Research Article

Effect of Nifedipine on the pharmacodynamic parameters of Simvastatin in hyperlipidemic rats

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ABSTRACT

The present study was aimed at investigating the effect of nifedipine (N) on the pharmacodynamics of simvastatin (S) in hyperlipidemic rats. The standard cholesterol diet was used to induce hyperlipidemia in Wister rats. The blood samples were collected from simvastatin treated and simvastatin along with nifedipine treated rats and analyzed for pharmacodynamics (lipid profiles) of simvastatin using reported methods. The combination therapy produced a significant change in lipid profiles which were comparable with simvastatin alone. The enhanced lipid lowering activity of S+N in hyperlipidemic rats suggests the combinational therapy can enhance the lipid lowering property of simvastatin.

Key words: Simvastatin, nifedipine, hyperlipidemia and lipid lowering activity

INTRODUCTION

Hyperlipidemia is 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 of differences in lipoprotein distribution and metabolism between humans and rats, hyperlipidemic rat models are extensively used in lipid research (1). The standard cholesterol diet has successfully been used to induce hyperlipidemia in rats in previous studies (2) and it was chosen as the hyperlipidemic model due to its convenience, reproducibility and availability. Simvastatin is,(1S,3R,7S,8S, 8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2(2R,4R)Tetrahydro-4- hydroxy- 6-OXO-2H-Pyran- 2 – y1) ethyl] – 1 napthalenyl 2,2 – dimethyl butyrate) (3), a lipid lowering agent , act by inhibiting HMG-CoA reductase, the rate limiting step in cholesterol synthesis (Mary j. Mycek). Nifedipine is (3,5 – pyridinedicarboxylic acid, 1,4 – dihydro 2,6 – dimethyl – 4 – (2 –nitropheny) – Dimethyl, ester), a dihydropyridine derivative and is widely prescribed agents for the management of mild to moderate and essential hypertension (4). In most of the cases, hyperlipidemia is coexisted with cardiovascular complications like hypertension in which calcium channel blockers are required along with statins for the effective treatment. Due to the lack of reports, the present study investigated the effect of nifedipine on pharmacodynamics of simvastatin in hyperlipidemic rats.

MATERIALS AND METHODS

Materials: Simvastatin pure drug was a kind gift from Orchid Pvt. ltd India and nifedipine pure drug was a kind gift from Nicholus Piramils India Ltd. Cholesterol kit (Enzymatic Method), HDL-C kit were procured from Qualigens

Diagnostics, Mumbai. Triglycerides kit was obtained from E-Merck Limited, Mumbai, India.

Study design

Wistar albino adult male rats weighing 200-230g were selected and allowed to acclimatize to the environment for 7 days and supplied with a standard pellet diet and water ad libitum. 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 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 hyperlipidemic rats were divided into three groups of each six and treated with (single dose /day for 7 days) simvastatin alone or in combination with nifedipine.

Group I**:** (HL) Control group of Hyperlipidemic rats received a dose of 1.5% CMC.

Group II**:** (S) Simvastatin (single dose of 80 mg/kg) alone in Hyperlipidemic (HL) rats.

Group III**:** (S-N) Simvastatin in combination with nifedipine (single dose of 20 mg/kg).

Collection of Blood samples

On 8th day, blood samples were withdrawn through retro-orbital sinus into heparinized eppendorff tubes and 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 carried out (5) using respective diagnostic commercial kits and LDL-C in plasma was calculated as per friedewald estimation (6-7**)**

(LDL-C=TC-(TG/5+HDL)-C).

Statistical Analysis: The results were expressed as mean ± SD. Statistical comparisons among, Non HL, HL, S and S-N groups were carried out using Dunnett test and the differences below P<0.05 implied statistically significance.

RESULTS AND DISCUSSION

The lipid profiles were estimated for all the groups on day 8. The Pharmacodynamic parameters (lipid profile) of simvastatin alone and in combination with nifedipine were shown in table 1. Standard cholesterol diet effectively induced hyperlipidemia by increasing the plasma TC, TG and LDL-C levels. In groups of III, IV, the lipid profiles were significantly changed than group II. Simvastatin significantly changed the lipid profiles in hyperlipidemic rats either alone or in combination with nifedipine. Simvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-COA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic low density lipoprotein (LDL) receptors on the cell surface for enhanced uptake and catabolism of low density lipoprotein (LDL) and also decreases triglycerides (TG) levels but, increases high density lipoprotein - cholesterol (HDL-C) (8). It was reported that the simvastatin therapy produced a statistically significant changes in total cholesterol, LDL-C, TG, HDL-C within 24 hours (7).

Simvastatin alone and in combination with nifedipine, significantly reduced the plasma cholesterol, triglycerides, low density lipoprotein-cholesterol levels in standard diet induced hyperlipidemic rats (P< 0.05), but the change in the lipid levels was more in S-N treated group than S group. There was a significant difference in change of lipid profiles in S and S-N treated groups (P< 0.005). These findings suggest the synergistic lipid lowering activity of nifedipine. In support of our investigations the lipid lowering activity of calcium channel blockers was also reported (9-10). This synergistic lipid lowering activity of nifedipine may suitable for the patients of hypertension associated with hyperlipidemia. It can be suggested that the combination of these two drugs have potential ben-

Table 1: Effect of Nifedipine on lipid parameters of simvastatin in Control and Experimental rats

Parameters	TC	TG	LDL	HDL
I: Normal rats	80.12 ± 0.09	118.9 ± 0.26	22.26 ± 0.14	33.5 ± 0.3
II: HL Control	193.12 ± 0.37^{b}	286.6 ± 0.55^{b}	81.5 ± 1.22^{b}	58.07 ± 0.25^{b}
III: ST treated	118.54 ± 0.21^{a}	130.2 ± 1.31^{a}	29.62 ± 0.40^{a}	62.5± 0.83^{a}
IV: ST +Nifedipine treated	112.16 ± 0.23^{a}	116.60 ± 1.21^{a}	25.31 ± 0.42^{a}	65.89 ± 1.51^{a}

Values are in mean ± SD; Number of animals in each group =6; a= p < 0.05 Vs Group II, b= p < 0.05 Vs Group I

efits in safety, efficacy and tolerability than individual drugs.

CONCLUSION

Nifedipine enhanced the lipid lowering property of simvastatin in hyperlipidemic rats. The current study demonstrated this combination therapy produces marked reduction in total lipid profile levels which were compared to simvastatin alone. The characteristic changes in pharmacodynamic profiles may be advantageous for the management of atherosclerosis.

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