.o.	0.9	0.4	>>30
Open-chest dogs:			
DBP ED_{25} μg/kg i.v.	5.2	2.9	>>30
Conscious dogs:			
TPR ED_{25} μg/kg i.v.	7.3	2.8	>>10

magnitude less than that of S-lercanidipine. The potential-dependent behavior of the racemate at the vascular and cardiac level is also shared by the S-enantiomer but not by R-lercanidipine. The differences in potency between the two enantiomers were generally observed also in the *in vivo* studies. The studies on blood pressure in normotensive and SH rats and in renal hypertensive dogs showed that the overall hypotensive or antihypertensive activity of lercanidipine may be ascribed to the S-enantiomer, since R-lercanidipine did not affect blood pressure at doses much higher than those active for the racemate and S-enantiomer. The effective dose of the S-enantiomer in reducing the DBP by 25% was generally the same or half of that of racemate after i.v. or p.o. administration in both dogs and rats, and no difference in potency was observed between the two animal species. The hemodynamic activity confirmed these results, with R-lercanidipine generally poorly or not active on peripheral and coronary resistances.

Antiatherosclerotic Properties

The prevention of hypertension should involve not only the correction of elevated blood pressure, but also the direct pharmacological control of atherogenic processes occurring in the arterial wall (54), since the presence of wall thickening in large arteries and small resistance vessels has been widely described in human hypertensive at autopsy (25). These modifications contribute to altered resistance vessel behavior and altered compliance of large conduit arteries (58), two key factors that participate in the biochemical regulation of arterial circulation. Calcium antagonists may exert an antiatherosclerotic effect by interfering with one or more mechanisms leading to atheroma formation (39,66,74). The *in vitro* effects of lercanidipine were, therefore, examined on several processes that play a role in the development of atherosclerotic lesions, such as smooth muscle cell migration and proliferation, lipid uptake by macrophages, and oxidation of low density lipoprotein (LDL).

Lercanidipine was effective in reducing proliferation and migration of rat arterial myo-

cytes, with a potency (IC_{50} = 31 μM) similar to that of lacidipine or nifedipine (15). Lercanidipine was able to modulate cholesterol metabolism by inhibiting the esterifying effect of the enzyme ACAT in normal and foam mouse peritoneal macrophages. Furthermore, lercanidipine did not impair the capability of the macrophages to hydrolyze the esterified cholesterol stored in the cytoplasm (Recordati, data on file). Finally, lercanidipine inhibited LDL oxidation induced by different agents by acting extra- as well as intracellularly (Recordati, data on file).

In vivo studies (Recordati, data on file) performed in cholesterol-fed rabbits, demonstrated that lercanidipine was markedly more potent than lacidipine or amlodipine in reducing the proliferative and fatty lesions induced by the diet.

SAFETY PHARMACOLOGY AND TOXICOLOGY

Several preclinical safety pharmacology studies were performed to evaluate the effects of lercanidipine in different organs and systems, according to the existing regulatory guidelines (Recordati, data on file). Administration of oral doses, generally much higher than those active on blood pressure, to different animal species did not produce relevant undesired effects.

An extensive toxicological investigation was conducted with lercanidipine (Recordati, data on file). Single dose toxicity studies were performed after the oral administration in mice, rats, and dogs and after intravenous administration in mice and rats. The calculated LD_{50} values and relative confidence limits from the single dose toxicity studies are summarized in Table 6. All the symptoms observed in the three animal animal species used (e.g. sedation, dyspnea, tachypnea, etc.), and the cause of the death in rats and in mice, are considered to be the consequence of exaggerated pharmacological effects due to the large doses used in the single administration studies.

There were no marked differences in the results obtained in the repeated dose toxicity studies conducted in rats and in dogs (4, 13, and 52 weeks). In most cases the findings were attributable to the pharmacological activity of lercanidipine and to the high dosages administered to the experimental animals (up to 120 mg/kg/d). In no case were symptoms or modifications observed that had not been previously described for other 1,4-DHPs.

The fertility and general reproductive performance (F2) study in rats did not show any modification of the general reproductive performance or fertility of either F0 or F1 parent

TABLE 6. *Acute toxicity of lercanidipine in different animal species*

Species	Route	Sex	LD_{50} mg/kg	confidence limits 95%
Mouse	p.o.	M	622	(481–805)
		F	438	(332–578)
	i.v.	M	15	(13–18)
		F	21	(17–25)
Rat	p.o.	M	939	(803–1098)
		F	574	(488–677)
	i.v.	M	10	(8–11)
		F	12	(10–14)
Dog	p.o.	M	>300	no limits
		F	>300	no limits

animals. No embryotoxic or fetotoxic effects were observed in the pups of either F1 or F2 generations. Lercanidipine seems to be free from teratogenic effect in rats or rabbits and does not affect the reproductive performance in rats other than by pharmacological action on the myometrium leading to difficulties in parturition.

A battery of mutagenic tests was performed with lercanidipine *in vitro* with and without metabolic activation (reverse mutation investigation in *Salmonella typhimurium,* mitotic gene conversion assay in *Saccaromyces cerevisiae,* chromosome aberrations and gene mutation) and *in vivo* (micronucleus test in mouse). The compound had no mutagenic activity.

Oncogenicity studies were performed in mice and rats for periods of up to 18 and 24 months, respectively. Macro- and microscopic evaluation performed at the postmortem examinations did not show changes considered of lercanidipine-related origin, indicating that lercanidipine has no oncogenic/carcinogenic potential in mice and rats.

PHARMACOKINETICS

Preclinical Pharmacokinetics

The kinetics of lercanidipine were investigated in the mouse, rat, rabbit, and dog using the drug labeled with ^{14}C at position 2 of the DHP ring (16,17). Labeling in this position was chosen to ensure metabolic stability.

Studies carried out with the radiolabeled drug showed that, after oral administration, lercanidipine was well absorbed in rats, dogs, mice, less in rabbits. Comparison of plasma concentrations of total radioactivity with those of parent drug after oral administration suggests that the systemic availability of lercanidipine is reduced by first-pass metabolism.

The main pharmacokinetic parameters evaluated after single intravenous or oral administration of labeled or unlabeled lercanidipine to different animal species are summarized in table 7. The absolute availability of lercanidipine was about 10% to 30% in mice, 17% in rats, 0.7% to 4% in dogs, and 0.3% in rabbits.

After 15 d of repeated oral administration of lercanidipine (3 mg/kg/d) to rats and dogs the excretion pattern did not differ from that seen after single administration and the recovery of the radioactivity was practically complete.

TABLE 7. *Pharmacokinetic parameters of unchanged lercanidipine after single i.v. or p.o. administration of [^{14}C]-labeled or unlabeled lercanidipine to different animal species*

Animal (Sex)	Dose mg/kg		C_{max} ng/ml	T_{max} h	half-life h	CL l/h/kg	Vdβ l/kg	AUC ng.h/ml
Rat (M)	0.5 (U)	i.v.	–	–	0.8	0.97	1.12	516
Dog (M)	0.25 (U)	i.v.	–	–	3.6	1.15	6.00	226
Rabbit (F)	4.0 (L)	i.v.	–	–	10.4	2.53	36.50	1576
Mouse (F)	10.0 (U)	p.o.	199	0.25	n.e.	–	–	n.e.
Rat (M)	3.0 (L)	p.o	218	0.50	1.4	–	–	396
Rat (F)	3.0 (L)	p.o.	162	0.50	1.6	–	–	313
Dog (M)	3.0 (L)	p.o.	87	0.70	9.1	–	–	224
Dog (F)	3.0 (L)	p.o.	89	3.30	5.2	–	–	404
Rabbit (F)	500 (U)	p.o.	44	2.00	2.6	–	–	650

M = male; F = female; U = unlabeled; L = labeled; n.e. = not evaluable.

The distribution profile of lercanidipine (17) reflects its high lipophilicity. After intravenous or oral administration of labeled compound to rats, radioactivity was rapidly and extensively distributed to organs and tissues. Concentrations higher than those in plasma were measured in the aorta, an organ largely investigated in pharmacological *in vitro* studies of lercanidipine and other 1,4-DHPs. In beagle dogs, after single oral administration, radioactivity was widely distributed throughout the body. Concentrations in the aorta were similar to those found in the plasma at 2 and 24 h after administration.

Following either oral and intravenous administration of [^{14}C]lercanidipine to rats, dogs, and mice, most of the radioactivity (about 81% of the dose) was excreted in the feces and only about 12% in the urine. Biliary excretion plays an important role in the disposition of lercanidipine in animals.

The radioactive components in the plasma and excreta of rats and dogs dosed orally with [^{14}C]lercanidipine were investigated for the metabolic profile in comparison with those of human subjects. Thin-layer chromatography separated up to eight radioactive components in the body fluids. Four of these have been isolated from human urine and identified: M8, the main metabolite, derived from aromatization of the 1,4-DHP ring and hydroxylation of the β carbon atom on the 1,1-dimethyl-substituted ester function, upon removal of the amino group; M4, corresponding to the O-glucuronide of M8; PA3, deriving from the reduction of the nitro group of M8 to amino group; and M5, a minor component, derived from N,N-bisdealkylation and nitro-reduction of lercanidipine (Fig. 9). Little or no unchanged drug was detected in the urine of any of the three species, demonstrating its essentially complete biotransformation prior to kidney excretion. No intact drug was detected in fecal extract, a finding that would be consistent with its extensive absorption. Although there were several distinct quantitative species differences, in particular the absence of glucuronide/sulphate conjugates of drug metabolites in rat urine and plasma, rat and dog metabolite profiles resembled those of human subjects.

Clinical Pharmacokinetics

After a 20 mg single dose of a solution of [^{14}C]lercanidipine, oral absorption was assumed to be complete, with 43% to 45% radioactivity recovered in urine and 49% to 51% in feces (5). Unchanged drug was absent in excreta. Absorption of radioactivity was rapid, with peak levels occurring at 1.2 h after administration; concentrations declined in a biphasic manner with a terminal half-life of about 12 h. Extensive first-pass metabolism was evident, with reduced systemic availability. The same phenomenon was reported in the literature for lacidipine, nimodipine, and nisoldipine (34,53). Lercanidipine, like most of the other 1,4-DHP calcium antagonists (34), was found to be extensively bound to plasma proteins (>98%).

A study involving crossover administration of single doses in soft gelatin capsules containing the drug in solution or tablet form indicated that the extent of absorption from tablets was good, 87% as relative AUC, with peak plasma concentrations equivalent to about 83% of those generated by the capsules. T_{max} was slightly shifted, 1.5 h compared with 1 h after capsules. In a crossover study to investigate kinetics linearity involving single doses of 10, 20, and 40 mg, plasma levels were not directly proportional to dosage; the AUC ratios were 1:4:18, and C_{max} ratios were 1:3:8. The results suggest that saturation of first-pass metabolism occurs with an increase in the dose, a phenomenon also observed for nicardipine (64).

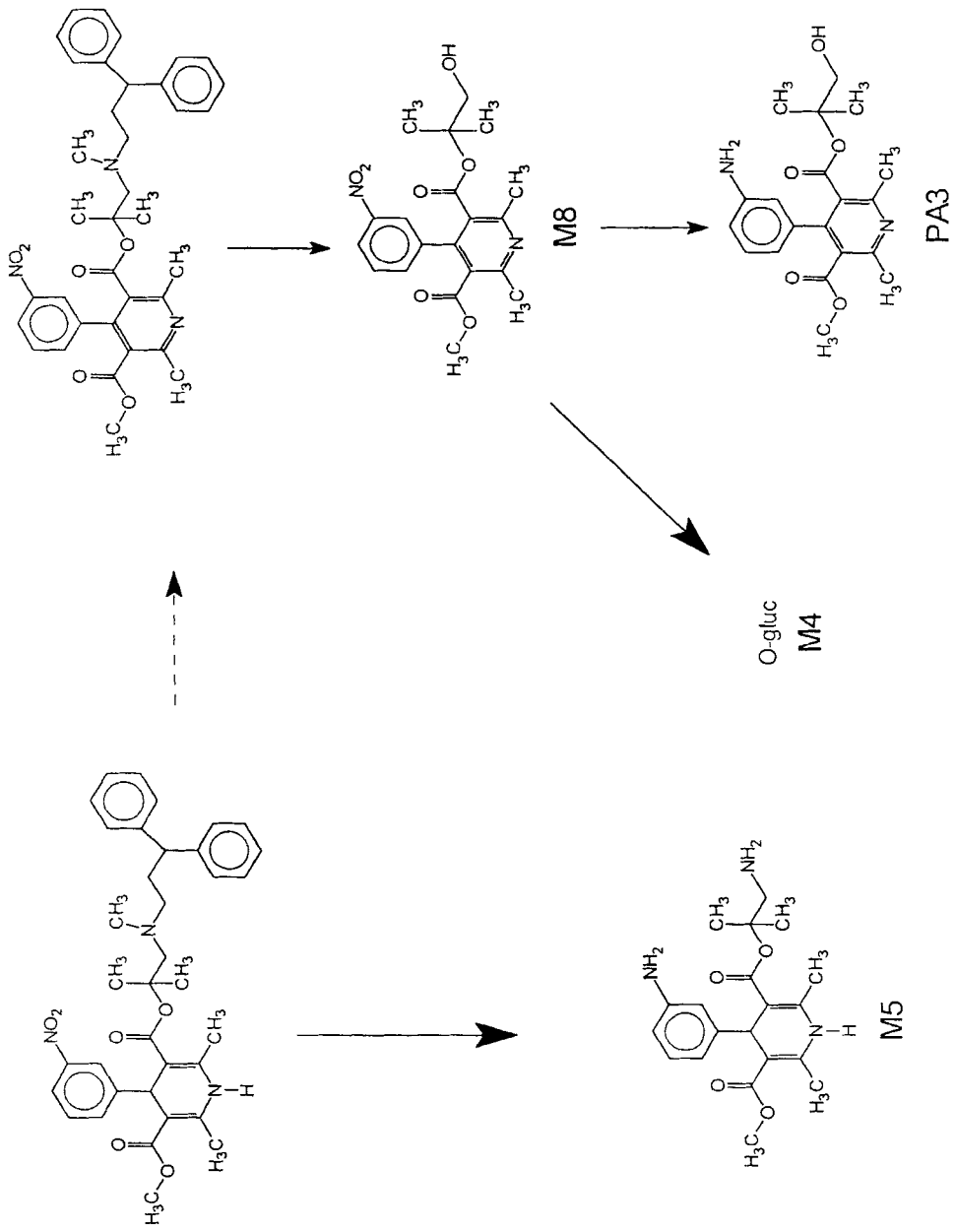


FIG. 9. Main metabolic pathways of lercanidipine in animals and humans.

Single and repeated-dose studies were carried out in patients with mild to moderate hypertension at 10 and 20 mg doses (5). Peak plasma concentration occurred at 1.5 to 3 h, and an apparent monophasic decay of lercanidipine plasma levels with a corresponding half-life of 2 to 5 h was observed. Plasma levels showed wide intersubject variability. No accumulation was seen upon repeated administration. Despite its relatively short plasma half-life, lercanidipine has a long duration of action, probably related to the high lipophilicity of the drug, which drives its preferential partitioning into the lipid bilayer of the cell membrane where lercanidipine appears to remain for a relatively long time, as shown in *in vitro* models (29).

No modification in plasma levels and no toxic effects were observed after co-administration with cimetidine and β-methyldigoxin, suggesting that there is no interaction with these drugs. A high-fat meal increased the availability of lercanidipine in healthy volunteers, either due to increase in hepatic blood flow induced by food (76) to the fact that food transiently inhibits the intrinsic ability of the liver to metabolize highly extracted drugs (67), or to lymphatic absorption, which could increase the systemic availability of this lipophilic drug. No increase in heart rate was observed in high-fat diet volunteers. On the basis of the results obtained to date, it is recommended that lercanidipine be taken before a meal.

The pharmacokinetics of lercanidipine in patients appeared to be unaffected by age, following a study with repeated treatment in 12 elderly patients. In hypertensive patients with renal impairment, drug plasma levels were elevated in those subjected to hemodialysis, indicating that a dosage reduction is necessary in the presence of severe renal insufficiency. Mild degrees of hepatic function impairment did not affect the bioavailability of lercanidipine; nevertheless, a reduction in starting dose and caution in dose incrementation is considered prudent.

Pharmacokinetics of Enantiomers

A crossover study involving single administration of either 10 mg of each of the two enantiomers or 20 mg of the racemate as solutions was performed. It was shown that after the administration of each single enantiomer the maximum plasma concentration occurred within 1 h, the decay of plasma levels was biphasic, with a distribution half-life of 20 min and an elimination half-life of about 3 h. Plasma concentrations were greater for the S-enantiomer, at all sampling times. No *in vivo* enantiomer interconversion was observed. After administration of the racemate, distribution and elimination half-lives remained unchanged while plasma concentrations of both enantiomers were higher than after dosing with the single isomer, most probably as a consequence of saturation of the first-pass metabolism. The availability of the S-enantiomer is, therefore, increased by the presence of R-lercanidipine. Following racemate administration, the C_{max} and AUC of the S-enantiomer were, on the average, 1.2-fold higher than those of the R-enantiomer.

CLINICAL PROFILE

Pharmacodynamic Properties

Hemodynamic Effects

The hemodynamic effects of single and repeated once-a-day doses of lercanidipine have been investigated during non-invasive and invasive studies. The administration of single

doses of 10, 20, and 30 mg, studied by using impedence cardiography, determined a dose-dependent increase in cardiac output. Echocardiographic evaluations after administration of 20 mg once a day showed that systolic function, both at rest and during handgrip and cold pressure tests, was well maintained and that diastolic function was improved, as indicated by an increase in mitral valve flow (Recordati, data on file).

During two invasive studies (cardiac catheterization), no signs of reduced cardiac inotropism were found 2 to 3 h after a single 20-mg oral dose of lercanidipine. No changes in ECG parameters, including PR and RR intervals, were observed (Recordati, data on file).

All the data obtained indicate the lack of negative inotropic effect of lercanidipine by oral administration and these findings confirm the observations recorded in preclinical studies.

Gradual Onset of Action

Lercanidipine, at a single daily dose, exerts a prolonged antihypertensive action lasting 24 h, as shown by measuring blood pressure in all pivotal studies at 24 h post-dose, and by ambulatory blood pressure monitoring in other placebo-controlled studies (3). Furthermore, lercanidipine differs from short-acting DHPs in its kinetic behaviour. It has a gradual onset of blood pressure-lowering activity, and the decrease in blood pressure over 24 h is smooth (Fig. 10). In particular, a study aimed to compare the 24 h profile of the antihypertensive action of lercanidipine with that of a well-known long-acting DHP,

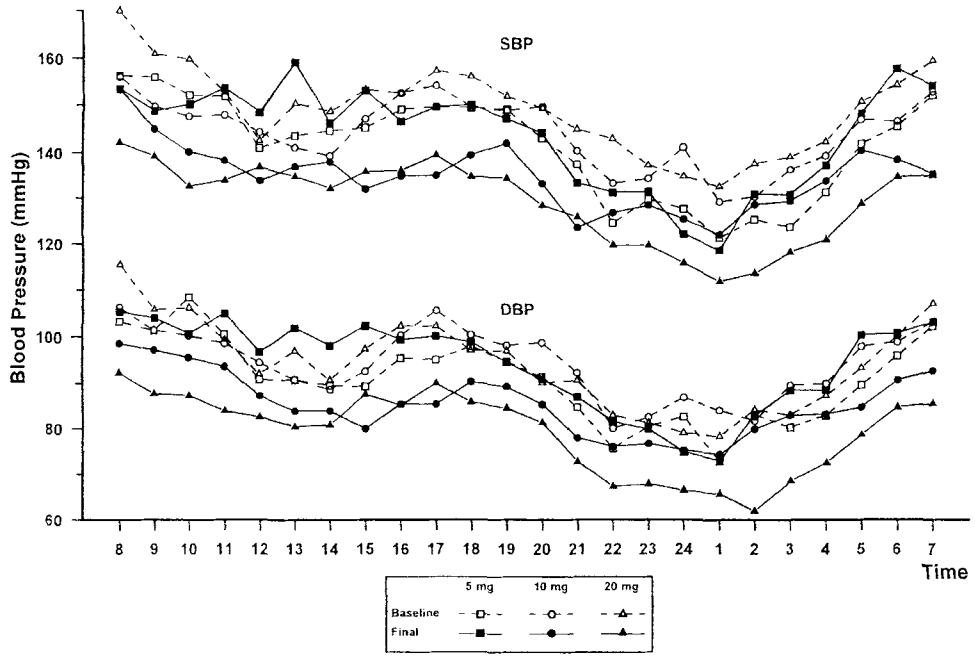


FIG. 10. Hourly averaging of blood pressure in mild to moderate hypertensive patients: curves taken before and after 4 weeks of treatment with lercanidipine 5, 10, or 20 mg p.o. daily, SBP, systolic blood pressure; DBP, diastolic blood pressure plotted against time in hours. Means of 8 patients per group.

amlodipine, showed that the antihypertensive effect of lercanidipine as well as that of amlodipine extends over the 24 h period (Recordati, data on file).

To demonstrate the gradual and smooth hypotensive effect of lercanidipine, the time-to-peak effect and the trough-to-peak ratio have been considered. The time-to-peak hypotensive effect ranged from 5 to 7 h after administration of lercanidipine, for both SBP and DBP (Recordati, data on file). The trough-to-peak ratio was very high, above 0.80 for lercanidipine 10 mg; when corrected for the placebo effect, the ratio further increased, indicating a very smooth antihypertensive activity of both 10 and 20 mg doses (14). In elderly patients the calculated trough-to-peak ratio was 0.77 (43).

Humoral Effects

In a placebo-controlled study performed in 16 patients to evaluate single and repeated dose effects on the renin-angiotensin-aldosterone (RAA) system, lercanidipine was administered at doses of 10 and 20 mg for 7 d, and did not show any modification in renin activity or aldosterone levels. During this study the effects were evaluated in standing and supine positions on days 1 and 7. The results suggest a lack of sympathetic activation by lercanidipine at either dose (Recordati, data on file). In the same study, no significant effects were found on renal function (urine volume, sodium and potassium excretion, PHA and creatinine clearance), both at a single or repeated doses. On the contrary, an increase in the plasma renin activity has been reported in the literature for other DHPs (30), as was a dose-related sympathetic activation (35,56).

Other Effects

Lercanidipine did not induce any change in plasma cholesterol or apolipoproteins after six months of treatment in a comparative study with hydrochlorotiazide performed on 52 hypertensive patients. Hydrochlorotiazide, on the contrary, caused an elevation in plasma triglycerides (Recordati, data on file).

A placebo-controlled study performed in hypertensive patients with non-insulin-dependent diabetes mellitus controlled by diet or oral hypoglycemic agents showed that lercanidipine, 10 and 20 mg, exerts an antihypertensive effect, after 4 weeks of treatment, similar to that seen in non-diabetic patients (DBP = −8 mmHg at either dose, and SBP = −16 and −14 mmHg at 10 or 20 mg respectively). Furthermore, a slight but significant decrease in fasting blood glucose, glycosylate hemoglobin, and fructosamine, and an improvement in oral glucose tolerance have been observed. These results suggest that lercanidipine has no negative effect on glucose levels in diabetic patients (Recordati, data on file).

Therapeutic Efficacy in Essential Hypertension

The therapeutic efficacy of lercanidipine in hypertension was evaluated by measuring SBP and DBP in standing and supine positions by a traditional method. Some studies also included ambulatory blood pressure monitoring. The rate of normalized (DBP $\leq$ 90 mmHg) and responder (DBP reduction of at least 10 mmHg from baseline value or $\leq$90 mmHg) patients was also evaluated.

Dose Finding Studies

The antihypertensive effects of 2.5, 5, 10, 20, and 30 mg of lercanidipine, given as single and once daily repeated doses, administered for 1 to 4 weeks, were investigated in double-blind, randomized studies. The 2.5 and 5 mg dosages were both found ineffective by conventional blood pressure measurements and 5 mg also by ambulatory blood pressure monitoring.

The results of a randomized, double-blind, placebo-controlled, crossover study, which involved 20 mild to moderate hypertensive patients, performed by using 24 h ambulatory blood pressure monitoring, confirmed the dose of 5 mg is not sufficiently potent (Recordati, data on file). The global analysis of the obtained data indicate the effective dose is 10 mg once a day, to be titrated up to 20 mg in non-responding patients. The direct comparison between 10 and 20 mg in a placebo-controlled, randomized study (14) did not show any statistical difference in terms of blood pressure response, although in the 20-mg dose group the rate of responding patients was higher (86% vs. 66%). A global evaluation (eight studies) of the rate of responding patients to dose titration up to 20 mg after 4 weeks of treatment at 10 mg showed that more than 60% of patients non-responding to the lower dose responded to the titrated dose (Recordati, data on file). The 30-mg daily dose did not appear to be more effective than 20 mg.

Comparison with Placebo

Placebo-controlled studies showed that either dose (10 or 20 mg) of lercanidipine once a day is significantly more effective than placebo in lowering SBP and DBP. In a multicentre study involving 132 patients with mild to moderate hypertension, treated with doses of 10 or 20 mg once a day and dose titration up to 40 mg/day in non-responders, a more significant decrease in DBP and SBP in comparison to placebo was observed after 4 weeks of treatment at either dose. The percentage of normalized patients was higher with lercanidipine at either dose (54 and 63 with 10 and 20 mg, respectively) in comparison with placebo (14). All other placebo-controlled studies gave similar results.

Comparison with Other Antihypertensive Agents

In double-blind studies, lercanidipine was shown to be at least equally effective and well-tolerated as other reference drugs. A total of 230 patients were enrolled in three clinical trials comparing lercanidipine with three other DHP calcium channel blockers: nitrendipine, nifedipine SR, and amlodipine, according to a crossover design and ambulatory blood pressure monitoring. In all trials lercanidipine exerted an antihypertensive effect similar to that of the reference compound, as shown in Figs. 11 and 12 (50, 52 and Recordati, data on file).

Four hundred and eight patients were evaluated in studies comparing the efficacy and safety of lercanidipine versus a β-blocker (atenolol) (70), a diuretic (hydrochlorotiazide) (Recordati, data on file), or an ACE-inhibitor (captopril) (4). In all studies lercanidipine showed a similar efficacy to standard drugs in reducing blood pressure, with a high rate of responding/normalized patients.

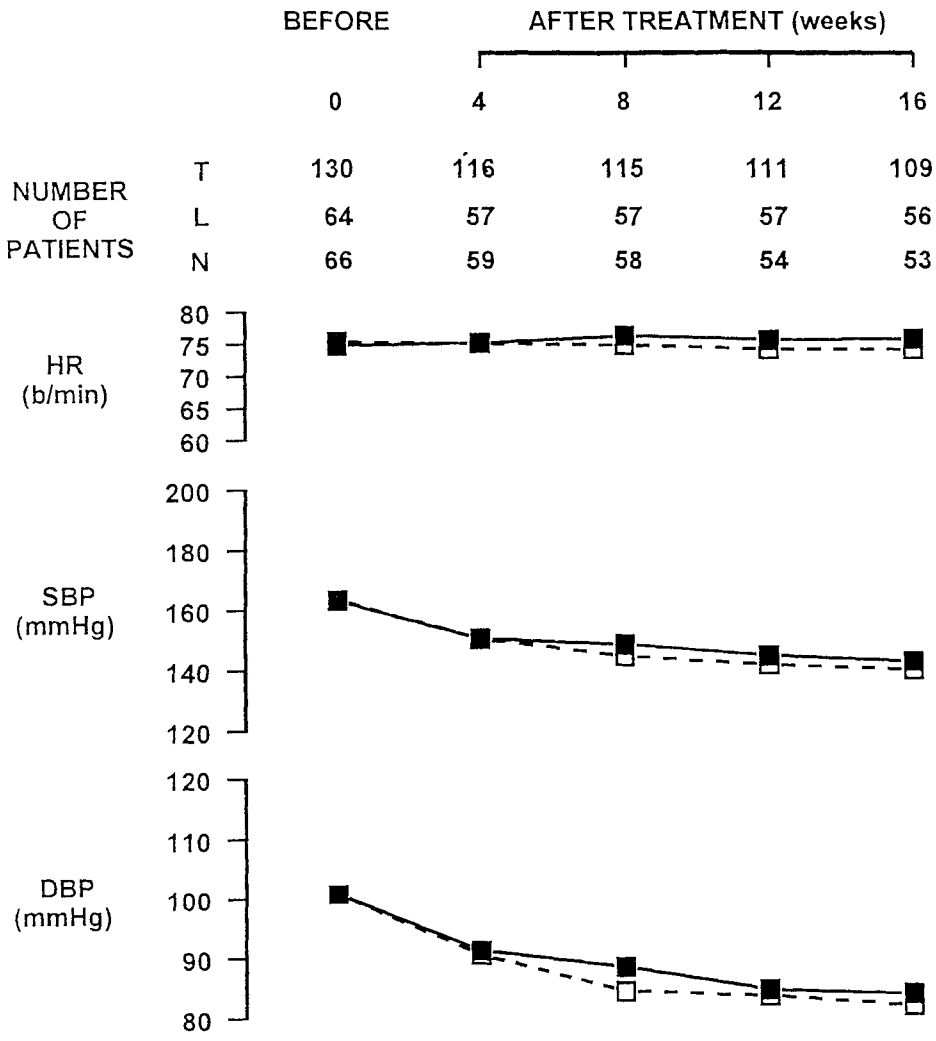


FIG. 11. Changes in supine blood pressure and heart rate (HR) during 16 weeks of active treatment with lercanidipine (10 to 20 mg/d) or nifedipine SR (40 to 80 mg/d) alone or in combination with hydrochlorothiazide (12.5 to 25 mg/d). T, total; L, lercanidipine (filled squares); N, nifedipine SR (open squares); SBP, systolic blood pressure; DBP, diastolic blood pressure.

Severe Hypertension

Two studies with different design were performed to evaluate the efficacy of lercanidipine in severe hypertension. The first one evaluated the effect of monotherapy with lercanidipine 20 mg administered once or twice a day, with an increase up to a maximum dose of 40 mg daily, to 50 patients with severe hypertension (DBP $\geqslant$ 110 mmHg). For ethical reasons there was no placebo comparison and the full course of treatment lasted 90 d, with follow-up visits performed every 5 d. The monotherapy with lercanidipine, once or twice a day produced a significant decrease in DBP (about 30 mmHg) within 60

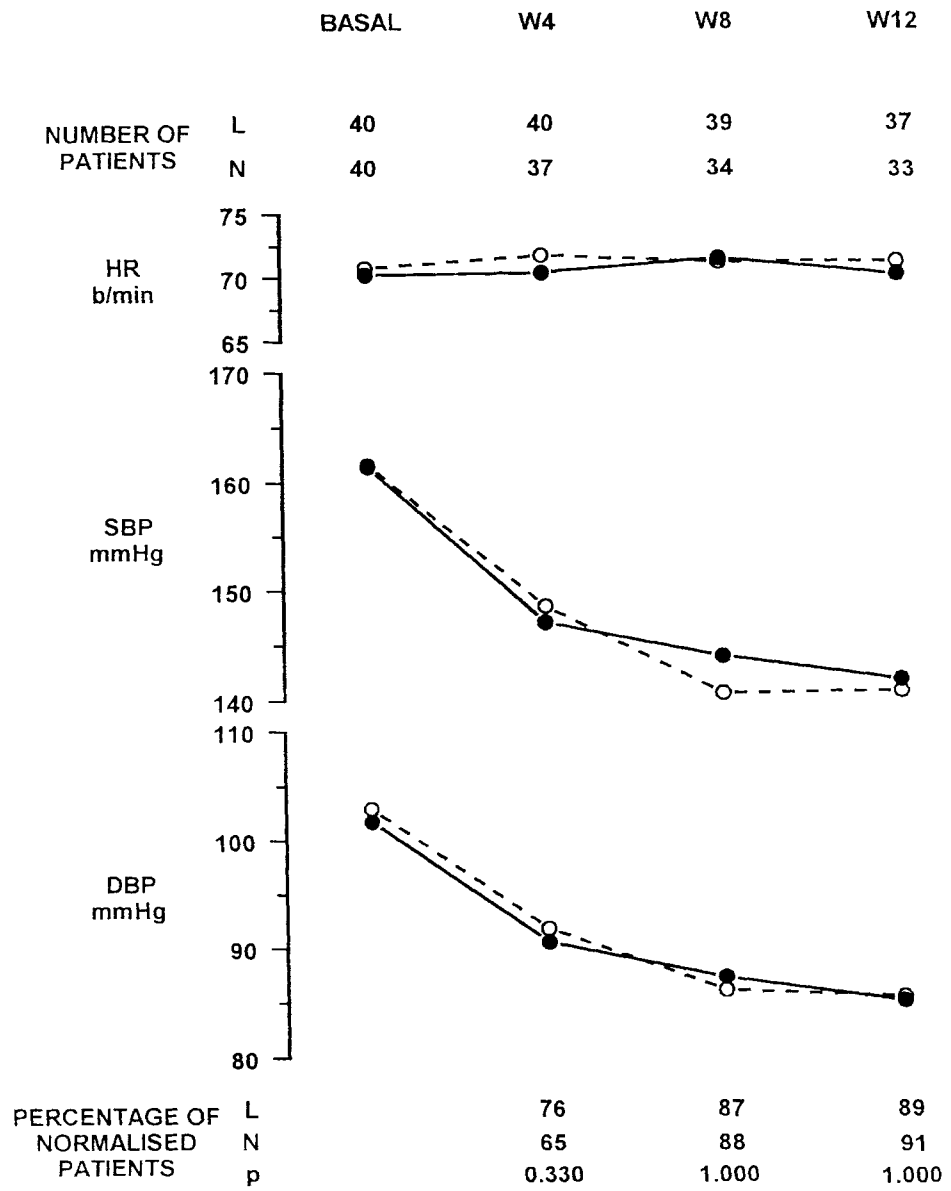


FIG. 12. Heart rate (HR), systolic (SBP), and diastolic (DBP) blood pressure values measured in patients before (basal) and after 4 (4W), 8 (8W), and 12 (12W) weeks of treatment with lercanidipine (L, filled circles) or nitrendipine (N, open circles) at 10 mg daily. In both groups the dose was titrated up to 20 mg and 30 mg in patients non-responding after 4 and 8 weeks of treatment, respectively.

d, with further improvement in the next 30 d. The efficacy was confirmed by the high percentage of responding (above 90%) and normalized (73% and 84% with the once and the b.i.d. regimens, respectively) patients. The results suggest that the once-a-day regimen is very effective also in this population, since no significant difference in achieved blood

pressure was detectable. From the point of view of patients compliance this regimen was also preferable (38).

The second study was a controlled, randomized, double-blind clinical trial in which 80 patients with uncontrolled hypertension received for 12 weeks either lercanidipine, 10 to 30 mg once a day, or nitrendipine, 10 to 30 mg once a day, in association with the pre-existing antihypertensive therapy (β-blocker, ACE-inhibitor, or diuretic). Lercanidipine reduced DBP by 13 mmHg after 4 weeks, similarly to nitrendipine (12 mmHg), with a high percentage of normalized patients and a lower incidence of adverse events (particularly ankle edema and flushing) than with nitrendipine (52).

Elderly

The antihypertensive activity of lercanidipine was also investigated in elderly patients with essential or isolated systolic hypertension (ISH).

In a placebo-controlled, parallel-group study involving 144 mild to moderate hypertensive patients, aged 68.4 ± 6.1 years, lercanidipine, 10 to 30 mg once a day, had a significantly greater effect on DBP and SBP, (measured at 4 and 24 h after treatment), than placebo (43).

A total of 83 patients of mean age 67 years affected by isolated systolic hypertension were included in a placebo-controlled study and treated with lercanidipine 10 mg (up to 20 mg for non-responders) once a day or placebo for 8 weeks. At the end of the study SBP decreased by 32 mmHg with lercanidipine and only by 10 mmHg with placebo, showing the efficacy of lercanidipine also in this type of patients (Recordati, data on file). In this respect, lercanidipine acts like other DHPs, which have been shown to be effective in the treatment of isolated systolic hypertension in elderly patients not only because they decrease peripheral vascular resistance, but also because they improve the compliance of large arteries, considered an important factor in the etiology of this type of hypertension (18).

Long-Term Studies

The long-term efficacy and tolerability of lercanidipine were studied in about 400 patients with mild to moderate hypertension, who received the drug in trials lasting 12 months (11). No tolerance to lercanidipine was evident during the studies, since the antihypertensive effect was progressively maintained while heart rate was not significantly affected. The consistent antihypertensive effect of lercanidipine 10 mg was also confirmed by long-term administration, since in only 91/350 patients the dose had to be increased to 20 mg/day. After a further 4 weeks of therapy, 37/350 patients required 30 mg of lercanidipine. These studies confirm that lercanidipine is an effective and well-tolerated drug for long-term use in patients with mild to moderate hypertension.

Tolerability

All data concerning the safety profile of lercanidipine, results of laboratory tests as well as adverse events, have been pooled and reviewed in comparison with placebo. The safety database included 1799 patients, 51% male and 49% female. The majority (71%) were 41–64 years old, and 23% were elderly (≥65 years); 74 of those were over 70 years and

27 over 75 years. Most had mild to moderate hypertension, with 12% recorded as having severe, resistant, or isolated systolic hypertension.

Heart Rate

During clinical trials lercanidipine had no relevant effect on heart rate and reflex tachycardia was an infrequent and transient event. An analysis performed after stratifying the database population in three major age classes (≤40 years; 41 to 64 years; ≥65 years), did not show an increase in heart rate in any of the groups. Similar results were also obtained after evaluating heart rate measurements of patients with severe hypertension (38). The global analysis of heart rate performed in a large sample of patients did not reveal any significant modification of this parameter, thus providing substantiate evidence for the lack of reflex tachycardia with lercanidipine at the recommended doses. Supporting data can be derived from heart rate measurements (Fig. 13) performed in some clinical trials at "peak" drug exposure, 4 to 5 h after lercanidipine administration, (14,43,70), by 24-h recording of heart rate with ABPM (3 and Recordati, data on file), Holter ECG monitoring (Recordati, data on file) or under stressing conditions, during the invasive hemodynamic investigation performed in some studies (Recordati, data on file). In no case, in fact, was an increase in heart rate observed. Therefore, lercanidipine at the recommended doses, seems to be free of any clinically detectable effect on the heart rate.

Vasodilation-Related Adverse Events

The evaluation of lercanidipine safety is based on 1317 patients who received the drug, 156 of whom experienced adverse effects (12%), in comparison with 16/227 (7%) patients treated with placebo. The adverse event profile of lercanidipine is typical of the pharmacological class, since the most commonly observed side effects were expected and related

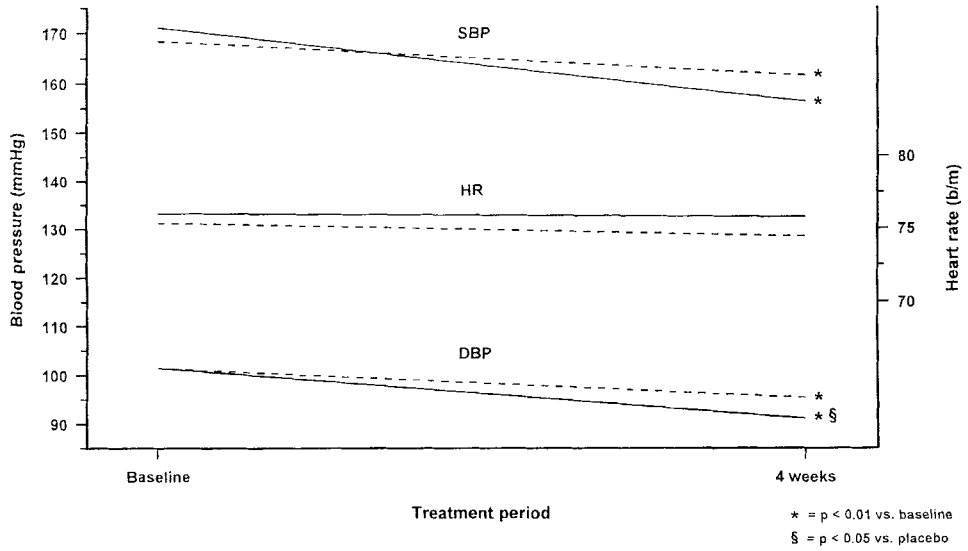


FIG. 13. Changes in blood pressure and heart rate (HR) during 4 weeks of treatment with placebo (dashed lines) or lercanidipine 10 mg daily (continuous lines). SBP, DBP, systolic, and diastolic blood pressures.

to the vasodilatory action of the drug (ankle edema, headache, flushing, and dizziness); in the majority of cases they were classified as mild-to-moderate in severity (Table 8). The tolerability of the 10 mg dose has been found superior to that of 20 mg as an initial dose. It is relevant that low incidence of the events occurred with the 10 mg dose, particularly tachycardia (0.62% with lercanidipine and 0.44% with placebo) and peripheral edema (0.89% and 1.32% with lercanidipine and placebo, respectively), and with 20 mg titrated (4.13% for tachycardia and 1.96% for peripheral edema). With 20 mg as an initial dose, these symptoms were reported more frequently, suggesting that tolerability is enhanced by starting treatment at 10 mg.

Data derived from all double-blind studies that compared lercanidipine with standard first-line antihypertensive agents (other calcium channel blockers, β-blocker, ACE-inhibitor, and diuretic) showed that lercanidipine was equally well-tolerated and in two cases (comparison with nifedipine SR and with nitrendipine) a lower incidence of adverse events and drop-outs due to adverse events were reported with lercanidipine (52). The large number of elderly patients (298) who received the 10 mg dose did not show a higher incidence of adverse effects than young and middle-aged patients. One hundred and sixty six (12.6%) of the 1317 patients treated with lercanidipine withdrew from treatment, 61 because of adverse events, versus 19 out of the 227 (8.4%) patients treated with placebo, 6 because of adverse events. The Odds ratio, percentage of total drop-outs with lercanidipine over that with placebo was 1.51. The incidence of withdrawal for adverse events was comparable for placebo (2.6%), 10 mg lercanidipine (2.6%), or 20 mg titrated lercanidipine (3.5%), but was slightly higher with 20 mg lercanidipine as initial dose (8%).

Cardiovascular Safety

The evaluation of ECGs recorded at different time during clinical trials with lercanidipine showed that the drug is free of any proischemic effect: only 1.9% of patients treated with lercanidipine presented electrocardiographic signs of ischemia during the treatment,

TABLE 8. *Most commonly reported Adverse Events (AEs) in each treatment group by different system/organ classes.*

	Placebo (n = 227)	10 mg (n = 1128)	20 mg (n = 180) Initial	20 mg (n = 460) Titrated	30 mg (n = 102)
Patients with AEs (%)					
Cardiovascular					
Peripheral oedema	1.32	0.89	6.11	1.96	3.92
Flushing	0.44	1.06	6.11	0.87	1.96
Tachycardia	0.44	0.62	8.89	4.13	0.00
Others	0.88	0.09	0.56	0.44	0.00
Body as a whole					
Asthenia	0.44	0.35	1.11	0.00	0.00
Others	1.32	0.36	0.56	0.65	0.00
Central Nervous System					
Headache	1.32	2.30	1.67	2.83	5.88
Dizziness	0.44	0.35	0.56	0.22	0.00
Others	0.00	0.18	0.00	0.00	0.00
Gastrointestinal					
Nausea	0.44	0.18	0.00	0.22	0.98
Abdominal pain	0.44	0.35	0.00	0.22	0.98
Others	0.88	0.18	0.56	0.00	0.00

and in 4.0% of them the signs disappeared. These findings, similar to those observed in the placebo-treated patients (2.1% and 1.4%), seem to be related to a normal evolution of ECG changes in hypertensive patients (Recordati, data on file).

The cardiovascular safety of lercanidipine is further supported by the observation that there were no reports of angina or myocardial infarction in more than one thousand patients receiving 10 mg/day and there were only 2 reports of chest pain (one of which was due to myocardial infarction) in more than 400 patients receiving 20 mg, in comparison with 1 patient with chest pain in more than 200 patients receiving placebo.

Furthermore, lercanidipine showed stable blood pressure control over the 24-h period without marked hypotension during night time (Recordati, data on file), which may be linked to the onset of coronary events and ischemic strokes and was reported for some other calcium channel blockers (19).

Finally, the pharmacokinetic and pharmacodynamic profile of lercanidipine, characterized by slow onset of the effect, absence of sympathetic activation and once a day administration, differentiate lercanidipine from the first generation short-acting DHPs that should be avoided in patients with ischemic heart disease.

Other Issues

In all the laboratory tests, including hematology and urinalysis, lercanidipine produced no clinically significant changes.

CONCLUSIONS

Calcium antagonists, in particular DHPs, are widely used in antihypertensive therapy because of their marked effectiveness in lowering blood pressure, and a mechanism of action leading to a decrease in peripheral vascular resistance.

It is commonly agreed that the benefits of antihypertensive therapy largely outweigh the risks, and that the benefits are directly correlated with the degree of decrease in blood pressure values. DHPs are amongst the most powerful antihypertensive agents available, and, among DHPs, lercanidipine shows pharmacodynamic properties and the therapeutic effect typical for the latest long-lasting agents.

The chemical properties of lercanidipine include a very high lipophilicity and membrane partitioning coefficient, which lead to a preferential distribution of the drug into the membranes of smooth muscle cells. This distribution results in a membrane-controlled kinetics, as opposed to plasma-controlled kinetics of most DHPs, including the short-acting compounds, and leads to a prolonged pharmacological effect on blood pressure that lasts 24 h in spite of a plasma half-life of 2 to 5 h.

These characteristics were confirmed in preclinical studies where the long-lasting effects of lercanidipine on blood pressure were associated with a marked vasoselectivity, both *in vitro* and *in vivo.*

Lercanidipine shows a sustained pharmacological action and a significant antihypertensive efficacy when administered once a day. The onset of its action is gradual. In placebo-controlled studies involving patients with mild to moderate hypertension, lercanidipine as monotherapy showed a clinically relevant antihypertensive effect. When compared with other calcium antagonists, β-blockers, diuretics, or ACE-inhibitors lercanidipine was at least as effective. In patients with more severe essential hypertension, also those uncontrolled by previous therapies, lercanidipine, as single treatment or "add-on"

therapy, demonstrated a significant antihypertensive efficacy. Furthermore, ambulatory blood pressure monitoring has shown that lercanidipine reduces blood pressure throughout 24 h without marked nocturnal hypotension and signs of reflex tachycardia. This finding, together with the favorable trough-to-peak ratio and the absence of sympathetic activation, demonstrates the smoothness of lercanidipine effect that leads to favorable cardiovascular and systemic tolerability.

Indeed, a clinically useful antihypertensive compound must couple effectiveness in lowering blood pressure with good tolerability. This is not universally true for all antihypertensive agents, and particularly for some DHPs (72). Flushing, headache, and palpitation have been frequently described as causes of withdrawal from medication with short-acting DHPs. Tachycardia, reflexly induced by a rapid fall in blood pressure, should not only be considered as an annoying side effect, but a possible risk for hypertensive patients with simultaneous, known or unknown, cardiac ischemia (21).

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