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RESEARCH ARTICLE

COMPARATIVE EFFECT OF HIGH DOSE VERSES LOW DOSE LOVASTATIN ON SERUM LIPID PARAMETERS OF RATS TREATED WITH ATHEROGENIC DIET

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ABSTRACT

Atherosclerotic disease**s** presently showing alarming trend in developing countries and has posed to be of major public health importance. Unhealthy diet practice and life style aggravates the condition. Studies show that Lipid lowering agents at different doses can alter the serum lipid profile favourably and can significantly reduce the complications. Present study aims to evaluate the role of lovastatin, a lipid lowering agent at two different doses on serum lipid profile of rats fed on Atherogenic diet.

Materials and Methods: 36 male albino rats were divided in to six groups of six rats each. Group 1,2 and 3 received standard diet and 4,5 and 6 received Atherogenic diet. Group 1 & 3 served as control while other two groups received lovastatin at 2mg and 4 mg per kg respectively on both diet groups. Serum lipd profile was estimated at start of the experiment, end of six and twelve weeks by using kits.

Result: Both the doses of lovastatin was capable of reducing serum LDL and Total cholesterol to a significant extent compared to their control. However 4mg dose is more effective than low dose (2mg). The magnitude of this beneficial effect is not translated into serum triglyceride. However Serum HDL cholesterol level showed increasing trend in both diet treatment groups.

Conclusion: Both the doses of lovastatin is capable of preventing diet induced dyslipidemia in rats. Thus lower dose can be more preferable for primary and higher dose for secondary prevention of dyslipidemia.

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INTRODUCTION

Dyslipidemia often coexists with diabetes mellitus and are strong risk factors for development of coronary artery disease. (Park and Park, 1991; Lozano *et al*., 2016) Several workers have found that HMG COA reductase inhibitors are endowed with serum cholesterol lowering effect. Studies also reveals that drugs like beta blockers and calcium channel blockers can alter serum lipid profile. (Ohata and Sakamoto, 1984; Willis and Nagel, 1986; Sugano and Nakashima, 1986; Panangiotopoulos and Nayler, 1984) However some workers have shown that role of statins can vary as per dietary conditions as both diet and drug can influence the development of atherosclerosis (Henry and Bentley, 1981). Present study was carried out, to study the effect of lovastatin, a HMG COA reductase inhibitor at two different doses in the background of both standard diet and atherogenic diet in albino rats.

MATERIALS AND METHODS

36 male albino rats from a single vendor (M/s. F.N. Chakraberty, Calcutta) weighing between 150-200 Grams were selected and placed under controlled conditions and randomly assigned to six equal diet and treatment groups; (1) standard diet and vehicle (2) standard diet and lovastatin 2 mg per kg (3) Standard diet with lovastatin 4 mg per Kg. Gr 4,5 and 6 received atherogenic diet (AD) that was prepared by adding 2% cholesterol and 3% coconut oil to the standard diet. Group -4 served as control and was treated with vehicle while Gr 5 and 6 received same two doses of lovastatin along with AD. The daily amount of diet was fixed per rat and water was given ad libitum. Blood was collected from tail vein after an over-night fast. Serum lipid profile was estimated at the beginning, before starting of diet/drug (Basal value) and at the end of 6th and 12th week by using kits (marketed by; GLAXO) following Wybenga and Pillegi's method (Wybenga and Pileggi, 1970). Reading was taken on a photo colorimeter with yellow green filter. The data was analysed by using Student's paired 't' test for the same group and Student's unpaired "t' test between the groups.

RESULTS

Mean Serum total cholesteral (T_c), Triglyceride (TG) $VLDL_c$, LDL_c and HDL_c at basal, end of 6th and 12 weeks of different groups of rats are depicted in Tables (1-4).

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Table 1. Effect of lovastatin on Sr. Total cholesterol in rats

		Sr Cholesterol in mg/ dl		
GROUPS	TREATMENT(Diet/Drug)	BASAL	6Week	12Week
Gr-1	SD(Control)	51.80± 1.3	53.50± 1.26	54.33±1.09
Gr-2	SD+Lova2mg/kg	53.53±0.8	62.67±0.62	50.17±*0.54
Gr-3	SD+Lova4mg/kg	49.50±1.26	48.67±**b 0.49	46.56c** 0.5
Gr-4	AD(Control)	49.50±1.09	84.54±3.05	128.6± 2.14
Gr-5	AD+Lova2mg/kg	49.00± 0.63	52.33**± 0.67	52.50***± 0.56
Gr-6	AD+lova4mg/kg	49.83± 0.54	50.67±** 1.09	49.67±*** 0.95
* p<0.05, ** p<0.01,*** p<0.001 compared to control				
a- p<0.05, b- p<0.01, c- p<0.001 compared between doses				

Table 2. Effect of lovastatin on Serum LDL Cholesterol in rats

		Sr LDL Cholesterol in mg/ dl		
GROUPS	TREATMENT(Diet/Drug)	BASAL	6Week	12Week
Gr-1	SD(Control)	26.87± 1.14	28.08±1.3	28.62±1.19
Gr-2	SD+Lova2mg/kg	25.02±1.01	24.48± 2.12	23.62±* 1.07
Gr-3	SD+Lova4mg/kg	29.58± 1.17	28.38 ± 1.13	20.10**±1.47
Gr-4	AD(Control)	27.63± 1.49	93.08±1.89	125.83±4.21
Gr-5	AD+Lova2mg/kg	30.87±0.87	45.28±***b 1.95	43.45±***1.99
Gr-6	AD+lova4mg/kg	32.36± 1.25	31.15±***c 1.09	29.70±***c0.38
* p<0.05, ** p<0.01,*** p<0.001 compared to control				
a- p<0.05, b- p<0.01, c- p<0.001 compared between doses				

Table 3. Effect of lovastatin on Sr Triglyceride levels in rats

		Sr Triglyceride levels in mg/ dl		
GROUPS	TREATMENT(Diet/Drug)	BASAL	6Week	12Week
Gr-1	SD(Control)	79.80±3.49	79.48± 3.66	81.15± 4.43
Gr-2	SD+Lova2mg/kg	83.25±2.47	85.90±1.85	79.93±2.49
Gr-3	SD+Lova4mg/kg	75.38±3.23	74.88± 3.36	67.85*± 2.79
Gr-4	AD(Control)	71.78± 3.45	86.58±1.94	105.93±* 2.08
Gr-5	AD+Lova2mg/kg	81.47±3.28	79.00±3.21	95.33±** 2.45
Gr-6	AD+lova4mg/kg	90.05±2.5	86.33±1.99	81.93±*b 1.82
* p<0.05, ** p<0.01,*** p<0.001 compared to control				
a- p<0.05, b- p<0.01, c- p<0.001 compared between doses				

Table 4. Effect of lovastatin on Serum HDL Cholesterol in rats

		Sr HDL Cholesterol in mg/ dl		
GROUPS	TREATMENT(Diet/Drug)	BASAL	6Week	12Week
Gr-1	SD(Control)	27.18± 1.54	24.4±1.37	23.20± 0.93
Gr-2	SD+Lova2mg/kg	31.88± 1.59	31.13±*1.22	31.75±** 0.4
Gr-3	SD+Lova4mg/kg	30.10± 0.55	31.27±* 0.83	31.60±** 0.49
Gr-4	AD(Control)	29.96±1.66	25.85±2.17	21.93± 0.99
Gr-5	AD+Lova2mg/kg	27.93± 1.21	30.53± 0.71	31.22±** 1.19
Gr-6	AD+lova4mg/kg	28.92±1.63	30.88±0.93	33.36±**1.01
* p<0.05, ** p<0.01,*** p<0.001 compared to control				
a- p<0.05, b- p<0.01, c- p<0.001 compared between doses				

In control rats on standard diet; Serum LDL level did not alter significantly both at 6th and 12th week of observation. But both low and normal dose of lovastatin could effectively prevent the rise of Sr. LDL at 12th week. In contrast to this finding both the low and normal dose of lovastatin could effectively prevent the rise of serum LDL levels at 6th and 12 weeks. Thus preventive action of lovastatin could be more appreceated in hyper lipidemic background and at the earlier period of observation. As both 6th week value of LDL has reduced to mean 45.28 mg/dl compared to corresponding control value of 93.08 and 12 weeks the value has reduced from 125.83 to 43.45 at 12 weeks. Serum total cholesterol, showed exactly the similar partern of alteration as that of Sr. LDL_c (Table-2). Only difference obsered was that high dose of lovatatin could prevent the rise of serum total cholesterol earlier i.e. at 6th week in rats treated with standard diet. Both the doses of lovantatin could effectively present the rise of total serum cholestrol at both the time of observation. Table-3, demonstrates the effect of both doses of lovastain at the 6th and 12 week. Both the doses of lovastatin, effectively prevented the fall of serum HDL both of 6th and 12th week along with standard diet. But the same doses of lovastatin could only prevent the fall of HDL level at 12th week. This suggests that lovastatin is very effective in normalizing the serum HDL level in the background of normal lipid level. In contrast to all favourable effect, normal doses of lovastatin could only prevent the rise of serum triglyceride at 12 the week of observation in both the diet treatment groups. As 6th week value of lovastatin treatment group (86.58) almost equal to that of corresponding control (86.58mg/dl) in hyperlipidemic rats. This suggests a variable response of Lovastatin on serum triglyceride values.

DISCUSSION

In this study, attempt has been made to emphasize both the preventive and therapeutic role of statins (Lovastatin). Albino rats were made dyslipidemic by adding 2% cholesterol and cocoanut oil to the standard rat diet. This diet-induced alteration in lipid profile was confirmed in two control groups

of rats (Gr. 1 & 4) who was being treated with standard diet and hyperlipidemic diet respectively. Hyper lipidemic diet was prepared by adding 2% cholesterol and coconut oil to the standard diet. Lovastatin prevented the rise of Sr. LDL cholesterol only at 12 weeks along with standard diet. In contrast, both doses of loventatin could effectively prevent the rise of Sr. LDL level both at 6 and 12 weeks in hyperlipidemic rats. This suggests that lovastatin being a standard lipid lowering drug acts better and earlier in the background of hyperlipidemia. The effect on Sr. Total cholesterol is almost similarly affected by both dose of lovastatin. Another important finding in the study is that, the preventive action is dose dependent. This suggests that lower dose of lovastotin can be initiated as a preventive therapy in persons with no primary lipid abnormality but have risk factors whereas high dose lovastatin is beneficial as a preventive therapy having more significant lipid abnormality and to prevent end point like stoke, M.I & post CABG patients. This dose dependent preventive action has been observed in another study involving humans. In this study in aggressive treatment group 66% of patients had and LDL cholesterol level below 100mg% and 6% had a level of 130mg/dl. In contrast to this In moderate treatment group 5% had a level below 100mg/dl and 58% had level of 130mg% and the mean difference in subsequent annual visits ranged from 37 to 40 percent for aggressive treatment and 13 to 15% for moderate treatment group and suspected adverse effect was only 3% in aggressive treatment group to 2% in moderate treatment groups. Beneficial effect of lovastatin in eliveting Sr. HDL levels is well documented. But in this study. Beneficial effect of lovastatin was more marked in rats teated with standard diet than with hyperlipidemic diet as both 6 week and 12 week value of HDL is significantly higher at the both doses of lovastatin elevation of HDL compared to control groups was observed only at 12 weeks in rats on hyperlipidemic diet. (Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study, 2004; Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: Results from the VOYAGER meta-analysis; Lozano *et al*., 2016) Effect of lovastatin on serum triglyceride was rather in conclusive. Lowering of triglyceride observed only at 12 weeks and at highter dose in rats on standard diet. But both the doses could prevent the rise of Sr. triglyoride in hyperlipidomic rats. Value with normal dose of lovastatin, in hyper lipidemic rats found to be equal at 6 weeks showing ineffectiveness of lovastatin at 6 weeks. This finding can be explained by the fact that statins are the groups of drugs which act by increasing LDL receptor population and they reduce both the number & composition of LDL and have no direct effect on Sr. triqlyceride. (Karlson *et al*., 2015) Through there was clean evidence of atherosclerotic patches (macroscopic) in the ascending thoracic aorta of hyperlipidemic rats at 12 weeks but it was not practically possible to quantify or analyse on size of plaque became of limitation of setup. Then to summarize, both the lower and usual dose of lovastasin are effective in preventing rise of LDL & TC in rats. Thus lower dose is preferable for primary and higher dose for secondary prevention of dyslipidemia. Lower dose of lovastatin can also change lipids favourably (low LDL & high HDL) in rats on standard diet. Thus further clinical studies confirming these finding may open up new avenues for future application of this drugs in preventing dyslipidemia and thus atherosclerosis.

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