

Lipid Lowering Activity of Lercanidipine in Hyperlipidemic Rats

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ABSTRACT

The present study was aimed at evaluating the lipid lowering activity of lercanidipine, a calcium channel blocker, in standard diet induced hyperlipidemic rats. Hyperlipidemic rats were divided into different groups and were treated with daily oral dose of lercanidipine and atorvastatin for 7 days. On 8th day, blood samples were collected and analyzed for serum lipid levels using commercial kits. The rats were fed with standard cholesterol diet to induce hyperlipidemia. The effect of lercanidipine on lipid profiles in hyperlipidemic rats was estimated. Like atorvastatin, a standard lipid lowering drug, lercanidipine reduced the cholesterol, triglycerides and low density lipoprotein levels. These findings suggest that anti-hyperlipidemic activity of lercanidipine, which may be used for the treatment of various cardiovascular diseases associated with hyperlipidemia.

Keywords: Lercanidipine, Lipid lowering activity, Hyperlipidemic rats, Atorvastatin

Hyperlipidemia is defined as an elevation of one or more of the plasma lipids, including cholesterol, cholesterol esters, triglycerides and phospholipids [1]. An elevation of plasma lipids may be caused by a primary genetic defect or secondary to diet, drugs or diseases. Despite differences in lipoprotein distribution and metabolism between humans and rats, hyperlipidemic rat models are extensively used in lipid research [1]. As described in previous studies, the standard cholesterol diet has been used successfully to induce hyperlipidemia in rats [2] and it was chosen as the hyperlipidemic model due to its convenience, reproducibility and availability. Elevated plasma levels of total cholesterol (TC), LDL-cholesterol (LDL-C) and apolipoprotein B (apoB) promote human atherosclerosis and are risk factors for developing cardiovascular diseases, while increased levels of high density lipoprotein (HDL) are associated with a decreased cardiovascular risk [3,4]. Lercanidipine is a novel dihydropyridine (DHP) calcium-channel blocker indicated for the treatment of mild-to-moderate hypertension [5]. Hyperlipidemia is one of the risk factor for most of the cardiovascular diseases like hypertension and coronary heart disease; hence the antihypertensive drugs having lipid lowering activity are suitable for treatment of these complications. So, the present study was aimed at evaluating the lipid lowering

activity of lercanidipine in standard diet induced hyperlipidemic rats.

MATERIALS AND METHODS

Lercanidipine pure drug was a kind gift from Nicholas Piramils India Ltd. Cholesterol (Enzymatic Method) and high density lipoprotein cholesterol kits were procured from Qualigens Diagnostics, Mumbai. Triglycerides kit was obtained from E-Merck Limited, Mumbai, India.

Experimental Animals

Wistar albino adult male rats weighing 200-220g were selected and housed in polypropylene cages in a room where the congenital temperature was 27°C ±1°C and 12 hrs light and dark cycles were maintained. The animals were allowed to acclimatize to the environment for 7 days and 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 diet along with butter (0.5 ml twice a day) was administered for 30 days to induce hyperlipidemia. At the end of the one month blood was withdrawn from the tail vein to analyze [6] lipid profiles (TC, TG, LDL-C and HDL-C levels) and to confirm the induction of hyperlipidemia.

Table 1. Effect of lercanidipine on TC, TG, LDL and HDL levels in plasma of Control and Experimental rats

Parameters	TC	TG	LDL	HDL
Group-I: Normal rats	83.16 ± 2.71	123.5 ± 2.16	21.5 ± 1.76	32.16 ± 3.06
Group-II: HL Control	179.16 ± 3.97 ^b	264.5 ± 9.48 ^b	74.16 ± 5.15 ^b	56.5 ± 1.64 ^b
Group-III: Lercanidipine Treated rats (20 mg kg-1)	109.83 ± 1.47 ^a	136 ± 1.54 ^a	34.66 ± 1.21 ^a	64.83 ± 0.75 ^a
Group-IV: Atorvastatin Treated rats	105.66 ± 1.63 ^a	119.83 ± 0.72 ^a	25.5 ± 1.37 ^a	

Values are in mean ± SD; Number of animals in each group =6; a= p < 0.001 Vs Group II, b= p < 0.001 Vs Group I

Anti-hyperlipidemic studies

The hyperlipidemic rats were divided into three groups of six rats each. **Group I:** Normal rats received a dose of 1.5% carboxy methyl cellulose (CMC) (p.o), **Group II:** Control hyperlipidemic (HL) rats received a dose of 1.5% CMC (p.o), **Group III:** HL rats received a daily oral dose of lercanidipine (20mg/kg [7] suspended in 1.5% CMC) and **Group IV:** HL rats received a daily oral dose of atorvastatin 40mg/kg. This study was carried out for 7 days. The protocol of the present study was approved [No: 09/IRB/VCP/2005] by the institutional animal ethical committee, Vel's College of Pharmacy, Chennai. India.

Collection of Blood samples

On the 8th day, blood was collected by retro orbital sinus puncture, under mild ether anaesthesia. 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.

Biochemical analysis

Plasma lipid levels include TC, TG and HDL-C were measured [6] using respective diagnostic commercial kits from Qualigens diagnostics, Mumbai, India and LDL-C in plasma was calculated as per friedewald estimation [8,9],

$$\text{LDL-C} = (\text{TC} - (\text{TG}/5 + \text{HDL-C})) \text{ mg/dl}$$

Statistical Analysis

The results were expressed as mean ± SD. Statistically analysis was carried out using t-test and differences below $p < 0.05$ implied as statistically significant.

RESULTS

The effect of lercanidipine on plasma lipids in hyperlipidemic rats was shown in table 1.

The rats of Group II, hyperlipidemic control showed a marked increase in plasma TC, LDL-C, and TG and a fall in HDL-C levels than normal control group indicating the induction of hyperlipidemia. However, following treatment with lercanidipine and atorvastatin for 7 days, the plasma TC, LDL-C and TG were reduced significantly ($p < 0.05$), while HDL-C levels were increased in treated group when compared with hyperlipidemic control group.

DISCUSSION

Lercanidipine, a dihydropyridine calcium-channel blocker (CCB), is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina [10]. Recent clinical trials support the efficacy and safety of long-acting dihydropyridine (DHP) CCBs for a wide spectrum of hypertensive patients, including diabetic hypertensive patients [10]. Among the calcium channel blockers (CCBs), the new and highly lipophilic calcium antagonists, such as lercanidipine and lacidipine, display the most promising anti atherosclerotic activities [11]. In the present study we evaluated the effect of lercanidipine on lipid profiles in cholesterol induced hyperlipidemic rats. Surprisingly lercanidipine significantly reduces the lipid levels; i.e decreased in the plasma TC, TG, LDL levels and increased the HDL-C levels in hyperlipidemic rats. A statistically significant change in lipid profile was observed with atorvastatin and lercanidipine treatments in HL rats ($p < 0.05$). The TC, TG and LDL-C content in plasma registered a significant hike in HL control group, which returned to near normal in lercanidipine treated HL rats. These observations indicate the lipid lowering potential of lercanidipine. In support of our investigations, the proposed synergistic effect of calcium channel blockers with lipid-lowering therapy in retarding progression of coronary atherosclerosis was also reported [12]. In addition to our investigations, the lipid lowering activity of calcium channel blockers were also reported by earlier studies [13,14]. This anti-hyperlipidemic activity of lercanidipine (20 mg kg-1) was comparable with atorvastatin treated groups.

CONCLUSION

The present investigations stated that the oral administration of lercanidipine has significantly reduced the plasma lipid levels and reversed to normal levels, thus emphasizing the protective role against standard cholesterol induced hyperlipidemia.

REFERENCES

1. Raasch RH, Hyperlipidemias, in *Applied Therapeutics. The Clinical Use of Drugs* edited by Young LY and Koda-Kimble MA (Edwards Brothers, Ann Arbor, MI) 1988;9: 1743.
2. Augusti KT, Narayana Aswathy, Lekhespillai, Razia S, Beneficial effects of garlic (allium sativum LMN) on rats fed with diets containing cholesterol and either of the oil seeds, coconuts (or) groundnuts, *Indian J Exp Biol.*2001;39: 660.
3. Markku J. Savolainen, Maire Rantala, Kari Kervinen, Leea Järvi, Kaisu Suvanto, Tapio Rantala & Y. Antero Kesäniemi,

- Magnitude of dietary effects on plasma cholesterol concentration: role of sex and apolipoprotein E phenotype, *Atherosclerosis*, 1991;86: 145.
4. Wanner C, Quaschnig T., Dyslipidemia and renal disease: pathogenesis and clinical consequences, *Curr Opin Nephrol Hypertens*, 2001; 10:195.
 5. Cherylyn Beckey, PharmD CDE, Lercanidipine in the Treatment of Hypertension, *The Annals of Pharmacotherapy*, 2007; 41:465.
 6. Gulati R, Agarwal DK, Hossain MM, Ali R, Srivastava U, Study of serum lipid profile changes in Met-Enkephalm treated rats, *Indian J. Physiol Pharmacol*, 2003; 47:357.
 7. Massicotte Julie, Viens antoine, Yao-Ming-Hui, et al., Effects of Lercanidipine on coronary reactivity and myocardial remodeling in transition to heart failure in cardiomyopathic hamsters, *Acta Pharmacol*, 2003;24:199.
 8. V.T. Friedewald, R.I. Levy and D.S. Fredrickson, Estimation of low-density lipoprotein cholesterol in plasma, without use of the preparative centrifuge, *Clin Chem*, 1972;18:499.
 9. Ralph H, Stern Ph.D M.D, Bing-Bing YoungPh.D, Neil J, Hormslow M.D, Mark MacMahon, M.D. Robert B. Abel Ph.D, and Stephen C, Olson Ph.D, Pharmacodynamics and pharmacokinetics pharmacodynamic relationships of atorvastatin, an HMG-COA reductase inhibitor, *J clin pharmacol* 2000;40:616.
 10. Epstein M, Lercanidipine: a novel dihydropyridine calcium-channel blocker, *Heart Dis.*, 2001; 3:398.
 11. Stefano Bellosta and Franco Bernini, Lipophilic calcium antagonists in antiatherosclerotic therapy, *J Curt Atherosclerosis Reports*, 2000; 2:76.
 12. J. Wouter Jukema, Ad J. van Boven, Aeilko H. Zwinderman, Arnoud Van der Laarse and Albert V.G. Bruschke' Proposed Synergistic Effect of Calcium Channel Blockers with Lipid-Lowering Therapy in Retarding Progression of Coronary Atherosclerosis, *Journal of Cardiovascular Drugs and Therapy*, 1998; 12:111.
 13. Maurizio R. Soma, Malvina Natali, Elena Donetti, Roberta Baetta, Pierluigi Farina, Amedeo Leonardi, Carmen Comparato, Laura Barberi & 1,2,5Alberico L. Catapano, Effect of lercanidipine and its (R)-enantiomer on atherosclerotic lesions induced in hypercholesterolemic rabbits, *British J Pharmacol* 1998;125:1471.
 14. Catapano, AL, Calcium antagonists and atherosclerosis. Experimental evidence, *Eur Heart J* 1997; 18:80.

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