

**EFFECT OF HYPERLIPIDEMIA ON THE PHARMACOKINETICS OF
LERCANIDIPINE IN EXPERIMENTAL RATS**

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Summary

The present study was aimed at investigating the effect of hyperlipidemia or hypercholesteramia on the pharmacokinetic parameters of lercanidipine in experimental rats. The standard cholesterol diet was used to induce hyperlipidemia in rats and was treated with lercanidipine. The blood samples were collected and estimated for plasma drug concentrations using HPLC and found a statistically significant change in pharmacokinetic parameters of lercanidipine in hyperlipidemic conditions.

Keywords: lercanidipine, hyperlipidemia, Pharmacokinetics

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Introduction

Lercanidipine hydrochloride, is (4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-[(3,3-diphenyl propyl) methylamino]-1,1-dimethyl ethyl methyl ester hydrochloride) (1) is a vasoselective dihydropyridine calcium channel blocker (CCB) that causes systemic vasodilation by blocking the influx of calcium systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes. It is a highly lipophilic drug that exhibits a slower onset and longer duration of action than other calcium channel antagonists. Further more, lercanidipine may have antiatherogenic activity unrelated to its antihypertensive effect (2). Lercanidipine has been shown to be effective in a wide range of hypertensive patients including mild to moderate hypertension, severe hypertension, the elderly and those with isolated systolic hypertension (3). Lercanidipine has now been shown to have one of the highest measured tolerances to cholesterol, which may indicate it's ability to treat a broad range of hypertensive patients with varying degrees of progressive atherosclerotic disease (4). In most of the cases, the CCB's are co administered with statins in the treatment of hyperlipidemia. The present study investigated the effect of hyperlipidemia on the pharmacokinetics of lercanidipine.

Methods

Materials: Lercanidipine pure drug was a kind gift from Nicholus Piramils India Ltd. HPLC grade acetonitrile, methanol and water were purchased form Qualigens Chemical Ltd.

Study design

Adult male wistar albino (200-220g) were selected and housed in polypropylene cages in a room where the congenial temperature was $27^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and 12 hrs light and dark cycles were maintained. The animals were supplied with a standard pellet diet and water ad libitum. Before induction of hyperlipidemia, the weight of the individual animal and plasma cholesterol levels were estimated. The standard cholesterol diet⁷ along with butter (0.5 ml twice a day) was administered for 30 days to induce hyperlipidemia. At the end of the one month the blood was withdrawn from tail vein to analyze (5) for lipid profiles (TC, TG, LDL-C and HDL-C levels) to confirm the induction of hyperlipidemia. The rats were divided into groups of six rats in each.

Group I: (Non-HL) Non-Hyperlipidemic rats received a dose of lercanidipine (20 mg/kg in 1.5% CMC/ day for 7 days).

Group II: (LER) Hyperlipidemic rats received a dose lercanidipine (20 mg/kg in 1.5% CMC/ day for 7 days). The protocol of the present study was approved by the institutional animal ethical committee.

Collection of Blood samples

On 1st and 8th day, blood samples of 0.5 mL were withdrawn at different time intervals through retro-orbital sinus into heparinized eppendorff tubes at 0.5, 1, 2, 4, 6, 8 and 24 hrs and equal amount of saline was administered to replace blood volume at every blood withdrawal time (6). Plasma was obtained by immediate centrifugation of blood samples using REMI ULTRA cooling centrifuge at 3000 rpm for 5 minutes at room temperature. All samples were stored at 4°C until analysis.

Method of analysis:

The plasma samples of lercanidipine were estimated by High Pressure Liquid Chromatography (HPLC) method (7). The results were expressed as mean \pm SD. Statistical comparisons for the pharmacokinetic study among, Non HL and LER groups were carried out using t-test and differences below $P < 0.05$ implied statistically significance.

Results and Discussion

Pharmacokinetic Analysis: Pharmacokinetic parameters like area under the curve [AUC], elimination half life [$t_{1/2}$], volume of distribution [V/f], total clearance [CL/f], peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were calculated for each subject using a non compartmental pharmacokinetic model "WIN NONLIN". The plasma levels ($\mu\text{g/ml}$) of lercanidipine in normal and hyperlipidemic groups at different time points, on day 1 and day 8 were shown in figure 1 and 2 and respective pharmacokinetic parameters were shown in table 1&2.

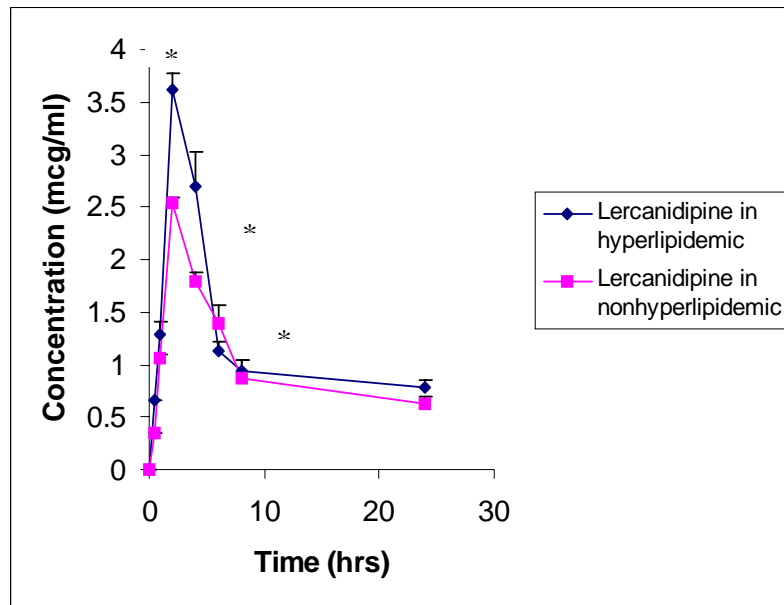
Table 1: Pharmacokinetic parameters of lercanidipine in hyperlipidemic versus non hyperlipidemic rats on day 1

Parameter	Lercanidipine in hyperlipidemic rats	Lercanidipine in non hyperlipidemic rats	Level of Significance ($P < 0.05$)
C_{max} ($\mu\text{g/ml}$)	3.61 \pm 0.32	2.53 \pm 0.08	S
T_{max}(h)	2	2	Ns
AUC_{0-t} ($\mu\text{g/ml/h}$)	27.76 \pm 0.65	24.45 \pm 1.02	S
AUC_{0-inf} ($\mu\text{g/ml/h}$)	42.09 \pm 1.39	39.54 \pm 1.36	S
T_{1/2}(h)	14.58 \pm 1.45	17.155 \pm 1.37	S
CL/f (ml/h/kg)	2486.13 \pm 93.694	2278.07 \pm 122.06	S
V/f (ml/kg)	51932.75 \pm 0.00	60568.02 \pm 2232.44	S

Table 2: Pharmacokinetic parameters of lercanidipine in hyperlipidemic versus non hyperlipidemic rats on day 8

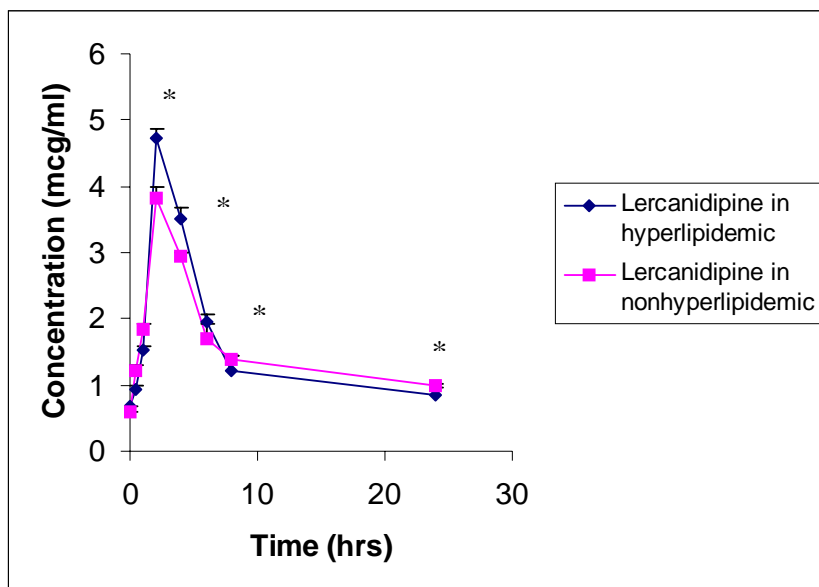
Parameter	Lercanidipine in hyperlipidemic rats	Lercanidipine in non hyperlipidemic rats	Level of Significance (P < 0.05)
Cmax (µg/ml)	4.73 ± 0.14	3.82 ± 0.05	S
Tmax(h)	2	2	NS
AUCo-t (µg/ml/h)	41.24 ± 1.33	39.74 ± 1.38	S
AUCo-inf (µg/ml/h)	41.64 ± 1.47	59.33 ± 2.92	S
T1/2(h)	14.58 ± 1.45	18.82 ± 0.23	S
CL/f (ml/h/kg)	2421.13 ± 105.51	1672.99 ± 99.11	S
V/f (ml/kg)	51937.64 ± 4363.67	36058.88 ± 1698.57	S

Fig.1 : Mean plasma concentrations (µg/ml) of lercanidipine in hyperlipidemic versus non hyperlipidemic rats on day 1 (n=6). * p < 0.05



There was a statistically significant change in the plasma concentrations were observed between two groups. There was increase in Cmax, AUC, clearance of lercanidipine in hyperlipidemic rats than normal rats, but the half life of the drug was more in normal rats than HL group. These findings suggest that hypercholesteramia changed the pharmacokinetics of lercanidipine.

Fig.2: Mean plasma concentrations ($\mu\text{g/ml}$) of lercanidipine in hyperlipidemic versus non hyperlipidemic on day 8 (n=6). *P < 0.05



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